PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

# CODE OF PRACTICE REVIEW

NUMBER 41 AUGUST 2003

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

## Annual Report for 2002

The Annual Report of the Prescription Medicines Code of Practice Authority for 2002 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 127 complaints in 2002 as compared with 138 in 2001. There were 121 complaints in 2000.

The 127 complaints in 2002 gave rise to 122 cases as compared to 147 cases in 2001. The reason that the number of cases usually differs from the number of complaints is because some complaints involve more than one respondent company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

Of the 404 rulings made by the Code of Practice Panel, 311 (77%) were accepted by the parties, 77 (19%) were unsuccessfully appealed and 16 (4%) were successfully appealed. This compares with the 4.6% of rulings which were successfully appealed in 2001.

The Code of Practice Panel met 79 times in 2002 (92 in 2001) and the Code of Practice Appeal Board met 9 times in 2002 (11 in 2001). The Appeal Board considered appeals in 26 cases as compared with 32 in 2001.

The number of complaints made by pharmaceutical companies in 2002 exceeded the number made by health professionals, there being 59 from companies and 45 from health professionals. This was also the case in 1996, 1999 and 2001. Historically the usual pattern has been that the highest number of complaints each year has come from health professionals.

## New Code of Practice and Constitution and Procedure now in operation

The 2003 edition of the Code of Practice for the Pharmaceutical Industry came into operation on 1 July but, during the period 1 July to 30 September inclusive, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements newly introduced.

The new Constitution and Procedure for the Prescription Medicines Code of Practice Authority applies to complaints received on and after 1 July.

Copies of the 2003 Code of Practice booklet, which incorporates the Constitution and Procedure, are available on request.

## New product? New indication?

Companies are reminded that Clause 3.1 of the Code of Practice states that a medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply.

It should be borne in mind that as required by Clause 3.2, the promotion of a medicine must always be in accordance with the terms of its marketing authorization and must not be inconsistent with its summary of product characteristics.

## Electronic submission of complaints/ responses

The Authority is now asking that where possible letters of complaint and response from pharmaceutical companies are submitted by email or on disk as well as on paper as some are extremely lengthy and detailed.

## Declaration of sponsorship

Clause 9.10 of the Code states:

"Material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company.

The only exception to this is market research material which need not reveal the name of the company involved but must state that it is sponsored by a pharmaceutical company."

Sponsorship must be indicated in a reasonably prominent up-front manner so that it will be seen by readers before they read the publication and not hidden in small print at the bottom of a page.

Disclosure of sponsorship must be a condition of providing sponsorship. It is not acceptable for no disclosure to be made because those receiving sponsorship wish to keep it secret. This point can be particularly relevant in relation to the sponsorship of meetings.

# CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis at the Royal College of Nursing in central London.

These seminars comprise a full day course offering lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

Forthcoming Code of Practice seminar dates on which places remain available are:

Friday, 26 September

Tuesday, 21 October

Tuesday, 18 November

Short training sessions on the Code or full all day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

***For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 1443).***

## How to contact the Authority

Our address is:

Prescription Medicines
Code of Practice Authority
12 Whitehall
London SW1A 2DY

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 1473).

Direct lines can be used to contact members of the Authority.

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| Heather Simmonds: | 020 7747 1438 |
| Etta Logan: | 020 7747 1405 |
| Jane Landles: | 020 7747 1415 |

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

**CASE AUTH/1281/2/02**

# BRITISH ASSOCIATION OF DERMATOLOGISTS v GALDERMA

## Proposed Silkis clinical studies

**The British Association of Dermatologists complained on 27 February 2002 that Galderma had asked some of its members to enter patients into a comparative study of Silkis (calcitriol) v Dovonex (calcipotriol), with a large amount of documentation. The study was scientifically lacking in validity as it was not being performed on a double-blind basis, nor did it appear to have been through any form of local or multicentre research ethics committee.**

**Other members had been asked to 'try out' calcitriol on six or eight patients, in return for, it was believed, £400; for the study mentioned above it was £400 per patient.**

**It was alleged that these were unethical forms of marketing. That any comparative trial should be considered with release of individual information and patient consent forms without having ethics committee approval was quite beyond belief from a pharmaceutical company. This form of marketing should be discontinued.**

**The Panel noted that ten key opinion leaders had been approached with the study protocol. The process had been stopped by Galderma on 4 February before the complaint had been received. Nevertheless the Panel still had to consider the case.**

**The Panel noted that the study protocol stated that the purpose of the study was to assess the efficacy and safety of Silkis compared to Dovonex when the products were applied on sensitive areas affected with psoriasis. The study was an open-label, parallel group, multicentre study with patients instructed to use either Silkis Ointment or Dovonex Ointment twice daily for six weeks. Each investigator was to enrol up to ten patients, five in each group; no indication was given as to the number of investigators involved. Physicians assessing patients were to choose a target sensitive area to be treated. It was Galderma's intention to supply free samples of Silkis and for Dovonex to be prescribed, although this was not mentioned in the protocol. Patients were to be assessed for efficacy and tolerability at weeks 1, 4 and 6. Investigators were asked to aim to complete patient enrolment within 4 weeks. Each investigator was to receive a medical education grant of £400 to cover the administrative costs of the study.**

**The Panel noted that ten clinicians had been approached with the study protocol; the study had not proceeded further and no monies had been paid. The Panel questioned whether the proposed study would have answered valid scientific questions. There was no indication as to the total number of patients required to provide the data such as to enable the safety and efficacy of Silkis and Dovonex to be compared. In the Panel's view the proposed study was unacceptable as it was not a *bona fide* study and the arrangements were such that it would amount to paying doctors to use samples of Silkis Ointment. A sample was defined in the Code as a small supply of medicine provided to health professionals so that they might familiarise themselves with it and acquire experience in dealing with it. In that regard the Panel noted Galderma's submission that the purpose of the proposed evaluation was to give key opinion leaders in psoriasis clinical experience of Silkis, prior to its UK launch, in order to answer any questions they might receive from either primary or secondary care.**

**The Panel considered that the proposed study constituted disguised promotion of Silkis and ruled a breach of the Code. As the study was considered to be disguised promotion it followed that payments offered for participation were inappropriate and a breach was also ruled in that regard. Clinicians had been approached with the study protocol after Silkis had been granted a marketing authorization and so the Panel ruled no breach in that respect.**

**Overall the Panel considered that high standards had not been maintained and that the proposed study brought discredit upon the pharmaceutical industry. Breaches of the Code were ruled, including a breach of Clause 2. The Panel also decided to report Galderma to the Code of Practice Appeal Board. Galderma accepted the Panel's rulings of breaches, provides the necessary undertaking and assurance and did not appeal any of the Panel's rulings.**

**The Appeal Board was concerned about the two activities, firstly, a comparative study of Silkis versus Dovonex and secondly, a clinical evaluation of Silkis involving the provision of samples to doctors. The only documentation provided, however, referred to the comparative study, but this in itself was confusing as it also referred to the study as a clinical evaluation; payments of £400 were involved in both activities. Both activities had been stopped by Galderma. The Panel had made a global ruling and the Appeal Board considered that it would be helpful if it were made clear to Galderma that the provision of samples was permitted provided the requirements of the Code were met. It was inappropriate to provide samples and £400. The Appeal Board considered that Galderma would be well advised to consider all of its activities in relation to the requirements of the Code.**

**The Appeal Board decided that Galderma should be required to undergo an audit of its procedures relating to the Code of Practice. This would be carried out by the Authority.**

**The Appeal Board considered the audit report, Galderma's comments upon it and a paper prepared by the Authority comparing the report and Galderma's position thereon. In the Appeal Board's view Galderma's comments indicated that it had decided not to amend some of its procedures. This was of serious concern. The Appeal Board decided to report Galderma to the ABPI Board of**

**Management. It recommended that it should be made clear to Galderma that its response to the audit report was incompatible with continued membership of the ABPI.**

**At a subsequent meeting the Appeal Board considered additional material and a letter from Galderma, together with a further paper prepared by the Authority on Galderma's position.**

**The Appeal Board noted the additional material supplied by Galderma. It had previously considered that Galderma's response to the audit report was incompatible with continued membership of the ABPI. The Appeal Board considered that what had happened as a result of the audit was unprecedented. It was very concerned about Galderma's attitude to its responsibilities under the Code. The Appeal Board decided that the matter should be reported to the ABPI Board of Management and that the ABPI Board should be provided with all the papers relating to the case.**

**The ABPI Board was extremely concerned about the attitude of Galderma in relation to compliance with the Code. The Code set out agreed standards. Some of these related to internal company arrangements. Most of the Code's requirements were also requirements of UK law. The ABPI Board noted that in a letter sent prior to its meeting, in relation to the report, Galderma appeared to accept all the disputed points arising out of the audit. From the Galderma representative's questions and comments at the meeting, however, it appeared that the company was still disputing some issues.**

**The ABPI Board decided that a further audit should be carried out by the Authority in six months' time to ensure that steps were rapidly put in place to prevent a recurrence. The audit report would be considered by the ABPI Board. A strongly worded letter would be sent to Galderma.**

The British Association of Dermatologists complained to Galderma (UK) Limited about its promotion of Silkis Ointment (calcitriol). The letter was copied to the Authority and, in accordance with established practice, taken up as a complaint under the Code.

## COMPLAINT

The complainant, the chair of an Association sub-committee, stated that his committee had been approached by various members regarding the marketing of Silkis Ointment. The complainant gathered that some members had been asked to enter patients into a comparative study of Silkis versus Dovonex (calcipotriol), with a large amount of documentation, patient satisfaction forms etc, and including a patient consent form. As far as the complainant could tell from the correspondence, this study was scientifically lacking in validity as it was not being performed on a double-blind basis, nor did it appear to have been through any form of local or multicentre research ethics committee.

The complainant had also been informed that other members had been asked to 'try out' calcitriol on six or eight patients, in return receiving a financial incentive to do this (the complainant believed the amount offered was £400; for the study mentioned above it was £400 per patient).

There was a unanimous view from the committee on behalf of the British Association of Dermatologists that these were unethical forms of marketing. That any comparative trial should be considered with release of individual information and patient consent forms without having ethics committee approval was quite beyond belief from a pharmaceutical company. The complainant stated that the unanimous advice from his committee was that this form of marketing should be discontinued.

When writing to Galderma the Authority drew attention to Clauses 2, 3.1, 9.1, 10.2 and 18.1 of the Code.

## RESPONSE

Galderma stated that this had been a case of someone within Galderma 'jumping the gun', in approaching the dermatologists with a clinical evaluation protocol prior to seeking the necessary internal approval or that from the British Association of Dermatologists.

In response to a request from the Authority for further information Galderma stated that at no time did it intend to discredit or harm confidence in the industry.

Regarding the comparative study of Silkis Ointment and calcipotriol ointment, ten key opinion leaders were approached with a study protocol once Silkis had been granted a marketing authorization (12 December 2001). However, the process was stopped on 4 February after receiving feedback from the consultants concerned and from completing an internal evaluation of the project. At no time was either product distributed. Galderma's intention was to supply free medical samples of Silkis and for the opinion leaders to prescribe calcipotriol. Galderma provided copies of the documentation sent to the opinion leaders, detailing the protocol for the comparative study of Silkis and calcipotriol.

The £400, offered as an educational grant, was to cover the administrative costs incurred for the entire project and not per patient enrolled. No monies had been paid to the investigators as the project did not proceed.

Regarding the clinical evaluation of Silkis, the purpose of the evaluation was to give key opinion leaders in psoriasis clinical experience of Silkis, prior to its mass UK launch, in order to answer any question they might receive from either primary or secondary care.

Once again, the £400 medical education grant was to cover the administrative costs incurred by assessing five patients six times, and was in no way an incentive to prescribe, as the Silkis Ointment was to be provided as a free medical sample.

Galderma had spoken directly with the complainant and he was now happy that there was a misunderstanding. He was reassured that the comparative study was discontinued prior to the complaint and that the sum of £400 was to cover total administrative costs and was not a payment per patient.

## PANEL RULING

The Panel noted that following a telephone call and a letter from Galderma the complainant had written to Galderma stating that the matter had been addressed and could be closed. A copy of the complainant's letter had been sent to the Authority.

Both Galderma and the complainant had been advised that it was not possible for the complaint to be withdrawn as a response from Galderma had been received. Paragraph 15.1 of the Constitution and Procedure stated that a complaint could only be withdrawn up until such time as the respondent company's comments on the complaint had been received by the Authority. The Panel was obliged to consider the case. [After the Panel had made its ruling in this case, but before the minutes had been finalised, the Authority received a further letter from the complainant stating that the general view of his committee was that it would not wish to withdraw the complaint as it felt it was valid; the committee was satisfied that the issues affecting the member of the British Association of Dermatologists had been addressed by Galderma.]

The Panel noted that ten key opinion leaders had been approached with the study protocol. The process had been stopped by Galderma on 4 February. Nevertheless the Panel still had to consider the case.

The Panel noted that the only requirement in the Code relating to clinical assessments and the like was Clause 10.2 which stated that such activities must not be disguised promotion.

The study protocol stated that the purpose of the study was to assess the efficacy and safety of Silkis compared to Dovonex when the products were applied on sensitive areas affected with psoriasis. A list of sensitive areas was given. The study was an open-label, parallel group, multicentre study with patients instructed to use either Silkis Ointment or Dovonex Ointment twice daily for six weeks. Each dermatologist and/or GP was to enrol up to ten patients, five in each group; no indication was given as to the number of investigators involved or the intended total size of the patient population. Galderma had submitted that ten key opinion leaders had been approached. Physicians assessing patients were to choose a target sensitive area to be treated with either Silkis or Dovonex (the first included patient would receive Silkis; the second one Dovonex etc). The Panel noted that it was Galderma's intention to supply free medical samples of Silkis and for the opinion leaders to prescribe Dovonex, although this was not mentioned in the protocol. Following their entry into the study patients were to be assessed for efficacy and tolerability at weeks 1, 4 and 6. Efficacy was to be assessed through erythema, plaque elevation, scaling and global assessment of improvement on a target lesion. Global tolerability was also to be assessed; patients were to be asked to complete a satisfaction questionnaire. Investigators were asked to aim for patient enrolment to be completed within 4 weeks. Each investigator was to receive a medical education grant of £400 to cover the administrative costs of the study.

The Panel noted that ten clinicians had been approached with the study protocol; the study had not proceeded further and no monies had been paid. The Panel questioned whether the proposed study would have answered valid scientific questions. The study was to have been an open label study and there was no indication as to the total number of patients required to provide the data such as to enable the safety and efficacy of Silkis and Dovonex to be compared. In the Panel's view the proposed study was unacceptable as it was not a *bona fide* study and the arrangements were such that it would amount to paying doctors to use samples of Silkis Ointment. The supplementary information to Clause 17, Definition of Sample, stated that a sample was a small supply of medicine provided to health professionals so that they might familiarise themselves with it and acquire experience in dealing with it. In that regard the Panel noted Galderma's submission that the purpose of the proposed evaluation was to give key opinion leaders in psoriasis clinical experience of Silkis, prior to its mass UK launch, in order to answer any questions they might receive from either primary or secondary care.

The Panel considered that the proposed study constituted disguised promotion of Silkis. The Panel therefore ruled a breach of Clause 10.2 of the Code. As the study was considered to be disguised promotion it followed that payments offered for participation were inappropriate and a breach of Clause 18.1 was ruled in this regard. Clinicians had been approached with the study protocol after Silkis had been granted a marketing authorization and so the Panel ruled no breach of Clause 3.1 of the Code.

Overall the Panel considered that high standards had not been maintained and that the proposed study brought discredit upon the pharmaceutical industry. Breaches of Clauses 9.1 and 2 were ruled. The Panel also decided to report Galderma to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

## GALDERMA'S COMMENTS ON THE REPORT TO THE APPEAL BOARD

Galderma provided the requisite form of undertaking and assurance and commented in detail on the case. It outlined the circumstances which gave rise to the case and commented on the Panel's rulings. It was concerned that it was defending a matter where Galderma had withdrawn the activity before any formal complaint was lodged. Galderma stated that an event which never happened had been ruled in breach of the Code. Galderma stated that it was facing censure for assumptions of how these non-occurring activities could have breached the Code.

The Galderma representatives explained that the clinical evaluation had been initiated in haste by a member of its staff and the company approval process had not been followed. The member of staff had been disciplined and had received some additional retraining. The representatives outlined the arrangements for the generation and approval of materials. These had been amended as a result of this case.

The company representatives stated that the comparative trial had been sent to ten people and as soon as this was discovered the trial was stopped. The company representatives said that with regard to the provision of samples and the £400 payment, this was not happening.

### REPORT TO APPEAL BOARD

The Appeal Board was concerned about the activities. It noted that there were two activities, firstly, a comparative study of Silkis versus Dovonex and secondly, a clinical evaluation of Silkis involving the provision of samples to doctors. The only documentation provided, however, referred to the comparative study, but this in itself was confusing as it also referred to the study as a clinical evaluation; payments of £400 were involved in both activities. Both activities had been stopped by Galderma. The Panel had made a global ruling and the Appeal Board considered that it would be helpful if it were made clear to Galderma that the provision of samples was permitted provided the requirements of Clause 17 were met. It was inappropriate to provide samples and £400.

The Appeal Board considered that Galderma would be well advised to consider all of its activities in relation to the requirements of the Code.

The Appeal Board decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Galderma should be required to undergo an audit of its procedures relating to the Code of Practice. This would be carried out by the Authority.

### FURTHER CONSIDERATION BY APPEAL BOARD

Before the Appeal Board were the audit report, Galderma's comments and a paper prepared by the Authority comparing the audit report with Galderma's position thereon.

In the Appeal Board's view Galderma's comments on the audit report indicated that it had decided not to amend some of its procedures. This was of serious concern. The Appeal Board decided to report Galderma to the ABPI Board of Management in accordance with Paragraph 12.2 of the Constitution and Procedure. It recommended that it should be made clear to Galderma that its response to the audit report was incompatible with continued membership of the ABPI.

### FURTHER CONSIDERATION BY APPEAL BOARD

Before the Appeal Board at a subsequent meeting were further material received from Galderma, a second paper prepared by the Authority comparing the audit report and Galderma's position thereon, and a letter from Galderma.

The Appeal Board noted all the additional material supplied by Galderma. It had previously considered that Galderma's response to the audit report was incompatible with continued membership of the ABPI. The Appeal Board considered that what had happened as a result of the audit was unprecedented. It was very concerned about Galderma's attitude to its responsibilities under the Code. The Appeal Board decided that the matter should be reported to the ABPI Board and that the ABPI Board should be provided with all the papers relating to the case.

### REPORT TO ABPI BOARD OF MANAGEMENT

The ABPI Board was extremely concerned about the attitude of Galderma in relation to compliance with the Code. The Code set out agreed standards. Some of these related to internal company arrangements. Most of the Code's requirements were also requirements of UK law. The ABPI Board noted that in a letter sent in relation to the report Galderma appeared to accept all the disputed points arising out of the audit. It appeared from the Galderma's representative's questions and comments that it was still disputing some issues.

The ABPI Board decided that a further audit should be carried out by the Authority in six months time to ensure that steps were rapidly put in place to prevent a recurrence. The audit report would be considered by the Board. A strongly worded letter would be sent to Galderma.

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| **Complaint received** | **27 February 2002** |
| **PMCPA proceedings completed** | **23 January 2003** |
| **ABPI Board consideration** | **3 April 2003** |

**CASE AUTH/1366/10/02**

# ORTHO BIOTECH v ROCHE

## Promotion of NeoRecormon

**Ortho Biotech complained about the promotion of NeoRecormon (epoetin beta) by Roche. The materials at issue were a loose insert, a company statement and a 'Dear Doctor' letter. Ortho Biotech marketed Eprex (epoetin alpha).**

**Ortho Biotech stated that erythropoietins were a common therapy for patients with various forms of anaemia. Recently, there had been an increased number of post-marketing reports of loss of effect where pure red cell aplasia (PRCA) was suspected in patients treated with Eprex and some with other erythropoietic products, including NeoRecormon. Ortho Biotech did not dispute that there had been more reports of PRCA with Eprex than NeoRecormon. However, Ortho Biotech's concerns related to the misleading and inappropriate manner in which Roche compared the two products in this respect.**

**The loose insert featured the headline 'Would you continue to drive People you feel Responsible for in a Car with a questionable sAfety record? Why take a risk?' This was followed by a discussion of data presented by Casadevall *et al* that suggested a link between PRCA and both Eprex and NeoRecormon. The advertisement concluded that 'Data clearly indicates that there is a difference between the Epoetins that can profoundly effect [sic] clinical outcomes'. The claim 'Starting treatment with NeoRecormon (Epoetin Beta) gives you and your patients the security of an unchanged formulation and the reassurance of a consistent 10-year safety record' appeared beneath a section headed 'Minimising risks Optimising outcomes'.**

**Ortho Biotech stated firstly that the insert drew a clear and inappropriate analogy between use of Eprex and travel in unsafe cars, with all the negative imagery that that entailed and alleged that this was tasteless, offensive and disparaging of Eprex. Secondly, the clear implication of the insert was that PRCA was not associated with NeoRecormon. This was inconsistent with the approved labelling for the product and failed to take into account the reports of PRCA experienced with it. Thirdly, the insert stated there had been no formulation changes for NeoRecormon. The Committee on Proprietary Medicinal Products (CPMP)'s Scientific Discussion during the approval of the product showed unequivocally that this was untrue.**

**Ortho Biotech alleged the headline failed to take into account the special nature of medicines and its intended audience and therefore fell well below the standards expected under the Code. Ortho Biotech queried whether the item had been certified in accordance with the Code and alleged that overall the item bought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2 of the Code.**

**The Panel noted that the journal within which the loose insert appeared, Nephrology Dialysis Transplantation, was published in English in the UK and circulated to UK doctors. Advertisements placed in the journal were thus subject to the Code.**

**The Panel noted that one half of one side of the insert featured the statement 'Would you continue to drive People you feel Responsible for in a Car with a questionable sAfety record? Why take a risk?' The statement was printed in white on a black background. The aim of the insert was to compare the incidence of PRCA observed with NeoRecormon with that seen with Eprex. In the Panel's view the statement was tantamount to comparing Eprex to an unsafe car. The Panel considered that describing Eprex in this way was disparaging and failed to recognise the special nature of medicines; breaches of the Code were ruled. The Panel considered that in this regard the insert had brought discredit upon the pharmaceutical industry and a breach of Clause 2 of the Code was ruled.**

**The Panel noted that Roche had not approved the insert for use in the UK due to the statement about car safety. The insert had appeared in the journal as part of an initiative by Roche, Switzerland and the instruction not to circulate the insert in the UK had not been followed. The Panel accepted that Roche in the UK had not wanted the insert to be distributed in the UK and had not approved its use. Nonetheless the Panel had to rule a breach of the Code as the insert had been distributed in the UK despite not being certified for such use.**

**The Panel noted that the incidence of PRCA in patients with renal failure was greater in Eprex – treated patients than in those treated with NeoRecormon. The Eprex summary of product characteristics (SPC) stated that PRCA was a rare event, reported in patients with chronic renal failure after months to years of treatment with Eprex or other erythropoietins. As the cases of PRCA were mainly associated with the subcutaneous route of administration, prescribers were advised to administer Eprex intravenously to patients with chronic renal failure where feasible. The SPC for NeoRecormon stated that in very rare cases, neutralising anti-erythropoietin antibodies with or without PRCA occurred during rHuEPO therapy.**

**The insert drew attention to a paper by Casadevall *et al* which was a study of 13 patients with chronic renal failure in whom severe transfusion-dependent anaemia developed after an initial haematological response to epoetin. In all 13 patients the anaemia was due to PRCA in association with neutralizing anti-erythropoietin antibodies. Eleven of the patients were receiving epoetin alpha (Eprex) at the time of onset of anaemia, another had been receiving epoetin alpha until just 1 month before diagnosis of anaemia and the last patient had only received epoetin beta (NeoRecormon).**

**The Panel noted that the insert discussed the characteristics of the 13 patients in Casadevall *et al*. It was stated that the patient who had only received epoetin beta had had an immunocomplex mediated nephropathy in a background of hypersensitivity.**

**'This may suggest a possible lack of a direct correlation between the development of PRCA and epoetin beta, and clarification of possible causative factors is on-going.' The Panel considered that the insert not only gave the impression that the PRCA reported in this patient was not connected to use of NeoRecormon but that it was not a problem associated with the product at all. The Panel accepted that while the definitive cause of the PRCA in the patient treated only with epoetin beta was not known, a case of PRCA had been reported and PRCA was referred to as a possible adverse effect of treatment in the NeoRecormon SPC. The Panel considered that the way in which the relationship between PRCA and NeoRecormon had been presented, and thus the relative difference between NeoRecormon and Eprex in that regard, was misleading. The Panel ruled breaches of the Code. The Panel considered that the information about PRCA and NeoRecormon was not consistent with the product's SPC. A breach of the Code was ruled. The Panel did not consider that the comparisons made with regard to PRCA disparaged Eprex *per se* and the Panel ruled no breach of the Code in that regard. The Panel did not consider that, in respect of the discussion generally about PRCA, the insert warranted a ruling of a breach of Clause 2.**

**The Panel noted that the pharmaceutical form of NeoRecormon had changed over the years; it had been formulated as a freeze-dried powder and then changed to a solution in pre-filled syringes. Roche stated in its response that NeoRecormon's formulation had remained essentially unchanged. The insert, however, referred a number of times, in absolute terms, to NeoRecormon's unchanged formulation. The Panel considered that these statements were thus misleading and ruled a breach of the Code.**

**Ortho Biotech complained about the following statements contained within the Roche company statement headed 'PRCA issue not linked to all EPO products':**

**'… other versions of EPO, such as epoetin beta (NeoRecormon), which is also administered primarily subcutaneously in the UK, is NOT associated with this increased risk of PRCA. There have been no cases of PRCA reported exclusively with epoetin beta (NeoRecormon) use in the UK.'**

**'In comparison with this 'background' occurrence of PRCA, since 1998 there have been reports of 141 cases of PRCA associated with Eprex worldwide. This should be compared to only one confirmed case in patients taking epoetin beta (NeoRecormon) exclusively, and two cases where it cannot be excluded. In the UK there have been 15 cases of PRCA associated with Eprex and NONE with epoetin beta (NeoRecormon).'**

**'… the increased rise in PRCA cases associated with epoetin alpha (Eprex) may be linked to this change in manufacturing process.'**

**Ortho Biotech's primary concern was the suggestion that there had been 141 cases of PRCA reported for Eprex and only one confirmed case with NeoRecormon. This failed to compare like with like. To have arrived at a figure of 141 cases Roche had to have included all suspected cases of PRCA reported for Eprex irrespective of whether the case had been confirmed by bone marrow biopsy or the detection of anti-erythropoietin antibodies and also cases where there had been combined erythropoietin therapy. However, when Roche cited cases of PRCA with its product, it used a much narrower case definition, and excluded all cases that had not been confirmed by antibody testing and also all cases of combined therapy.**

**Ortho Biotech alleged that the selective use of UK safety data resulted in misleading and unfair comparisons between the products. Such comparisons unfairly disparaged Eprex. The statements made in relation to the safety profile for NeoRecormon were inconsistent with both the NeoRecormon marketing authorization and its SPC.**

**Finally, Ortho Biotech was concerned about Roche's untrue assertion that the manufacturing process for its product 'has remained identical over the 10 years since epoetin beta (NeoRecormon) was launched'. This was clearly not so.**

**Ortho Biotech further alleged that the company statement, issued as a press release, constituted an illegal and misleading advertisement to the general public. It clearly included product claims intended to promote the prescription of NeoRecormon or to encourage patients to ask their doctors for it.**

**The Panel noted that the first paragraph of the Roche company statement discussed a letter issued by Ortho Biotech warning doctors that, as the risk of PRCA was associated with subcutaneous administration, they should use intravenous Eprex in patients with chronic renal failure. The second paragraph explained that subcutaneous injections were more convenient for the patient. The third paragraph reminded readers that NeoRecormon could be used subcutaneously and 'is NOT associated with this increased incidence of PRCA. There have been no cases of PRCA reported with exclusively epoetin beta (NeoRecormon) use in the UK'. The Panel considered that the company statement by referring to UK-only data gave the impression that NeoRecormon was not associated with any risk of PRCA; this impression was strengthened by the heading 'PRCA issue not linked to all EPO products'. The Panel noted its comments and rulings above regarding PRCA. The company statement was misleading and inconsistent with the SPC. Breaches of the Code were ruled. These rulings were appealed by Roche. The Panel did not consider that the company statement was such as to disparage Eprex or that it warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.**

**The Appeal Board noted that the company statement cited reports of 141 cases of PRCA 'associated with Eprex worldwide' since 1998 and the number of cases for NeoRecormon were 'only one confirmed case in patients taking [NeoRecormon] exclusively, and two cases where it cannot be excluded'. At the appeal hearing Roche stated that at the time of the company statement the company was aware of at**

**least 12 cases of PRCA on the Roche database where patients had received both Eprex and NeoRecormon. The Appeal Board considered that the criteria for determining the number of cases of PRCA associated with each product was not the same; like was not being compared with like.**

**The Appeal Board considered that the claim 'epoetin beta … is NOT associated with this increased incidence of PRCA', followed by 'There have been no cases of PRCA reported with exclusively epoetin beta (NeoRecormon) use in the UK', gave the impression that NeoRecormon was not associated with any risk of PRCA. The Appeal Board noted that this was not consistent with the SPC and upheld the Panel's ruling of a breach of the Code. The Appeal Board considered that the statements about PRCA and NeoRecormon were misleading and upheld the Panel's rulings of breaches of the Code.**

**With regard to the manufacturing process of NeoRecormon, it was stated that 'this process has remained identical over the 10 years since epoetin beta (NeoRecormon) was launched'. The Panel noted its previous comments and considered that the claim that the manufacturing process had remained identical over 10 years was misleading. A breach of the Code was ruled. Upon appeal by Roche the Appeal Board upheld the Panel's ruling.**

**The Panel noted that the company statement was given to the press. It was not an advertisement for a prescription only medicine to the public and no breach of the Code was ruled. The Code required that information about medicines which was made available to the public either directly or indirectly must be factual and presented in a balanced way; *inter alia* it must not be misleading with respect to the safety of the product. The Panel noted its rulings above and ruled a breach of the Code. Upon appeal by Roche the Appeal Board upheld the Panel's ruling.**

**Ortho Biotech noted that a letter about the use of NeoRecormon for anaemia of malignancy following recent advice on route of administration of Eprex in chronic renal failure which had been sent to oncologists, haematologists and palliative care physicians referred to a communication that had been sent to members of the chronic renal failure community recommending a change in the route of administration of Eprex and sought to provide information 'to clarify the situation'. The discussion that followed made a number of comparisons between the products and concluded that no alteration to the route of administration of NeoRecormon was necessary. Ortho Biotech alleged that the letter made misleading comparisons and sought to unfairly disparage Eprex. Ortho Biotech also objected to Roche's assertion that 'NeoRecormon had had no major reformulation change since introduction'.**

**The Panel noted that the letter in question had been sent to those health professionals with an interest in treating anaemia of malignancy. The letter began by stating 'You may recently have received a communication letter from Ortho Biotech which provided amended advice on the route of administration of epoetin alfa (Eprex) in Chronic Renal Failure (CRF) patients because of reports of PRCA occurring in this population'. The letter continued by comparing the differences between Eprex and NeoRecormon with regard to product and formulation, storage and case incidence of PRCA. With regard to the incidence of PRCA in patients with chronic renal failure, the letter stated that there was only one confirmed case in patients taking epoetin beta exclusively and two cases where the association could not be excluded. The penultimate paragraph of the letter reassured the reader that NeoRecormon could continue to be administered subcutaneously and stated in bold 'The Summary of Product Characteristics (SmPC) for NeoRecormon has not changed in this regard. No alteration to the route of administration is necessary'.**

**The Panel noted that there had been no reports of PRCA in patients receiving epoetin for the treatment of anaemia of malignancy. Ortho Biotech thus had not had to write to oncologists, and others in the same therapy area, to advise them to administer Eprex intravenously where feasible. The Panel considered that the letter disparaged Eprex by highlighting a problem in one therapy area which had no clinical relevance to the audience to which the letter was sent. The Panel ruled a breach of the Code. This ruling was appealed by Roche.**

**The Appeal Board noted that in July 2002 Ortho Biotech had issued a 'Dear Doctor' letter regarding Eprex and PRCA. That letter had contained amended advice on route of administration and reminded readers of the correct storage and handling of Eprex. As a result of that letter Roche had received a number of enquiries from clinicians concerned that the information they had received about Eprex might also apply to NeoRecormon. Some of these enquiries had come from oncologists and haematologists. As a response to this Roche had issued the letter in question, dated 21 August 2002, to oncologists, haematologists and palliative care physicians.**

**The Appeal Board considered that although there had been no reports of PRCA in patients being treated for anaemia of malignancy, Roche was nonetheless justified in making clinicians involved in their care aware of the issues regarding PRCA and epoetin therapy. The Appeal Board noted that some of the target audience, ie haematologists, might be involved in the care of renal patients who had developed PRCA as a result of treatment with Eprex. In that respect the Appeal Board did not consider that the letter had disparaged Eprex and thus ruled no breach of the Code.**

**The Panel noted its comments above with regard to PRCA. The Panel considered that the letter minimised the risk of PRCA in patients with chronic renal failure treated with NeoRecormon and did not give the reader enough information about Eprex such that a valid comparison of the two products could be made. Given the audience to which the letter was directed the Panel considered that the letter was misleading. Breaches of the Code were ruled. Upon appeal by Roche the Appeal Board upheld the Panel's rulings.**

**The letter stated that '… NeoRecormon has had no major reformulation change since its introduction'. The Panel noted that this statement was different to those considered above which were absolute statements of no change. The Panel considered that the claim now at issue reflected Roche's submission that the formulation had remained essentially unchanged. No breach of the Code was ruled. This ruling was appealed by Ortho Biotech. The Appeal Board referred to its previous comments and considered that the claim was misleading in breach of the Code.**

Ortho Biotech complained about the promotion of NeoRecormon (epoetin beta) by Roche Products Limited. Ortho Biotech marketed Eprex (epoetin alpha). The materials at issue were a loose insert, a company statement and a 'Dear Doctor' letter. Ortho Biotech stated that it had attempted to resolve the issues with Roche.

### Background Information from Ortho Biotech

Ortho Biotech stated that erythropoietins were a common therapy for patients with various forms of anaemia. Recently, there had been an increased number of post-marketing reports of loss of effect where pure red cell aplasia (PRCA) was suspected in patients treated with Eprex and some with other erythropoietic products, including NeoRecormon. Ortho Biotech did not dispute that there had been cases of PRCA in patients receiving Eprex, or indeed that there had been more reports of PRCA with Eprex than NeoRecormon. However, Ortho Biotech's concerns related to the misleading and inappropriate manner in which Roche compared the two products in this respect.

The NeoRecormon summary of product characteristics (SPC) stated 'In very rare cases, neutralizing anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO [recombinant human erythropoietin] therapy'. Any assertion that PRCA was not associated with NeoRecormon treatment was inconsistent with the approved labelling for that product.

Ortho Biotech had, through its parent company (Johnson & Johnson), conducted full analysis of all reports of PRCA according to common definitions, testing methodologies and accepted practices within the pharmacovigilance community. The company had adopted a broad case definition and analysis to include any report of a patient who was administered some form of epoetin therapy, experienced a loss of therapeutic effect which was suspected to be related to PRCA, regardless of availability of bone marrow examination results or evidence of anti-erythropoietin antibodies. This case definition included cases where treatment with multiple erythropoietic products was reported (ie combined cases).

Up until the end of May 2002, antibodies against erythropoietin in 66 patients of the 141 with suspected PRCA had been identified. Among these 66 case reports, there were 12 in which the patient also received NeoRecormon. In addition to these combined cases, Roche had stated that there was at least one case of PRCA where the patient had only received NeoRecormon, and two cases where it could not be excluded.

Ortho Biotech noted that NeoRecormon was a successor to Recormon, originally marketed by Boehringer Mannheim. Although Ortho Biotech did not know the full regulatory history of Recormon, the product was authorised in the UK as early as 1991. It was initially formulated as a freeze-dried powder, with ampoules of water for injection, in doses of 1000, 2000 and 5000 IU. The Committee on Proprietary Medicinal Product's (CPMP) Scientific Discussion included in the EMEA's European Public Assessment Report (EPAR) for NeoRecormon made it clear that the product had been reformulated on numerous occasions, to include products such as pre-filled syringes with solution for injection and two-chamber cartridges to be used with a pen system. Both of these must be new formulations, since they were legally-classified as new pharmaceutical forms, and all of these would inevitably have resulted in changes in the manufacturing processes for the product.

Roche had claimed that its product benefited from unchanged formulation and/or manufacturing processes since its introduction; this clearly had no basis in science, law or fact.

### Background Information from Roche

Roche stated that epoetin alpha (Eprex) and epoetin beta (NeoRecormon) were synthetic versions of the endogenous compound, erythropoietin. Recently a longer acting epoetin, darbepoietin alfa had also been introduced in the UK. They stimulated production of red blood cells in the bone marrow and were licensed for the treatment of anaemia secondary to chronic renal dysfunction and cancer chemotherapy. Although often viewed by the medical community as being the same, there were important differences in pharmacology and formulations of epoetin alpha and beta. For example they had different plasma half-lives, receptor affinities, and effects on the haemoglobin levels for a given dose; also different posologies, and formulation stability. However the molecular structure of the synthetic epoetins was almost identical to endogenous erythropoietin such that the body recognised them as self and normally did not mount an antibody response.

The differences in formulation were relevant in respect of recent increasing reports of antibody formation and PRCA associated with Eprex.

PRCA was a rare haematological condition in which the bone marrow failed to produce red blood cells whilst production of other blood cell lines remained unaffected. In the past it had been seen following certain viral infections, malignancies and medicines. However anti-erythropoietin antibodies were a newly described cause of this condition. Antibodies neutralised systemic erythropoietin (both endogenous and injected) and therefore removed the stimulus to invoke red blood cell progenitor maturation in the bone marrow. This led to a severe form of anaemia with the reduction or absence of red blood cells and the absence of the production of new red blood cells in the bone marrow (PRCA). The patient had to stop

all epoetins because antibodies to one particular epoetin cross-reacted with all. This was a serious safety issue, as the patient might have to be on regular blood transfusions indefinitely. The number of reports of PRCA for Eprex was higher than that for NeoRecormon.

Epoetins were administered subcutaneously or intravenously in microscopic amounts via various 'presentations' (single and multi-dose vials, pre-filled syringes, etc). Therefore epoetins must be formulated with other materials to ensure that the three-dimensional structure remained stable. If the molecular structure was altered epoetins might no longer be recognised as self and neutralising antibodies produced. In particular epoetin formulations contained stabilisers to prevent aggregation or other structural changes which resulted in lost efficacy, and/or an immune response. Ortho Biotech and Roche formulated their respective epoetins in different ways.

Originally Eprex was formulated with human serum albumin (HSA). Eprex was the brand marketed in Europe and many other countries in the world excluding the US. A similar HSA formulation was used in two brands of epoetin alpha marketed in the US under the names of Epogen and Procrit. In 1998 HSA was removed from Eprex, following an EU directive aimed at reducing the risk of transmissible spongiform encephalopathy, and replaced with new excipients. Roche believed that this was the current formulation as marketed in Europe, Canada and other countries apart from the US where Epogen and Procrit were not changed and remained formulated with HSA.

In contrast, NeoRecormon had never contained human derived products such as HSA. Instead a stable formulation was developed using a variety of synthetic stabilisers including 5 amino acids. This formulation, which had remained essentially unchanged since introduction, was more stable than Eprex as shown by a comparison of the relevant SPCs. Thus Eprex should be kept cooled at 2-8°C and must not be shaken, exposed to light or have the cooling chain broken. In contrast NeoRecormon, which must also be kept at the 2-8°C, did not have light exposure or shaking restrictions and for some presentations the cooling chain could be broken for up to 5 days at room temperature for a single period. NeoRecormon also had a longer shelf life than Eprex.

Roche submitted that these formulation differences were possibly the most important single factor in explaining the differences in incidence of anti-epoetin antibodies and PRCA. These important differences were not mentioned in Ortho Biotech's complaint.

Roche agreed that the SPC for NeoRecormon was as stated by Ortho Biotech. Prior to March 2001 however the SPC stated 'there is no evidence of the development of neutralising antibodies to epoetin beta in humans'. This was based on all available data at that time including results of testing more than 4600 patients in 35 clinical trials.

In July 1999, Professor Nicole Casadevall, a haematologist in Paris, had reported three cases of anti-erythropoietin antibodies associated with PRCA in renal dialysis patients to the French health authorities. By January 2000 Roche was aware of 5 reports in Casadevall's series; three with epoetin alpha, one beta and one mixed. Roche concluded that the SPC should be changed to reflect these new data from Casadevall even though there was no indication that this was a specific epoetin beta effect. This change to the SPC came into effect in March 2001 (the variation was submitted in July 2000) with the statement 'In very rare cases, neutralising anti-erythropoietin antibodies with or without PRCA occurred during rHuEPO therapy'. Roche informed Ortho Biotech of the intention to change the SPC based on an analysis of known data for all epoetins; a similar change was not made to the SPC for Eprex at that time.

Thereafter the number of reports increased markedly for Eprex before Ortho Biotech altered its SPC. Eventually Roche presumed the company was directed by the CPMP to change the SPC for Eprex and inform health professionals about the change via a 'Dear Doctor' letter in November 2001. According to the letter, there were by then 40 confirmed or suspected cases of PRCA, mostly occurring after 1998. Casadevall published her case series in February 2002.

Roche stated that all of its statements or 'assertions' about antibodies and PRCA had been consistent with the SPC, the above facts and with those detailed further below.

Roche noted that Ortho Biotech appeared to suggest that it had a larger number of reports of PRCA with Eprex due entirely to its 'broad case definition' and that its number was not out of line with the number of reports of PRCA with NeoRecormon. The company continued later in its complaint to assert that Roche's comparisons were selective and not based on an up-to-date evaluation. In this regard, Ortho Biotech claimed to have done a full and expansive research and analysis of all reports. However, Ortho Biotech only quoted the number of reports up to May 2002. The letter of complaint was dated 1 October. Given that Ortho Biotech itself made the point that particular care should be taken to ensure that emerging clinical or scientific opinion was presented in a balanced manner and with a sound statistical basis it was misleading to use figures that were several months out of date in its complaint. Clearly it could not be full or expansive unless there had been no further reports of PRCA since May 2002; unlikely in view of the increases month on month up to then.

Roche believed that Ortho Biotech's statement that it had identified only 66 patients with PRCA and antibodies, of whom 12 had also received NeoRecormon, was misleading. It did not indicate how many of the 141 cases identified by the end of May 2002 had been tested for antibodies. The French regulatory authority which was the Rapporteur for Eprex in the EU stated in July 2002 that of the 141 cases, 114 were confirmed by marrow biopsy and 66 out of 80 tested patients had antibodies. Thus a simple inspection of these numbers indicated that 34 patients with marrow confirmed PRCA had not been tested for antibodies and at least a proportion of these would be expected to have neutralising antibodies.

Ortho Biotech referred to 12 combined cases. It should be noted that switching of epoetins was relatively common, sometimes for commercial reasons, but also when there was lack of efficacy with a particular epoetin. This was highly relevant when investigating cases of PRCA. The fact that 12 patients had also taken NeoRecormon was not evidence that PRCA was caused by NeoRecormon in these patients. In the series reported by Casadevall at least one such patient was switched just before final diagnosis of PRCA. However PRCA was often not suspected as a cause of anaemia and it was usually several months from the onset of antibodies until PRCA developed and was diagnosed. Patients might have switched epoetins during this times often as a last resort (particularly before doctors became aware of PRCA as an issue) if the haemoglobin concentration had fallen despite increasing the dose.

Roche noted that three of these 12 cases were forwarded to Roche UK as part of the earlier correspondence in this complaint and these and other aspects of the complaint had been settled between the companies. Roche stated then, as now, that all requirements for safety reporting had been adhered to in this regard. However it was relevant that of the three cases cited at that time two were originally reported as Eprex cases and the third was a case of haemolytic anaemia, not PRCA.

In addition even if one accepted that there were only 66 patients with antibodies and suspected PRCA and that 12 were mixed cases then this would indicate that 54 were related purely to Eprex which was some 18 times higher than exclusive reports for NeoRecormon.

In certain countries both epoetins were marketed so there could be difficulty in determining which brand was used. However this was not the case in Canada where only Eprex was available.

According to a joint communication of Ortho Biotech and the Canadian Health Authority, up to 30 April 2002, there were 27 cases of PRCA. All of these cases, if confirmed, would have been exclusively due to Eprex as there was no possibility of the patients having NeoRecormon or any other epoetin. This allowed a direct comparison of exclusive cases between products. Thus, at the time of the communication, whereas Roche had only one confirmed case and possibly 2 others throughout the world, Ortho Biotech had 27 cases in Canada alone and at least 54 cases with confirmed PRCA and confirmed antibodies in patients exclusively treated with Eprex.

Roche stood by the statement it had made about reports of PRCA with NeoRecormon. These statements were consistent with the statement of 19 July 2002 (in relation to the emergency restriction on Eprex) mentioned in the communication from the French regulatory authority, which had responsibility for Eprex in EU. This stated: 'Although a few cases of (PRCA) have also been observed with other marketed erythropoietins (less than about 10 cases throughout the world) the great majority of these cases were reported with Eprex'. Other erythropoietins would include Epogen, Procrit, NeoRecormon and darbepoetin.

Roche noted that, whatever the number of individual reports with different definitions and different dates raised by Ortho Biotech in its complaint, the real issue was that the number of reports escalated with Eprex which had resulted in restrictions on its use in Europe.

Roche stated that Ortho Biotech appeared to be confused by the difference between formulation, presentation or 'pharmaceutical form' (the wording used in the SPC). These terms might be frequently interchangeable but in the context of Roche's communications the meaning was clear. Moreover Ortho Biotech did not mention the relevance of formulation to the issue of PRCA. Roche had introduced new presentations (pharmaceutical forms) over the years including the pre-filled syringe, multi-dose vial and the RecoPen. However in each of these presentations the active ingredient, epoetin beta, had been formulated with essentially the same excipients. In particular the excipients responsible for stabilising the epoetin molecule to prevent aggregation or molecular structural change had remained essentially the same. This was important as Roche and many others believed that instability leading to aggregation etc might reduce the potency and expose molecular sites that acted as antigens.

The NeoRecormon formulation had been found to be stable at different physical conditions of temperature, light and shaking. As detailed above these characteristics differed from those of Eprex as detailed in the relevant SPCs, and NeoRecormon was clearly a more intrinsically stable product because of this.

The change in formulation of Eprex to an HAS-free formulation was a likely cause of the increased susceptibility to antibody formation. Although subcutaneous administration was also more likely to induce antibody formation compared to intravenous administration this was true for all epoetins and did not explain the excess reports for Eprex which had mostly occurred after 1998 as stated by Ortho Biotech. The relevance of the change in formulation was originally suggested in an editorial of the New England Journal of Medicine discussed below.

Although the relevance of formulation change had not been mentioned in any of Ortho Biotech's communications in the UK, it was cited as one probable cause by a senior scientist of Ortho Biotech's parent company in a presentation to US financial analysts. The web-cast of this meeting was posted on the investor's page of the parent company's web-site. The relevant sections were highlighted. In addition several countries in which Eprex was marketed had sent out similar 'Dear Doctor' letters as in Europe including the regulatory authority in Singapore in conjunction with Ortho Biotech which in addition cited formulation change and poor handling techniques as likely causes of PRCA. In addition Ortho Biotech alluded to the problem of stability in its 'Dear Doctor' letters of November 2001 and July 2002 when emphasising the need for strict handling procedures in the distribution chain. However Ortho Biotech did not mention why this was so important.

Roche noted that Ortho Biotech asserted that Roche had made repeated claims that its products benefited

from unchanged formulation and/or manufacturing processes and that this had no basis in science, law or fact. The issue with Eprex had been an increased incidence of reports of PRCA since 1998; the changes to the formulation to remove HSA had been postulated as a likely reason for this. No such changes had to be made to NeoRecormon and there had been no similar increase in the incidence of PRCA.

### 1 Loose leaf journal insert in Nephrology Dialysis Transplantation

This insert appeared in the April 2002 edition of the journal.

The insert featured the headline 'Would you continue to drive **P**eople you feel **R**esponsible for in a **C**ar with a questionable s**A**fety record? **Why take a risk?**' This was followed by a discussion of data presented by Casadevall *et al* and associated editorial in the New England Journal of Medicine that suggested a link between PRCA and both Eprex and NeoRecormon. The advertisement concluded that 'Data clearly indicates that there is a difference between the Epoetins that can profoundly effect [sic] clinical outcomes'. The claim 'Starting treatment with NeoRecormon (Epoetin Beta) gives you and your patients the security of an unchanged formulation and the reassurance of a consistent 10-year safety record' appeared beneath a section headed 'Minimising risks Optimising outcomes'.

#### COMPLAINT

Ortho Biotech stated that it had three main concerns. Firstly, the insert drew a clear and inappropriate analogy between use of Eprex and travel in unsafe cars, with all the negative imagery that that entailed. Ortho Biotech alleged that this was tasteless, offensive and disparaging of Eprex. Secondly, the clear implication of the insert was that PRCA was not associated with NeoRecormon. This was inconsistent with the approved labelling for the product and failed to take into account the reports of PRCA experienced with it. Finally, the insert stated there had been no formulation changes for NeoRecormon. The CPMP's Scientific Discussion during the approval of the product showed unequivocally that this was untrue.

Ortho Biotech alleged that the insert breached the Code in numerous ways, the cumulative effect of which was to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The most significant of these alleged breaches were:

***Clause 9.1*** The headline drew an analogy between the use of Eprex and the possibility of a motor accident and was therefore in poor taste and likely to cause offence. It failed to take into account the special nature of medicines and its intended audience and therefore fell well below the standards expected under the Code.

***Clause 8.1*** Critical references to another company's products must be substantiated, fair, balanced and accurate. The suggestion that NeoRecormon had been associated with only a single report of PRCA, which the insert simply dismissed, was factually inaccurate and misleading. Ortho Biotech strongly believed that the manner in which Eprex and NeoRecormon were compared unfairly disparaged and denigrated Eprex. There could be no justification for drawing an analogy between use of an approved medicine and travel in an unsafe car. Such unjustified knocking copy was a clear breach of the Code.

***Clause 7.2*** Roche's comparison was based on a selective interpretation of the results of a single publication, rather than reflecting an up-to-date evaluation of all the evidence, including reports of PRCA Roche had received for NeoRecormon. The Code made it clear that particular care should be taken to ensure that emerging clinical or scientific opinion, that had yet to be resolved in favour of one generally accepted viewpoint, was presented in a balanced manner and with a sound statistical basis. In light of Roche's own prescribing information and reports of PRCA that Ortho Biotech knew Roche had received, it believed that reference to the New England Journal of Medicine article alone did not accurately reflect Roche's knowledge about epoetin beta and its association with PRCA at the time that the insert was used. There could also be no basis for its assertion that NeoRecormon had not been the subject of reformulation during its lifetime.

***Clause 7.3*** The advertisement failed to comply with the requirements for comparative advertising of medicines. These failures included the presentation of the existing data in a misleading manner and the unfair denigration of Ortho Biotech and Eprex.

***Clause 7.9*** The advertisement contained claims about the safety of NeoRecormon that were not reflected in the available evidence or clinical experience.

***Clause 3.2*** The advertisement was inconsistent with both the NeoRecormon marketing authorization its SPC.

***Clause 2*** Taken as a whole, the breaches of the Code outlined above and the advertisement's poor taste, disregarded the spirit and the letter of the Code and the available clinical evidence. They could only bring discredit upon, and reduce confidence in, the pharmaceutical industry.

***Clause 14.1*** Ortho Biotech stated that when it approached Roche about this insert, it was informed that the company needed to take 'instructions from the NeoRecormon team at Roche's Headquarters in Basel, Switzerland, which was responsible for the advertisement'. However, Roche UK, not its Swiss parent, was the marketing authorization holder for the product. Moreover, the advertisement was placed in a UK journal in the UK subsidiary's name and it alone was legally responsible for the content of this insert and its dissemination. Clause 14.1 of the Code required that all promotional material was pre-approved by two qualified signatories, whose names had been notified to the MCA's Advertising Unit and to the Authority. Ortho Biotech could only assume that it was not done.

#### RESPONSE

Roche stated that this insert was discussed by the two companies earlier in the year and the complaint

resolved. Copies of emails were provided. Roche had given an undertaking that this insert would not be used again in the UK and this had been adhered to. Roche was surprised that this item was subject to the same complaint that had been resolved between companies.

Roche explained that the insert was prepared and released by its parent company, F Hoffman-La-Roche Switzerland. Roche examined the insert as part of the UK approval system and decided that although the claims relating to the incidence of antibodies and PRCA were valid, the imagery on the front page was probably not appropriate for a UK audience. It was therefore not approved for use in the UK and it was agreed within the company that it would not be so distributed. However, as it was an insert in a journal which had a wide circulation throughout Europe this posed logistical problems in excluding the UK from the usual distribution chain. In the event the instruction to restrict the circulation of the insert to countries other than the UK was not successful and Roche was made aware of this only after it had appeared in the journal.

Firstly Roche addressed the main contents of the item. There was a clear statement in the heading that it was based on the article by Casadevall *et al*. This was the first paper of its kind so it reflected most of the available world literature on this topic. It was claimed that the 'NEJM [New England Journal of Medicine] analysis points to key differences between epoetins'. This was supported by the data presented by Casadevall and the accompanying editorial in the New England Journal of Medicine. As the editorial raised the issue of formulation change as a possible explanation for these differences it was justifiable to point out in the insert that no formulation changes had been made to NeoRecormon. Roche referred to its statements above regarding formulation changes.

The NeoRecormon SPC referred to reports of antibodies and PRCA associated with epoetins in general (rHuEPO). At the time the only confirmed case with NeoRecormon was the one mentioned in Casadevall's report and the insert discussed the relevance of this patient's history of hypersensitivity and unique antibody profile which differed from that of the other Eprex patients. The claims in the insert were justified.

Casadevall *et al* pointed out that before its case series there had only been three previous cases of PRCA associated with epoetin therapy. The 13 cases in the main part of the article were identified between May 1998 and November 2000, that was after the change in formulation of Eprex. Twelve of the patients were treated in France and one in the UK. All received epoetin by the subcutaneous route. Twelve received epoetin alpha in the previous few months before onset of PRCA. Only one was treated exclusively with NeoRecormon (epoetin beta) and this patient had a different antibody profile to the other cases. According to 'note added in proof' at the end of the article another nine patients all treated with Eprex were identified with PRCA and antibodies. The chances that 21 of 22 spontaneously reported cases of this previously almost unheard of condition could be due to chance were remote. In the editorial concern was expressed that the majority of PRCA reports had occurred after Eprex was reformulated. It was stated that there were a further 25 cases in Europe but that PRCA was encountered less frequently in USA.

Thus the statement in the insert that 'NEJM analysis points to key differences between epoetins' was justified by the data presented. In addition the New England Journal of Medicine editorial suggested that the differences in incidence between Europe and USA raised the question whether the antigenicity of the European product had been slightly enhanced by a change in the manufacturing process. It was therefore reasonable and balanced to state in the insert that 'should the hypothesis about manufacturing prove to be correct it would solely relate to epoetin alpha' and that no changes in the formulation of NeoRecormon had occurred.

This was also justified as the editorial referred to the major change of formulation of Eprex. It was clear that the author was not referring to additional presentations of epoetins introduced over the years by Roche. In this regard the company was curious that no response, written or verbal had been made by Ortho Biotech to this article and editorial. The Panel might consider why Ortho Biotech should split hairs about the meaning of formulation yet make no statement in its complaint about the relevance.

Based on the evidence published in the New England Journal of Medicine, and in view of the serious consequences of developing PRCA, a condition that could lead to a life time dependence on blood transfusions, Roche considered that it was justified in bringing this to the attention of prescribers, and highlighting that they had a choice when prescribing epoetin. In addition, every event since this insert justified the general question posed in this item, that was 'knowing the data which would you prescribe?'

Following publication the FDA wrote a letter to the New England Journal of Medicine in response to the Casadevall article which stated:

- Data submitted to the FDA suggested important differences among brands of epoetin with regard to PRCA reports.
- For the period July 1997 to December 2001, 82 cases of PRCA were reported of which 4 were on Epogen (epoetin alpha in USA), none on Procrit (epoetin alpha in USA), and 78 on Eprex (including the Casadevall reports).
- The amount of medicine distributed appeared not to account for differences of reporting among brands.

Casadevall, in response to this letter, stated, also in the New England Journal of Medicine, '[FDA] support our conclusions that *Eprex is involved* [emphasis added] in the recent occurrence of [PRCA] …'. This was her clearly stated conclusion of her data. Indeed she added that since her publication another 19 patients had been identified so that 39 patients in total were known in her series of which 36 were on Eprex at the time of the onset of anaemia, and one received NeoRecormon exclusively. (Please note there was an error in the publication which she corrected later.) These patients had been collected from France (26), UK (6), Australia, Switzerland and Canada.

In May a 'Dear Doctor' letter was issued in Switzerland recommending intravenous Eprex instead of subcutaneous administration in predialysis, peritoneal and haemodialysis patients and suggested that the risk benefit of subcutaneous administration be weighed in chronic renal insufficiency. In June a similar warning was issued in Canada advising use of the intravenous route where feasible. However it was not until July 2002, following the urgent safety restriction imposed on Eprex by the EU Pharmacovigilance working party, that Ortho Biotech finally advised UK health professionals of similar recommendations incorporated into a major change to the SPC. The Eprex Rapporteur, the French regulatory authority, stated: 'Although a few cases of (PRCA) have also been observed with other marketed erythropoietins (less than about 10 cases throughout the world) the great majority of these cases were reported with Eprex'.

Roche stated that it had not been mandated to make similar changes to the NeoRecormon SPC in any country including those of the EU. The SPC had not been changed in respect to the licensed route of administration. Roche had not seen a similar rise in the rate of reporting of PRCA exclusively to NeoRecormon.

Roche stated that the insert, based on all data available at the time, had been vindicated by these subsequent events. The main point of the item was to bring this problem to the attention of the profession because this was an extremely serious safety issue, which had not previously been published in such numbers and where there were differences in incidence between epoetins. The means by which the attention of the profession could be attracted were various. Standards of suitability and taste varied throughout Europe; what was considered unsuitable in one country might be entirely acceptable in another. In addition what one person considered suitable might be deemed unacceptable by another. This was a serious safety issue and as such it justified an image that demanded attention. This was approved at the highest levels of Roche. It was approved for countries in Europe which took a different view from the UK about the taste or otherwise of such imagery. In no country in the EU had Ortho Biotech or its subsidiaries complained to Roche which suggested the imagery was not considered tasteless, offensive etc to its affiliates in these countries. At no point in the insert was Eprex disparaged. In addition Roche was not aware of any complaint from the medical profession in Europe including the UK. Roche categorically denied that the insert brought the industry into disrepute.

***Clause 9.1*** As stated above the analogy with the car was used to bring this serious condition to the attention of the prescriber. The insert was used throughout Europe. As such the means by which attention was sought should be seen as European wide rather than as a purely UK issue. Europe was composed of different cultures, languages etc and as such what might be considered insensitive in one country might be entirely acceptable in others. The insert was approved at senior level in the company with due consideration for the special nature of medicines and its intended heterogeneous audience. Arbiters of taste or suitability should put themselves in the position of a patient about to be treated with subcutaneous epoetin. Such arbiters now had the advantage of hindsight in that they knew that within weeks of this insert's appearance Ortho Biotech would be warning doctors in Switzerland, and Canada (but not in the UK at that time) not to use subcutaneous Eprex in certain patients because of fears about PRCA. In addition by July the Pharmacovigilance working party of the CPMP would be issuing an urgent safety warning which would mandate Ortho Biotech to issue the same warning throughout Europe. Roche submitted that with such knowledge any judgement of the suitability of the insert would acknowledge that although stark it was not altogether inappropriate in the circumstances. Indeed any doctor whose attention was attracted by the headline and who subsequently took heed of the advice might well have saved his patient from a serious life long adverse reaction. Roche denied any breach of Clause 9.1.

***Clause 8.1*** Roche stated that the insert was fair and accurate and based on the article in the New England Journal of Medicine. The piece commented only on the cases reported in the New England Journal of Medicine article and did not comment on the overall incidence of PRCA cases with one or the other product. Otherwise, instead of mentioning only 12 cases it would have referred to the additional 9 cases described in the addendum to the paper all on Eprex and at least 40 Eprex cases reported in the 'Dear Doctor' letter of the 19 November 2001. However the statements in the insert reflected the totality of data available, which included the 'Dear Doctor' letter, and Roche did not accept that it disparaged Eprex.

The insert provided the profession with a comment about the mechanism postulated in the editorial, stating that should the hypothesis about manufacturing be correct it could not relate to NeoRecormon. In addition the insert pointed out the imbalance in reports in the New England Journal of Medicine.

Roche noted that Ortho Biotech's statement that 'the suggestion that NeoRecormon had been associated with only a single report of PRCA, which the advertisement dismissed' was inaccurate and misleading. Casadevall's paper and her subsequent follow up letter in the New England Journal of Medicine made clear that there was only one case with NeoRecormon. The advertisement discussed this in the context of the patient's previous history and antibody profile, which was uniquely different to the other cases. The fact of the matter was that in this one publication based on post marketing reports only one of 22 such reports implicated NeoRecormon. It made statements about the safety profile of NeoRecormon which were accurate. The advertisement then justifiably stated, based on the evidence available, that there was a difference between the two referenced epoetins that could affect outcomes. This was self evident from the data. Roche denied any breach of Clause 8.1.

***Clause 7.2*** Roche stated that the comparison regarding the safety concerns was based on all of the Casadevall's paper, data available at that time and not

just on a single publication. These included the 'Dear Doctor' letter sent by Ortho Biotech on 19 November 2001 which stated 40 cases of confirmed or suspected PRCA with Eprex, and Roche's own database. As stated above 'Roche's own prescribing information' was based on a complete review of all the known reports of antibodies with or without PRCA associated with epoetins in general. This included the one confirmed case described by Casadevall. The statements in this promotional piece accurately reflected the information. This was supported by the fact that: Roche had not been required to send a 'Dear Doctor' letter warning about antibodies and PRCA; the company had not sequentially warned countries that its product should not be given subcutaneously, NeoRecormon had not been the cause of an urgent safety restriction requiring a major change to its SPC and a further 'Dear Doctor' letter throughout EU restricting its subcutaneous administration.

In addition the insert was consistent with the statement from the French regulatory authority that: 'Although a few cases of (PRCA) have also been observed with other marketed erythropoietins (less than about 10 cases throughout the world) the great majority of these cases were reported with Eprex'.

The postulation turned out to be correct with the advice given by Ortho Biotech in its letter of 17 July. This made far-reaching and drastic recommendations as to how Eprex should be administered. Roche was not required to make any such recommendations.

Roche stated that the issues about reformulation had been covered already in detail above. In 1998 the stabiliser in EU formulations of Eprex was changed from HSA to HAS to polysorbate 80 and glycine. The stabilizers in NeoRecormon had remained essentially unchanged. Although Ortho Biotech was arguing over the minutiae of the formulation, the fact remained that the formulation remained essentially the same. This could not be said for Eprex. Roche denied any breach of Clause 7.2.

***Clause 7.3*** Roche reiterated that the claims made in the insert were substantiable.

***Clause 7.9*** Roche stated that the claims made about the safety concerns were justified as noted above. The advertisement reflected the data available and as presented by Casadevall *et al*. At the time of going to press the situation was as stated, that only one case of PRCA with anti-erythropoietin antibodies related to exclusive NeoRecormon treatment was known to Roche. Roche stated that the quoted data from its clinical development programme had never been contested. In addition the claims were consistent with the NeoRecormon SPC and with the information provided by the regulatory authorities. Roche denied any breach of Clause 7.9.

***Clause 3.2*** The prescribing information, which formed part of the insert, included the information about PRCA that was compliant with Roche's marketing authorisation.

***Clause 2*** For the reasons outlined above Roche denied that the insert brought discredit upon, and reduced confidence in, the pharmaceutical industry. The contents of the insert were fair and balanced and reflected the data. The imagery of the front page was not considered appropriate for the UK but was approved at the highest level in Switzerland and in other EU countries. As evidence that this imagery was acceptable in other countries in the EU it was relevant that no affiliate of Ortho Biotech in the EU had complained and nor was Roche aware of any complaint from the members of the medical profession in the UK or Europe. If on seeing this advertisement in the UK a doctor decided he would not put a particular new patient on subcutaneous Eprex he would have minimised the possibility of PRCA, action that was now finally, at last, recommended by Ortho Biotech.

***Clause 14.1*** Roche referred to its explanation above regarding the use of the insert in the journal. Although Nephrology Dialysis Transplantation was published in the UK, it was the official publication of the European Dialysis and Transplant Association. It had a widespread circulation in Europe. In addition there had been no complaint from any other affiliate as pointed out above. However as stated above, the insert was seen by Roche and was not approved for distribution in the UK. Roche carried out its responsibilities in this regard and denied breach of Clause 14.1.

## PANEL RULING

The Panel noted that the journal Nephrology Dialysis Transplantation was published in English in the UK (ref Willings Press Guide) and circulated to UK doctors. Advertisements placed in the journal were thus subject to the Code. The insert at issue had been approved for use by Roche's parent company in Switzerland. It was, however, an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas divisions. Roche in the UK was therefore responsible under the Code for the insert.

The Panel noted that one half of one side of the insert featured the statement 'Would you continue to drive **P**eople you feel **R**esponsible for in a **C**ar with a questionable s**A**fety record? **Why take a risk?** The statement was printed in white on a black background. The aim of the insert was to compare the incidence of PRCA observed with NeoRecormon with that seen with Eprex. In the Panel's view the statement at issue was tantamount to comparing Eprex to an unsafe car. The Panel considered that describing Eprex in this way was disparaging and ruled that there had been a breach of Clause 8.1 of the Code. The Panel also considered that to describe a licensed medicine so, failed to recognise the special nature of medicines. A breach of Clause 9.1 was ruled. The Panel considered that in this regard the insert had brought discredit upon the pharmaceutical industry and ruled that there had been a breach of Clause 2 of the Code.

The Panel noted that Roche had examined the insert as part of the UK approval system and decided that the statement about car safety was probably not suitable for a UK audience. The insert was therefore not approved for use in the UK. It had appeared in the journal Nephrology Dialysis Transplantation as

part of a European initiative by Roche in Switzerland and the practicalities of the journal's distribution were such that the insert could not be removed from those copies being delivered in the UK. The Panel accepted that Roche in the UK had not wanted the insert to be distributed in this country and had therefore not approved its use. Nonetheless the Panel had to rule a breach of Clause 14.1 of the Code as the insert had been distributed in the UK despite not being certified for such use.

The Panel noted that the incidence of PRCA in patients with renal failure was greater in Eprex – treated patients than in those treated with NeoRecormon. The Eprex SPC stated that PRCA was a rare event, reported in patients with chronic renal failure after months to years of treatment with Eprex or other erythropoietins. As the cases of PRCA were mainly associated with the subcutaneous route of administration, prescribers were advised to administer Eprex intravenously to patients with chronic renal failure where feasible. The SPC for NeoRecormon stated that in very rare cases, neutralising anti-erythropoietin antibodies with or without PRCA occurred during rHuEPO therapy.

The insert drew attention to a paper by Casadevall *et al* which had been published in the New England Journal of Medicine. The authors studied 13 patients with chronic renal failure in whom severe transfusion-dependent anaemia developed after an initial haematological response to epoetin. In all 13 patients the anaemia was due to PRCA in association with neutralizing anti-erythropoietin antibodies. Eleven of the patients were receiving epoetin alpha (Eprex) at the time of onset of anaemia, another had been receiving epoetin alpha until just 1 month before diagnosis of anaemia and the last patient had only received epoetin beta (NeoRecormon). An editorial which highlighted the Casadevall paper and discussed drug-induced autoimmune red-cell aplasia appeared in the same edition of the journal.

The Panel noted that the insert discussed the characteristics of the 13 patients. It was stated that the patient who had only received epoetin beta had had an immunocomplex mediated nephropathy in a background of hypersensitivity. 'This may suggest a possible lack of a direct correlation between the development of PRCA and epoetin beta, and clarification of possible causative factors is on-going.' The Panel considered that the insert not only gave the impression that the PRCA reported in this patient was not connected to use of NeoRecormon but that it was not a problem associated with the product at all. The Panel accepted that while the definitive cause of the PRCA in the patient treated only with epoetin beta was not known, a case of PRCA had been reported and PRCA was referred to as a possible adverse effect of treatment in the NeoRecormon SPC. The Panel considered that the way in which the relationship between PRCA and NeoRecormon had been presented, and thus the relative difference between NeoRecormon and Eprex in that regard, was misleading. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.9 of the Code. The Panel considered that the information given about PRCA and NeoRecormon was not consistent with the product's SPC. A breach of Clause 3.2 was ruled. The Panel did not consider that the comparisons made with regard to PRCA disparaged Eprex *per se*; critical references to another company's products were acceptable under the Code provided that they were accurate, balanced, fair, etc. The Panel ruled no breach of Clause 8.1 in that regard. The Panel noted that rulings of breaches of Clause 2 of the Code were regarded as a sign of particular censure and reserved for such. The Panel did not consider that, in respect of the discussion generally about PRCA, the insert warranted a ruling of a breach of Clause 2.

The Panel noted that the pharmaceutical form of NeoRecormon had changed over the years; it had been formulated as a freeze-dried powder and then changed to a solution in pre-filled syringes. Roche stated in its response that NeoRecormon's formulation had remained essentially unchanged. The insert, however, referred a number of times, in absolute terms, to NeoRecormon's unchanged formulation. The Panel considered that these statements were thus misleading and ruled a breach of Clause 7.2 of the Code.

During its consideration of the journal insert the Panel was concerned to note that it was not made clear that PRCA had only been reported in patients with chronic renal failure. In other patient groups for whom epoetin treatment was indicated, ie patients receiving chemotherapy, this complication of therapy had not been reported. There was no complaint in this regard. The Panel was also concerned that prescribing information was difficult to read. Its type size was smaller than that recommended in the supplementary information to Clause 4.1 of the Code. The Panel requested that Roche be advised of its concerns.

### 2 Roche company statement

The Roche company statement headed 'PRCA issue not linked to all EPO products' was issued as a press release (dated 19 July 2002) to specialist medical and scientific journals and health correspondents in the UK.

## COMPLAINT

Ortho Biotech complained about the following statements:

'… other versions of EPO, such as epoetin **beta** (NeoRecormon), which is also administered primarily subcutaneously in the UK, is **NOT** associated with this increased risk of PRCA. There have been no cases of PRCA reported exclusively with epoetin **beta** (NeoRecormon) use in the UK.'

'In comparison with this 'background' occurrence of PRCA, since 1998 there have been reports of 141 cases of PRCA associated with Eprex worldwide. This should be compared to only one confirmed case in patients taking epoetin **beta** (NeoRecormon) exclusively, and two cases where it cannot be excluded. In the UK there have been 15 cases of PRCA associated with Eprex and NONE with epoetin **beta** (NeoRecormon).'

'… the increased rise in PRCA cases associated with epoetin alpha (Eprex) may be linked to this change in manufacturing process.'

Ortho Biotech's primary concern was the suggestion that there had been 141 cases of PRCA reported for Eprex and only one confirmed case with NeoRecormon. This failed to compare like with like. To have arrived at a figure of 141 cases Roche had to have included all suspected cases of PRCA reported for Eprex irrespective of whether the case had been confirmed by bone marrow biopsy or the detection of anti-erythropoietin antibodies and also cases where there had been combined erythropoietin therapy. However, when Roche cited cases of PRCA with its product, it used a much narrower case definition, and excluded all cases that had not been confirmed by antibody testing and also all cases of combined therapy. If one applied the same case definition to NeoRecormon as Roche did for Eprex, one could identify at least two cases of antibody-mediated PRCA in patients who received only NeoRecormon, and several other cases in which patients received both NeoRecormon and Eprex. Ortho Biotech stated that this obviously did not include NeoRecormon PRCA reports of which it was unaware. However, the prescribing information suggested that such cases existed.

Ortho Biotech was also concerned about the selective use of UK safety data, which Roche used to give the misleading impression that there had been no reports where NeoRecormon had been used exclusively. This could not be justified on the basis that the advertisement was aimed at a UK audience.

Finally, Ortho Biotech was concerned about Roche's untrue assertion that the manufacturing process for its product 'has remained identical over the 10 years since epoetin beta (NeoRecormon) was launched'. This was clearly not the case.

Roche would undoubtedly argue that the issue that its company statement sought to address was what it alleged was an increased rate of PRCA with Eprex. However, this was not relevant to the basis of the complaint. Ortho Biotech's concern was Roche's selective use of safety data to make misleading and unfair comparisons between the products. Roche might also argue that it had simply quoted figures regarding Eprex from company sources and various regulatory bodies. Again, this was irrelevant. It was the misleading way Roche had done this that concerned Ortho Biotech.

Ortho Biotech alleged that the company statement breached the following provisions of the Code:

***Clause 8.1*** The comparisons contained in the document were unsubstantiated, unfair, unbalanced and inaccurate. The suggestion that NeoRecormon had been associated with only a single report of PRCA, was factually inaccurate and misleading, as was the assertion that its manufacture had remained unchanged for 10 years. The manner in which the comparison of the products was made unfairly disparaged and denigrated Eprex.

***Clause 7.2*** The comparison Roche made was based on a selective interpretation and misleading presentation of certain limited data, rather than reflecting a balanced evaluation of evidence available to it.

***Clause 7.3*** The statement failed to comply with the requirements for comparative advertising of medicines. These failures included the presentation of the existing data in a misleading manner and the unfair denigration of Eprex.

***Clause 7.9*** The document contained claims about the safety of NeoRecormon that were not reflected in the available evidence or clinical experience.

***Clause 3.2*** The statements made in relation to the safety profile for NeoRecormon in the UK were inconsistent with the terms of both the NeoRecormon marketing authorization and its SPC.

***Clause 20*** The document constituted an illegal and misleading advertisement to the general public. The Code considered that this encompassed promotional materials made available to the general public either directly or indirectly 'via press conferences, press announcements, television and radio reports, public relations activities and the like'. For the reasons outlined above, there was no realistic argument that this document simply comprised factual, balanced, non-promotional information, since it clearly included product claims intended to promote the prescription of NeoRecormon or to encourage patients to ask their doctors for it. (Ortho Biotech referred to Cases AUTH/624/10/97, AUTH/830/1/99 and AUTH/804/11/98).

## RESPONSE

Roche stated that in view of the importance of PRCA as a safety issue, the fact that 'Dear Doctor' letters had been sent by Ortho Biotech, and because of publicity in the medical and financial press, it was justified in making such a statement. Roche stated that it thought the issues regarding this statement had been resolved in intercompany correspondence.

Roche stated that the context in which this press release was written must be emphasised. Following the New England Journal of Medicine article in February 2002 PRCA had become a pressing issue for the medical community. From the start there had been an excess of cases associated with Eprex administration. This was reflected in the subsequent change of route of administration recommended for Eprex but not for NeoRecormon. There was speculation in the scientific and financial media about this in relation to both products. Unfortunately before definitive guidance from the European Agency there was some confusion and concern amongst clinical staff as to the significance of the problem.

Roche stated that it largely refrained from commenting on the increasing incidence of PRCA as it did not consider that there existed an increasing incidence with its product. The SPC stated that very rarely antibodies had been detected with epoetins. The Roche database, which included all reports, was frequently analysed and there was no indication of an increasing incidence of antibodies or PRCA with NeoRecormon, nor any evidence that the SPC should be changed.

The company statement was, however, prepared and approved in the UK and released to the medical press and selected health correspondents as a response to much media speculation following the 'Dear Doctor'

letters in Switzerland and Canada referred to above, and statements made by Ortho Biotech to the media in the States. In addition Ortho Biotech circulated a statement at the European Renal Association-European Dialysis and Transplant Congress meeting in Copenhagen in July that the company was about to send a 'Dear Doctor' letter throughout Europe recommending the change in administration advice referred to above.

The company statement came out after the 'Dear Doctor' letters from Ortho Biotech of the 17 July indicating that the recommended route of administration of Eprex should be changed. No explanation was offered to clinicians as to why this issue had arisen but it 'reminded' the medical community about how to store the product. The letter also contained a suggestion that the issue was likely to be similar for other products. Following this letter Roche had several enquiries from the media and health professionals as to whether NeoRecormon would be subject to similar restrictions.

The letter stated that Ortho Biotech was aware of 141 post marketing reports of PRCA of which 114 were confirmed with bone marrow examination. Roche noted that Ortho Biotech had questioned how it had arrived at 114 cases; Roche had used only the numbers referred to in Ortho Biotech's letters to the health professions. Roche resented very much, and denied, the repeated allegations that it had misled the community about the incidence of PRCA associated with NeoRecormon.

All of these assertions flew in the face of the facts and actions taken by the regulatory authorities in Europe to limit the prescribing of Eprex but not other epoetins. Roche had fulfilled all of its reporting responsibilities to the European regulatory authorities that, based on routine surveillance, had not restricted the marketing authorization for NeoRecormon.

Roche noted that Ortho Biotech also alleged that it was misleading to state that there had been no reports of PRCA exclusively with NeoRecormon in the UK and that this could not be justified on the basis that the advertisement was aimed at a UK audience. Roche stated that actually, this seemed to it to be a major justification. In addition the UK was an excellent model for comparing incidences in situations where both products were available and treatments were switched between products for various reason. According to the Ortho Biotech Swiss letter there were 15 PRCA cases in the UK as at 31 March 2002. At the time no UK physician had informed Roche of a case with NeoRecormon. Thus the statement made in Roche's company statement was accurate. Over the time period 1998-2002 it was relevant that the market share in the UK was Eprex 60%: NeoRecormon 40%, so these reporting figures reflected a surprising excess in cases of Eprex if this was truly a generic phenomenon.

Roche stated that it had already answered the complaint about the manufacturing process above.

Overall Roche denied any selectivity or imbalance in the use of data. The statements made in its company statement reflected the overall data as was known and the situation as it was at that time with regard to safety warnings about Eprex.

The statement that other versions of epoetin including NeoRecormon were not associated with the increased incidence of PRCA was consistent with: the data available at the time; the fact that the Pharmacovigilance working party had required an urgent safety restriction only for Eprex; the fact that no similar restriction was required for NeoRecormon or darbepoetin and the statements in the NeoRecormon SPC.

Roche considered its company statement was factual, presented in a balanced way and not misleading with respect to the safety of NeoRecormon as required in Clause 20.2 of the Code. It was not intended to promote prescription of the product therefore it was not to be considered as an advertisement.

***Clause 8.1*** At the time of the release, NeoRecormon was associated with one confirmed case in patients taking epoetin beta exclusively and two further cases where it could not be excluded. Roche failed to see how this could be construed as misleading. Roche disagreed that this unfairly denigrated Eprex. Ortho Biotech's own communication (17 July 2002) reported 114 biopsy-confirmed cases of PRCA associated with Eprex. This did not unfairly denigrate Eprex.

The letter sent out by the French regulatory authority on 19 July stated that 'Although a few cases of erythroblastopenia have also been observed with other marketed erythropoietins (less than about ten cases throughout the world), the great majority of these cases were reported with Eprex'. The press release was consistent with this information (bearing in mind that the agency included other product data eg Epogen, Procrit, darbepoetin), which was from a reliable source and could not be construed as misleading. Roche rejected the assertions made by Ortho Biotech.

***Clause 7.2*** Again the number of NeoRecormon cases reported at the relevant date remained as above. These data were not open to interpretation but reflected an up-to-date assessment of all the evidence and clinical expertise. Although no formal statistical analysis of the cases had been performed, it was clear that there was a large imbalance in the numbers of PRCA with anti-erythropoietin antibodies between epoetins. This was reflected in Ortho Biotech's 'Dear Doctor' letter of 17 July. Roche denied a breach of Clause 7.2.

***Clause 7.3*** Roche denied that that the company statement was misleading. Much of the data presented came from Ortho Biotech's own figures, and the rest was reflected in the plethora of communications from regulatory bodies throughout Europe and Canada. The statement would only be considered unfairly denigrating to Eprex if it was factually incorrect at the time of press.

***Clause 7.9*** Roche strenuously denied that the statement contained claims about the safety of NeoRecormon that were not reflected in the available evidence or clinical experience. At the time of writing the company had not been required to advise the medical community anywhere in the world of any change to NeoRecormon's route of administration.

***Clause 3.2*** The statement of one confirmed case and two further cases where the causation could not be

excluded was entirely consistent with Roche's label. NeoRecormon was not subject to the same recommendations about its route of administration as Eprex.

***Clause 20*** Again for the reasons stated above the provision of factual and balanced data clearly spelling out safety information, supported by Ortho Biotech's and the European agency's own data, was permitted. Therefore this did not constitute an advertisement and Roche robustly defended its right to provide this information, much of which was already in the public domain.

## PANEL RULING

The first paragraph discussed a letter issued by Ortho Biotech warning doctors that, as the risk of PRCA was associated with subcutaneous administration, they should use intravenous Eprex in patients with chronic renal failure. The second paragraph explained that subcutaneous injections were more convenient for the patient. The third paragraph reminded readers that NeoRecormon could be used subcutaneously and 'is **NOT** associated with this increased incidence of PRCA. There have been no cases of PRCA reported with exclusively epoetin **beta** (NeoRecormon) use in the UK'. The Panel considered that the company statement by referring to UK-only data gave the impression that NeoRecormon was not associated with any risk of PRCA; this impression was strengthened by the heading 'PRCA issue not linked to all EPO products'. The Panel noted its comments and rulings regarding PRCA in point 1. The Panel considered that the company statement about PRCA and NeoRecormon was misleading. Breaches of Clauses 7.2, 7.3 and 7.9 were ruled. The information given about NeoRecormon and PRCA was not consistent with the SPC. A breach of Clause 3.2 was ruled. These rulings were appealed by Roche. The Panel did not consider that the company statement was such as to disparage Eprex or that it warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 8.1 and Clause 2 was ruled.

The Panel noted that the company statement, with regard to the manufacturing process of NeoRecormon, stated that 'this process has remained identical over the 10 years since epoetin **beta** (NeoRecormon) was launched'. The Panel noted its comments in point 1 about the manufacture of NeoRecormon. The Panel considered that the claim that the manufacturing process had remained identical over 10 years was misleading. A breach of Clause 7.2 was ruled. This ruling was appealed by Roche.

The Panel noted that the company statement was released to the medical press and selected health correspondents. The Panel did not consider that the statement was an advertisement for a prescription only medicine to the public and so ruled no breach of Clause 20.1 of the Code.

Clause 20.2 of the Code required that information about medicines which was made available to the public either directly or indirectly must be factual and presented in a balanced way; *inter alia* it must not be misleading with respect to the safety of the product. The Panel noted its rulings above and ruled a breach of Clause 20.2. This ruling was appealed by Roche.

## APPEAL BY ROCHE

Roche noted the Panel's reference to its use of UK-only data. Roche stated that the press release contained clear information about the worldwide incidence of PRCA in addition to the clarification about case numbers in the UK, and submitted that it was reasonable and fair to provide both sets of data because: 15 suspected cases of PRCA had been reported with Eprex in the UK; the relative use of subcutaneous (SC) versus intravenous (IV) administration of epoetins varied within different countries in Europe and worldwide; in the UK the SC route accounted for at least 90% of renal patient use whereas it was much less than this in Germany. Roche further noted that a recommendation for using Eprex IV only (or where feasible) had particular importance for the UK health professionals. Quoting figures from the UK helped people evaluate claims that it was the route of administration rather than the product causing the problem as both products were given SC. The numbers of case reports had varied between countries and thus the overall worldwide data did not necessarily reflect local experience and this was relevant to prescribers.

Roche noted that the Panel had considered that the company statement gave the impression that NeoRecormon was not associated with any risk of PRCA. Roche denied that it had ever stated that NeoRecormon *per se* was not associated with PRCA; the company statement set the context by using the term, *'PRCA issue'*. The issue referred to in the company statement was both the recent upsurge in incidence of PRCA (not PRCA *itself*) in patients treated with SC Eprex and the subsequent restriction on Eprex's recommended route of administration; the restriction placed upon Eprex as described in the 'Dear Doctor' letter from Ortho Biotech did not apply to NeoRecormon. Roche submitted that in the established context, it was then and was now accurate to state 'this increased incidence of PRCA' (ie the recent upsurge) was not associated with NeoRecormon. If the issue had been associated with NeoRecormon it was almost certain that the EU regulatory bodies would have imposed a similar restriction to that placed on Eprex and this was not the case.

Roche stated that publications provided in its response to the complaint clearly showed large differences in incidence of PRCA between epoetins. These included data from the FDA, which had responded to the article by Casadevall *et al* pointing out that this was a brand issue. Casadevall's follow-up letter confirmed this. A change in the manufacture of epoetins had been cited as a possible cause of these differences between epoetins by the editorial in the New England Journal of Medicine. Roche submitted that it was justified in referring to the differences in epoetins and the change in manufacture because these were emerging data relevant to the issue and it had not been mentioned in the 'Dear Doctor' letters sent by Ortho Biotech in November 2001 or July 2002.

Roche stated that the context in which the company statement was sent was highly relevant. This was not a proactive spontaneous media release but one in response to a nationwide 'Dear Doctor' letter announcing a major change to the licence of one epoetin but not to the others. The 'Dear Doctor' letter did not state that the decision only applied to Eprex nor that the SC route for NeoRecormon had not been affected nor was any reference made to the above publications. Roche submitted that it was entitled to clarify this, particularly as there was confusion on these points.

Casadevall had collected most of the cases prior to the first 'Dear Doctor' letter. These cases were spontaneously referred to her from various centres throughout Europe and beyond because she had first reported the phenomenon and had a validated antibody assay. Casadevall *et al* published these data in 2002 showing that of 39 cases in its series only one was exclusively with NeoRecormon. The probability that this was a chance finding was remote. Moreover the reference member state under the mutual recognition procedure for Eprex noted the imbalance in reports, at the time of the urgent safety restriction and Roche presented these data as evidence. Thus the issue was about an increasing number of cases with Eprex and not with NeoRecormon although the SPC for NeoRecormon included a warning that PRCA was possible with all epoetins. Roche referred to its response above for further information.

In summary Roche submitted that the NeoRecormon SPC was amended very early in the history of this problem to warn that very rarely antibodies with or without PRCA had been reported with epoetins. Subsequent to that amendment, based on early data on this issue, the number of reports increased markedly; the vast majority associated with Eprex. This led to a similar warning on the SPC for Eprex in November 2001. However the numbers continued to increase such that a decision had to be taken to restrict the licence of Eprex only, and this was the basis of the second 'Dear Doctor' letter sent by Ortho Biotech in July 2002.

Roche stated that the situation for NeoRecormon had not changed since the amendment to the SPC and pharmacovigilance did not suggest that there was a similar growing issue with the product. The company statement contained information on the worldwide incidence of PRCA with NeoRecormon which was entirely consistent with the SPC in that it provided numbers of suspected cases reported to Roche and noted that no change was necessary to the prescribing information. Roche contended that the company statement was both accurate and balanced and consistent with the SPC.

Roche submitted that the formulation change to Eprex was crucial in the causality of PRCA. Data from Casadevall *et al* and the FDA, provided above, clearly showed differences in incidence of PRCA with different formulations and brands of epoetins: the New England Journal of Medicine speculated that this might reflect a manufacturing change; the majority of cases with Eprex had occurred since the removal of human serum albumin (HSA) as the main stabilizer of the Eprex formulation; Ortho Biotech's 'Dear Doctor' letters had included advice about adhering to storage and handling instructions for Eprex which reflected the stability concerns (although no reasons were given as to why this was important). Roche submitted that its company statement had explained all of this in a balanced and fair way, it was noted that if the issue was associated with a change in formulation as suggested, this would not involve NeoRecormon which had never contained HSA; differences between formulations such as shelf-life and storage conditions might result in differences in stability between the products. In this regard NeoRecormon had a longer shelf-life, and different handling instructions etc compared to Eprex.

Roche accepted that although there could be differences in opinion as to the exact meaning of words like formulation, manufacturing process, presentations etc its statement did not mislead in terms of the overall points made. All NeoRecormon formulations contained similar stabilizers and these had not changed over the years. In contrast the change in formulation of Eprex was strongly associated with the emergence of an increased incidence of PRCA and had been cited as such in several publications. Roche submitted that its statement reflected these data and had not misled.

Roche submitted that its justification for the company statement and the response to the other rulings would suggest that the breach of Clause 20.2 no longer stood.

Roche did not accept that it was misleading to state that there was a large difference in incidence of a serious adverse event between two products such that only one was the subject of an urgent safety restriction resulting in major restrictions to its use, but not the other. Roche submitted that if it had assumed the differences between epoetin brands in terms of PRCA and changes to prescribing information had occurred as a result of changes in formulation then it was not misleading to point out that the only stabiliser used in one formulation was replaced with synthetic materials and that the timing of this change was highly associated with the emerging problem.

Roche submitted that if it had misled on this matter then it had to be assumed that equally important changes to the formulation of NeoRecormon had also occurred (which they had not) and the formulation argument dismissed as irrelevant as it did not explain the differences in incidence. Roche submitted that the statement about the formulation taken overall and put into the context of the situation at the time did not mislead.

## COMMENTS FROM ORTHO BIOTECH

Ortho Biotech stated that it had never disputed that there had been reports of PRCA in patients receiving Eprex, or that there had been more spontaneous reports of PRCA with Eprex than with NeoRecormon; it had made this clear in its complaint. Ortho Biotech objected to the misleading and inappropriate manner in which Roche compared the two products in this respect.

Ortho Biotech stated that there were fundamental flaws in Roche's appeal. These included the

misguided and inappropriate reliance on spontaneous adverse event reporting data as a basis for assertions about the relative safety of two products, and Roche's inappropriate interference with due regulatory process. Both formed common themes throughout Roche's advertising and its submissions to the Authority.

Ortho Biotech noted that the full extent to which PRCA occurred in all erythropoietin products and its cause(s) had yet to be fully determined. In the absence of comparative clinical or suitable epidemiological data, Roche's advertising and grounds for appeal appeared to be based solely on spontaneous adverse event reporting data. However, spontaneous adverse event reporting data was not a suitable basis for such evaluations or comparisons. A review of any reputable text on adverse drug reactions highlighted the numerous possible confounding factors and biases that affected the validity of spontaneous reporting data and highlighted the problems with their meaningful interpretation in this context. Spontaneous reporting had significant limitations because it depended on voluntary reporting of suspected reactions encountered during regular clinical practice, which inevitably led to severe bias. Reporting was usually incomplete, perturbed by promotional claims and media attention, and declined with time after marketing. Other possible confounding factors included prescription volume, the date of marketing, the age and sex groups in which a product was most used, the duration of its therapy, dose and route of administration, etc. Diseases could also alter in terms of their natural history and might be complicated or complex, making diagnosis and identification of cases difficult or inaccurate. Medicines could also rapidly acquire an adverse profile because they were, in the beginning, considered to be safer than alternative agents. They might therefore have been promoted for use in vulnerable groups of patients. Even if they were actually safer, reported adverse event data could soon appear worrying. For these and other reasons, Ortho Biotech submitted that spontaneous reporting schemes were generally only considered to be useful methods for the identification of new hazards, ie as an early warning system, and for the identification of risk factors for particular adverse reactions, but no more.

Ortho Biotech noted that many of these possible confounding factors had applied in this case, details were provided. Ortho Biotech noted that spontaneous reporting schemes were not considered to be a realistic basis for estimating the relative safety of medicines within the same therapeutic class.

Ortho Biotech noted that Roche had consistently referred to spontaneous reporting data when seeking to draw conclusions regarding the incidences of PRCA with NeoRecormon and Eprex. However, spontaneous reports could not be used as a basis for determining the incidence of an adverse reaction. This was because neither the numerator (number of reports) nor the denominator (number of patients exposed) could be accurately determined, and there was therefore no way of knowing what proportion of suspected adverse reactions had been reported. Outside the context of controlled study, it was also almost impossible to identify precisely the number of patients exposed. Sales figures and information on the number of prescriptions represented a flawed source of such information because medicines were given in varying doses and for different durations. In addition, data on the number of prescriptions was meaningless without knowledge of the proportion of these that were repeat prescriptions, etc.

To substantiate comparative safety claims, Ortho Biotech stated that it was preferable to rely on head-to-head comparative clinical data. If this was not possible, sound epidemiological data might suffice. For this reason, many medicines advertising regulators expressly prohibited the use of spontaneous adverse event reporting data alone in comparative advertising, on the basis that it was inherently misleading.

Ortho Biotech referred to the requirements of Clauses 7.2, 7.3, 7.4, 7.5 and 7.9 and to two sections of the supplementary information to Clause 7.2, use of data derived from *in vitro* studies and emerging clinical or scientific opinion.

Ortho Biotech noted the previous published cases on comparative safety claims, in which the Panel had, on numerous occasions, found claims based only on spontaneous adverse event reporting data to be misleading, even where they cited published analyses of such data. Previous cases also made clear that head-to-head clinical data were required in order to make comparative safety claims. Ortho Biotech noted that other self-regulatory bodies, regulators and the courts had also adopted similar stances. Details were provided. In Switzerland Roche had been prohibited from making comparative claims about Eprex and NeoRecormon in its promotional materials unless the comparison was based on direct comparative studies. Under Dutch case law comparative claims must generally be substantiated by at least two independent, head-to-head clinical trials. These studies must be published in peer-reviewed journals and consistent with the results of other published clinical studies. Given the totality of the above, Ortho Biotech alleged that Roche had failed to substantiate any of its comparative safety claims and that they were all misleading.

Ortho Biotech acknowledged that some of the issues raised by Roche were legitimate ones that all the manufacturers of erythropoietin products and the regulators needed to address. However, the correct approach was to raise and resolve such issues during formal discussions with the regulatory authorities; it was both inappropriate and irresponsible to do so via advertising.

The basic message in Roche's advertising was that Eprex was unsafe, and that patients on it should be switched to NeoRecormon. The fact remained, however, that Eprex was a licensed product approved for use in accordance with its SPC. The regulators had made and communicated, and would continue to do so, all necessary changes in the product's labelling, as data relating to PRCA and its association with erythropoietin therapy continued to emerge. If Roche had concerns about the safety of Eprex or the

adequacy of these regulatory communications, it should express these concerns to the relevant regulators and/or the marketing authorization holders which had access to all relevant data and were competent to make decisions regarding both the regulatory status of a product and their conditions for use. It was not for Roche to second guess the regulators or to interfere with this process, and it was certainly inappropriate to do so in promotional material. What Roche had chosen to do could only undermine confidence in the regulatory system, in licensed products and the pharmaceutical industry. Preventing such damage was one of the principal purposes of the Code.

It appeared that Roche had conceded the primary basis for Ortho Biotech's complaints. This was that the overriding impression given by Roche's advertisements was that PRCA was a problem associated exclusively with Eprex, not NeoRecormon. From the Panel's ruling, it appeared that it shared this impression. In its appeal Roche appeared to accept that PRCA also occurred with its product and had now changed its focus to argue that PRCA was much more of a problem with Eprex than with NeoRecormon. If this was the case, Roche must also concede that its advertising was misleading.

Ortho Biotech noted that Roche had suggested that the basis for the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.9 was that Roche had referred only to UK data. This misstated the ruling. The Panel found that the company statement, taken as a whole, suggested that NeoRecormon was not associated with any risk of PRCA. In doing so, it cited a number of factors, including the misleading and selective use of UK safety data and the title of the statement, ie 'PRCA issue not linked to all EPO products.' This, as the Panel indicated, was misleading.

Ortho Biotech alleged that Roche had sought to justify its selective reference to UK spontaneous reporting figures on the basis that they were, in some way, more relevant to a UK audience, and that worldwide safety data were not. This was clearly inconsistent with the provisions of the Code and rulings made in previous cases (Case AUTH/1221/8/01).

Ortho Biotech stated that this selective use of spontaneous reporting data added to the already insurmountable problems associated with use of such data as a basis for comparative safety claims. Careful selection of jurisdiction gave fundamentally different impressions. For example, according to a recent statement by SwissMedic, the Swiss medicines regulator:

'Up to mid-December 2002 seven cases of pure red cell aplasia in patients with renal anaemia which were treated with erythropoietins were reported to the SwissMedic Pharmacovigilance Centre. In 4 of the patients the diagnosis has been proven by bone-marrow examination and presence of anti-EPO-antibodies … in one of the four cases epoetin alfa [Eprex] seems to be the cause, in the second case only epoetin beta [NeoRecormon] has been given and in the remaining two cases epoetin alfa or beta [Eprex or NeoRecormon] could be the cause. In other two reports the diagnosis has been confirmed by bone-marrow examination – in one patient the antibody-test was negative, in the other antibody-test was not available. One of these patients only received epoetin alfa in the others both epoetins can be taken into consideration. Also, in a further case, where bone-marrow and antibody-testing are not available, both epoetins could be the cause. SwissMedic will carefully supervise all recombinant epoetins including the worldwide available data and recommendations.' [Translated from the original German text.]

Ortho Biotech stated that it was hardly surprising that Roche did not rely on these figures when promoting NeoRecormon in its home market, despite the fact that its arguments above, if true, would suggest the figures were of greater relevance to a Swiss audience.

Ortho Biotech stated that Roche's view was also not shared by the European Agency for the Evaluation of Medicinal Products (EMEA) and the EEA's national regulators. NeoRecormon was centrally-approved and, as such, was sold under a single authorization and on the basis of an SPC that was harmonised throughout the European Community. If the regulators could identify no basis for presenting physicians in different countries with different prescribing information, Ortho Biotech found it difficult to see why Roche was competent to provide them with different safety data.

Ortho Biotech reiterated its objection to Roche's use of spontaneous reporting data as a basis for comparative safety claims. Ortho Biotech repeated its observation that Roche had eliminated all NeoRecormon cases that did not fit a very narrow definition of antibody-mediated PRCA; this excluded cases in which there was no information about antibody status, where patients were taking more than one erythropoietin, or had other conditions or were taking other medicines traditionally associated with PRCA.

Conversely Roche had applied a much broader definition when discussing reports of PRCA associated with Eprex. This definition included all reported cases of suspected PRCA, regardless of bone marrow or antibody status, and included all cases where patients were treated with more than one erythropoietin.

Ortho Biotech considered that Roche's statement that its company statement 'contained clear information about the worldwide incidence of [PRCA]' was misleading. For the reasons set out above, spontaneous adverse event reporting data could not be used as a basis for determining the incidence of a particular condition. The same argument applied to Roche's insistence that it was highlighting 'the recent upsurge in incidence of PRCA (not PRCA *itself*)' and its citation of FDA figures and Casedevall *et al* as substantiation for its claims. Whether or not they were published or quoted by regulators, Roche could not rely on spontaneous adverse event data as substantiation for any claim relating to the incidence of a condition or the comparative safety of products.

Ortho Biotech considered that Roche's suggestion that any increase in PRCA associated with Eprex had resulted from changes in its manufacture and/or formulation, and that NeoRecormon had been subject to no such changes since launch was also misleading.

This was another example of Roche acting as a regulator, by making unsubstantiated pronouncements and determinations about another company's licensed product. A definitive cause of the increase in spontaneous reports for Eprex was still being investigated. Roche's pronouncement that it was linked to manufacturing changes was unsupported by current data. Roche had conceded that the relevant data were emerging. However, it had singularly failed to treat them in a balanced manner, as required by the Code. Ortho Biotech stated that the issue was very complex and possible factors included: stimulated reporting resulting from increased awareness of the condition; manufacturing changes; changes in the formulation of the finished product, including the removal of HSA and presentation as a pre-filled syringe; failure to comply with cold-chain distribution requirements and increased prevalence of SC administration of the product. It was for this reason that neither Ortho Biotech nor the regulators had made definitive statements as to the cause of this phenomenon. To suggest that there was a single, well-established cause was clearly misleading.

Ortho Biotech was alarmed that Roche had insisted that its company statement was issued 'in response to a nationwide 'Dear Doctor' letter announcing a major change to the licence of one epoetin but not to others.' Roche must be aware that 'Dear Doctor' letters following urgent safety restrictions and/or variations of this type were a regulatory requirement and that their contents were subject to regulatory approval. If these communications had not contained pronouncements as to the cause of an issue, that was most likely because the regulators had reviewed the available data and were, nevertheless, unsure of its cause.

Ortho Biotech stated that if Roche was concerned about the content of the 'Dear Doctor' letters, either because the regulators did not share its views on the issue of causation and/or because it was worried about confusion that might have arisen, it should have raised its concerns with the relevant regulators, rather than assuming the regulatory mantle itself and second-guessing the authorities by making misleading statements of its own. Such unwarranted interference with a regulatory process could only undermine the regulatory system, confidence in licensed products and the pharmaceutical industry.

Ortho Biotech did not see the relevance of Roche's grounds for appealing the Panel's ruling of a breach of Clause 3.2. Community guidance on SPCs stated:

'The SPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. It is the definitive statement between the competent authority and the marketing authorisation holder and it is the common basis of communication between the competent authorities of all the Member States. As such the content cannot be changed except with the approval of the originating competent authority.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The content of the package leaflet must be consistent with the SPC but in a wording that can be easily understood by non-professionals.'

Ortho Biotech stated that the SPC was an integral part of a product's marketing authorization, and that regulations made it clear that advertising must be consistent with it. If a company no longer considered that its SPC was a suitable basis for informing health professionals on how to use the product safely and effectively, it could apply to vary its authorization. Roche appeared to argue that the background to the introduction of the relevant section of its SPC provided some form of justification for its circumvention of these regulatory procedures. This clearly could not be true, and marketing authorization holders could not simply choose to circulate inconsistent statements. Rulings made in previous cases were clear on this point eg Case AUTH/1221/8/01 as noted above.

Ortho Biotech stated that neither it nor the regulators had determined the cause(s) of PRCA. Based on the totality of the available data, it was possible only to identify a number of possible causes. Ortho Biotech questioned what data Roche had to substantiate its claims in this respect.

There was no basis for Roche's argument that the formulation change to Eprex was crucial in the causality of PRCA. Furthermore Roche suggested that it could be done based on spontaneous adverse event data although such data provided no basis for determining the incidence of an adverse reaction, let alone its causation.

Ortho Biotech noted that Roche had not acknowledged the changes in formulation and manufacturing process that had occurred with NeoRecormon. According to section 8 (Steps Taken After Authorization) of the EPAR for NeoRecormon, this even included the removal of human serum albumin (HSA) from the manufacturing process in April 1998. Roche again did not acknowledge that Ortho Biotech's 'Dear Doctor' letters were regulatory communications, subjected to regulatory approval. If Roche objected to the regulator's terms, it should have raised its concerns with the relevant authorities, rather than issuing inconsistent statements to the medical profession.

Ortho Biotech reiterated that the EPAR for NeoRecormon made it clear that the product had been subject to major changes in its manufacturing processes and formulation over time. Most of these had involved Type II 'major' variations in the terms of its marketing authorization, and one was considered so significant that it justified an entirely new application. Roche justified its divergent stance on this issue by arguing that 'there can be differences in opinion as to the exact meaning of words like formulation, manufacturing process, presentations, etc'. Ortho Biotech alleged that any 'differences', to the extent that they existed, should be resolved in favour of the regulators. The CPMP's interpretation of these terms was unambiguous.

Ortho Biotech submitted that for the reasons set out above, Roche's grounds for appeal were based on pure speculation and an erroneous, misleading and selective interpretation of limited spontaneous adverse event reporting data. Moreover, as Roche

appeared to now admit, it was based on a number of assumptions. These were, at best, unsubstantiated, and at worst unscientific.

Ortho Biotech concluded that spontaneous adverse event data provided no basis for determining the incidence of an adverse reaction. Roche had therefore provided no meaningful substantiation for its comparative safety claims regarding the association of PRCA with Eprex and NeoRecormon; Roche had provided no meaningful substantiation for its claim that any safety differences had resulted from changes in Eprex's formulation. NeoRecormon had also been subject to major reformulations and changes in its manufacturing process, including the removal of HSA and Roche's claims were inconsistent with regulatory statements on this issue, including the Ortho Biotech 'Dear Doctor' letters it cited.

Ortho Biotech alleged that there could therefore be no basis for Roche's claims. They were unsubstantiated and misleading.

### APPEAL BOARD RULING

The Appeal Board noted that the incidence of PRCA in patients with renal failure was greater in Eprex-treated patients than in those treated with NeoRecormon. The Eprex SPC stated that PRCA was a rare event, reported in patients with chronic renal failure after months to years of treatment with Eprex or other erythropoietins. As the cases of PRCA were mainly associated with the subcutaneous route of administration, prescribers were advised to administer Eprex intravenously to patients with chronic renal failure where feasible. The SPC for NeoRecormon stated that in very rare cases, neutralising anti-erythropoietin antibodies with or without PRCA occurred during rHuEPO therapy.

The Appeal Board noted that the company statement cited reports of 141 cases of PRCA 'associated with Eprex worldwide' since 1998 and the number of cases for NeoRecormon were 'only one confirmed case in patients taking [NeoRecormon] exclusively, and two cases where it cannot be excluded'. At the appeal hearing itself Roche's representatives stated that at the time of the company statement the company was aware of at least 12 cases of PRCA on the Roche database where patients had received both Eprex and NeoRecormon. The Appeal Board considered that the criteria for determining the number of cases of PRCA associated with each product was not the same; like was not being compared with like.

The Appeal Board considered that the claim 'epoetin **beta** … is **NOT** associated with this increased incidence of PRCA', followed by 'There have been no cases of PRCA reported with exclusively epoetin **beta** (NeoRecormon) use in the UK', gave the impression that NeoRecormon was not associated with any risk of PRCA. The Appeal Board noted that this was not consistent with the SPC and upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful. The Appeal Board considered that the statements about PRCA and NeoRecormon were misleading and upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.9. The appeal on this point was unsuccessful.

With regard to the manufacture of NeoRecormon the Appeal Board considered the change in presentation from a freeze-dried form to a liquid form represented a significant change in the manufacturing process. The Appeal Board noted that when presented as a freeze-dried powder the cold-chain for NeoRecormon could be interrupted for a single period of up to 5 days. When presented as a solution the cold-chain could only be interrupted for a single period of 3 days. In the Appeal Board's view this suggested that the stability of the two forms was not identical. The Appeal Board noted that NeoRecormon was introduced, as a freeze-dried powder, in 1997 and its liquid form was introduced in 1998. The Appeal Board considered that the claim that the manufacturing process had remained identical over 10 years was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that the company statement was not in accordance with Clause 20.2 of the Code which required that information to the public be factual, presented in a balanced way and not be misleading with regard to the safety of the product. The Appeal Board upheld the Panel's ruling of a breach of Clause 20.2. The appeal on this point was unsuccessful.

## 3 Letter dated 21 August 2002 (ref P589399)

This letter was about the use of NeoRecormon for anaemia of malignancy following recent advice on route of administration of Eprex in chronic renal failure. It had been sent to oncologists, haematologists and palliative care physicians.

### COMPLAINT

Ortho Biotech noted that the letter referred to a communication that it had sent to members of the chronic renal failure community recommending a change in the route of administration of Eprex and sought to provide information 'to clarify the situation'. The discussion that followed made a number of comparisons between Eprex and NeoRecormon and concluded that no alteration to the route of administration of NeoRecormon was necessary.

Ortho Biotech alleged that the letter was misleading and sought to unfairly disparage Eprex. The company's primary concern was that it did not make the communication referred to by Roche to UK oncologists. Indeed, Roche acknowledged that Ortho Biotech's communication related only to chronic renal failure patients in the first two paragraphs of their letter.

There had been no reported cases or PRCA with Eprex in oncology patients and neither Ortho Biotech nor the regulatory authorities had made any recommendation that oncology patients on Eprex changed their route of administration. There was no reason for Ortho Biotech to communicate with oncologists on these issues and there was therefore clearly no objectively justifiable reason for Roche to do so. Although Roche's letter was carefully drafted,

the only possible explanation for its circulation was that Roche was seeking to unfairly disparage Eprex by suggesting that there might be safety concerns with this product in the oncology field.

Ortho Biotech also objected to Roche's assertion the 'NeoRecormon had had no major reformulation change since introduction'.

Ortho Biotech alleged that the letter breached the following provisions of the Code:

***Clause 8.1*** Ortho Biotech considered that the comparisons contained in the letter were unsubstantiated, unfair, unbalanced and inaccurate. The manner in which the comparison of the products was made unfairly disparaged and denigrated Eprex.

***Clause 7.2*** The comparison Roche made was based on an unfair, unbalanced and inaccurate interpretation of the available information.

***Clause 7.3*** The letter failed to comply with the requirements for comparative advertising of medicines set out in Clause 7.3 of the Code. These failures included the presentation of the existing information in a misleading manner and the unfair denigration of Eprex.

## RESPONSE

Roche stated that this was not a 'Dear Doctor' letter, a term which usually referred to a letter informing health professionals of safety issues with a product usually in conjunction with the regulatory authorities. This was a letter to consultant oncologists, haematologists and palliative care physicians who might prescribe NeoRecormon for its oncology indication according to the SPC. The letter was to inform these professionals about PRCA as it might affect their practice. In fact the letter was to reassure such prescribers that PRCA had not occurred in this indication with any of the epoetins as far as Roche was aware.

Following Ortho Biotech's 'Dear Doctor' letter of 17 July Roche fielded a number of inquiries regarding the safety of its product, many of which originated from the oncologists and haematologists. As Ortho Biotech promoted Eprex to oncologists it was reasonable that there would have been discussions about its safety with this customer group too. Roche understood that Ortho Biotech's sales force had been, quite appropriately, advising their customers that the subcutaneous route of administration for Eprex remained the route of choice in this indication. Roche rigorously defended the right to communicate to its customers in like manner when it considered that relevant information was appropriate.

Roche failed to see how this letter might be construed as misleading and it clearly did not disparage Eprex. It merely confirmed what was already in the public domain. Roche neither insinuated that Eprex could not be given by the subcutaneous route nor stated nor implied that there had been any cases of PRCA in oncology patients on Eprex. Roche also stood by the assertion that there had been no major reformulation change since introduction.

This piece contained information on NeoRecormon in response to numerous requests about the product. Roche neither compared, nor disparaged Eprex. Roche denied any breach of the Code in respect to Clauses 8.1, 7.2 or 7.3.

## PANEL RULING

The Panel noted that the letter in question had been sent to those health professionals with an interest in treating anaemia of malignancy. The letter began by stating 'You may recently have received a communication letter from Ortho Biotech which provided amended advice on the route of administration of epoetin alfa (Eprex) in Chronic **Renal Failure (CRF) patients** because of reports of PRCA occurring **in this population**'. The letter continued by comparing the differences between Eprex and NeoRecormon with regard to product and formulation, storage and case incidence of PRCA. With regard to the incidence of PRCA in patients with chronic renal failure the letter stated that there was only one confirmed case in patients taking epoetin beta exclusively and two cases where the association could not be excluded. The penultimate paragraph of the letter reassured the reader that NeoRecormon could continue to be administered subcutaneously and stated in bold **'The Summary of Product Characteristics (SmPC) for NeoRecormon has not changed in this regard. No alteration to the route of administration is necessary'**.

The Panel noted that there had been no reports of PRCA in patients receiving epoetin for the treatment of anaemia of malignancy. Ortho Biotech thus had not had to write to oncologists, and others in the same therapy area, to advise them to administer Eprex intravenously where feasible. The Panel considered that the letter disparaged Eprex by highlighting a problem in one therapy area which had no clinical relevance to the audience to which the letter was sent. The Panel ruled a breach of Clause 8.1. The Panel noted its comments in point 1 with regard to PRCA. The Panel considered that the letter minimised the risk of PRCA in patients with chronic renal failure treated with NeoRecormon and did not give the reader enough information about Eprex such that a valid comparison of the two products could be made. Given the audience to while the letter was directed the Panel considered that the letter was misleading. Breaches of Clauses 7.2 and 7.3 were ruled. These rulings were appealed by Roche.

The letter stated that '… NeoRecormon has had no major reformulation change since its introduction'. The Panel noted that this statement was different to those considered in points 1 and 2 above which were absolute statements of no change. (In point 1 the claim at issue referred to an 'unchanged formulation'.) The Panel considered that the claim now at issue reflected Roche's submission that the formulation had remained essentially unchanged. No breach of Clause 7.2 was ruled. This ruling was appealed by Ortho Biotech.

## APPEAL BY ROCHE

Roche re-iterated that oncologists and haematologists had telephoned the company, and asked its

representatives, about the safety of NeoRecormon. This implied that the issue was of relevance to these prescribers; their concerns could only have arisen as a result of them hearing about the recent announcement about Eprex or indeed seeing the 'Dear Doctor' letter of July from Ortho Biotech. Roche did not know to whom Ortho Biotech had sent that letter. Roche noted the following: SPCs for epoetins were common for both indications and thus a major change for a safety reason must concern all prescribers; the NeoRecormon SPC included information about antibodies and PRCA within the Undesirable Effects section without relating this to any particular indication (oncology or nephrology). In addition, information about PRCA was included in the one SPC for Eprex that would be used by both oncologists and haematologists (in addition to renal specialists); that this particular safety issue had not yet been reported in oncology or haematology did not mean it was clinically irrelevant to doctors in those therapy areas. It might, for example, reflect the current size of this patient group, where epoetin use was less well established than with nephrology patients. Haematologists treated haematological malignancies but were likely also to be involved in the diagnosis and management of patients with PRCA, a haematological condition, even if the adverse event occurred while the patient was under the supervision of a nephrologist.

Roche submitted that it did not suggest that there was, or was likely to be, a problem at the time of the letter. The letter stated that PRCA had not been observed in oncological or haematological patients. Roche submitted that it was highly relevant for it to notify oncologists and haematologists of the issue as long as this was in a fair and balanced way, which was what was done.

Roche submitted that the Panel's ruling in point 1 supported its position here. On the issue of notifying PRCA to different specialities the Panel was concerned that it was not made clear that PRCA had only been reported in patients with chronic renal failure. In other patient groups for whom treatment was indicated, ie patients receiving chemotherapy, this complication had not been reported. Roche submitted that the Panel supported informing nephrologists that PRCA had not occurred in the oncology/haematology indication but ruled against informing oncologists/haematologists that PRCA had not occurred in the oncology/haematology indication ie their own speciality. Roche submitted that the Panel seemed to concur that the safety of a medicine in one therapeutic area was of concern to clinicians prescribing in another with regard to point 1, but then ruled that such action was disparaging with regard to point 4 because it 'highlighted a problem in one therapy area which had no clinical relevance to the audience to which the letter was sent'.

Roche noted that PRCA was a haematological condition and those charged with helping nephrologists to diagnose and understand it were the same haematologists to whom this letter was sent. Roche disagreed that this issue was not clinically relevant to oncologists and haematologists; it was highly relevant and in the interests of both clinicians and patients to be aware of all the risks of taking a medicine particularly as there had been a major change to the SPC which was common for both indications. Roche repeated that there was not a separate SPC for each indication. Clause 3.2 permitted promotion which was not inconsistent with the particulars of the SPC.

Roche submitted that the logic of the Panel's ruling of a breach of Clause 8.1 was that if an oncologist or haematologist asked a representative for a SPC for either Eprex or NeoRecormon this could be provided together with the advice that the section on antibodies should be ignored because it was not clinically relevant.

Roche noted that the Panel had considered that the company had minimised the risks of PRCA in patients with chronic renal failure treated with NeoRecormon and did not give enough information about Eprex such that a valid comparison could be made. Roche submitted that this seemed to go against the Panel's ruling that a company should not highlight safety in one therapeutic area, which had 'no clinical relevance' to physicians in another. Roche also submitted that the Panel had not taken full account of the circumstances of the letter when ruling about it minimising the risk of PRCA. The facts were that the relevant regulatory authorities had assessed the risks of epoetins and had decided to issue an urgent safety restriction for only one product.

Roche submitted that the statement from the reference member state for Eprex made clear what the risks were in the statement that the majority of cases had occurred with Eprex. The English translation of this statement was, 'Although a few cases of PRCA have also been observed with other marketed erythropoietins (less that about 10 cases throughout the world) the great majority of these cases were reported with Eprex'. Roche disagreed that it was necessary in this sense to justify the actions of the regulatory authorities in this regard.

### COMMENTS FROM ORTHO BIOTECH

Ortho Biotech stated that Roche appeared to make regulatory pronouncements about another company's product. There had been no reported cases of PRCA with Eprex in oncology patients. Therefore, while Ortho Biotech and the regulators had made label changes and associated communications in respect of the administration of Eprex for chronic renal failure patients, neither Ortho Biotech nor the authorities had considered that similar steps were necessary for oncology patients. If the regulators had considered that communication with oncologists was necessary, eg because they considered that the spontaneous reports emerging in the renal area were potentially clinically relevant to the oncology field, they could have requested that Ortho Biotech did so. Roche should have raised any concerns it had about the clinical relevance of Ortho Biotech's 'Dear Doctor' letters with the regulators that had approved them, rather than seeking to undermine the regulatory process by issuing its own inconsistent statements regarding another company's licensed product.

Ortho Biotech alleged that there was no objectively justifiable reason for Roche to communicate with

oncologists on these issues. It had not demonstrated the clinical relevance that it suggested and the only possible explanation for its letter was that Roche was seeking to unfairly disparage Eprex by implying that there might be safety concerns with it in the oncology field.

Ortho Biotech stated that Roche had failed to grasp that all claims must be capable of substantiation. The central thrust of all of its communications was that Eprex was associated with an increased incidence of PRCA, that NeoRecormon was not, and that NeoRecormon was therefore safer. Ortho Biotech alleged that Roche had made such claims on the basis of a mixture of unfounded assumptions, unreliable spontaneous adverse reporting data and pseudoscience.

Ortho Biotech noted that Roche persistently refused to accept regulatory communications for what they were. Eprex was a licensed product approved for use in accordance with its SPC. Its marketing authorization holders and the relevant regulators had made, and would continue to make, any changes in the product's labelling that were justified by the emerging data relating to PRCA and its association with erythropoietin therapy. These changes had been, and would continue to be, communicated in accordance with all relevant regulatory and legal requirements in an approved form. If Roche had concerns about the safety of Eprex and/or the suitability of these approved communications, it should express these concerns to the marketing authorization holder and relevant regulators who alone had access to all relevant data and were competent to make decisions regarding the regulatory status of a product and its conditions for use. Roche was not in a position to second-guess the regulators or to interfere with this process, and it was certainly inappropriate to do so in its advertisements.

Ortho Biotech noted that spontaneous adverse event reporting data alone were an unsuitable basis for comparative safety claims in advertising, in the absence of supporting controlled clinical and/or epidemiological study data. Ortho Biotech, in line with the Authority and numerous regulatory authorities, alleged that to do so was inherently misleading and that Roche should be prevented from repeating such claims.

Ortho Biotech alleged that it was inappropriate for Roche to second guess the regulatory process by issuing 'statements' or advertisements that were inconsistent with regulatory communications about labelling changes for another company's product. Ortho Biotech alleged that this was also inherently misleading. Roche's actions could only undermine the regulatory system, confidence in licensed products and the pharmaceutical industry, the protection of which were the principal aims of the Code.

Ortho Biotech alleged that it was inappropriate for Roche to use data and regulatory or third party communications regarding the use of Eprex in chronic renal failure patients as a basis for unfounded and misleading communications to haematologists and oncologists. Roche should be prevented from the unjustified use of safety concerns in one field as a basis for its advertisements in unrelated fields.

**APPEAL BY ORTHO BIOTECH**

Ortho Biotech noted that in the background information supplied upon the case, Roche had argued that Ortho Biotech was 'confused by the difference between formulation, presentation or 'pharmaceutical form'' and that it 'had introduced new presentations (pharmaceutical forms) over the years, including the pre-filled syringe, multidose vial and RecoPen. However, in each of these presentations the active ingredient, epoetin beta, had been formulated with essentially the same excipients'. The Panel concluded that the claim was not an absolute statement of change and reflected Roche's submission that the formulation had remained essentially unchanged. Ortho Biotech alleged that Roche misled the Authority in its response in this respect.

Ortho Biotech referred to sections of the NeoRecormon EPAR; details were provided. Ortho Biotech noted it was made clear that the product had been the subject of major reformulations on numerous occasions over the last decade, and Roche's statement that NeoRecormon had 'been formulated with essentially the same excipients' since launch was untrue.

NeoRecormon was first introduced as a freeze-dried powder which had to be reconstituted using sterile water prior to injection. The product had since been reformulated as a solution for injection so that it could be presented as pre-filled syringes, two-chamber cartridges to be used with a pen system, etc. The Scientific Discussion stated:

'Recormon is currently marketed under 4 dosage strengths (1,000 IU, 2,000 IU, 5,000 IU and 10,000 IU/vial), each presentation being for single use.

The solvent is provided in two presentations: ampoule or prefilled syringe.

On the occasion of the new application, the company [Roche] introduced two new dosage strengths of 500 IU and 20,000 IU as well as multidose vials containing 50,000 and 100,000 and new pharmaceutical presentations (two-chamber cartridges to be used with a pen system) for 10,000 and 20,000 IU.

A new pharmaceutical form (solution for injection) in 7 strengths was introduced as an extension of the marketing authorisation. These new presentations are provided in pre-filled syringes. Subsequent extension applications added two more strengths of the solution for injection in pre-filled syringe to the marketing authorisation, together with one additional strength of the powder and solvent for solution for injection in cartridge (for use with Reco-pen).

Finally, there are 24 forms and strengths in total which, in combination with different packaging sizes, result in 44 presentations.'

Ortho Biotech alleged that this was a clear and unambiguous statement from the regulatory body responsible for NeoRecormon that the product had been subject to at least one major reformulation and change in excipients since it was launched. There could be no sensible argument that the reformulation was not major.

Ortho Biotech noted that since NeoRecormon was centrally-approved, variations in the terms of its

marketing authorization were governed by Regulation (EC) No 541/95 under which changes to a marketing authorization were classified as either a 'minor variation' (type I), a 'major variation' (or type II), or a change that fell within Annex II to the Regulation. The latter were 'considered to fundamentally alter the terms of [the] authorisation and therefore cannot be considered as a variation .... For these changes … any application has to be considered within a complete scientific evaluation procedure (as for the granting of a marketing authorisation). As the case may be, an authorisation or a modification to the existing marketing authorisation will have to be issued by the competent national authorities'.

Ortho Biotech noted the Steps Taken After Authorization for NeoRecormon section of the EPAR included the following statement in respect of the introduction of the solution for injection formulation: 'On 2 April 1998, the European Commission approved an Annex II application (Extension of the Marketing Authorisation) for 7 additional strengths/ pharmaceutical forms (solution for injection). The relevant amendments have been incorporated in the relevant sections of the Commission Decision and of this EPAR'.

Ortho Biotech noted that the CPMP's view was therefore that this reformulation of NeoRecormon from a freeze-dried powder into a solution for injection was, in the words of the Regulation, 'considered to fundamentally alter the terms of [the] authorisation' and therefore necessitated the submission of a new marketing authorization application, rather than simply the variation of an existing authorization. Ortho Biotech therefore could not see any basis in law or fact for Roche's assertions that its product had had 'no major reformulation change since its introduction.' This view was certainly not shared by the CPMP.

Ortho Biotech alleged that there had been other significant changes in the formulation of NeoRecormon. In discussing some of these changes, the Scientific Discussion added that:

'The proposed new 'optimised formulation' consists of a revision of the content in some excipients keeping in mind the need to keep as closely as possible to the already approved formulation. Most of the adjustments made in the content of the excipients are self-explanatory (to keep the solution isotonic after reconstruction).

Supportive experimental data have been provided for the reduction in $CaCl_2$ content; all formulations still comply with the requirements of the E.P. This optimised formulation has been already approved as a variation for the 5,000 and 10,000 IU/1ml presentations of Recormon. Its use is extended also for the 1,000 and 2,000 IU/vials. This formulation allows the reduction of the volume to be injected into patients and enables more convenient subcutaneous administration.

The rationale for the development of the multi-dose presentations is to avoid any wastage of reconstituted product where the optimised dose cannot be achieved using one of the single-use products. The aim is to provide a preserved solvent compatible with the 'optimised formulation' of the lyophilisate. The excipients contained are the same as those for the single use formulations. However, for the three of them (urea, calcium chloride and L-phenylalanine), the quantitative composition was decreased in order to avoid any risk of particle formation during shelf life and after reconstitution.'

Ortho Biotech noted that in respect of these changes, the CPMP's discussion of the Steps Taken After Authorisation stated: 'On 11 November 1998, the European Commission approved a type II variation for the extension of the shelf life to 3 years at 2–8ºC for NeoRecormon (powder and solvent for solution for injection) for the following strengths: 500 IU, 1,000 IU, 2,000 IU, 5,000 IU and 10,000 IU single dose and 50,000 IU and 10,000 IU multidose. The relevant amendments have been incorporated in the relevant sections of the Commission Directive and of this EPAR'.

Ortho Biotech stated that if the CPMP considered that these constituted a type II variation to Roche's authorization, it was difficult to see how Roche could argue otherwise. The meaning of the term 'major' was, after all, set out in Community law.

## COMMENTS FROM ROCHE

Roche stood by its assertion made in the background information above that it 'had introduced new presentations (pharmaceutical forms) over the years …. However, in each of these presentations the active ingredient epoetin beta, had been formulated with essentially the same excipients'. NeoRecormon had not undergone a major change of formulation in the way that Eprex had with the replacement of the principal stabilising agent, human serum albumin. This was of fundamental importance. Roche noted that Johnson & Johnson's presentation to financial journalists had cited the change in formulation of Eprex as a probable cause of the reports of PRCA.

Roche noted that the claim at issue 'NeoRecormon had had no major formulation change since introduction', referred clearly to the history of NeoRecormon not Recormon, its predecessor. NeoRecormon had only existed subsequent to the changes in presentation of Recormon detailed in the EPAR scientific discussion cited.

Roche submitted that the EPAR taken in its entirety supported its claim there was no major formulation change, regardless of product name. For example it stated 'The excipients contained are the same as those for the single use formulations'. A clear distinction must be made between the terms 'major formulation change' and 'major variation (type II)' to Roche's authorization (in respect of an extension in shelf life) or 'Annex II' type variation (for additional strengths/pharmaceutical forms). Roche submitted that the essence of its statement was that the formulation had essentially remained unchanged, and that was how the target audience, oncologists and haematologists would have read the statement. They would not have been misled into considering that there were not small adjustments to the relative proportions of various excipients.

Roche noted the editorial in the February 2002 New England Journal of Medicine which accompanied the original paper by Casadevall *et al* on PRCA with anti-erythropoietin antibodies. Commenting on the emergence of PRCA since 1998 and the difference in incidence seen in Europe and the USA, it stated 'This state of affairs raises the question whether the antigenicity of the European product has been slightly enhanced by a change in the manufacturing process that has altered either the formulation or the carbohydrate structure of epoetin'. Roche stated that this was why the understanding of the changes to manufacturing and formulation was so important.

Roche noted that in its appeal Ortho Biotech had contested that the scientific discussion within the NeoRecormon EPAR made it clear that the product had been the subject of major reformulations on numerous occasions over the past decade. It was important to understand that 'the product' in Roche's original statement was NeoRecormon not Recormon. NeoRecormon received market authorization in October 1997, hence comments pertaining to 'the past decade' were clearly inaccurate. Roche noted that it was subsequently claimed that its statement that NeoRecormon had 'been formulated with essentially the same excipients' since launch 'was also untrue'. Roche disputed these assertions. Roche noted that at no time in its appeal did Ortho Biotech detail a single ingredient that had been either added, removed or replaced in the formulation of NeoRecormon. Thus it was hard to see how any of the small changes Ortho Biotech examined in minute detail could constitute a major reformulation.

Roche noted that the confusions between 'Recormon' and 'NeoRecormon' and 'formulation' and 'pharmaceutical form' persisted with the statement 'NeoRecormon was first introduced as a freeze-dried powder formulation'. To support this was a quotation from the scientific discussion of the EPAR which started 'Recormon is currently …' followed by 'the company introduced two new dosage strengths … and new pharmaceutical presentations …. A new pharmaceutical form (solution for injection) in 7 strengths was introduced'. Even if this statement did refer to NeoRecormon, it was not an 'unambiguous statement from the regulatory body … that the product had been subject to at least one major reformulation and change in excipients since it was launched'. Instead it was a statement that Recormon was available in different dosage strengths, pharmaceutical presentations and pharmaceutical forms. There was no mention here of reformulation.

Roche noted Ortho Biotech's comment that 'There could be no sensible argument that the reformulation of the product's original freeze-dried powder formulation as a solution for injection was not major'. (The 'original freeze-dried powder' referred to here was Recormon.) Roche submitted that it interpreted the scientific discussion in the EPAR differently to Ortho Biotech, and submitted that the entire document, not just the selected quotations, should be read. This document considered the composition of 4 entities: the new dosage strength (500 IU/0.5ml); the new formulation for 1,000 IU/ml and 2,000 IU/ml dosage strengths; the new multidose presentations in two chamber cartridge 10,000 IU/1ml and 20,000 IU/1ml; new multidose presentations in vial 50,000 IU/10ml and 100,000 IU/5ml.

Roche noted that of these only the new dosage strengths of 1,000 IU/ml and 2,000 IU/ml were described as having a 'new formulation'. However Roche noted that if it read on it saw that this 'new formulation' did not represent any major differences from the others:

'The proposed new 'optimised formulation' consists of a revision of the content in some excipients keeping in mind the need to keep as closely as possible to the already approved formulation. Most of the adjustments made in the content of the excipients are self-explanatory (to keep the solution isotonic after reconstitution) …. This optimised formulation has already been approved as a variation …'

In respect of the multi-dose presentations:

'The aim is to provide a preserved solution compatible with the 'optimised formulation' of the lyophilisate. The excipients are the same as for the single use formulations. However, for three of them … The quantitative composition was decreased in order to avoid any risk of particle formation during shelf life and after reconstitution.'

Regarding specifications and routine tests:

'The same set of specifications and test procedures had been submitted as already reviewed and approved.'

Other ingredients:

'All the excipients were contained in the already approved presentations and had been checked.'

On stability tests on the finished medicinal product:

'For the powder for solution for injection: identical protocols to those used for the already approved formulations have been employed also for the new formulation of 500 IU/0.5ml and 1,000 and 2,000 IU/1ml. The same assessment criteria, tests, parameters and storage conditions were applied. All parameters recorded during the stability studies at 5°C met the specifications for the samples whatever the dosage strength.'

Roche submitted that any changes to the old Recormon formulation were relatively small, involving variations in quantitative composition of the stabilising excipients and did not affect the stability of the finished product. This was the crucial point about the claim with regard to changes in formulation.

Roche referred to Ortho Biotech's discussion of type I, type II (minor and major) and Annex II variations in a marketing authorization. This was highly technical regulatory terminology. Roche did not agree that an Annex II amendment to a marketing authorization for additional strength/pharmaceutical forms would translate into a 'major formulation change' in the parlance of a normal physician not versed in regulatory affairs. A regulatory submission under Annex II did not necessarily imply that there had been a major formulation change. On the contrary, Roche argued that a physician reading its statement

would regard the adjustments in strengths and pharmaceutical forms not to represent a major formulation change, regardless of its Annex categorisation. This would certainly be the case if they were also aware that, having undergone the complete scientific evaluation process required, the findings were as above ie changes in quantitative composition of stabilising excipients did not affect the stability of the finished product. Roche submitted that its statement did not concern new strengths/presentations, it was about stability formulation.

Roche questioned Ortho Biotech's statement that Roche's assertion that NeoRecormon had had no reformulation change since its introduction was 'certainly not a view shared by the CPMP'. As the CPMP was discussing, in a highly technical manner, variations to a marketing authorization not the specific term 'major reformulation' as would concern a lay clinician, Roche submitted that this view could not be presumed from this quotation.

Roche stated that the next section of quotation from the EPAR discussion document clearly stated that it concerned 'a revision of the content in some excipients'. Roche emphasised that this referred to quantities of various agents not changes in the constituent agents. Indeed the quotation contained the statement 'The excipients contained are the same as those for the single use formulations'. Roche agreed that these changes constituted a type II (ie major) variation in market authorization, after all the meaning of the term was set out in Community law. Roche submitted however that its audience was not European Community lawyers but physicians not versed in these matters, trying to evaluate a safety issue and make informed decisions for their patients. Roche's view was that it had provided them with a statement which simplified the complexities detailed above, in the context of the change in Eprex formulation, which it submitted was not misleading in the essence of this matter and would be helpful to their decision making process.

Roche submitted that in essence the matter came down to two questions. Should a statement clearly referring to NeoRecormon also be taken to refer to Recormon? If so, were the recipients of the letter, oncologists and haematologists, to read the EPAR document would they consider the small variations in relative amounts of various excipients, which did not alter the stability of the finished product, to constitute a major reformulation or would they reserve such a term for total change in formulation excipients eg from human serum albumin to tween (as had happened with Eprex)? Roche submitted that the original context for it releasing this statement was the marked increase in PRCA cases associated with Eprex which had not been seen with NeoRecormon, to inform prescribers of the situation with its product and to offer some theoretical explanation as to why there should be such a difference. The editorial in the New England Journal of Medicine made it clear that changes to the manufacturing and formulation of the 'European product' could be responsible for this phenomenon. Roche stated that it was important that it informed its customers that changes such as those to the Eprex formulation had not occurred for NeoRecormon.

## FURTHER COMMENTS FROM ORTHO BIOTECH

Ortho Biotech stated that any comments by Roche in respect of formulation changes for Eprex were not relevant to its appeal. Roche had attempted to justify a claim that did not take into account the clear regulatory pronouncement on the basis that, even though there had been numerous reformulations, the product had been formulated with essentially the same excipients.

Ortho Biotech stated that the term 'excipient' was understood by most people in the pharmaceutical industry and in the medical profession to be a largely inactive substance used as a diluent, vehicle or to give form or consistency. When Roche reformulated the original freeze-dried powder presentation of NeoRecormon to a solution for injection it was obviously necessary to introduce a significant amount of a new excipient ie water. It was therefore difficult to understand Roche's statement that 'in each of these presentations the active ingredient, epoetin beta, had been formulated with essentially the same excipients'. There was no water present in the lyophilized powder presentation. Water was present in the solution for injection. Water was an excipient. These presentations were therefore clearly not 'formulated with essentially the same excipients'.

Ortho Biotech admitted that, at the request of the European regulators, Eprex had been reformulated to remove human serum albumin. This was to minimise the risk of transmitting new variant CJD. Roche had argued that this change was in some way more 'major' than its formulation changes. This was not borne out by the facts. Ortho Biotech stated that the removal of human serum albumin from Eprex formulations required a type II variation of the relevant marketing authorizations. Ortho Biotech stated that because the reformulation of NeoRecormon to a solution for injection involved changes in the strength and pharmaceutical form of the product, a type II variation would not suffice, and an entirely new marketing authorization application was required. Ortho Biotech alleged that under Community law, and in the eyes of the CPMP, this reformulation was clearly more significant than its change in excipients.

Ortho Biotech stated that what another company might or might not have done with its product did not substantiate Roche's claims. The issue was whether NeoRecormon had been the subject of a major reformulation. The CPMP and the product's regulatory history made clear that it had. Any changes made to Eprex could not change that fact.

Ortho Biotech noted that Roche had argued that its reference to 'the product' related to NeoRecormon, not Recormon, and that NeoRecormon only received marketing authorization in October 1997. Ortho Biotech did not understand the relevance of this statement, since the CPMP's discussion of the steps taken after the approval of NeoRecormon made clear that the CPMP approved its reformulation as a

solution for injection in April 1998, ie after Recormon was renamed NeoRecormon. Roche's sudden insistence that 'NeoRecormon received marketing authorisation in October 1997' also meant that its comments pertaining to 'the past decade' were inaccurate. Ortho Biotech alleged that this was inconsistent with other statements in its advertisements. In the company statement at issue at point 2 above Roche stated that the manufacturing process for its product 'has remained identical over the 10 years since epoetin beta (NeoRecormon) was launched'. The Panel had ruled this statement in breach of the Code. Ortho Biotech noted that throughout its advertising, Roche had consistently made claims related to the safety of NeoRecormon on the basis of over 10 years' market experience. If Roche now asserted that 'comments pertaining to 'the past decade' were clearly inaccurate', then all of these claims must also have been misleading.

Ortho Biotech noted Roche's observation that Ortho Biotech had not identified any ingredient that had 'been either added, removed or replaced in the original formulation of NeoRecormon'; this was an oversight. Ortho Biotech confirmed that the excipient added to the lyophilized powder during its reformulation to a solution for injection was water.

Ortho Biotech stated that Roche had discussed the EPAR for NeoRecormon at some length and alleged a degree of confusion over the terms 'NeoRecormon', 'Recormon', formulation and pharmaceutical form. There was no need for confusion since the facts were straightforward. In April 1998, after Recormon had become NeoRecormon, the original powder form of the product was reformulated as a solution for injection. This reformulation was, according to Community law and the EPAR, so major that it could not be made by a type II variation but required an entirely new marketing authorization application.

Ortho Biotech noted that Roche had misleadingly asserted that the EPAR for NeoRecormon considered the composition of four entities and then listed a number of 'new' dosage strengths, formulations, multidose presentations, all of which were solutions for injection. This was not correct. The EPAR also discussed the lyophilised powder formulation of NeoRecormon. Roche had focused attention on the changes in the formulation of the lyophilisate, including the reduction in urea, calcium chloride and L-phenylalanine. However, this did not change the fact that the lyophilised powder had been reformulated as a solution for injection. It was this reformulation which Ortho Biotech considered major and hence formed the basis of its appeal. Ortho Biotech did not see the relevance of the discussion about stability tests. However the extract Roche quoted from the EPAR made it clear that there were both lyophilised powder and solution for injection formulations for NeoRecormon.

Ortho Biotech noted that Roche had argued that the legal classifications of its reformulations as 'fundamental' and 'major' was in some way irrelevant. Roche did not dispute that these were the correct legal and regulatory classifications. Instead Roche sought to argue that this was 'highly technical regulatory terminology' and that the introduction of 'additional strengths/pharmaceutical forms' would not translate to 'a 'major formulation change' in the parlance of a normal physician not versed in regulatory affairs'. Ortho Biotech noted that even if doctors knew about the formulation changes to NeoRecormon, Roche argued that they would not consider them to be major. In essence Roche suggested that it was justified in providing UK physicians with misleading information because they were unable to understand the significance of the relevant terms; this significantly underestimated the medical community. In Ortho Biotech's view the medical community would consider the difference between NeoRecormon in its powdered form and in a solution to be 'a major formulation change'. Ortho Biotech did not consider that Roche's view of the 'lay physician' justified inclusion of inaccurate statements in its public communications. It would be preferable to provide the medical community with the facts, and allow it to decide on the significance of any reformulation. Roche operated in a highly regulated area; a level of precision and accuracy was required when it sought approval of its products and a similar level of precision was required when it made public statements about them.

Ortho Biotech considered that Roche's only remaining argument was that the reformulations of its product were in some way less 'major' than the formulation change in Eprex and that this justified informing the medical community that the changes that had occurred with Eprex had not occurred with NeoRecormon. Ortho Biotech alleged that there were a number of problems with this argument. Firstly, that that was not what Roche had told the medical community; its claim was that 'NeoRecormon had had no major reformulation change since introduction'. Secondly, Roche's argument presupposed that its reformulations could not affect the stability of its product. If this was the case, Ortho Biotech questioned why Roche had had to submit stability data to support its reformulation. Contrary to Roche's assertions it was well known to academics and regulators that changes in formulation of recombinant proteins from lyophilised powder to solution could significantly affect the equivalence, or comparability, of the different formulations. For example the FDA's Center for Biologics Evaluation and Research (CBER), had specifically cited the reformulation of a lyophilised powder formulation of a recombinant protein to a liquid as an example of a change which should trigger a requirement to prove equivalence on the basis of new clinical data. The FDA had cited only two examples of formulation changes requiring equivalence data and these were 'lyophilized to liquid', ie the change Roche had made to NeoRecormon, and 'remove protein carrier', ie the change Ortho Biotech made to Eprex. In the FDA's view at least the significance and regulatory status of these changes were equivalent.

Ortho Biotech considered that Roche's grounds for disputing its appeal were without merit.

## APPEAL BOARD RULING

The Appeal Board noted that in July 2002 Ortho Biotech had issued a 'Dear Doctor' letter regarding

Eprex and PRCA. That letter had contained amended advice on route of administration and reminded readers of the correct storage and handling of Eprex. As a result of that letter Roche had received a number of enquiries from clinicians concerned that the information they had received about Eprex might also apply to NeoRecormon. Some of these enquiries had come from oncologists and haematologists. As a response to this Roche had issued the letter in question, dated 21 August 2002, to oncologists, haematologists and palliative care physicians.

The Appeal Board considered that although there had been no reports of PRCA in patients being treated for anaemia of malignancy, Roche was nonetheless justified in making clinicians involved in their care aware of the issues regarding PRCA and epoetin therapy. The Appeal Board noted that some of the target audience, ie haematologists, might get involved in the care of renal patients who had developed PRCA as a result of treatment with Eprex. In that respect the Appeal Board did not consider that the letter had disparaged Eprex and thus ruled no breach of Clause 8.1 of the Code. Roche's appeal on this point was successful.

The Appeal Board considered, however, that the letter minimised the risk of PRCA in patients with chronic renal failure treated with NeoRecormon and did not give the reader enough information about Eprex such that a valid comparison of the two products could be made. The Appeal Board considered that the letter was misleading in this regard and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3. Roche's appeal on this point was unsuccessful.

With regard to the claim that '… NeoRecormon has had no major reformulation change since its introduction' the Appeal Board referred to its comments in point 2. The Appeal Board considered that the change in presentations from a freeze-dried powder to a liquid form did represent a major reformulation of the product. The Appeal Board considered that the claim was misleading and ruled a breach of Clause 7.2. Ortho Biotech's appeal on this point was successful.

**Complaint received** **2 October 2002**

**Case completed** **8 April 2003**

CASE AUTH/1379/10/02

# FUJISAWA v NOVARTIS

## Promotion of Neoral

Fujisawa complained about a leavepiece issued by Novartis which promoted Neoral (cyclosporin) for use in organ transplants. A page headed 'Optimising Efficacy and Tolerability for Transplant Patients' featured five bullet points, the last of which read 'PTDM [post-transplant diabetes mellitus] incidence is up to four times greater with tacrolimus than Neoral'. Fujisawa marketed tacrolimus (Prograf).

Fujisawa did not consider that this final bullet point represented a fair comparison; the supporting reference (Moore 2001) related to the original formulation of cyclosporin (Sandimmun) and not Neoral. Furthermore Fujisawa alleged that the claim disparaged Prograf.

Fujisawa noted that it had had similar concerns regarding a previous claim 'tacrolimus is 4 times more likely to cause post-transplant diabetes than Neoral' and following correspondence with Novartis had considered the matter closed. To use an almost identical claim in a second leavepiece, and to quote the same reference, was a deliberate attempt by Novartis to mislead. Fujisawa alleged that this sort of activity was likely to bring discredit upon the pharmaceutical industry and reduce confidence in it in breach of Clause 2.

Fujisawa explained that Moore was an abstract given at a Novartis sponsored meeting in 2001. The presentation reported on a 'database' of 860 patients. Fujisawa stated that its analysis led it to conclude that the database included only the results of two early studies that compared the results of tacrolimus and cyclosporin (original formulation) treatment in renal transplant patients. Patients were recruited during 1993-1995; doses of tacrolimus and steroids used at that time tended to be higher than current practice.

Analysis of comparative studies since showed a much lower incidence of diabetes than those earlier reports. In particular in a report of a prospective randomised trial of tacrolimus/prednisolone versus tacrolimus/prednisolone/mycophenolate mofetil (MMF) in 208 renal transplant patients, the reported incidence of PTDM was 7% initially with a final incidence of 2.9% (Shapiro *et al* 1999). Johnson *et al* 2000 showed the incidence of PTDM was the same (6.5%) in renal recipients receiving a regimen including tacrolimus and MMF and those receiving Neoral and MMF. The group receiving tacrolimus and azathioprine had a somewhat higher initial incidence of PTDM (14%). At 12 months the incidence of persisting PTDM was actually lowest in the tacrolimus/MMF group (2.2%) compared with 6.5% in the Neoral/MMF group and 12.3% in the tacrolimus/azathioprine group. Fujisawa stated that these papers represented only a sample of publications where the relative incidence of PTDM was at odds with the claim in the leavepiece.

Fujisawa noted that two papers had been published since the leavepiece was produced. Margreiter *et al* (2002) reported the results of a randomised study involving 506 patients. Half received Prograf/azathioprine/steroids and half received Neoral/azathioprine/steroids. Using the same definition of PTDM the proportions of patients with new-onset diabetes mellitus were 4.5% for the Prograf group and 2% for the Neoral group. The other recent paper reported the results of a large study carried out in 196 paediatric renal transplant patients treated with either Prograf or Neoral in combination with azathioprine and prednisolone. Using the same definition of PTDM the proportions of patients with new-onset diabetes mellitus were 3% for the Prograf group and 2.2% for the Neoral group (Trompeter *et al* 2002).

Fujisawa alleged that the original presentation and abstract were very misleading, as the data gave the appearance of being recent when it actually related to a period some six years ago.

The Panel noted that Prograf was indicated for immunosuppression in patients with liver or kidney transplants, either to prevent organ rejection in the first place or to treat it if patients became resistant to other immunosuppressive regimes. Neoral had a much wider range of indications but was licensed for use in the same patient groups as Prograf. The Prograf summary of product characteristics (SPC) listed both hyperglycaemia and diabetes mellitus as very common (> 10%) adverse reactions to therapy. The Neoral SPC listed hyperglycaemia as a rare (≥ 0.01% to < 0.1%) adverse reaction to therapy. There was no mention of diabetes mellitus being associated with Neoral treatment.

The claim at issue 'PTDM incidence is up to four times greater with tacrolimus than Neoral' appeared twice in the leavepiece – once at the bottom of a page which specifically discussed renal transplant patients and again as the last bullet point on a page where the preceding bullet points referred to both renal and liver transplant patients. The cited reference, Moore, was a pooled analysis of data to compare the incidence of PTDM in renal transplant patients treated either with tacrolimus or cyclosporin. The study identified a consistent trend in renal transplant recipients where initial incidence of PTDM in the first year was four times higher in the tacrolimus treated group than in those treated with cyclosporin.

The Panel noted that the parties had referred to a number of clinical studies. Johnson *et al* (2000) had investigated the optimal combination of immunosuppressants for renal transplantation using three regimens: tacrolimus plus azathioprine (n=76); cyclosporin plus MMF (n=75) and tacrolimus plus MMF (n=72). There were no significant differences between the treatment groups with regard to efficacy. With regard to adverse events, the incidence of new onset PTDM was identical in the cyclosporin plus MMF and the tacrolimus plus MMF treatment groups (6.5%) and was higher in the tacrolimus and azathoprine group (14%).

**In a retrospective analysis of the records of 427 patients Bloom *et al* (2002) re-examined the risk factors for PTDM and concluded that the hepatitis C virus was strongly associated with PTDM in renal transplant patients and appeared to account for the increased diabetogenicity observed with tacrolimus.**

**O'Grady *et al* (2002) compared the use of tacrolimus and cyclosporin in 606 liver transplant patients and showed that diabetes after 3 months was more frequent in the tacrolimus group (2.06 [1.36-3.12] p=0.0006).**

**The Panel understood that two relevant papers had been published since the leavepiece was issued. Margreiter *et al* had examined the efficacy and safety of tacrolimus-based therapy (n=287) compared with that based on cyclosporin (n=273) in renal transplantation. Concomitant corticosteroid and azathoprine therapy was identical in both groups. The proportion of patients with PTDM was similar for the two groups (4.5% in the tacrolimus group v 2% in the cyclosporin group; p=0.105). Trompeter *et al* compared the safety and efficacy of tacrolimus (n=103) with cyclosporin (n=93) in children undergoing renal transplantation; PTDM was reported in 3% of the tacrolimus group and in 2.2% of the cyclosporin group.**

**Finally the Panel noted the Prograf product information issued in the US (May 2002). Under a heading of 'Warnings' the following appeared:**

> **'Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients without pre-transplant history of diabetes mellitus in the Phase III study …. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.'**

**The product information also included a table of data comparing Prograf (n=151) with cyclosporin based therapy (n=151) which showed an incidence of new onset PTDM at one year of 20% and 4% respectively; by two years those figures had fallen to 11% and 3% respectively.**

**The Panel considered that the claim at issue 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was too simplistic. Although most authors had reported a higher incidence of PTDM in tacrolimus-treated patients than in those receiving cyclosporin this was not always the case; the difference between the two was not always four fold. The incidence of PTDM appeared to depend upon a number of factors such as dose, time, race, type of transplant and concomitant therapy. The situation was not as straightforward as the claim implied. Although the claim stated '… *up to* four times greater …' (emphasis added), the Panel's view was that use of the phrase 'up to' did not negate the impression that the incidence of PTDM was always four times greater with tacrolimus than with cyclosporin which was not so. The Panel considered that the claim was misleading as alleged and ruled a breach of the Code. This ruling was appealed.**

**The Panel did not consider that the claim disparaged Prograf and so ruled no breach of the Code in that regard. Rulings of a breach of Clause 2 of the Code were reserved as signs of particular censure. The Panel did not consider that the claim warranted such a ruling.**

**Upon appeal by Novartis, the Appeal Board noted that the claim at issue 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was based upon a pooled analysis of comparative studies in which Sandimmun had been used, not Neoral. The two formulations of cyclosporin differed in their absorption characteristics; Neoral had better bioavailability than Sandimmun and there was less variability between patients in cyclosporin absorption. The Appeal Board noted the submission by Novartis that the formulation of cyclosporin was not an issue. Any difference in bioavailability between the two products, that might lead to a difference in the incidence of PTDM, was accounted for by the fact that a patient's dose of cyclosporin was titrated to a particular blood level of cyclosporin regardless of the formulation administered. Nonetheless the Appeal Board noted that no data had been submitted to confirm that the incidence of PTDM was the same for both Sandimmun and Neoral.**

**The Appeal Board noted that the incidence of PTDM was influenced by a range of complex factors. The Appeal Board considered that the claim at issue was a strong claim; it gave the impression that the incidence of PTDM was always four times greater with tacrolimus than with Neoral and this was not so; the use of the phrase '*up to* four times greater' (emphasis added) did not negate this impression. The Appeal Board considered that the claim was too simplistic and was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code.**

Fujisawa Limited complained about a Neoral (cyclosporin) A5 leavepiece (ref TXN 02/17) issued by Novartis Pharmaceuticals UK Ltd. The 6 page, gate folded leavepiece promoted Neoral for use in organ transplants; page 5, headed 'Optimising Efficacy and Tolerability for Transplant Patients', featured five bullet points, the last of which read 'PTDM [post-transplant diabetes mellitus] incidence is up to four times greater with tacrolimus than Neoral'.

Fujisawa marketed tacrolimus (Prograf).

## COMPLAINT

Fujisawa did not consider that the claim 'PTDM incidence is up to four times greater with tacrolimus than Neoral' represented a fair comparison; the reference cited in support of the claim, Moore (2001), related to the original formulation of cyclosporin (Sandimmun) and not Neoral. A breach of Clause 7.2 was alleged. Furthermore Fujisawa alleged that the claim was unjustifiably disparaging of Prograf and in breach of Clause 8.1.

Fujisawa stated that it had previously contacted Novartis regarding the unfair and unbalanced comparison. The company had also pointed out that

an error had been made in using the cited reference to refer to Neoral as the patients in the database had been treated with the original formulation of cyclosporin and following the response from Novartis had considered the matter closed. Fujisawa considered that to use an almost identical claim in a second leavepiece, and to quote the same reference could only be seen as a deliberate attempt by Novartis to mislead the reader. This, unfortunately, was the very sort of activity that was likely to bring discredit upon the pharmaceutical industry and reduce confidence in it. Fujisawa alleged a breach of Clause 2.

Fujisawa explained that the original leavepiece (ref TXN01/058) contained the claim 'tacrolimus is 4 times more likely to cause post-transplant diabetes than Neoral' referenced to Moore which was an abstract of a presentation that was given at a Novartis sponsored meeting in 2001. The presentation reported on a 'database' of 860 patients. Fujisawa stated that its analysis of the patient data led it to conclude that the database actually included only the results of two early studies that compared the results of tacrolimus and cyclosporin (original formulation) treatment in renal transplant patients. Patients were recruited during the years 1993-1995; doses of tacrolimus and steroids used at that time tended to be higher than current practice.

Analysis of comparative studies since showed a much lower incidence of diabetes than these earlier reports. In particular in a report of a prospective randomised trial of tacrolimus/prednisolone versus tacrolimus/prednisolone/mycophenolate mofetil (MMF) in 208 renal transplant patients, the reported incidence of PTDM was 7% initially with a final incidence of 2.9% (Shapiro *et al* 1999). A further comparative study showed the incidence of PTDM was the same (6.5%) in renal recipients receiving a regimen including tacrolimus and MMF and those receiving a cyclosporin microemulsion and MMF (Johnson *et al* 2000). The group receiving tacrolimus and azathioprine had a somewhat higher initial incidence of PTDM (14%). At 12 months the incidence of persisting PTDM was actually lowest in the tacrolimus/MMF group (2.2%) compared with 6.5% in the Neoral/MMF group and 12.3% in the tacrolimus/azathioprine group.

Fujisawa stated that these papers represented only a sample of publications where the relative incidence of PTDM was at odds with the claim in the leavepiece.

Fujisawa noted that two papers had been published since the leavepiece was produced. Margreiter *et al* (2002) reported the results of a randomised study involving 506 patients. Half received Prograf/azathioprine/steroids and half received Neoral/azathioprine/steroids. Using the same definition of PTDM the proportions of patients with new-onset diabetes mellitus were 4.5% for the Prograf group and 2% for the Neoral group. Trompeter *et al* 2002 reported the results of a large study carried out in 196 paediatric renal transplant patients treated with either Prograf or Neoral in combination with azathioprine and prednisolone. Using the same definition of PTDM the proportions of patients with new-onset diabetes mellitus were 3% for the Prograf group and 2.2% for the Neoral group.

Fujisawa alleged that the original presentation and abstract were very misleading, as the data gave the appearance of being recent when it actually related to a period some six years ago. Fujisawa assumed that Novartis was initially unaware of the misleading aspects of this presentation until Fujisawa pointed it out. Fujisawa stated that to continue to cite this misleading reference following its previous correspondence could not be excused in the same way.

## RESPONSE

Novartis stated that in view of the wealth of data now available comparing cyclosporin (both Sandimmun and Neoral) with tacrolimus, it did not consider that the statement 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was either misleading or an unfair comparison. It clearly stated that the incidence was up to 4 times higher with tacrolimus, as compared to Neoral based regimens. Whilst the company acknowledged that the abstract by Moore did not state which cyclosporin formulation was used, there had been no evidence of any difference in the incidence of PTDM between Sandimmun and Neoral. Further, the following studies all used Neoral and all showed a higher incidence of PTDM with tacrolimus than with Neoral based regimens: Bloom *et al* (2000); O'Grady *et al* (2002); Johnson *et al* (2000); Trompeter *et al* (2002); Margreiter *et al* (2002).

Bloom *et al* cited an incidence of PTDM that was up to 7.5 times higher with tacrolimus based immunosuppression than that noted with the Neoral based regimen.

Novartis noted that the current American product information for Prograf included a summary table in the 'Warnings' section. This table clearly showed a 20% incidence of new onset PTDM during the first year of treatment with tacrolimus, as compared to only a 4% increase with cyclosporin based regimes (ie a 5 fold increase in incidence with tacrolimus). The American product information also carried a written warning relating to the occurrence of PTDM with tacrolimus.

In view of the above, the claim 'up to 4 times' was a very reasonable view of the current literature. Thus, since the company did not consider that the claim constituted either an unfair comparison or a misleading one, it concluded that Clause 7.2 had not been breached. It followed therefore, that the claim in question was clearly not unjustifiably disparaging of tacrolimus and Novartis did not consider it was in breach of Clause 8.1.

With regard to Fujisawa's contention that the doses of tacrolimus and steroids used at that time tended to be higher than current practice, suggesting that the use of data from these studies might not be acceptable, Novartis noted that Fujisawa had used data from these studies extensively in promotional materials and continued to do so. Moreover, the issue of using studies which had employed such dosing regimens was the subject of an earlier complaint (Case AUTH/513/2/97). In that case, the Panel ruled that 'because the area of immunosuppression was

complicated with regards to the dose of agents used' it was justifiable to cite studies using high doses of tacrolimus (higher than the maximum licensed dose in one case) to support efficacy claims. Therefore, it seemed contradictory that Fujisawa was now suggesting that the use of such studies might not be acceptable after all. Novartis concluded from this that Fujisawa was less inclined to accept this principle in relation to safety data.

Novartis acknowledged that there had been previous correspondence. In particular, Fujisawa had concerns relating to the statement 'Tacrolimus is 4 times more likely to cause PTDM than Neoral'. As a result of this correspondence, the original leavepiece was withdrawn, as requested by Fujisawa, and the statement in question amended to read 'PTDM incidence is up to four times greater with tacrolimus than Neoral'. Such direct and prompt action in response to Fujisawa's initial concern, and the company's belief that use of the amended statement was fully justifiable, meant that Novartis strongly refuted Fujisawa's suggestion that its actions discredited the pharmaceutical industry or reduced confidence in it. Thus, Clause 2 had clearly not been breached.

Novartis did not consider that it was the place of the pharmaceutical industry to comment on the quality or impartiality of data presented by independent clinicians. At the very least, the company suggested that the Panel was an inappropriate forum in which to discuss such matters.

In conclusion, Novartis strongly contended that it had conducted itself entirely within the Code in these matters. It had acted upon Fujisawa's concerns, had kept its materials updated to reflect this, and had sought to present a balanced and fair account of the data throughout.

## PANEL RULING

Prograf was indicated for immunosuppression in patients with liver or kidney transplants, either to prevent organ rejection in the first place or to treat it if patients became resistant to other immunosuppressive regimes. Neoral had a much wider range of indications but was licensed for use in the same patient groups as Prograf. The Prograf summary of product characteristics (SPC) listed both hyperglycaemia and diabetes mellitus as very common (> 10%) adverse reactions to therapy. The Neoral SPC listed hyperglycaemia as a rare (≥ 0.01% to < 0.1%) adverse reaction to therapy. There was no mention of diabetes mellitus being associated with Neoral treatment.

The claim 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was referenced to a paper by Moore. The claim appeared twice in the leavepiece – once at the bottom of page 4 which specifically discussed renal transplant patients and again as the last bullet point on page 5; the preceding bullet points referred to both renal and liver transplant patients. Moore was a pooled analysis of data to compare the incidence of PTDM in renal transplant patients treated either with tacrolimus or cyclosporin. The study identified a consistent trend in renal transplant recipients where initial incidence of PTDM in the first year was four times higher in the tacrolimus treated group than in those treated with cyclosporin.

The Panel noted that the parties had referred to a number of clinical studies in which the effects of tacrolimus and cyclosporin in transplant patients had been compared.

Johnson *et al* (2000) had investigated the optimal combination of immunosuppressants for renal transplantation using three regimens: tacrolimus plus azathioprine (n=76); cyclosporin plus MMF (n=75) and tacrolimus plus MMF (n=72). There was no significant differences between the treatment groups with regard to efficacy. With regard to adverse events, the incidence of new onset PTDM was identical in the cyclosporin plus MMF and the tacrolimus plus MMF treatment groups (6.5%) and was higher in the tacrolimus and azathoprine group (14%). The authors noted that a reduced incidence of PTDM had been observed in other clinical trials where tacrolimus had been combined with MMF. The tacrolimus target blood concentrations and maintenance steroid dosing used in the trial were lower than in a previous trial and this appeared to have lowered the risk of PTDM compared to previous experience. The authors stated that no relationship of PTDM and patient race was evident.

In a retrospective analysis of the records of 427 patients Bloom *et al* (2002) re-examined the risk factors for PTDM and looked to see whether there was any association between the hepatitis C virus and PTDM in renal transplant patients on tacrolimus. The authors concluded that the hepatitis C virus was strongly associated with PTDM in renal transplant patients and appeared to account for the increased diabetogenicity observed with tacrolimus. The authors noted that previous studies had observed an association of black race with PTDM. They also noted that the results of their study suggested that the relationship between race and PTDM was potentially confounded by a patient's hepatitis C status.

O'Grady *et al* (2002) compared the use of tacrolimus and cyclosporin in 606 liver transplant patients and showed that diabetes after 3 months was more frequent in the tacrolimus group (2.06 [1.36-3.12] p=0.0006).

The Panel understood that two relevant papers had been published since the leavepiece was issued. Margreiter *et al* (2002) had examined the efficacy and safety of tacrolimus-based therapy (n=287) compared with that based on cyclosporin (n=273) in renal transplantation. Concomitant corticosteroid and azathoprine therapy was identical in both groups. The proportion of patients with PTDM was similar for the two groups (4.5% in the tacrolimus group v 2% in the cyclosporin group; p=0.105). Trompeter *et al* compared the safety and efficacy of tacrolimus (n=103) with cyclosporin (n=93) in children undergoing renal transplantation; PTDM was reported in 3% of the tacrolimus group and in 2.2% of the cyclosporin group.

Finally the Panel noted the Prograf product information issued in the US (May 2002). Under a heading of 'Warnings' the following appeared:

> 'Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-

treated kidney transplant patients without pre-transplant history of diabetes mellitus in the Phase III study …. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.'

The product information also included a table of data comparing Prograf (n=151) with cyclosporin based therapy (n=151) which showed an incidence of new onset PTDM at one year of 20% and 4% respectively; by two years those figures had fallen to 11% and 3% respectively.

The Panel considered that the claim at issue 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was too simplistic. Although most authors had reported a higher incidence of PTDM in tacrolimus-treated patients than in those receiving cyclosporin this was not always the case; the difference between the two was not always four fold. The incidence of PTDM appeared to depend upon a number of factors such as dose, time, race, type of transplant and concomitant therapy. The situation was not as straightforward as the claim implied. Although the claim stated '… **up to** four times greater …' (emphasis added), the Panel's view was that use of the phrase 'up to' did not negate the impression that the incidence of PTDM was always four times greater with tacrolimus than with cyclosporin which was not so. The Panel considered that the claim was misleading as alleged and ruled a breach of Clause 7.2. This ruling was appealed. The Panel did not consider that the claim disparaged Prograf and so ruled no breach of Clause 8.1. Rulings of a breach of Clause 2 of the Code were reserved as signs of particular censure. The Panel did not consider that the claim warranted such a ruling.

During its consideration of this case the Panel noted that the leavepiece in question had no date of production on it. Clause 4.9 of the Code stated that promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised. The Panel requested that Novartis be reminded of its obligations in this regard.

## APPEAL BY NOVARTIS

Novartis submitted that the claim 'PTDM incidence is up to four times greater with tacrolimus than Neoral' gave a fair and balanced overview of the data. Moore was a pooled analysis of renal transplant patients treated with either cyclosporin or tacrolimus, which gave a PTDM incidence in the first year post-transplant four times greater with tacrolimus than cyclosporin.

Novartis stated that this was supported by both the UK SPCs and US product information:

| UK SPC | Hyperglycaemia | Diabetes Mellitus |
|---|---|---|
| Tacrolimus | Very common (>10%) | Very common (>10%) |
| Cyclosporin | Rare (≥ 0.001 –<0.1%) | No mention |

| US Product Information | New Onset PTDM at 1 Year |
|---|---|
| Tacrolimus | 20% |
| Cyclosporin | 4% |

Since Novartis' response to the complaint, a meta-analysis of patients receiving cyclosporin or tacrolimus was presented at the American Society of Nephrology, Heisel *et al* (2002). This meta-analysis clearly stated that 'the odds of PTDM are increased four-fold in patients receiving tacrolimus compared with cyclosporin'.

Novartis considered that the statement 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was supported by the Moore data, the UK SPC and US product information and was confirmed by the very recent meta-analysis from Heisel *et al* and was therefore not misleading nor simplistic.

## COMMENTS FROM FUJISAWA

Fujisawa noted that the patient cohorts referred to in Moore (2001) were not treated with Neoral; these patients received the original Sandimmun formulation of cyclosporin. Novartis introduced Neoral because the unreliable absorption of the original formulation led to inadequate levels in some patients. The use of Neoral had therefore resulted in a more reliable absorption and associated higher blood levels. There was no suggestion that the products were bioequivalent. According to the Neoral SPC, the bioavailability of Neoral was on average 29% higher in terms of area under curve (AUC). As PTDM was known to be related (at least in part) to the level of exposure to the particular immunosuppressant there was no reason to assume that the incidence of PTDM seen with Sandimmun would remain the same in patients treated with Neoral.

Fujisawa referred to Cosio *et al* (2001), 'Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years', which included 2078 non-diabetic renal transplant recipients transplanted since 1983. All patients received cyclosporin. None received tacrolimus. The percentage of patients with PTDM had increased since 1995 from 5.9% to 10.5% at one year and from 8.8% to 16.9% at three years, compared with the incidence reported prior to 1995 when Neoral was launched. It was noted that average cyclosporin levels had increased significantly ($p<0.0001$) and steroid doses had decreased ($p<0.0001$). (Recipients had also got older and heavier ($p<0.0001$).) The authors postulated that this increase in PTDM might be 'due to the introduction of better absorbed cyclosporin formulations' … (ie Neoral) … that resulted in 'higher blood levels and higher cumulative exposure to this diabetogenic drug'.

In view of the above Fujisawa did not consider that it was reasonable to claim that 'there is no evidence of any difference in the incidence of PTDM between Sandimmun and Neoral' as a legitimate reason for citing a reference based on the old formulation to support a claim based on the new. Fujisawa considered that the burden of proof should lie with

those making the claim that the old and new products had the same incidence of the particular adverse event. The evidence that was available would seem to suggest the opposite and therefore the reference (Moore, 2001) quoted did not support the disputed statement. Fujisawa noted that in advertisements for Neoral originating in the US it was made clear in relation to claims regarding the relative incidence of PTDM that reference was being made to the Sandimmun formulation and the 'risk of PTDM in patients taking Neoral remains to be determined'.

Fujisawa noted that in Moore (2001) the author was careful to use the phrase '*initial* incidence of PTDM in the *first* year is four times higher in the [tacrolimus] versus [cyclosporin] *treated* groups' which took account of two additional factors. Firstly, PTDM appeared to be particularly related to the higher blood levels of tacrolimus seen in the early months after transplantation. As a consequence, approaching half of all tacrolimus-treated patients who developed PTDM over the first year discontinued insulin whilst remaining on tacrolimus therapy (First *et al*, 2002). Thus the prevalence of PTDM in tacrolimus-treated patients decreased with time. Cosio *et al* (2001) indicated an increasing incidence of PTDM in cyclosporin-treated patients as time progressed post-transplantation. Secondly, use of the expression '[cyclosporin]-t*reated*' acknowledged the importance of considering the totality of the immunosuppressive regimen rather than the overly simplistic and now outdated direct comparisons of individual medicines as represented in the disputed phrase. It was generally accepted that in the complicated area of immunosuppressive therapy one must compare regimen to regimen rather than medicine to medicine.

Fujisawa stated that the SPC was as an important medium of communication between the company and the medical profession; this was particularly important when dealing with safety issues. The emphasis that Fujisawa applied to this was to ensure that potential adverse events associated with its products were adequately communicated. It was particularly important to alert doctors to a possible adverse event that might be remedied by either decreasing the dose used or, on occasions, discontinuing the medicine. As a result Fujisawa would rather err on the side of over-emphasising safety concerns than underestimating them. Fujisawa did not regard the SPC as an area where it would seek to gain competitive advantage. Fujisawa considered that describing the incidence of PTDM as being very common (>10%) in the UK SPC for tacrolimus merely reflected this responsible approach and despite the significantly lower incidence of PTDM seen with tacrolimus in more recent years Fujisawa had not sought to change this wording. Fujisawa was surprised that the UK SPC for Neoral did not mention PTDM at all and listed the incidence of hyperglycaemia as rare (> 0.01% – < 0.1%) which would appear to be somewhat at odds with the figures quoted by Novartis and with Cosio *et al* (2001).

Fujisawa noted that no details had been provided on the Heisel *et al* poster regarding the papers included in the 'meta-analysis'. However, Fujisawa understood that the same two studies which provided all the patients in the Moore (2001) abstract accounted for more than half of the tacrolimus patients included in the Heisel *et al* poster (508/1000). It was likely that some if not all of the remaining studies included patients treated with the original formulation of cyclosporin and would reflect the higher incidence of PTDM associated with Prograf seen in the earlier studies, but did not reflect the current era. Unfortunately the studies considered in the meta-analysis had not been disclosed. Although '9 randomised comparative studies provided detailed information on the incidence of insulin-dependent diabetes mellitus (IDDM) suitable for meta-analysis' there was confusion later in the abstract as 5 kidney studies, 4 liver studies and an unknown number of lung and heart studies had rates of PTDM quoted. Further confusion was then provided by a later reference to a meta-analysis of 9 studies in kidney, liver and heart transplantation.

Fujisawa considered that the inclusion of any data from heart transplant recipients to support a claim relating to the relative incidence of PTDM in tacrolimus and cyclosporin patients was inappropriate as tacrolimus was only licensed in liver and kidney transplantation. Data published on tacrolimus in heart transplantation should be regarded as experimental and referred to early studies in this indication using various doses.

Fujisawa further noted that the 'meta-analysis' concentrated on randomised controlled studies which in transplantation might not always reflect the true clinical situation. For that reason, more naturalistic studies (like the Cosio study) might sometimes more closely reflect the true situation.

Fujisawa therefore agreed with the Panel that the phrase used in the leavepiece was too simplistic. Fujisawa referred to a review by First *et al* of 435 kidney transplant recipients carried out to determine risk factors, incidence and management strategies for post-transplant glucose intolerance which demonstrated the complex nature of the issue of PTDM. Although the study showed a rate of PTDM of 3.3% in the cyclosporin cohort compared with 5.7% in the tacrolimus-treated cohort, a multivariate analysis identified the only significantly related variable to be the absence of an anti-proliferative agent (MMF, azathioprine, rapamycin, everolimus). There was a trend towards higher tacrolimus doses in patients who developed PTDM compared with those who did not. The authors of this paper concluded that the incidence of PTDM was low under current immunosuppressive protocols, prompting reconsideration of previously identified risk factors. Transplant clinicians all accepted that in comparisons of immunosuppression, what was relevant was generally a comparison of one regimen with another rather than individual medicines. This appeared to be particularly true for the risk of PTDM and to make the claim quoted in the leavepiece in question was in Fujisawa's opinion oversimplistic and misleading.

In summary Fujisawa alleged that the disputed phrase 'PTDM incidence was up to four times greater with tacrolimus than Neoral' did not represent a fair comparison and was misleading. The reference used to support the claim referred to patients treated with

Sandimmun rather than the Neoral formulation of cyclosporin. The two formulations were not bioequivalent and bioavailability was on average 29% higher in terms of AUC according to Neoral SPC. There was no evidence to suggest that the incidence of PTDM for Neoral was the same as for Sandimmun. There was no evidence to suggest that the incidence of PTDM might be substantially higher in Neoral-treated patients than in Sandimmun-treated patients. The Heisel *et al* poster included patients treated with Sandimmun and included heart transplant patients for which tacrolimus did not hold a licence. The incidence of PTDM in tacrolimus-treated patients in studies published in more recent years was much lower than the 'historical' data referred to in both Moore and Heisel *et al*.

## FURTHER INFORMATION FROM NOVARTIS

Novartis noted that PTDM made a significant contribution to the burden of co-morbidity and mortality caused by cardiovascular disease. Indeed, as in the normal population, the incidence and prevalence of type 2 diabetes mellitus appeared to be increasing such that in some ethnic groups an incidence of around 50% was seen in the first year after transplantation.

Novartis noted that one of the difficulties that the transplant literature had in the context of PTDM was the lack of conformity in the adopted criteria to define PTDM which essentially had ignored the new American Diabetes Association/World Health Organisation definition of diabetes and was crudely defined as need for insulin for some thirty days.

Novartis considered that PTDM was under recognised and was associated with significant co-morbidity and co-mortality resulting in decreased graft and patient survival, diminished quality of life and increased health care costs.

The risk factors for PTDM included those present in the normal population such as age, family history, race and obesity, as well as the immunosuppressive regimen adopted after transplantation. In particular, corticosteroids and calcinurine inhibitors (cyclosporin and tacrolimus) both had important roles.

There were many postulated mechanisms for development of PTDM including beta cell toxicity, decreasing insulin secretion and increasing insulin resistance. Both cyclosporin and tacrolimus inhibited insulin secretion and were beta cell toxic. In addition, tacrolimus might have a role in increasing insulin resistance (Fernandez *et al* 1999; Strumph *et al* 1995; Tamura *et al* 1995; Van Duijnhoven *et al* 2001; Dmitrewski *et al* 2001). Novartis considered that the hypothesis that the different mechanisms of action ie to an increased incidence with tacrolimus appeared to be borne out in clinical practice. Moore (2001) was a pooled analysis of two pivotal studies of tacrolimus compared to cyclosporin; Mac *et al* (1997) [this should be Mayer *et al* (1997)] and Mayer (1998) [this should be Pirsch *et al* (1997)]. PTDM incidence was 2.6% on cyclosporin and 10.8% on tacrolimus.

Novartis noted that in Knoll and Bell (1999) the odds ratio for tacrolimus versus cyclosporin was 5.03 (2.04-12.36) which it considered to be a true meta-analysis.

Novartis noted that in the Heisel *et al* abstract the average PTDM rate in five randomised kidney transplant studies was 16.1% on tacrolimus and 4.2% on cyclosporin which was based on detailed literature review and meta-analysis.

Novartis noted that in Margreiter *et al* PTDM was 2% on cyclosporin versus 4.5% on tacrolimus; in First *et al* the PTDM was 3.3% on cyclosporin versus 5.7% on tacrolimus. Novartis submitted that Maes *et al* (2001) was an important study adopting the American Diabetes Association criteria for impaired fasting glucose and diabetes mellitus at one year in patients taking tacrolimus with 32% diabetes mellitus; 15% impaired fasting glucose; 53% normal glucose tolerance. In Greenspan *et al* (2002) the odds ratio for development of PTDM on tacrolimus was 9.1 versus cyclosporin. In Neylan *et al* (1998) the incidence of PTDM at one year post-transplant in different ethnic groups was: Caucasian 1.1% on cyclosporin versus 12.2% on tacrolimus; African/American 8.3% on cyclosporin versus 36.6% on tacrolimus and Hispanic 5.6% on cyclosporin versus 29.4% on tacrolimus.

Novartis stated that there was no doubt that failure to adopt the current criteria for definition of disorders of glucose metabolism used in the normal population had led to an underestimate of the incidence and prevalence of PTDM in the transplant population.

Novartis noted that although it had been suggested that the initial high doses utilised in both cyclosporin and tacrolimus based regimens had led to increased incidence. There was limited clinical evidence to suggest that the lower doses currently adopted would lead to a diminution of risk. Indeed, Cosio *et al* suggested an increase in cumulative incidence since 1995.

Finally, Novartis considered that clinical evidence suggested that PTDM was a significant cause of co-morbidity and co-mortality following transplantation that was contributed to a certain extent by the chosen immunosuppressive regimen. The burden of published evidence supported the contention that there was a high risk of developing PTDM in patients on tacrolimus versus cyclosporin, especially in certain ethnic groups and in those individuals at high risk of developing diabetes such as the obese or with a strong family history. Novartis disagreed that the statement PTDM incidence is 'up to four times greater with tacrolimus than Neoral' was misleading or unfair.

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Novartis advised that there had been an error in the referencing of the papers. Details were provided and were as stated in Fujisawa's comments below.

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## COMMENTS FROM FUJISAWA

Fujisawa noted that it had complained that the claim 'PTDM incidence is up to four times greater with tacrolimus than Neoral' did not represent a fair comparison and used a reference which related to the

original formulation of cyclosporin [Sandimmun] and not Neoral, and was therefore in breach of Clause 7.2.

Fujisawa noted that the majority of the references quoted by Novartis referred to the original formulation of cyclosporin and several of the references related to the same cohort of patients.

In general Fujisawa agreed with the first three statements regarding the problem of PTDM in transplant patients; the problem of PTDM being under recognised emphasised the importance of ensuring information was transmitted to doctors via an appropriately worded SPC. Fujisawa preferred to err on the side of overstating the risk of PTDM in the Prograf SPC and was surprised by the omission of this information in the Neoral SPC.

Fujisawa noted that Novartis had wrongly cited the two papers which formed the basis for the abstract by Moore (2001). The reference Mac *et al* (1997) should be Mayer *et al* (1997). The pages referred to in the second reference Mayer (1998) actually referred to a paper by Neylan which was quoted in a later paragraph. [Novartis confirmed that this was so.] Fujisawa considered the reference that Novartis intended to refer to was Pirsch *et al* (1997) (although as the two papers referred to the same cohort of patients it perhaps did not matter which was intended). As indicated in previous correspondence these studies referred to the original formulation of cyclosporin (Sandimmun) and reflected a historical period when doses of tacrolimus and steroids tended to be higher than in the modern era.

Fujisawa noted that the next paper, Knoll and Bell, was a meta-analysis and closer examination of this paper showed that only 3 studies were considered regarding the prevalence of PTDM. This was recognised by the authors to be a weakness of the meta-analysis. The papers cited were Pirsch *et al*, Mayer and Vincenti *et al* (1996). Only the Pirsch and Vincenti papers were considered by the author to permit inclusion in a summary odds ratio. Vincenti *et al* referred to a phase II dose-finding study where extremely high doses of tacrolimus were used in some of the patients (significantly higher than the licensed starting dose). Target trough levels, in retrospect, were well into the toxic range. But after all, the purpose of the study was to define an appropriate dose and target level to use in further development of tacrolimus in renal transplantation. All cyclosporin treated patients for whom an incidence of PTDM was quoted received Sandimmun and not Neoral.

Fujisawa noted that Heisel *et al* referred to data presented after the original complaint was made. Nevertheless Fujisawa believed that this reference also considered patients treated with the original formulation of cyclosporin and also included heart transplant patients for whom tacrolimus held no licence.

Fujisawa noted that Margreiter *et al* and First *et al* related to Neoral and showed an incidence of PTDM of 4.5% versus 2% and 5.7% versus 3.3% (tacrolimus versus Neoral). Fujisawa considered that this was a significantly lower relative incidence of PTDM than Novartis was alleging and was supported by references already quoted in Fujisawa's appeal where the relative incidences were 3% and 2.2% (tacrolimus versus Neoral) (Trompeter *et al*) and 7% and 7% for tacrolimus + MMF versus Neoral + MMF patients (Johnson *et al* 2000). These studies reflected the small increased risk of PTDM seen for tacrolimus in modern usage of this agent and the importance in considering the overall regimen rather than the over-simplistic comparison of two medicines.

Fujisawa noted that in Maes *et al* no patients treated with cyclosporin were considered and in patients treated with tacrolimus the incidence of PTDM requiring insulin use at 1 year was 5%. As Novartis pointed out, although there were other potential ways of describing the incidence of PTDM the transplant literature had generally 'crudely' defined this as 'a need for insulin therapy for some thirty days'. In current clinical practice in transplantation this was what clinicians would generally assume to be meant by PTDM. PTDM differed significantly from diabetes mellitus in non-transplant patients, particularly in the likelihood of reversal of diabetes (in a significant proportion of transplant patients), and this was the likely reason for the 'cruder' definition being preferred.

Fujisawa noted in Greenspan *et al*, 16 children (between 1989 and 1999) were defined as having PTDM and compared to 32 case controls. However, in this study PTDM was defined clinically by serum glucose greater than 200mg/dl on more than one occasion and the need for anti-hyperglycaemic medication. Although 13 patients were receiving tacrolimus at the time of diagnosis of PTDM, compared to 3 receiving cyclosporin (not possible to obtain information regarding formulation), one of the tacrolimus-treated patients had previously received cyclosporin. Of the thirteen patients, 9 were subsequently switched to cyclosporin. Of these 9, PTDM resolved in 5 following a switch to cyclosporin. Of 4 patients remaining on tacrolimus PTDM resolved in 3. In 3 patients who received cyclosporin from the time of transplant all 3 continued to suffer from PTDM. Therefore the final numbers of patients with PTDM were 5 for tacrolimus versus 3 for cyclosporin. In considering the risk for PTDM in paediatric renal transplant patients it was perhaps more reliable to refer to the data contained in the randomised controlled study in 196 patients reported by Trompeter *et al*.

Fujisawa considered Neylan *et al* was yet again the identical cohort of patients included in Pirsch *et al* and included in the original Moore abstract and included in the Knoll and Bell meta-analysis. These patients were recruited to the study between November 1993 and August 1995. This predated the Neoral era (therefore all cyclosporin-treated patients received the original formulation) and represented a time when significantly higher doses of tacrolimus and steroids were used.

Unfortunately, quoting four different references relating to various ways of analysing the same cohort of patients reported originally by Pirsch (Moore, 2001, Knoll and Bell, 1999, Heisel *et al*, 2002, and Neylan *et al*, 1998) did not help to clarify the debate.

In relation to Novartis' comments regarding the reasons why there was an under estimate of incidence

and prevalence of PTDM, Fujisawa referred to its comments above regarding definition of PTDM.

Fujisawa noted that Novartis had referred to the increased incidence of PTDM seen since 1995 and quoted in Cosio *et al*. As Fujisawa had noted in previous correspondence this study included 2078 non-diabetic renal transplant recipients transplanted since 1983. All patients received cyclosporin. None received tacrolimus. The percentage of patients with PTDM had increased since 1995 from 5.9% to 10.5% at one year and from 8.8% to 16.9% at three years, compared with the incidence reported prior to 1995 when Neoral was launched. It was noted that average cyclosporin levels had increased significantly ($p<0.0001$) and steroid doses had decreased ($p<0.0001$). (Recipients had also got older and heavier ($p<0.0001$).) The authors postulated that this increase in PTDM might be 'due to the introduction of better absorbed cyclosporin formulations' … (ie Neoral) … that resulted in 'higher blood levels and higher cumulative exposure to this diabetogenic drug'. Therefore perhaps Novartis was indicating that there might be an increasing risk for PTDM since 1995, although the reference was only to cyclosporin-treated patients. All the other published evidence pointed to a decreasing incidence in tacrolimus-treated patients.

In summary, Fujisawa considered, therefore, that Novartis had emphasised the complex nature of PTDM and the possible differences in the incidence of PTDM in cohorts treated with the different formulations of cyclosporin. This seemed to support the original findings of the Panel that the phrase used in the leavepiece was too simplistic and was therefore in breach of Clause 7.2 of the Code.

## APPEAL BOARD RULING

The Appeal Board noted that the claim at issue 'PTDM incidence is up to four times greater with tacrolimus than Neoral' was referenced to Moore (2001), a pooled analysis of comparative studies which were based on the original Sandimmun formulation of cyclosporin and not Neoral for which the claim was made. The two formulations differed in their absorption characteristics; Neoral had better bioavailability than Sandimmun and there was less variability between patients in cyclosporin absorption. The Appeal Board noted the submission by Novartis' representatives at the appeal that the formulation of cyclosporin was not an issue. Any difference in bioavailability between the two products, that might lead to a difference in the incidence of PTDM, was accounted for by the fact that a patient's dose of cyclosporin was titrated to a particular blood level of cyclosporin regardless of the formulation administered. Nonetheless the Appeal Board noted that no data had been submitted to confirm that the incidence of PTDM was the same for both Sandimmun and Neoral.

The Appeal Board noted that the incidence of PTDM was influenced by a range of complex factors. The Appeal Board considered that the claim at issue was a strong claim; it gave the impression that the incidence of PTDM was always four times greater with tacrolimus than with Neoral and this was not so; the use of the phrase '**up to** four times greater' [emphasis added] did not negate this impression. The Appeal Board considered that the claim was too simplistic and was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

During its consideration of this case the Appeal Board noted that in its initial response to the complaint Novartis had stated that it did not consider that it was the place of the pharmaceutical industry to comment on the quality or impartiality of data presented by independent clinicians. The company had further suggested that at the very least the Panel was an inappropriate forum in which to discuss such matters. The Appeal Board strongly disagreed with this view. While clinicians were entitled to publish what they liked the use of such data in the promotion of medicines must always stand up to scrutiny and comply with the Code.

**Complaint received** **18 October 2002**

**Case completed** **20 March 2003**

**CASES AUTH/1382/10/02 and AUTH/1386/11/02**

# GLAXOSMITHKLINE v BOEHRINGER INGELHEIM and PFIZER

## Promotion of Spiriva

**GlaxoSmithKline complained about the promotion of Spiriva (tiotropium) by Boehringer Ingelheim and Pfizer. The materials at issue were a detail aid, a leavepiece and two journal advertisements.**

**Page 1 (front cover) of the detail aid was headed 'Introducing Spiriva' and included the strapline 'Changing expectations in COPD'. Page 1 was not as wide as the rest of the pages of the detail aid such that a question on page 3 'What do you expect from a COPD treatment?', and the product logo, were visible. To the left of the question on page 3, and visible once the front cover had been turned, was a list of treatment attributes including 'Efficacy vs salmeterol'; alongside each attribute was a tick. GlaxoSmithKline considered that the list of ticked attributes appeared to be attributes of Spiriva itself and not simply of chronic obstructive pulmonary disease (COPD) treatments in general. In the second half of the list, 'Efficacy vs. salmeterol' followed several positive items (simple dosing, convenient delivery device) inviting the conclusion that this too was a positive comparison for Spiriva compared with salmeterol. GlaxoSmithKline alleged that the use of this statement followed by a tick on a page branded with Spiriva was an exaggerated claim. The evidence for a superior effect of Spiriva over salmeterol was based on two clinical trials which did not support an overall positive claim of 'efficacy vs salmeterol'.**

**Given the context in which the list of attributes appeared the Panel considered that 'Efficacy vs. salmeterol' implied that Spiriva had superior efficacy to salmeterol. The Panel noted the companies' submission that Spiriva outperformed salmeterol in comparisons with placebo and in some of the direct comparisons. There were two studies directly comparing Spiriva and salmeterol. There were some differences between Spiriva and salmeterol and some of these were in favour of Spiriva. Some measures had shown no difference. A number of specific comparisons were the subject of further allegations. The Panel did not consider that the data were sufficient to support a general claim that Spiriva had superior efficacy to salmeterol. The claim was misleading and exaggerated and breaches of the Code were ruled. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's rulings.**

**GlaxoSmithKline alleged that the claim 'Spiriva can make a life-changing difference in COPD' which appeared on page 4 of the detail aid, as well as on a number of other pages, was exaggerated. Boehringer Ingelheim had stated that it was an overall claim based on the total properties of Spiriva and should not be interpreted as being specifically supported by the data contained on one particular page. The company had also stated that based on the evidence (four studies of 1 year and two of 6 months) Spiriva was capable of producing statistically significant benefits in many instances and clinically significant benefits in some.**

**GlaxoSmithKline considered that the phrase 'can make a life-changing difference' was strongly positive and implied a strong likelihood of an effect. However, as Boehringer Ingelheim stated, clinically significant benefits were seen only in some instances.**

**The Panel noted that the claim appeared on almost every alternate page of the detail aid. The Panel considered that the claim 'Spiriva can make a life-changing difference in COPD' was a strong claim. Page 4 of the detail aid, headed 'Significant and sustained improvement in lung function', compared trough $FEV_1$ of Spiriva in placebo controlled studies over a one-year period. The Panel considered that in the context of a page comparing Spiriva and placebo the claim was exaggerated as a positive result was no more than would be expected. A breach of the Code was ruled.**

**Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board considered that the claim 'Spiriva can make a life-changing difference in COPD' implied a major impact. This was not supported by the data. In the context of a page comparing Spiriva and placebo the claim was exaggerated and all embracing. The Appeal Board upheld the Panel's ruling.**

**The claim 'Health-related quality of life' appeared as the heading on page 6 which featured a bar chart, adapted from Casaburi *et al*, comparing the change in St George's Respiratory Questionnaire (SGRQ) total and impact scores for placebo and Spiriva at one year. Beneath the bar chart was the claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores'. GlaxoSmithKline stated that with regard to the SGRQ a 4-unit change from baseline in total score represented a clinically meaningful improvement in health status. In Casaburi *et al* patients receiving tiotropium did not achieve this 4-unit change. Although attention was drawn to the probity of the SGRQ at the side of the page, readers were not told of the level of change that was clinically meaningful, and it was not made clear that a clinically meaningful improvement was not achieved. The inclusion of the strap-line 'Spiriva can make a life-changing difference in COPD' implied that Spiriva achieved meaningful improvements in quality of life which was not so. GlaxoSmithKline alleged that the presentation of the quality of life data was misleading.**

**The Panel noted that in a review of evidence for the validity of health status or health related quality of life measurement in COPD it was stated that there was no universally agreed definition of worthwhile benefit in chronic disease but a common view was that if a patient could detect a definite reduction in symptoms or the impact of the disease on their daily life, that was clinically significant (Jones 2001). The issue of clinically noticeable differences and thresholds for clinical significance was complex but**

**the suggested threshold of 4 units for the SGRQ appeared to be reliable. The short term repeatability of the SGRQ questionnaires was described as 'good' by reference to the correlation coefficient. Jones stated that the correlation coefficient did not give the full picture and referred to a situation where approximately half the patients showed a change in SGRQ score that was greater or less than the 4 unit threshold for a clinically significant change whether or not there had been a real change in their state. Equally in other patients who had a 'true' worthwhile benefit, the health status score might change by less than the clinically significant threshold. This was described as a problem.**

**Casaburi *et al* was a long-term evaluation of once daily tiotropium. The primary outcome was trough $FEV_1$ (prior to dosing). Changes in dyspnoea were measured using the Transitional Dyspnoea Index (TDI). Health status was evaluated using SGRQ. At each visit the investigator recorded COPD symptoms after reviewing the patient's daily diary for wheezing, shortness of breath, coughing and chest tightness and recorded a global evaluation of the patient's overall condition. Tiotropium demonstrated improvements in each domain as well as in total score with statistically significant improvements relative to placebo ($p<0.05$). In addition to a statistically significant improvement in mean response, a significantly greater percentage of patients in the tiotropium group (49%) showed at least a four unit improvement in total score compared to those in the placebo group (30%).**

**The Panel noted that the data presented in the bar chart on page 6 did not reach a mean change from baseline of four units with regard to total and impact scores for Spiriva at one year. The difference between Spiriva and placebo was statistically significant ($p<0.05$). With regard to impact scores the difference between the two was a total of 4.04 units and therefore at a level to be judged clinically significant. The Panel noted that more patients in the tiotropium group showed at least a four unit improvement in total score compared to those in the placebo group. In the Panel's view there was a difference between a 4 unit reduction in mean SGRQ score ie achieving clinical significance and the numbers of patients achieving a change of 4 units or more. The Panel considered that this was a complex issue as noted by Jones. In the Panel's view the basis of the claim should be made clear. The claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores' was a general claim for the population as a whole. The Panel considered, however, that the overall impression of the heading 'Health-related quality of life', the strapline 'Spiriva can make a life-changing difference in COPD' and the differences depicted in the bar chart, was that all the results were clinically significant and this was not so. Insufficient explanation had been provided. The Panel considered that the presentation of the data was misleading and ruled a breach of the Code.**

**Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board considered that the claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores' was true but did not reflect the results with regard to clinical significance. There was a difference between statistical significance and clinical significance. The Appeal Board considered that the overall impression of the heading 'Health-related quality of life', the strapline 'Spiriva can make a life-changing difference in COPD' and the differences depicted in the bar chart, was that all the results were clinically significant and this was not so. Insufficient explanation had been provided. The Appeal Board considered that the presentation of the data was misleading and upheld the Panel's ruling.**

**The claim 'Significantly reduces exacerbations and related hospitalisations' appeared as the heading to page 7 which featured a bar chart headed 'Exacerbations and exacerbation-related hospitalisations compared with placebo per patient-year'. The data were adapted from Casaburi *et al*. GlaxoSmithKline alleged that the presentation of the data misled as to the significance of the exacerbation-related hospitalisation data, which were of an order of magnitude smaller than for exacerbations. Although the different scales were given on the two y-axes, the visual impression was that the exacerbation and exacerbation-related hospitalisation data were on the same scale, thus exaggerating the effect of tiotropium on hospitalisations. Although the difference in hospitalisations was statistically significant, the reduction compared with placebo was only 0.075 hospitalisations per patient-year (equivalent to around 1 event every 13 years per patient) – a reduction from 0.161 to 0.086 was rather less impressive than the visual impression the graph conveyed.**

**The Panel noted that the two y-axes were the same height. The scale for the number of exacerbations per patient-year, on the left-hand side of the bar chart, started at zero and finished at 1.6 with intervals of 0.2. The scale for the mean number of hospitalisations due to exacerbations per patient-year, on the right-hand side of the bar chart, started at zero and finished at 0.18 with intervals of 0.02. The bar charts appeared beneath the same heading. Both showed a statistically significant advantage for Spiriva over placebo and the details were given. The Panel's view was that the presentation was visually misleading. The bar charts were in the same visual field. The mean number of hospitalisations due to exacerbations per patient year appeared to be numerically greater than the mean number of exacerbations. The Panel considered that the change in scale for the hospitalisation data exaggerated the benefit for Spiriva compared to placebo and a breach of the Code was ruled.**

**Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board considered that the presentation was visually misleading and upheld the Panel's ruling of a breach of the Code.**

**The claim 'Spiriva delivered via the HandiHaler encourages good compliance' was referenced to**

Kesten *et al* (2000) and appeared beneath the heading 'Tailored for COPD'. GlaxoSmithKline alleged that the claim implied there was something specific about Spiriva delivered via the HandiHaler which meant compliance would be encouraged.

Kesten *et al*, was an abstract that evaluated compliance by capsule counting from two tiotropium vs placebo studies. Good compliance was shown in both groups but there was no difference between tiotropium and placebo. It could not be concluded that Spiriva through the HandiHaler encouraged good compliance, since compliance was the same with placebo via HandiHaler.

The Panel noted that Kesten *et al* stated that one advantage of tiotropium was once daily dosing which presumably should improve compliance. The abstract concluded that counts of pierced capsules suggested a high compliance rate with tiotropium prescribed once daily via a capsule based system.

Boehringer Ingelheim had some evidence in relation to compliance but there was no data to compare compliance with the HandiHaler and compliance with other methods of administration. There was an implication that good compliance with Spiriva was achieved through use of the HandiHaler as opposed to any other inhalation device. There was no data in this regard. The Panel considered the claim was misleading as it had not been substantiated. The Panel therefore ruled breaches of the Code. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.

Page 9 of the detail aid demonstrated the use of the HandiHaler by use of three illustrations labelled 'Drop…press… and inhale'. GlaxoSmithKline stated that the illustrations suggested that the HandiHaler could be used in three steps. This was not so: seven steps were outlined in the SPC with the exhalation/inhalation cycle repeated in order to empty the capsule and inhale the whole dose. GlaxoSmithKline alleged that it was misleading to make it appear that using the HandiHaler consisted of three simple steps.

The Panel considered that the impression given was that there were three steps for taking Spiriva via the HandiHaler. The correct administration was more complicated than that implied by the illustration and the phrase 'Drop…press…and inhale'. In the Panel's view page 9 would be seen as providing the instructions needed for the administration of Spiriva and it was misleading in that regard. A breach of the Code was ruled. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.

The claim 'Spiriva can make a life-changing difference in COPD' appeared as the heading to page 11 of the detail aid. The page presented three comparisons; Spiriva with placebo, with ipratropium and with salmeterol. GlaxoSmithKline stated that the claim implied that Spiriva was likely to make a life-changing difference compared with all three and that the data provided substantiated this.

GlaxoSmithKline alleged that the placebo comparison health-related quality of life data did not reflect 'life-changing' differences. Over one year, tiotropium did not produce a clinically relevant difference in quality of life. In addition the reduction in hospitalisations was only 0.075 hospitalisations per patient per year compared with placebo (equivalent to the prevention of one hospitalisation event per patient every 13 years).

GlaxoSmithKline stated that the improvement over ipratropium in breathlessness (TDI focal score) did not reach a clinically relevant difference. In addition, the difference in terms of quality of life between the two was not clinically significant. It was misleading to suggest the differences were 'life-changing'.

Comparing salmeterol and tiotropium, there was no evidence of either a clinical or statistical difference in breathlessness score, or quality of life. Furthermore, Boehringer Ingelheim had stated that there was no basis for a claim of superiority of Spiriva over salmeterol for either parameter. Thus the heading that 'Spiriva can make a life-changing difference …' was misleading in connection with these claims.

GlaxoSmithKline alleged that the implication that tiotropium could make a life-changing difference in COPD compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. Furthermore, the breathlessness data for tiotropium compared with salmeterol had been presented selectively. This data was referenced to Witek. GlaxoSmithKline stated that in these six-month studies, the primary analysis of this endpoint was defined as the percentage of TDI responders (that was, the percentage of patients in each group achieving a one unit or greater improvement in TDI score, Donohue *et al*).

The outcome measure presented in the detail aid was not the primary endpoint, but was an additional secondary outcome measure for breathlessness in which the mean TDI score was given as a unit.

For the primary analysis of this co-primary endpoint, in the Donohue study (Study 205.130), 42% of patients on tiotropium responded, compared with 35% receiving salmeterol, with no statistical difference between the groups. In study 205.137, 45% patients on tiotropium responded, compared with 48% on salmeterol – again with no statistical difference between the groups.

The claim in the detail aid implied that patients would not achieve a clinically relevant improvement with salmeterol, whereas the primary endpoint of the study refuted this (35-48% would improve to a clinically relevant degree).

GlaxoSmithKline alleged that the claim derived from these data did not reflect the balance of evidence.

The Panel noted that the data comparing Spiriva with placebo was referenced to Casaburi *et al* and considered that its previous comments on this study were relevant. The Panel considered that the claim

**referring to health-related quality of life scores was too simplistic given the complexity of the use of such data. There were statistically significant differences with placebo in relation to exacerbations and exacerbation-related hospitalisations.**

**The comparison with ipratropium, 'Significant improvement in lung function, and a statistically significant improvement in breathlessness scores and health-related quality of life scores, with a significant reduction in exacerbations' was referenced to Vincken *et al*. Breathlessness scores were measured by using the TDI focal score. The Panel noted that the differences between ipratropium and Spiriva were statistically significantly in favour of Spiriva, however they were less than one and hence did not achieve a clinically meaningful difference for that measure. The proportion of patients who achieved a clinically meaningful difference in TDI total score (improvement of ≥ 1 unit) was statistically significantly greater in the Spiriva group (31%) than in the ipratropium group (18%) (p=0.004). Similarly the difference between the products in terms of quality of life was statistically significantly in favour of Spiriva but was less than 4 units and hence did not achieve a clinically meaningful difference. More patients in the Spiriva group achieved a clinically meaningful improvement of 4 units (52% v 35% p< 0.01). There was a difference between a 4 unit reduction in mean SGRQ score ie achieving clinical significance and the numbers of patients achieving a change of 4 units or more. In the Panel's view the basis of the claim should be made clear. The Panel noted its previous comments regarding quality of life data.**

**With regard to the comparison with salmeterol in relation to breathlessness score and health-related quality of life scores, the Panel noted Boehringer Ingelheim and Pfizer's submission that the comparisons with salmeterol were not direct comparative claims. Each medicine had been compared with placebo. The claims appeared beneath the heading 'In a comparison with salmeterol, Spiriva delivered a: …'. The Panel considered that in conjunction with the heading the claims would be read as direct comparisons between the two products.**

**The Panel noted its comments above regarding the claim 'Spiriva can make a life-changing difference in COPD'. The Panel noted the submission from Boehringer Ingelheim and Pfizer that Spiriva could produce, for individual patients, differences that were life-changing. The claims in the detail aid, however, would be assumed to represent the expected response in most patients. In the Panel's view the word 'can' rarely negated the impression of 'will'. The Panel considered that given its comments above overall, the implication that Spiriva could make a life-changing difference in COPD generally or in relation to all the parameters listed compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. The Panel ruled breaches of the Code.**

**The Panel considered that although the claim that in a comparison with salmeterol, Spiriva delivered a 'Clinically significant difference in breathlessness score (1.1 units) after 6 months compared with placebo, whereas salmeterol did not (0.7 units) …', was consistent with the findings of Witek *et al* it was not sufficiently clear given that there was data to show that the numbers of patients who responded, ie achieved a one unit or greater improvement for TDI for Spiriva compared to salmeterol, was not statistically different, Donohoe and data on file.**

**The Panel considered that the claim was misleading as it had not been put into the context of the other results and it appeared that salmeterol did not produce a clinically significant difference in breathlessness score. Insufficient explanation had been provided. A breach of the Code was ruled.**

**Upon appeal by Boehringer Ingelheim and Pfizer with regard to the comparison of Spiriva with placebo, referenced to Casaburi *et al*, the Appeal Board considered that its comments on this study above were relevant. The Appeal Board considered that the claim referring to health-related quality of life scores was too simplistic given the complexity of the use of SGRQ. There were statistically significant differences with placebo in relation to exacerbations and exacerbation-related hospitalisations.**

**The comparison with ipratropium, 'Significant improvement in lung function, and a statistically significant improvement in breathlessness scores and health-related quality of life scores, with a significant reduction in exacerbations', was referenced to Vincken *et al*. The Appeal Board noted that the differences between ipratropium and Spiriva were statistically significantly in favour of Spiriva, however they did not achieve a clinically meaningful difference for that measure. The proportion of patients who achieved a clinically meaningful difference in TDI total score (improvement of ≥ 1 unit) was statistically significantly greater in the Spiriva group (31%) than in the ipratropium group (18%) (p=0.004). Similarly the difference between the products' quality of life scores was statistically significant in favour of Spiriva but did not achieve a clinically meaningful difference. More patients in the Spiriva group achieved a clinically meaningful improvement (52% v 35% p< 0.01). The basis of the claim had not been made sufficiently clear. The Appeal Board noted previous comments regarding the SGRQ above.**

**With regard to the comparison with salmeterol in relation to breathlessness score and health-related quality of life scores, the Appeal Board noted that the comparisons with salmeterol were not direct comparative claims. Each medicine had been compared with placebo. The claims appeared beneath the heading 'In a comparison with salmeterol, Spiriva delivered a: …'. The Appeal Board considered that in conjunction with the heading the claims would be read as direct comparisons between the two products.**

**With regard to the claim 'Spiriva can make a life-changing difference in COPD', the Appeal Board noted the submission from Boehringer Ingelheim**

and Pfizer that Spiriva could produce, for individual patients, differences that were life-changing. The claims in the detail aid, however, would be assumed to represent the expected response in most patients. The Appeal Board considered that given its comments above overall, the implication that Spiriva could make a life-changing difference in COPD generally or in relation to all the parameters listed compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. The Appeal Board upheld the Panel's rulings.

The Appeal Board considered that the claim that in a comparison with salmeterol, Spiriva delivered a 'Clinically significant difference in breathlessness score (1.1 units) after 6 months compared with placebo, whereas salmeterol did not (0.7 units) …' was consistent with the findings of Witek *et al*. It was not sufficiently clear given that there was data to show that the numbers of patients who responded, ie achieved a one unit or greater improvement for TDI for Spiriva compared to salmeterol, was not statistically different (the primary endpoint in the study), Donohoe and data on file.

The Appeal Board considered that the claim was misleading as it had not been put into the context of the other results and it appeared that salmeterol did not produce a clinically significant difference in breathlessness score. Insufficient explanation had been provided. The Appeal Board upheld the Panel's ruling.

The claim 'Efficacy vs. ipratropium' was the heading to page 16 of the detail aid which compared Spiriva with ipratropium and stated that 'In a comparison with ipratropium, Spiriva delivered a:
Significant improvement in lung function
Sustained improvement in lung function
Statistically significant improvement in breathlessness scores…'.

The claims were referenced to Vincken *et al*. GlaxoSmithKline stated that although statistically significant, the improvement over ipratropium in breathlessness (TDI focal score) was not clinically significant.

As TDI focal score had a validated threshold of clinical significance, it was misleading not to make this clear. TDI was relatively unfamiliar to most UK health professionals and they could not be expected to know that the improvement reported (0.9) was not a clinically relevant difference. Since it appeared on a page which concluded with the claim 'Spiriva can make a life-changing difference in COPD', the implication was that there was a difference that would be noticed by patients.

The Panel noted its previous comments. The difference between breathlessness scores was statistically significant not clinically so. The Panel ruled that the claim with regard to breathlessness, in conjunction with the strapline 'Spiriva can make a life-changing difference in COPD', was misleading in breach of the Code. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.

The claim 'Statistically significant improvement in health-related quality of life scores' was on page 16 of the detail aid and introduced with the statement 'In a comparison with ipratropium, Spiriva delivered a: ...'. The claim was referenced to Vincken *et al*. GlaxoSmithKline stated that the difference in qualify of life score between Spiriva and ipratropium was statistically significant but not clinically meaningful. There was no mention on this page of the level at which a change in quality of life achieved clinical relevance. The claim implied there was a difference that would be noticed by patients – however the improvement with tiotropium over ipratropium did not reach the validated threshold for a clinically meaningful difference. GlaxoSmithKline alleged that the claim was misleading.

The Panel noted its previous comments. The Panel considered that the claim, in the context in which it was used, was misleading. Insufficient explanation had been provided. The Panel ruled a breach of the Code. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.

The claim 'In a comparison with salmeterol: Spiriva showed no evidence of tachyphylaxis' referenced to Donohue *et al* appeared on page 18 of the detail aid which was headed 'Efficacy vs. salmeterol'. GlaxoSmithKline alleged that the apposition of the claim implied that salmeterol showed tachyphylaxis. The balance of evidence from a range of clinical studies was that salmeterol showed a sustained bronchodilator effect vs placebo in studies of 6 months to 1 year with no evidence of tachyphylaxis. GlaxoSmithKline alleged that the claim was misleading as it did not reflect the balance of evidence.

The Panel considered that given that the claim that 'Spiriva showed no evidence of tachyphylaxis' appeared on a page headed 'Efficacy vs. salmeterol', the failure to give any information about salmeterol and tachyphylaxis gave the impression that salmeterol caused tachyphylaxis. In the Panel's view the claim, in the context in which it was used, was misleading and a breach of the Code was ruled. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.

The claim 'In a comparison with salmeterol: Spiriva patients achieved a clinically significant difference in breathlessness score (1.1 units) at 6 months compared with placebo whereas salmeterol did not (0.7 units)', referenced to Witek, appeared on page 18 of the detail aid. GlaxoSmithKline alleged that this was a selective use of a secondary endpoint for breathlessness, where the primary endpoint showed a different result. The page also carried the strapline 'Spiriva can make a life-changing difference in COPD'. GlaxoSmithKline alleged that the claim did not reflect the balance of evidence and was misleading. The Panel noted its previous comments. The Panel considered that one of its previous rulings also applied here and therefore ruled a breach of the Code. This ruling was upheld on appeal.

The claim 'In a comparison with placebo, Spiriva significantly reduced the number of exacerbations

**while salmeterol did not' appeared on a page headed 'Efficacy vs. salmeterol'. GlaxoSmithKline alleged that the claim implied that salmeterol had no effect on exacerbations compared with placebo. This was selective use of the available data, and did not reflect the balance of evidence.**

**The Panel noted that Boehringer Ingelheim and Pfizer were referring to the only study comparing Spiriva and salmeterol (data on file (SP102-2). GlaxoSmithKline had data from two large studies to show that salmeterol was associated with a mean reduction in exacerbation rate compared to placebo. The Panel considered that the claim implied that the balance of the data was such that salmeterol was no different to placebo with regard to reductions in numbers of exacerbations and this was not so. The claim was misleading and the Panel ruled a breach of the Code. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.**

**The leavepiece included a number of claims that appeared in the detail aid and had been ruled in breach of the Code.**

**GlaxoSmithKline alleged that the claim 'Introducing Spiriva Open up to a new world of COPD management' which appeared in journal advertisements was exaggerated and implied a major step forward compared with existing therapy for COPD management (ie anticholinergics such as ipratropium bromide and long acting ß2 agonists such as salmeterol). Such a claim was not supported by the data.**

**GlaxoSmithKline noted that tiotropium was not a new class of medicine – anticholinergics had been well established for many years. Essentially, tiotropium and ipratropium bromide had the same mode of action, although tiotripium had a longer duration of action and was taken once daily – but there was no evidence that once daily dosing regimens improved compliance compared with twice daily. Compared with ipratropium, there was little evidence of clinically relevant improvements in breathlessness scores or health-related quality of life and no difference in hospitalisations for exacerbation. Compared with salmeterol there was little evidence of clinically relevant differences for lung function, and no statistical or clinical differences with regard to breathlessness (either in terms of the primary analysis – percentage responders or secondary endpoint – mean scores), health-related quality of life or exacerbations. GlaxoSmithKline alleged that the claim was exaggerated and all embracing and not substantiated by the available evidence.**

**The Panel noted that before Spiriva was launched ipratropium and salmeterol had been available for use in COPD. The Panel noted that there were differences between the indication for Spiriva compared to ipratropium and salmeterol. Spiriva was not a new class of medicine but it had additional properties to other medicines eg it was long-acting and therefore only needed to be given once a day compared to ipratropium and salmeterol. The Panel considered that the claim was a broad claim and although Spiriva was different to other medicines it was not sufficiently so to justify the claim 'Open up to a new world of COPD management'. The Panel decided that the claim was exaggerated as alleged and ruled a breach of the Code. Upon appeal by Boehringer Ingelheim and Pfizer, the Appeal Board upheld the Panel's ruling.**

GlaxoSmithKline UK Limited complained about the promotion of Spiriva (tiotropium) by Boehringer Ingelheim Limited and Pfizer Limited. The materials at issue were a detail aid, a leavepiece and two journal advertisements.

Spiriva was a long-acting, once daily, anticholinergic bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease (COPD). GlaxoSmithKline marketed Serevent (salmeterol, a long-acting ß2 agonist), a bronchodilator for treating reversible airways obstruction including COPD. Boehringer Ingelheim also marketed ipratropium (Atrovent, a short-acting anticholinergic bronchodilater) which was licensed for the treatment of chronic reversible airways obstruction particularly in asthma and chronic bronchitis.

Boehringer Ingelheim and Pfizer submitted a joint response.

### A Detail Aid (ref SPI 61/SPV 30)

#### 1 Claim 'Efficacy vs. salmeterol'

Page 1 (front cover) of the detail aid was headed 'Introducing Spiriva' and also included the strapline 'Changing expectations in COPD'. Page 1 was not as wide as the rest of the pages of the detail aid such that a question on page 3 'What do you expect from a COPD treatment?', and the product logo, were visible. To the left of the question on page 3, and visible once the front cover had been turned, was a list of treatment attributes; alongside each attribute was a tick.

#### COMPLAINT

GlaxoSmithKline noted that page 2 of the detail aid introduced Spiriva as the first once daily inhaled maintenance therapy specifically for COPD. Page 3 included the Spiriva logo. GlaxoSmithKline stated that Boehringer Ingelheim had maintained that the list of treatment attributes on page 3 applied to COPD therapy in general.

GlaxoSmithKline considered, however, that as it was positioned within the double-page spread, the list of ticked attributes appeared to be attributes of Spiriva itself and not simply of COPD treatments in general.

In particular, in the second half of the list, 'Efficacy vs. salmeterol' followed several positive items (simple dosing, convenient delivery device) inviting the conclusion that this too was a positive comparison for Spiriva compared with salmeterol. GlaxoSmithKline alleged that the use of this statement followed by a tick on a page branded with Spiriva was an exaggerated claim. Efficacy was not defined and the implication was that for a range of endpoints, Spiriva was superior to salmeterol. The evidence for a superior effect of

Spiriva over salmeterol was based on two clinical trials (study 205.130 published as Donohue *et al* 2002 and study 205.137). These data did not support an overall positive (by reason of the tick) claim of 'efficacy vs salmeterol'. GlaxoSmithKline provided a table summarising the results of the studies.

GlaxoSmithKline alleged that this claim, associated with Spiriva, was both exaggerated and misleading in breach of Clauses 7.2 and 7.10 of the Code.

## RESPONSE

Boehringer Ingelheim and Pfizer provided details about the efficacy of Spiriva, comparative efficacy with ipratropium and salmeterol. With regard to the efficacy of Spiriva the companies referred to Section 5.1 of the summary of product characteristics (SPC) that:

> 'The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnea, exacerbations and health-related quality of life.
>
> In the aforementioned studies, tiotropium bromide, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, $FEV_1$, and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance.'

and

> 'Tiotropium bromide significantly improved dyspnea (as evaluated using the Mahler Transition Dyspnea Index). This improvement was maintained throughout the treatment period.'

The companies submitted that data on comparative efficacy could be considered under three headings:

### Lung function

In all studies Spiriva was found to achieve a statistically significant improvement in the primary endpoint, trough $FEV_1$, compared with placebo and active comparators. Data from Casaburi *et al* 2002, Vincken *et al* 2002 and data on file studies 205.137 and 205.130 were provided.

### Mahler Dyspnea Index

Boehringer Ingelheim and Pfizer submitted that the Mahler Dyspnea Index was an internationally validated scale. The TDI (transition dyspnea index) assessed changes in breathlessness following treatment, with the BDI (baseline dyspnea index) giving a baseline which allowed comparison of severity of breathlessness across treatment groups. An improvement of at least 1 unit was clinically meaningful and for the patient could be described as being 'able to return to work at reduced pace or has resumed some customary activities with more vigour than previously due to improvement in shortness of breath'.

Spiriva produced a clinically significant improvement in a significant number of patients. See table below.

### St George's Respiratory Questionnaire (SGRQ)

The companies submitted that this internationally accepted and validated health status measure was widely used. However, the determination of what constituted a clinically meaningful change was not as clear as suggested by GlaxoSmithKline.

This questionnaire presented the summation of three domains (symptoms, impacts and activities) as a score out of 100 – the lower the score the better the health status of the population studied. However, the interpretation of the differences in these scores between groups, within groups and over time (ie versus baseline) was the subject of some debate.

Traditionally, a clinically meaningful change had been interpreted as approximately a 4-unit reduction in mean score compared with that group's baseline score. For an individual patient, this 4-unit reduction in score compared with their baseline could mean that

**% responder data for TDI ≥1 unit improvement**

| | Spiriva versus placebo (Casaburi *et al*) | Spiriva versus ipratropium (Vincken *et al*) | Spiriva versus salmeterol and placebo (data on file studies 205.130 and 205.137) |
|---|---|---|---|
| Percent of patients achieving an improvement of ≥1 unit | Spiriva 42-47%<br>placebo 29-34%<br>p<0.01 | Spiriva 31%<br>ipratropium 18%<br>p=0.004 | Spiriva 43.1%<br>salmeterol 41.2%<br>placebo 29.8%<br>p<0.01 for both active treatments compared with placebo<br>p NS<br>Spiriva vs salmeterol |

**% responders (exceeding 4 units)**

| Comparators | Spiriva versus placebo (Casaburi *et al*) | Spiriva versus ipratropium (Vincken *et al*) | Spiriva versus salmeterol and placebo (data on file studies 205.130 and 205.137) |
|---|---|---|---|
| tiotropium | 49% | 52% | 48.9% |
| placebo | 30% | | 39.3% |
| | p<0.05 | | p<0.05 vs placebo |
| ipratropium | | 35%<br>p<0.01 | |
| salmeterol | | | 43.2%<br>p NS vs placebo<br><br>tiotropium (48.9%)<br>vs salmeterol (43.2%)<br>p NS |

'he or she no longer takes so long to wash or dress, can now walk upstairs without stopping, and is now able to leave the house for shopping or entertainment'.

This interpretation per patient against their own baseline score could then be used to determine the proportion of patients exceeding the 4-unit threshold. For Boehringer Ingelheim and Pfizer's studies the data were as in the table above.

### Comparative efficacy versus salmeterol

Boehringer Ingelheim and Pfizer stated that two six-month studies were performed, studies 205.130 and 205.137. The data summarised in the table in GlaxoSmithKline's complaint were sourced from an appendix of clinical study reports prepared for the Food and Drug Administration (FDA).

The two studies were performed in parallel, with the main difference between the studies being the time period over which spirometry was performed (see point A7 below). The results from the two studies were analysed separately and then combined for statistical analysis, as pre-specified in the study protocols.

Data from these studies specific to Spiriva and salmeterol could be summarised and are set out in the table at the top of the next page.

The companies submitted that it was apparent from this analysis that Spiriva showed a consistency of response in the variables measured that indicated that it outperformed salmeterol in comparisons with placebo and in some of the direct comparisons in the management of patients with COPD.

### Expert opinion

Boehringer Ingelheim and Pfizer referred to expert comments on the place of anticholinergics in general and of Spiriva in particular in the management of COPD:

> 'Anticholinergics are the bronchodilators of choice for COPD and in many studies have been shown to be more effective than ß2 agonists.' Barnes (1999)
>
> 'It is almost self evident that a drug with a long duration of action has considerable advantages in both preventing symptoms developing and also in simplifying the treatment regime.' Calverley (2000)
>
> 'Anticholinergic agents have proven to be of particular value in the treatment of COPD, as vagal cholinergic tone appears to be the only reversible component of airway narrowing.' Barnes (2000)

The companies stated that the purpose of a detail aid was also to promote discussion. A piece within a detail aid might require elaboration during discussions with a doctor and might require further explanation by a representative. In the companies' view, if an issue was raised by a GP in relation to a detail aid, this should not be regarded as clarification by the representative of a misleading item. Rather, it should simply be regarded as an additional means of ensuring that a GP was fully informed about the issue in question.

Whilst the detail aid was a stand-alone item, the companies also believed that the context in which a detail aid was used (ie during detailing by a representative) must also be taken into account in considering any suggestion that an item in it might be misleading. The representative and the detail aid comprised an integral promotional activity, the end result of which was a well-informed health professional who would not have been misled by the material presented.

The companies pointed out that the question 'What do you expect from a COPD treatment?' on page 3 was followed by a list of items prompting responses. Certainly the page was branded with the Spiriva logo and the items listed were relevant to the properties of Spiriva as presented in the detail aid. The specific complaint was that the tick against 'Efficacy vs. salmeterol' was a claim that Spiriva had superior efficacy to salmeterol. Boehringer Ingelheim and

| End point | Results | Statistical significance |
|---|---|---|
| Trough $FEV_1$ | tiotropium 120ml<br>salmeterol 90ml<br>tiotropium > salmeterol 30ml | Tiotropium >salmeterol **p<0.05**<br>**p<0.01** for both active treatments vs placebo<br>[note 1] |
| am PEFR | tiotropium 266.1<br>salmeterol 265.8<br>placebo 244.5 | **p<0.0001** for both active treatments compared with placebo<br>tiotropium-salmeterol **p=NS** |
| pm PEFR | tiotropium 281.8<br>salmeterol 270.8<br>placebo 249.4 | **p<0.0001** for both active treatments compared with placebo<br>tiotropium >salmeterol **p<0.01** [note 1] |
| % TDI responders | tiotropium 43.1%<br>salmeterol 41.2%<br>placebo 29.8% | **p<0.05** for both active treatments compared with placebo<br>tiotropium-salmeterol **p=NS** |
| TDI focal score compared to placebo (Witek *et al* 2000) | tiotropium 1.1<br>salmeterol 0.7 | tiotropium>placebo **p<0.001**<br>salmeterol>placebo **p<0.05**<br>tiotropium> 1 unit threshold of clinical significance<br>salmeterol< 1 unit threshold of clinical significance [note 2] |
| SGRQ total score | tiotropium 4.2<br>salmeterol 2.8<br>placebo 1.5 | tiotropium>placebo **p<0.01**<br>tiotropium-salmeterol **p=NS** [note 3]<br>salmeterol-placebo **p=NS**<br>tiotropium > 4 threshold of clinical significance [note 2]<br>salmeterol < 4 threshold of clinical significance [note 2] |
| % SGRQ responders (at least – 4 unit change) | tiotropium 48.9%<br>salmeterol 43.2%<br>placebo 39.3% | tiotropium>placebo **p<0.05**<br>tiotropium-salmeterol **p=NS** [note 3]<br>salmeterol-placebo **p=NS** |
| Rescue salbutamol use week 24 | tiotropium 3.13<br>salmeterol 2.93<br>placebo 3.88 | **p<0.001** for both active treatments<br>tiotropium-salmeterol **p=NS** |

note 1: the superiority for tiotropium over salmeterol was statistically significant.
note 2: the change for tiotropium was clinically significant but for salmeterol it was not.
note 3: tiotropium was clinically relevant but not statistically different from salmeterol.

Pfizer submitted that no such claim was being made here. The page simply indexed those elements regarding the management of COPD on which a new treatment might be expected to have information. The comparative data on Spiriva and salmeterol were elaborated upon later in the detail aid.

The companies did not accept that this statement was either exaggerated or misleading and was therefore not in breach of Clauses 7.2 or 7.10 of the Code.

## PANEL RULING

The Panel noted that the detail aid was headed (page 1) 'Introducing Spiriva' followed by the claim 'Changing expectations in COPD'. Page 2 included the claim 'Spiriva is the first once daily inhaled maintenance therapy, specifically for COPD, delivering full 24 hour control, day after day, when a short-acting ß2 agonist prn is not enough'. Page 3 included the question 'What do you expect from a COPD treatment?' and a list of attributes including, *inter alia*, simple dosing, convenient delivery service and efficacy vs. placebo. Given that these were all desirable attributes the Panel considered that 'Efficacy vs. salmeterol' would be viewed in the same way as 'Efficacy vs. placebo' ie in the same way as the reader would expect a product to be more efficacious than placebo so it was suggested that greater efficacy vs salmeterol was also desirable. The list of attributes appeared after a statement on page 2 of the detail aid which introduced Spiriva, and on a page which included the Spiriva logo. Given the context in which the list of attributes appeared the Panel considered that 'Efficacy vs. salmeterol' implied that Spiriva had superior efficacy to salmeterol.

The Panel noted that both parties had submitted detailed data. The Panel noted the companies' submission that Spiriva outperformed salmeterol in comparisons with placebo and in some of the direct comparisons. There were two studies directly comparing Spiriva and salmeterol; studies 205.130 (Donohue *et al*) and 205.137. There were some differences between Spiriva and salmeterol and some of these were in favour of Spiriva. Some measures had shown no difference. A number of specific comparisons were the subject of further allegations (points A7, A10, A11 and A12). The Panel did not consider that the data were sufficient to support a general claim that Spiriva had superior efficacy to salmeterol. The claim was misleading and

exaggerated and breaches of Clauses 7.2 and 7.10 of the Code were ruled.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer explained that the detail aid was written and distributed to its representatives in September 2002. It was never left with a health professional and was only ever used in the context of an explanatory discussion with a representative.

The companies considered that the Panel had pre-judged this item by describing it as a 'claim'. It was not a claim but rather it was a response to the question 'What do you expect from a COPD treatment?'

The first page was headed 'Introducing Spiriva' and was followed by the claim 'Changing expectations in COPD'. Page 2 continued the introduction by referring to the disease state of COPD and by describing the basic properties of Spiriva. Half of page 3 had already been disclosed when considering page 1 and it contained the question 'What do you expect from a COPD treatment?' The health professional was invited to consider this question and was then given a number of prompts as to what these expectations might be. These prompts referred to items on which information would be required in order to fulfil the expectations of a COPD treatment: information that was contained within the detail aid as it applied to Spiriva, including information on the efficacy of Spiriva compared with salmeterol.

The companies noted that the Panel, however, concluded that these prompts constituted claims for Spiriva on no better grounds than that they appeared after the introduction to Spiriva and the fact that the Spiriva logo was at the bottom of the page. Furthermore, the Panel not only concluded that these were claims for Spiriva but that the statement 'Efficacy vs. salmeterol' was a claim for superior efficacy to salmeterol, based on the observation that 'Efficacy vs. placebo' would be expected to mean superior efficacy to placebo. The companies submitted that these conclusions were unreasonable and unjustified.

Since Boehringer Ingelheim and Pfizer did not accept that the statement 'Efficacy vs. salmeterol' was a superiority claim for Spiriva, the companies would not consider here whether Spiriva could be justifiably claimed to have superior efficacy to salmeterol. This was dealt with at point A7 below.

Boehringer Ingelheim and Pfizer concluded that since 'Efficacy vs. salmeterol' was not a claim for Spiriva, it could not be considered to be a claim that was misleading or exaggerated.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline considered that the issues under question had been sufficiently detailed in its original letter of complaint. GlaxoSmithKline also considered that the Panel's ruling covered all the points raised both by Boehringer Ingelheim and Pfizer and itself.

### APPEAL BOARD RULING

The Appeal Board noted that the list of attributes on page 3 followed a statement on page 2 of the detail aid which introduced Spiriva. Page 3 included the Spiriva logo. Given the context in which the list of attributes appeared, the Appeal Board considered that the impression was given that they were all claims for Spiriva. In that regard the statement 'Efficacy vs. salmeterol' would be taken to mean that Spiriva had superior efficacy to salmeterol.

The Appeal Board did not consider that the data comparing Spiriva and salmeterol were sufficient to support the general claim that Spiriva had superior efficacy to salmeterol. The claim was misleading and exaggerated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal was unsuccessful.

## 2 Claim 'Spiriva can make a life-changing difference in COPD'

This claim appeared at the bottom of page 4 and on almost every alternate page throughout the detail aid. Page 4 was headed 'Significant and sustained improvement in lung function'.

### COMPLAINT

GlaxoSmithKline alleged that the claim was exaggerated. Boehringer Ingelheim had stated that it was an overall claim based on the total properties of Spiriva and should not be interpreted as being specifically supported by the data contained on one particular page. The company had also stated in correspondence that based on the evidence (four studies of 1 year and two of 6 months) Spiriva was capable of producing statistically significant benefits in many instances and clinically significant benefits in some.

GlaxoSmithKline considered that the phrase 'can make a life-changing difference' was strongly positive compared to, for instance 'can help' or 'may make a life-changing difference' and implied a strong likelihood of an effect. However, as Boehringer Ingelheim stated, clinically significant benefits were seen only in 'some (instances)'.

GlaxoSmithKline considered that it was important to distinguish between differences that were statistically significant, which might be a product of features of study design such as patient numbers, and differences that were clinically relevant.

In COPD some debate existed around what constituted a clinically relevant difference in lung function. However, two important instruments which were used to measure changes in breathlessness (Transitional Dyspnoea Index (TDI)) and health status (St George's Respiratory Questionnaire (SGRQ)) had validated thresholds for clinically relevant differences, which could be defined as the point at which patients would feel a difference. For the TDI, a change of 1 unit or more was clinically relevant (Mahler *et al* 1984), whilst for the SGRQ, a 4 unit change was clinically relevant (Jones 2001). It was accepted, when these instruments were used, that changes which did

not reach threshold levels for clinical relevance should not be considered as clinically relevant.

The claim implied that patients were likely to attain these thresholds with Spiriva, compared with other available therapies. The balance of evidence did not support the claim. Statistically significant changes alone, without evidence of clinically relevant change, were insufficient to support the claim.

Since clinically relevant differences were only achieved in some instances, according to Boehringer Ingelheim, the claim could not be substantiated and a breach of Clause 7.10 of the Code was alleged.

### RESPONSE

Boehringer Ingelheim and Pfizer stated that the same claim was used on page 11 of the detail aid (point A7). The companies addressed the concerns with the claim and made comments of a more general nature under point A7. In relation to point A2 and its use on page 4 of the detail aid, Boehringer Ingelheim and Pfizer submitted that the claim appeared as a strap-line on every alternate page. It was based on the total properties of Spiriva and should not be interpreted as being exclusively supported by the data contained on only one particular page, in this instance a page containing the measure of lung function. The companies did not therefore accept that it was an exaggerated claim with regard to measures of lung function. It was not in breach of Clause 7.10 of the Code.

### PANEL RULING

The Panel noted that the claim appeared on almost every alternate page of the detail aid. The Panel considered that the claim 'Spiriva can make a life-changing difference in COPD' was a strong claim. In this instance it appeared on a page headed 'Significant and sustained improvement in lung function' which compared trough $FEV_1$ of Spiriva in placebo controlled studies over a one-year period. Spiriva would and should make a difference in COPD compared to placebo. The Panel considered that in the context of a page comparing Spiriva and placebo controlled studies, the claim was exaggerated as a positive result was no more than would be expected. A breach of Clause 7.10 of the Code was ruled.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer stated that the claim 'Spiriva can make a life-changing difference in COPD' was a strapline reflecting the overall consistent benefits seen in extensive comparative clinical trials of Spiriva. Although supporting the claim, it was not fully substantiated by data appearing on any given page. It was a general statement for Spiriva and the frequency of its use and its positioning in isolation at the bottom of several pages meant that the reader was highly unlikely to regard it as a claim relating to a specific set of data presented on one page. The overall data contributing to this strapline were detailed and discussed in point A7, where 'Spiriva can make a life-changing difference in COPD' appeared as a title to the summary page.

Boehringer Ingelheim and Pfizer noted that this strapline was part of the Panel's rulings in other points; the overall truth that this was a general statement about Spiriva remained the same for each but would be referred to at appropriate points in this submission.

The companies noted that the Panel considered that in the context of a page comparing Spiriva and placebo-controlled studies, the claim that 'Spiriva can make a life-changing difference' was exaggerated, as a positive result was no more than would be expected. As noted above, this general statement was not intended to be fully substantiated solely by the data on placebo studies.

### COMMENTS FROM GLAXOSMITHKLINE

With regard to this allegation and point A7 below, GlaxoSmithKline noted Boehringer Ingelheim and Pfizer's submission that some patients achieved clinically significant improvements in quality of life scores and further stated that the percentage of patients achieving a clinically significant improvement was greater with Spiriva than comparators. GlaxoSmithKline did not consider that this was a valid argument in defence of the way in which the quality of life data had been presented.

Although more patients on Spiriva might have experienced a clinically significant change in quality of life compared with ipratropium (or salmeterol or placebo), if the overall mean (or median) result was that patients on Spiriva did not achieve a clinically significant result, then this should be made clear. If Boehringer Ingelheim and Pfizer wished to make a claim concerning the different percentages who achieved particular scores, GlaxoSmithKline considered that this would be acceptable providing it was made clear that there was no clinically significant result in respect of the overall group.

### APPEAL BOARD RULING

The Appeal Board considered that the claim 'Spiriva can make a life-changing difference in COPD' was a strong claim that implied a major impact. This was not supported by the data. The Appeal Board considered that in the context of a page comparing Spiriva and placebo the claim was exaggerated and all embracing as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10 of the Code. The appeal was unsuccessful.

### 3 Claim 'Health-related quality of life'

This claim appeared as the heading on page 6 which featured a bar chart, adapted from Casaburi *et al*, comparing the change in SGRQ total and impact scores for placebo and Spiriva at one year. Beneath the bar chart was the claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores'.

## COMPLAINT

GlaxoSmithKline stated that the important measure for the SGRQ was the change from baseline within treatment groups. In the Casaburi study patients receiving tiotropium did not achieve the 4-unit change from baseline in total score, which had been validated as representing a clinically meaningful improvement in health status. Although attention was drawn to the probity of the SGRQ at the side of the page, there was no attempt to make the reader aware of the level of change that was clinically meaningful, and it was not made clear that a clinically meaningful improvement was not achieved.

The page included the strap-line 'Spiriva can make a life-changing difference in COPD'. The implication was that Spiriva achieved meaningful improvements in quality of life. This was clearly not the case from the evidence shown.

GlaxoSmithKline alleged that, because health professionals were being encouraged to believe the improvement was clinically relevant, the presentation of the quality of life data was misleading in breach of Clause 7.2 of the Code.

## RESPONSE

Boehringer Ingelheim and Pfizer stated that the graph was an accurate presentation of the Casaburi *et al* results, with Spiriva achieving statistically significantly better scores than placebo.

In discussing their findings the authors commented: 'Health status was improved with tiotropium relative to placebo, confirming the overall benefit of therapy to the patient. Improvements that were at or around the level of clinical significance (a decrease of 4 units) were observed in all SGRQ domains compared with placebo. Further, a significantly higher proportion of patients exceeded a 4-unit improvement in the group receiving tiotropium'.

Thus, a clinically meaningful improvement was achieved, but as the histogram did not show an average 4-unit improvement, the companies considered it inappropriate to make a claim beyond statistical significance.

The representative would have had the full paper by Casaburi *et al* so that this could have been elaborated upon if the health professional had asked.

The companies' response to GlaxoSmithKline's allegation regarding the strap-line 'Spiriva can make a life-changing difference in COPD' was the same as for point A2 above.

The companies did not accept that the presentation of the data was misleading and it was not in breach of Clause 7.2 of the Code.

## PANEL RULING

The Panel noted that Jones (2001) reviewed recent evidence for the validity of health status or health related quality of life measurement in COPD. Health status measurement was a means of quantifying the impact of disease on patients' daily lives, health and wellbeing. The process was described as being essentially similar to a highly structured clinical history although the end product was not a clinical impression but an objective measurement that could be used for scientific purposes. Jones stated that the SGRQ and others tended to have a degree of complexity that made them unsuitable for routine use. Jones stated that there was no universally agreed definition of worthwhile benefit in chronic disease but a common view was that if a patient could detect a definite reduction in symptoms or the impact of the disease on their daily life, that was clinically significant. The issue of clinically noticeable differences and thresholds for clinical significance was a complex topic sufficient to say that the suggested threshold of 4 units for the SGRQ appeared to be reliable. Jones discussed statistical issues and referred to patients with stable COPD. The short term repeatability of the SGRQ questionnaires was described as 'good' by reference to the correlation coefficient. Jones stated that the correlation coefficient did not give the full picture and referred to a situation where approximately half the patients showed a change in SGRQ score that was greater or less than the 4 unit threshold for a clinically significant change whether or not there had been a real change in their state. Equally in other patients who had a 'true' worthwhile benefit, the health status score might change by less than the clinically significant threshold. This was described as a problem.

The Panel noted the companies' submission in point 1 above that traditionally a clinically meaningful change in SGRQ had been interpreted as approximately a 4-unit reduction in mean score compared with that group's baseline score.

Casaburi *et al* was a long-term evaluation of once daily tiotropium. The primary spirometric outcome was trough $FEV_1$ (prior to dosing). Changes in dyspnoea were measured using the TDI. Health status was evaluated using SGRQ. At each visit the investigator recorded COPD symptoms after reviewing the patient's daily diary for wheezing, shortness of breath, coughing and chest tightness and recorded a global evaluation of the patient's overall condition. Tiotropium demonstrated improvements in each domain as well as in total score with statistically significant improvements relative to placebo ($p<0.05$). In addition to a statistically significant improvement in mean response, a significantly greater percentage of patients in the tiotropium group (49%) showed at least a four unit improvement in total score compared to those in the placebo group (30%).

The Panel noted that the data presented in the bar chart did not reach a mean change from baseline of four units with regard to total (–3.18) and impact (–2.68) scores for Spiriva at one year. The difference between Spiriva and placebo (total score +0.50, impact score +1.36) was statistically significant ($p<0.05$). With regard to impact scores the difference between the two was a total of 4.04 units and therefore at a level to be judged clinically significant. The Panel noted that more patients in the tiotropium group showed at least a four unit improvement in total score compared to those in the placebo group. In the Panel's view there was a difference between a 4 unit reduction in mean

SGRQ score ie achieving clinical significance and the numbers of patients achieving a change of 4 units or more. The Panel considered that this was a complex issue as noted by Jones. In the Panel's view the basis of the claim should be made clear. The claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores' was a general claim for the population as a whole. The Panel considered, however, that the overall impression of the heading 'Health-related quality of life', the strapline 'Spiriva can make a life-changing difference in COPD' and the differences depicted in the bar chart, was that all the results were clinically significant and this was not so. Insufficient explanation had been provided.

The Panel considered that the presentation of the data was misleading and ruled a breach of Clause 7.2 of the Code.

## APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer repeated that the strapline 'Spiriva can make a life-changing difference in COPD' was an overall statement and did not directly relate to the outcome of any one endpoint (points A2 and A7).

The heading 'Health-related Quality of Life' simply introduced the subject matter on the page and described the results using the SGRQ. As the strapline was not specific to the heading, it was unreasonable to incorporate it into the interpretation of the results presented on this page.

## COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

## APPEAL BOARD RULING

The Appeal Board considered that the claim 'In comparison with placebo, Spiriva delivered a statistically significant improvement in health-related quality of life scores' was true but did not reflect the results with regard to clinical significance. There was a difference between statistical significance and clinical significance. Traditionally a clinically meaningful change in SGRQ had been interpreted as a 4-unit reduction in mean score compared to baseline score. The Appeal Board noted that with regard to total scores the difference between Spiriva and placebo was less than 4 units. With regard to impact scores the difference between the two was 4.04 units and therefore at a level judged to be clinically significant. This had not been made sufficiently clear.

The Appeal Board considered that the overall impression of the heading 'Health-related quality of life', the strapline 'Spiriva can make a life-changing difference in COPD' and the differences depicted in the bar chart, was that all the results were clinically significant and this was not so. Insufficient explanation had been provided. The Appeal Board considered that the presentation of the data was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

### 4 Claim 'Significantly reduces exacerbations and related hospitalisations'

This claim appeared as the heading to page 7 which featured a bar chart headed 'Exacerbations and exacerbation-related hospitalisations compared with placebo per patient-year'. The data were adapted from Casaburi *et al*.

## COMPLAINT

GlaxoSmithKline alleged that the data for two different endpoints were presented in such a way as to mislead as to the significance of the exacerbation-related hospitalisation data, which were of an order of magnitude smaller than for exacerbations. Although the different scales were given on the two y-axes, the visual impression was that the exacerbation and exacerbation-related hospitalisation data were on the same scale, thus exaggerating the effect of tiotropium on hospitalisations.

Although the difference in hospitalisations was statistically significant, the reduction compared with placebo was only 0.075 hospitalisations per patient-year (equivalent to around 1 event every 13 years per patient) – a reduction from 0.161 to 0.086 was rather less impressive than the visual impression the graph conveyed. GlaxoSmithKline illustrated this by plotting the two outcome measures on the same scale.

GlaxoSmithKline alleged that, because of the use of two scales on the same graph, this representation of the data was misleading as to the significance of the data presented in breach of Clause 7.8 of the Code.

## RESPONSE

Boehringer Ingelheim and Pfizer stated that the technique of having two sets of results presented in a single bar chart with differing y-axis scales was widely adopted in scientific presentations, especially when the two bar charts were on closely related matters as in this instance. The percent changes and their statistical significance were clearly presented.

GlaxoSmithKline tried to give support to its complaint by referring to the interpretation of the data meaning that treatment with Spiriva would cause a reduction in the incidence of hospitalisations that was 'equivalent to around 1 event every 13 years per patient'. However, a more meaningful interpretation of the results was that treating 1000 patients with Spiriva would result in 75 fewer hospitalisations per year. Such an effect was of benefit to patients and hospital services.

The companies did not accept that the presentation of the data was misleading as to the significance of these findings and there was no breach of Clause 7.8.

## PANEL RULING

The Panel noted that the y-axes were the same height on both sides of the bar chart. The scale for the number of exacerbations per patient-year, on the left-hand side of the bar chart, started at zero and finished at 1.6 with intervals of 0.2. The scale for the mean number of hospitalisations due to exacerbations per patient-year, on the right-hand side of the bar chart,

started at zero and finished at 0.18 with intervals of 0.02. The bar charts appeared beneath the same heading. Both showed a statistically significant advantage for Spiriva over placebo and the details were given. The Panel's view was that the presentation was visually misleading. The bar charts were in the same visual field. The mean number of hospitalisations due to exacerbations per patient year appeared to be numerically greater than the mean number of exacerbations. The Panel considered that the change in scale for the hospitalisation data exaggerated the benefit for Spiriva compared to placebo. The Panel ruled a breach of Clause 7.8 of the Code.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer submitted that the presentation of related data in this way was common in scientific papers and was accepted practice. Further the bar charts were not misleading. They were clearly labelled, both the reduction in hospitalisations and in exacerbations compared with placebo were statistically significant for patients taking Spiriva and all health professionals would know that most exacerbations of COPD did not require hospitalisation and therefore the numbers of patients involved in each histogram would be different. The number of hospitalisations could not possibly be numerically larger than the number of exacerbations.

The companies noted that the Panel also considered that the presentation of the data exaggerated the benefit of Spiriva compared with placebo. This view was possibly influenced by GlaxoSmithKline's statement that the difference in hospitalisations (0.075 per patient year) (Casaburi *et al* 2002) would be equivalent to 'around 1 event every 13 years per patient'. However Boehringer Ingelheim and Pfizer noted that the more meaningful interpretation of these data was that the difference in hospitalisations would be equivalent to 75 hospitalisations prevented per year per thousand patients treated; a response of beneficial significance to the patients concerned and to the NHS.

Boehringer Ingelheim and Pfizer did not accept that the presentation of these data misled as to their significance.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

### APPEAL BOARD RULING

The Appeal Board considered that the bar charts gave the impression that the mean number of hospitalisations due to exacerbations per patient year was numerically greater than the mean number of exacerbations. The Appeal Board considered that the presentation was visually misleading. The change in scale for the hospitalisation data exaggerated the benefit for Spiriva compared to placebo. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8 of the Code. The appeal was unsuccessful.

## 5 Claim 'Spiriva delivered via the HandiHaler encourages good compliance'

This claim was referenced to Kesten *et al* (2000) and appeared on page 9 beneath the heading 'Tailored for COPD'.

### COMPLAINT

GlaxoSmithKline alleged that the claim implied there was something specific about Spiriva delivered via the HandiHaler which meant compliance would be encouraged.

Kesten *et al* was an abstract that evaluated compliance by capsule counting from two tiotropium vs placebo studies. These studies were identical in design, being double-blind, double-dummy and using the same device (HandiHaler) and dosing regimen in both groups. The results of the study showed good compliance in both groups but no difference between tiotropium and placebo. It could not be concluded that Spiriva through the HandiHaler encouraged good compliance, since compliance was the same with placebo via HandiHaler. Therefore the reference did not substantiate the claim.

Boehringer Ingelheim had stated to GlaxoSmithKline that there was evidence to support the fact that the lower the frequency of dose the better the compliance and that the clinical trial results supported this conclusion. A systematic review across a range of therapeutic areas had shown that compliance was higher for once and twice daily versus four times daily doses, but there was no difference in compliance between once daily and twice daily dosing (Claxton *et al* 2001).

GlaxoSmithKline had not been provided with evidence to show that Boehringer Ingelheim's clinical trials supported the conclusion that a once daily regimen provided better compliance than twice daily and was unsure how this could be shown. All the studies were of double-blind double-dummy design and therefore within a particular trial all patients would have been on the same dosing regimen, making different regimens impossible to compare. Furthermore, in the Boehringer Ingelheim trials comparing salmeterol with tiotropium and placebo, patients tended to prefer more frequent dosing to once daily.

GlaxoSmithKline alleged that the claim was misleading and not supported by the evidence in breach of Clauses 7.2 and 7.4 of the Code.

### RESPONSE

Boehringer Ingelheim and Pfizer stated that Kesten *et al* compared the compliance rate on Spiriva with placebo, both given once daily via the HandiHaler. GlaxoSmithKline was correct in noting that no difference was found between the groups but its conclusion that the reference did not substantiate the claim was wrong. The fact that the compliance rate with a once daily treatment was the same in both groups was a measure of the reliability of the method and that once daily administration via the HandiHaler

had a particular compliance rate regardless of the therapeutic response.

Kesten *et al* showed that 'greater than 85% of all patients took their study drug 90% of the time or better' and the authors concluded that 'Counts of pierced capsules suggest a high compliance rate with tiotropium prescribed once daily via a capsule based system in patients with COPD'.

GlaxoSmithKline acknowledged that compliance was higher for once and twice daily versus four times daily doses. It was on this basis and the evidence of Kesten *et al* that the claim for Spiriva of encouraging good compliance was made. This claim did not state that Spiriva delivered by the HandiHaler produced good compliance nor that it achieved better compliance than other therapies, it merely noted that it encouraged good compliance.

The companies did not accept that the claim was misleading and considered that it was adequately supported by the evidence and therefore not in breach of Clauses 7.2 or 7.4 of the Code.

## PANEL RULING

The Panel noted that Kesten *et al* stated that one advantage of tiotropium was once daily dosing which presumably should improve compliance. The abstract concluded that counts of pierced capsules suggested a high compliance rate with tiotropium prescribed once daily via a capsule based system.

The Panel noted that Claxton *et al*, a review of 76 studies, stated that there were no significant differences in compliance between once daily and twice daily regimens or between twice daily and 3 times daily regimens. Statistically significant differences were found between once daily versus 3 times daily, once daily versus 4 times daily, and twice daily versus 4 times daily. GlaxoSmithKline's product Serevent was to be used twice daily. Compliance was inversely related to the number of doses per day.

The page in the detail aid made no mention of frequency of dosage. Boehringer Ingelheim had some evidence in relation to compliance but there was no data to compare compliance with the HandiHaler and compliance with other methods of administration. There was an implication that good compliance with Spiriva was achieved through use of the HandiHaler as opposed to any other inhalational device. There was no data in this regard. The Panel considered the claim was misleading as it had not been substantiated. The Panel therefore ruled breaches of Clauses 7.2 and 7.4 of the Code.

## APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

With regard to frequency of dosage, Boehringer Ingelheim and Pfizer stated that it was not necessary to refer to it here as there were several references to the once daily dosage for Spiriva in the rest of the detail aid, not least in the introductory paragraph on page 2 and in the prescribing information inside the back cover.

The Panel had also noted that there were no data to compare compliance with the HandiHaler and compliance with other methods of administration. Boehringer Ingelheim and Pfizer submitted that as Spiriva was only delivered by the HandiHaler, such a comparison was not possible. Yet the Panel considered that there was an implication that good compliance was achieved through use of the HandiHaler as opposed to any other inhalation device. The companies submitted that no such implication existed.

The claim was a non-comparative claim based on the fact that patients treated with Spiriva (necessarily by way of the HandiHaler) demonstrated good compliance in clinical studies. The evidence for this was the capsule count study by Kesten *et al* (2000) and the authors' conclusions that 'greater than 85% of all patients took their study drug 90% of the time or better' and that 'counts of pierced capsules suggest a high compliance rate with tiotropium prescribed once daily via a capsule based system in patients with COPD'.

The companies stated that the compliance rate was deemed to be 'good', and was consistent with descriptions of good compliance in other COPD studies.

Boehringer Ingelheim and Pfizer submitted that the claim 'Spiriva delivered via the HandiHaler encourages good compliance' was a statement of fact substantiated by Kesten *et al* and was not misleading.

## COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline noted that compliance rates such as those found by Kesten *et al* were normal in that kind of study. Kesten *et al* was a post-hoc analysis of dose counting from two tiotropium studies. As the studies were double-blind and placebo-controlled, a claim for compliance could only be made if there was a significant difference between tiotropium and placebo. This was not the case. The results were similar to those found in many other studies. Two recent GlaxoSmithKline studies, Chapman *et al* (1999) and Aubier *et al* (1999), on Seretide found similar rates of between 94% and 96%. Such studies were very different from studies where the primary outcome measure was compliance and methods such as electronic dose counting were used.

GlaxoSmithKline noted that there was also no evidence that there was any difference between once daily dosing and twice daily dosing in terms of compliance (Claxton *et al* 2001).

## APPEAL BOARD RULING

The Appeal Board considered that there was an implication that good compliance with Spiriva was positively promoted by the use of the HandiHaler as opposed to any other inhalational device; there was no data in this regard. The Appeal Board considered the claim was misleading and that it had not been substantiated. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4 of the Code. The appeal was unsuccessful.

## 6 Using the HandiHaler

Page 9 demonstrated the use of the HandiHaler by use of three illustrations labelled 'Drop…press… and inhale'.

### COMPLAINT

GlaxoSmithKline stated that the illustrations suggested that the HandiHaler could be used in three steps. This was not so: seven steps were outlined in the SPC with the last two repeated, details were provided. In particular, GlaxoSmithKline noted that according to the SPC, the patient must repeat the exhalation/inhalation cycle twice in order to empty the capsule and inhale the whole dose. GlaxoSmithKline alleged that it was misleading to make it appear that using the HandiHaler consisted of three simple steps.

In addition, the first suggested step was 'Drop' – trying to achieve this in practice proved extremely difficult – it was almost impossible to get the capsule in the chamber by following this oversimplified instruction. The word 'Drop', as used in the detail aid, had very different implications from 'place', which was used in the SPC.

Boehringer Ingelheim had stated that these instructions were by no means a substitute for a full and thorough demonstration and that the representative had other materials to educate the health professional as to the proper use of the device. However, the detail aid should be seen as a stand-alone item and therefore comply with the Code. If the representative needed to clarify the use of the HandiHaler, this implied that the information in the detail aid was not a clear reflection of how the device should be used.

GlaxoSmithKline alleged that the illustrations and the accompanying text were an oversimplification of the method of use of the HandiHaler, were misleading and did not accurately reflect the SPC in breach of Clause 7.2 of the Code.

### RESPONSE

Boehringer Ingelheim and Pfizer submitted that 'Drop…press…and inhale' was simply intended to highlight the three main steps in taking a dose of Spiriva. The statement also confirmed that the capsules were not ingested, that Spiriva was not an aerosol and that the device was breath actuated. These steps clearly distinguished Spiriva from aerosol medications with which respiratory patients would be particularly familiar.

This statement was not intended to be, nor was it likely to be construed by a doctor as, a definitive instruction for the administration of Spiriva. As noted by GlaxoSmithKline, the representative, in conjunction with the detail aid, would also use additional information aids containing full instructions for the use of the HandiHaler. A demonstration might also be given to the doctor on how to use the HandiHaler. There was no question therefore that a doctor would either regard or be given the impression that the statement constituted instructions on how to use the HandiHaler.

Boehringer Ingelheim and Pfizer did not accept that the statement was misleading and considered that it was therefore not in breach of Clause 7.2 of the Code. GlaxoSmithKline's reference to the SPC was irrelevant.

### PANEL RULING

The Panel considered that the impression from the page was that there were three steps for taking Spiriva via the HandiHaler. The correct administration was more complicated than the impression given by the illustration and the phrase 'Drop…press…and inhale'. For example, the SPC stated that inhalation had to be repeated and this was not made clear in the detail aid. The Panel noted that the representatives had other resources to use when discussing the use of the HandiHaler. Nevertheless the detail aid was a stand-alone piece. In the Panel's view this page of the detail aid would be seen as providing the instructions needed for the administration of Spiriva and it was misleading in that regard. A breach of Clause 7.2 of the Code was ruled.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer submitted that this page, headed 'Tailored for COPD', was a general description of the properties of the HandiHaler. It contained information relating to compliance, the physical attributes of the HandiHaler, an outline of its use, the effectiveness of the system at low inspiratory flow rates, the benefits of breath-actuation and the pack-size availability. The companies submitted that this outline of its use was an illustration of the capsule/inhaler technology employed by the HandiHaler. This page was not intended as instructions for use nor was it a reasonable conclusion to be drawn from the whole page. As had been pointed out, the representative had samples of the HandiHaler and of laminated cards with instructions for use which could be presented to the health professional on request.

Boehringer Ingelheim and Pfizer did not accept that this reference to the way the HandiHaler was used was an instruction for use and that it was thereby a misleading claim.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its comments in point A1.

### APPEAL BOARD RULING

The Appeal Board considered that the correct administration of the HandiHaler was more complicated than the impression given by the illustration and the phrase 'Drop…press…and inhale'. In particular the SPC stated that inhalation had to be repeated and this was not made clear on the page at issue. In the Appeal Board's view this page of the detail aid would be seen as providing the instructions

needed for the administration of Spiriva and it was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

### 7 Claim 'Spiriva can make a life-changing difference in COPD'

This claim appeared as the heading to page 11. The page presented three comparisons: Spiriva with placebo, with ipratropium and with salmeterol.

#### COMPLAINT

GlaxoSmithKline stated that the claim implied that Spiriva was likely to make a life-changing difference compared with placebo, ipratropium and salmeterol and that the data provided substantiated this (ie that the differences between treatments represented clinically relevant differences).

GlaxoSmithKline alleged that the placebo comparison health-related quality of life data did not reflect 'life-changing' differences. Over one year, tiotropium did not reach a mean improvement of 4 units in the SGRQ total score, which had been validated as a clinically relevant difference in quality of life. In addition the reduction in hospitalisations was only 0.075 hospitalisations per patient per year compared with placebo (equivalent to the prevention of one hospitalisation event per patient every 13 years).

GlaxoSmithKline stated that the improvement over ipratropium in breathlessness (TDI focal score) was 0.9: this did not reach the clinically relevant difference of 1 unit for this instrument (Claxton *et al* 2001). In addition, the difference in terms of SGRQ total score was less than 4 units between these two treatments. It was misleading to suggest the differences were 'life-changing'.

As discussed above, the three claims given against salmeterol should be read in the context of the heading, which implied 'life-changing differences'.

Comparing salmeterol and tiotropium, there was no evidence of either a clinical or statistical difference in breathlessness score, or SGRQ total score. Furthermore, Boehringer Ingelheim had stated that there was no basis for a claim of superiority of Spiriva over salmeterol for either breathlessness score or SGRQ. Thus the heading that 'Spiriva can make a life-changing difference …' was misleading in connection with these claims.

GlaxoSmithKline alleged that the implication that tiotropium could make a life-changing difference in COPD compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

Furthermore, the breathlessness data for tiotropium compared with salmeterol had been presented selectively. This data was referenced to Witek. GlaxoSmithKline stated that in these six-month studies, the primary analysis of this endpoint was defined as the percentage of TDI responders (that was, the percentage of patients in each group achieving a one unit or greater improvement in TDI score, Donohue *et al*).

The outcome measure presented in the detail aid was not the primary endpoint, but was an additional secondary outcome measure for breathlessness in which the mean TDI score was given as a unit.

For the primary analysis of this co-primary endpoint, in the Donohue study (Study 205.130), 42% of patients on tiotropium responded, compared with 35% receiving salmeterol, with no statistical difference between the groups. In study 205.137, 45% patients on tiotropium responded, compared with 48% on salmeterol – again with no statistical difference between the groups.

The claim in the detail aid implied that patients would not achieve a clinically relevant improvement with salmeterol, whereas the primary endpoint of the study refuted this (35-48% would improve to a clinically relevant degree).

GlaxoSmithKline alleged that the claim derived from these data did not reflect the balance of evidence in breach of Clause 7.2 of the Code.

#### RESPONSE

Boehringer Ingelheim and Pfizer stated that their comments in point A1 provided the evidence supporting the efficacy of Spiriva and were particularly relevant here.

With regard to the comparison with placebo, Boehringer Ingelheim and Pfizer's response to these two points had been given in points A3 and A4 above. The companies did not accept that there was an issue here on the stab-point statements concerning the effects of Spiriva compared with placebo in respect to lung function, breathlessness, health-related quality of life scores nor exacerbations and hospitalisations.

With regard to the comparison with ipratropium, as stated in the detail aid, Spiriva produced a statistically significant improvement in breathlessness scores and health-related quality of life scores. Vincken *et al* stated that: 'The difference in TDI focal score between the tiotropium and ipratropium groups at 9 and 12 months were 0.97+/–0.25 and 0.90+/–0.26, respectively. The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1unit) at 1 yr was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%, p=0.04)'.

With regard to the health-related quality of life scores, the authors stated that: 'More patients in the tiotropium group than in the ipratropium group achieved the clinically meaningful improvement of 4 units in the SGRQ total score after 9 and 12 months (52 versus 35% respectively, at 1 yr, p=0.001)'.

Thus, a clinically meaningful result was achieved in comparison with ipratropium, in addition to the statistically significant differences.

With regard to the first stab-point in the section comparing Spiriva with salmeterol 'Significant

improvement in lung function over 12 hours at 6 months', Donohue *et al* 2002 concluded that: 'Tiotropium once daily produces superior bronchodilation, improvements in dyspnea, and proportion of patients achieving meaningful changes in [health-related quality of life] compared with twice-daily salmeterol in patients with COPD'.

Donohue *et al* reported on the results of study 130 alone. The primary lung function measure was 12 hour spirometry, as opposed to 3 hour spirometry performed in study 137. Twelve hour spirometry was performed in order to reflect the duration of action of salmeterol.

The second and third stab-points, 'Clinically significant difference in breathlessness score (1.1 units) after 6 months compared with placebo, whereas salmeterol did not (0.7 units). Both active substances showed statistically significant differences vs placebo' (Witek), and 'Statistically significant improvement in health-related quality of life scores vs placebo (p=0.003), whereas salmeterol did not (p=0.156)' (data on file) did not make a direct comparative claim with regard to salmeterol. Both points accurately stated the findings in relation to breathlessness scores and health-related quality of life scores. In the former, Spiriva produced a clinically significant improvement against placebo whereas salmeterol did not and in the latter, Spiriva produced a statistically significant improvement in score against placebo whereas salmeterol did not.

GlaxoSmithKline argued that in the results of the two studies (130 and 137) the dyspnoea data showed that 35% and 48% of salmeterol patients improved to a clinically relevant degree. Boehringer Ingelheim did not disagree with this for by the same token, 42% and 45% of Spiriva patients responded to a clinically relevant degree. Thus both Spiriva and salmeterol showed statistically significant differences compared to placebo but in the case of salmeterol this average difference across the two studies (pre-specified combined analysis – see point A3) did not reach clinical significance. Many individual patients on both treatments achieved a clinical response. It was worth highlighting the fact that all the clinical trial results for Spiriva had been consistent.

Boehringer Ingelheim and Pfizer stated that in point A2 GlaxoSmithKline played with words in regard to the meaning of 'can make', 'can help make' and 'may make'. The companies' view was that they all had an essentially similar meaning. The companies had chosen to claim 'Spiriva can make a life-changing difference in COPD' because they believed it to be true and proven in a clinically relevant proportion of the patient population studied.

Evidence on the properties of Spiriva clearly showed that it could produce, for individual patients, differences in their well-being that were life changing. In addition to the clinical effects, it could benefit patients by not requiring more than once daily dosage and by reducing the possibility of having to be admitted to hospital with an acute exacerbation. The claim was not therefore exaggerated.

Boehringer Ingelheim and Pfizer did not accept that the claim 'Spiriva can make a life-changing difference in COPD' was misleading and not capable of substantiation nor that it was an exaggerated claim and denied breaches of Clauses 7.2, 7.4 or 7.10 of the Code.

Likewise the companies did not accept that the presentation of data on breathlessness (dyspnoea) did not reflect the balance of evidence and therefore it did not breach Clause 7.2 of the Code.

## PANEL RULING

The Panel noted that GlaxoSmithKline had criticised certain parts of the three comparisons.

The Panel noted that the data comparing Spiriva with placebo was referenced to Casaburi *et al* and considered that its comments on this study in point A3 above were relevant. The Panel considered that the claim referring to health-related quality of life scores was too simplistic given the complexity of the use of SGRQ. There were statistically significant differences with placebo in relation to exacerbations and exacerbation-related hospitalisations. Boehringer Ingelheim and Pfizer had previously stated that the difference between placebo and Spiriva would mean that treating 1000 patients with Spiriva would result in 75 few hospitalisations per year (point A4).

The comparison with ipratropium, 'Significant improvement in lung function, and a statistically significant improvement in breathlessness scores and health-related quality of life scores, with a significant reduction in exacerbations' was referenced to Vincken *et al*. Breathlessness scores were measured by using the Mean Transition Dyspnoea Index (TDI) focal score. The Panel noted that the differences between ipratropium and Spiriva were statistically significantly in favour of Spiriva, however they were less than one and hence did not achieve a clinically meaningful difference for that measure. The proportion of patients who achieved a clinically meaningful difference in TDI total score (improvement of ≥ 1 unit) was statistically significantly greater in the Spiriva group (31%) than in the ipratropium group (18%) (p=0.004). Similarly the difference between the products' SGRQ total scores was statistically significant in favour of Spiriva but was less than 4 units and hence did not achieve a clinically meaningful difference. More patients in the Spiriva group achieved a clinically meaningful improvement of 4 units (52% v 35% p< 0.01). There was a difference between a 4 unit reduction in mean SGRQ score ie achieving clinical significance and the numbers of patients achieving a change of 4 units or more. In the Panel's view the basis of the claim should be made clear. The Panel noted its previous comments regarding the SGRQ (point A3 above).

With regard to the comparison with salmeterol in relation to breathlessness score and health-related quality of life scores, the Panel noted Boehringer Ingelheim and Pfizer's submission that the comparisons with salmeterol were not direct comparative claims. Each medicine had been compared with placebo. The claims appeared beneath the heading 'In a comparison with salmeterol, Spiriva delivered a: …'. The Panel considered that in conjunction with the heading the claims would be read as direct comparisons between the two products.

The Panel noted its comments in A2 above regarding the claim 'Spiriva can make a life-changing difference in COPD'. The Panel noted the submission from Boehringer Ingelheim and Pfizer that Spiriva could produce, for individual patients, differences that were life-changing. The claims in the detail aid, however, would be assumed to represent the expected response in most patients. In the Panel's view the word 'can' rarely negated the impression of 'will'. The Panel considered that given its comments above overall, the implication that Spiriva could make a life-changing difference in COPD generally or in relation to all the parameters listed compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

Witek *et al* was a retrospective analysis of 997 COPD patients who received tiotropium, salmeterol or placebo. It appeared that Witek *et al* was an analysis of studies 205.130 (Donohue *et al*) and 205.137.

The Panel considered that although the claim that in a comparison with salmeterol, Spiriva delivered a 'Clinically significant difference in breathlessness score (1.1 units) after 6 months compared with placebo, whereas salmeterol did not (0.7 units) …' was consistent with the findings of Witek *et al* it was not sufficiently clear that there was other data to show that the numbers of patients who responded ie achieved a one unit or greater improvement for TDI for Spiriva compared to salmeterol was not statistically different, Donohoe and data on file.

The Panel considered that the claim was misleading as it had not been put into the context of the other results and it appeared that salmeterol did not produce a clinically significant difference in breathlessness score. Insufficient explanation had been provided. A breach of Clause 7.2 of the Code was ruled.

## APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer noted that there were several parts to this item of complaint and to the Panel's conclusions and rulings. The rulings challenged the scientific basis of the claim 'Spiriva can make a life-changing difference in COPD'.

An understanding of this progressive disease and the influence it had on the individual patient would help in the understanding of the results from the Spiriva clinical trial programme that supported this claim.

### The disease

The British Thoracic Society guidelines defined COPD as '… a chronic, slowly progressive disorder, characterised by airflow obstruction that does not change markedly over several months. It is a major cause of morbidity with frequent use of hospital and general practice services'.

COPD caused a decline in lung function that was continuous if the causative agent (eg smoking) was not eliminated. Patients suffering from COPD might not notice anything wrong at first. Slowly, however, as their lung function deteriorated, they became breathless on exertion. Sufferers often experienced a chronic smokers cough, productive of sputum and associated with wheeze. Patients might be so disabled by breathlessness as to be unable to wash or dress themselves. Patients with COPD could have sudden worsening of their symptoms; an acute exacerbation usually because of a respiratory infection. Severe exacerbations of COPD might necessitate treatment in hospital and might ultimately prove to be fatal.

### Diagnosis

COPD was diagnosed by history and examination along with objective measures of lung function using spirometry. The most important measure of lung function in COPD, assessed by spirometry, was the forced expiratory volume in one second ($FEV_1$). This was used in diagnosis and was also an important measure of the progress of the disease.

### The patient's perspective

Boehringer Ingelheim and Pfizer noted that this had received attention in a recent editorial by Dekhuijzen (2002): 'Relatively little is known about the patient's own perception of their health status with regard to COPD. Obviously, it is important to explore this significant issue because there may be a discrepancy between the doctor's perception of the impact of COPD in the patient and the patient's own perception of their health status'.

The companies noted that as a surrogate measure of this phenomenon, the term health status, or health-related quality of life, was used to describe the multi-dimensional influence of COPD and its effects on everyday life.

The influence of the disease was best understood through the words of patients. The companies noted that a sub-group of patients from a randomised controlled trial of nebulised therapy were interviewed to find out their perceptions of COPD (Guthrie *et al* 2001). The following quote conveyed the stark reality of one patient's experience: Patient 1 Mrs D 60 year old married woman, 'I don't go out hardly at all now…I've had a few bad experiences – it really frightens you. You try to slow your breathing down, and then I feel dizzy… you feel such a fool, people stare at you. It's a horrible feeling – I don't go out unless I really have to, just really to doctor's or chemist; and that's often not as much as once a week'.

### Measurement of COPD

Boehringer Ingelheim and Pfizer considered that the interpretation of the Spiriva clinical trial results should be made with reference to the disease and any improvements, although perceived as small for a normal population, were very significant for these patients. To make a life-changing difference, a COPD therapy must consistently demonstrate improvements not only in lung function, but also in those areas that were relevant to patients: dyspnoea (breathlessness); health status and exacerbations.

*Dypsnoea*

Boehringer Ingelheim and Pfizer noted that in Spiriva clinical trials dyspnoea had been assessed using the Mahler BDI (Baseline Dyspnoea Index) and TDI, multidimensional instruments measuring the impact of the most disabling symptom in this disease. As COPD was a progressive disease, it was known that there was worsening of breathlessness over time – by approximately 0.7 units of the TDI over 2 years (Mahler, 2002).

The TDI demonstrated mean study group results, where an improvement of 1 unit was clearly and unambiguously defined as a clinically important difference (Mahler *et al*, 1984, Witek, 2002).

Boehringer Ingelheim and Pfizer stated that according to Mahler *et al* a 1-unit change could be described as the ability to: return to work at a reduced pace; resume some customary activities with more vigour than previously due to an improvement in shortness of breath. These changes in this group of patients could significantly improve the quality of their lives.

*Health status, SGRQ*

'The primary aim in developing the SGRQ was to provide an instrument that had the ability to measure the patient's status with reference to other groups of patients and also to measure response to treatment' (Jones *et al* 2000).

Boehringer Ingelheim and Pfizer noted that this disease-specific questionnaire was used to measure health status in asthma and COPD patients. The questionnaire consisted of 3 domains, impacts, symptoms and activities, which were combined to make a total score out of 100. A score of 0 represented best possible health, and a score of 100 represented worst possible health. A reduction in score represented health status improvement.

The companies stated that a 4-point reduction in total or impacts score could be defined as either the difference between: mean values for each group compared with baseline; difference between the values in each group at a given time point; proportion of patients exceeding a 4-point improvement in their own baseline score – 'responder analysis' (Jones *et al* 1992, Jones 2002a, Jones 2002b).

Boehringer Ingelheim and Pfizer noted that according to Jones (2002c) a 4-point reduction for a patient could mean that 'they no longer walk more slowly than others of their age and are not breathless on bending over, and in addition that they are not breathless when washing and dressing'.

Boehringer Ingelheim and Pfizer also noted that the difference of 4 points was said by Jones (2002a) to be '3.9. For convenience this was rounded up to 4'. The study also discussed the merits of using the threshold of 4 plus or minus that population's confidence intervals to determine clinical significance.

*Lung function efficacy vs placebo*

The companies noted the page relating to point A2 featured a graph showing significant and sustained improvements in trough $FEV_1$ over 1 year with Spiriva in placebo-controlled studies (Casaburi *et al*). Boehringer Ingelheim and Pfizer noted the footnotes on the graph which explained that all patients continued their current respiratory medicines. Those in the placebo arm, therefore, were permitted to continue on their usual therapy in accordance with the study protocol. Thus, this was not a simple placebo comparison but rather a comparison of the 'add-on' effect of Spiriva or placebo to patients who were already receiving treatment.

The companies noted that $FEV_1$ inevitably declined in COPD at an annual rate of approximately 60-90mls (Fletcher *et al* 1997).

In these studies, after 1 year, patients taking Spiriva had on average a 110 ml improvement above baseline in pre-dose lung function. Those on placebo had an average worsening of 40ml compared with baseline. This improvement in lung function represented a 12% improvement from baseline, in a population with an average lung function of less than 40% of predicted values (Casaburi *et al*).

The companies submitted that the Panel's ruling on point A2 was unreasonable. A positive result in a comparison with placebo was a very important factor in establishing the efficacy of a product and that it could not be taken as 'no more than expected'. The fact that these were not simple placebo studies added to the importance of these results. This statistically and clinically significant response on lung function for Spiriva compared with placebo was a part of the evidence that substantiated the claim that 'Spiriva can make a life-changing difference in COPD'.

*Health-related quality of life efficacy vs placebo*

Boehringer Ingelheim and Pfizer addressed the Panel's comments, emphasising the nature of the placebo group as discussed above.

The information on page 6 of the detail aid stated 'Spiriva delivered a statistically significant improvement in health-related quality of life score'. No claim was made with regard to clinical significance and it was difficult to see how the graphic representation of the scores could be interpreted to mean that all the results were clinically significant, as proposed by the Panel.

The fact that Spiriva produced a statistically significant improvement in these scores meant that Spiriva was more effective than placebo in this measure of health-related quality of life and supported the only claim made from these data.

The Panel noted that in Casaburi *et al*, in addition to a statistically significant improvement in mean response for Spiriva over placebo, a significantly greater percentage of patients in the Spiriva group (49%) showed at least a 4-point improvement in total score (equated with clinical significance) compared with the placebo group (30%).

These results were summarised by Casaburi *et al*: 'Health status was improved with tiotropium relative to placebo, confirming the overall benefit of therapy to the patient. Improvements that were at or around

the level of clinical significance (a decrease of 4 units) were observed in all SGRQ domains compared with placebo. Further, a significantly higher proportion of patients exceeded a 4-unit improvement in the group receiving tiotropium'.

Boehringer Ingelheim and Pfizer noted that Jones (2002b) discussed these data and their clinical relevance. When considering the impact domain data from Casaburi *et al*, displayed in a histogram exactly like the one in the detail aid, the author stated: 'The difference between the two [tiotropium and placebo] groups was 4.04 units, so it may be concluded that, on average, patients in the study had an improvement in health that could be considered clinically significant'.

Even though the detail aid clearly stated the statistically significant improvement with Spiriva and did not refer to the clinical significance, the Panel considered that further explanation should have been given to describe what was not being claimed (ie clinical significance). Boehringer Ingelheim and Pfizer submitted that this page provided good evidence for the superiority of Spiriva over placebo with regard to health-related quality of life scores and that the presentation of the data was not misleading.

The Panel, in its ruling in point A7, considered that 'the claim referring to health-related quality of life was too simplistic given the complexity of the use of the SGRQ'. The companies noted as discussed above that they had chosen to quote the SGRQ results directly from the study findings with no further interpretation. This was neither over simplistic nor misleading. The companies submitted that this statistically significant response for Spiriva on health-related quality of life scores in comparison with placebo was a part of the evidence that substantiated the claim 'Spiriva can make a life-changing difference in COPD'. With regard to the effect on exacerbations and hospital admissions for Spiriva compared with placebo, the companies submitted that this response for Spiriva in comparison with placebo was a part of the evidence that substantiated the claim that 'Spiriva can make a life-changing difference in COPD'.

*Health-related quality of life efficacy vs ipratropium*

With regard to the comparison of Spiriva and ipratropium in relation to breathlessness scores, the companies submitted that there was evidence that the reduction in cholinergic tone, the dominant reversible element in COPD, was important in this patient group (Barnes 1999). Ipratropium was currently the most widely prescribed anticholinergic for the treatment of COPD. The statistically significant improvements demonstrated by Spiriva over the improvements seen in the ipratropium group were therefore of undoubted clinical relevance and were part of the evidence that substantiated the claim that 'Spiriva can make a life-changing difference in COPD'.

The companies noted that significantly more patients achieved a 4 unit or more improvement in SGRQ with Spiriva compared with ipratropium (Vinken *et al*). The difference between the groups' mean impact scores at one year was greater than 4 units, a clinically significant result. These results were part of the evidence that substantiated the claim that 'Spiriva can make a life-changing difference in COPD'.

*Lung function efficacy vs salmeterol*

The companies noted the claim that Spiriva delivered a 'Significant improvement in lung function over 12 hours at 6 months' was referenced to Donohue *et al* and was a direct comparison between Spiriva and salmeterol. The Panel appeared to have overlooked this significant result in its assessment.

Boehringer Ingelheim and Pfizer stated that the claims that Spiriva delivered a 'Clinically significant difference in breathlessness score (1.1 units) at 6 months compared with placebo, whereas salmeterol did not (0.7 units). Both active substances showed statistically significant differences vs. placebo' and 'Statistically significant improvement in health-related quality of life scores vs. placebo (p=0.003), whereas salmeterol did not (p=0.156)' were explicit in their description of the results from the studies of Spiriva, salmeterol and placebo. However, the Panel considered that these two claims would be read as direct comparisons between Spiriva and salmeterol despite the clear reference to them being comparisons with placebo.

The companies did not accept this interpretation of these claims. Furthermore, their position on the comparison with salmeterol added further evidence in support of the claim that 'Spiriva can make a life changing difference in COPD'; it was also relevant to the response in point A1.

Boehringer Ingelheim and Pfizer noted that in its ruling on point A7 the Panel referred to its comments in point A2 regarding the claim that 'Spiriva can make a life-changing difference in COPD'. The Panel noted that it was a strong claim that was exaggerated when based only on the lung function data comparing Spiriva with placebo. The companies submitted that this, however, was not the basis for this claim and in the context of point A7, was clearly only one part of the evidence provided on this page of the detail aid.

The companies rejected the Panel's conclusion that the overall impression that Spiriva could make a life-changing difference in COPD generally or in relation to all the parameters listed compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. The companies submitted that the data referred to in the detail aid showed statistically and clinically significant advantages for Spiriva over placebo (Casaburi *et al*), ipratropium (Vincken *et al*) and salmeterol (Donohue *et al*) as described above. These significant advantages taken together clearly supported the conclusion that 'Spiriva can make a life-changing difference in COPD'.

The companies considered that the Panel's view that the word 'can' rarely negated the impression 'will', implied that the Panel assumed that 'will' was the interpretation here. Boehringer Ingelheim and Pfizer did not accept this interpretation. The word 'can' explicitly meant 'was capable of'. It meant that many patients, unquantified but not all, would enjoy a life-changing difference in their COPD. The word 'will'

would mean that all would enjoy such an effect. This was a totally unreasonable inference from this page of the detail aid. This claim did not require all patients to experience a life-changing difference, but certainly the available data meant that many of them would do so.

### Exercise tolerance, dypsnoea and quality of life

Boehringer Ingelheim and Pfizer noted that Huchon *et al* 2002, a 12-week, double-blind, placebo-controlled study assessed exercise tolerance (as measured by shuttle walk test), breathlessness (TDI) and health status (SGRQ). After 84 days the Spiriva group had a total SGRQ that had improved by 6.52 units compared to placebo ($p<0.05$). TDI scores on day 84 were 1.3 units better than placebo ($p<0.05$). Patients taking Spiriva had a difference of 36m in the shuttle walk test compared with placebo ($p<0.05$) and had a 110ml improvement in trough FEV1 at the end of the study.

A further 6-week placebo-controlled study assessed dynamic ventilatory parameters, exercise tolerance (measured by endurance time) and intensity of dyspnoea during exercise (O'Donnell *et al* 2002). The companies submitted that improvements in dynamic lung function, as seen by the reduction in operating lung volumes during exercise suggested that there was a physiological advantage conveyed to the patient by 24-hour bronchodilatation produced by Spiriva. Patients were able to exercise for longer than those on placebo (treatment difference 105 seconds, $p<0.05$), and breathlessness was less likely to ultimately limit them.

Boehringer Ingelheim and Pfizer submitted that the findings offered an explanation of the mechanism by which Spiriva produced its benefits, and confirmed the improvements in activities of daily living seen in other placebo-controlled studies.

### Exacerbations and quality of life

As shown by Jones *et al* (2001), exacerbations of COPD reduced the health status of patients and Spiriva attenuated this deterioration (see table below). Jones *et al* concluded: 'Tiotropium prevented the decline in health status that is associated with increasing exacerbations. Tiotropium improved and maintained health status over 1 year irrespective of exacerbation frequency'.

| Medicine | Number of Exacer-bations | N | Impacts domain SGRQ (mean +/– SE) | Total domain SGRQ (mean +/– SE) |
|---|---|---|---|---|
| Tiotropium | 0 | 326 | –3.1 (0.8) | –4.0 (0.7) |
| | 1 | 111 | –3.0 (1.3) | –2.7 (1.1) |
| | 2 | 44 | –1.6 (2.1) | –1.3 (1.8) |
| | >2 | 35 | –2.9 (2.4) | –3.4 (2.0) |
| Placebo | 0 | 175 | –0.2 (1.1) | –1.5 (0.9) |
| | 1 | 92 | 1.2 (1.5) | 0.9 (1.2) |
| | 2 | 34 | 3.9 (2.4) | 2.6 (2.0) |
| | >2 | 23 | 4.7 (2.9) | 5.3 (2.5) |

(Negative results indicated improvement for the patient)

Boehringer Ingelheim and Pfizer submitted that combining the fact that Spiriva reduced exacerbations compared to placebo (Casaburi *et al*) and ipratropium (Vincken *et al*) in one-year studies, and to placebo (Friedman *et al*) in the six-month studies, further reinforced the life-changing aspect of Spiriva in the management of COPD.

Boehringer Ingelheim and Pfizer referred again to the claim 'In a comparison with salmeterol, Spiriva delivered a: Clinically significant difference in breathlessness score (1.1 units) at 6 months compared with placebo, whereas salmeterol did not (0.7 units). Both active substances showed statistically significant differences vs placebo' and noted that although the Panel acknowledged that the first sentence was consistent with the findings of Witek *et al* it went on to allege that 'it was not sufficiently clear that there was data to show that the numbers of patients who responded ie achieved a one unit or greater improvement for TDI for Spiriva compared to salmeterol was not statistically significant'.

Boehringer Ingelheim and Pfizer noted the presentation of combined data from the whole pool of patients in the Witek *et al* poster was used to support this claim as it represented the full population studied. As shown by Donohue *et al* (2002), the results from the single trial (205.130) for TDI score were far less favourable for salmeterol (TDI score 0.24 units above placebo). Selective use of these results could have been misleading. By showing the combined results (salmeterol TDI score 0.7 units above placebo) and stating that salmeterol showed statistically significant improvements versus placebo, the companies had accurately and fairly displayed the study findings.

Boehringer Ingelheim and Pfizer stated that an improvement in 1 unit in the TDI between mean study groups was clearly and unambiguously defined as a clinically important difference.

According to Mahler *et al* (1984) a 1 unit change could be described as the ability to: return to work at a reduced pace; resume some customary activities with more vigour than previously due to an improvement in shortness of breath.

Whilst the percentage of patients achieving a 1 unit improvement was accepted by the FDA as a co-primary endpoint in this study, the mean results remained the validated and most widely accepted way of expressing TDI results in clinical practice.

Following a literature search the companies provided additional references which they submitted confirmed that the accepted method of displaying TDI results in COPD literature was mean differences. The companies provided a table summarising the available TDI results for both Spiriva and salmeterol and this appears at the top of the next page.

Boehringer Ingelheim and Pfizer noted that salmeterol did not achieve a clinically meaningful difference in mean score in the studies referenced in the detail aid, and failed to do so in all the other studies listed above. Salmeterol produced statistically significantly better breathlessness scores compared with placebo, and this was accurately written in the detail aid.

| STUDY | n (Salmeterol arm) | DURATION | Salmeterol vs. placebo mean TDI score |
|---|---|---|---|
| Mahler *et al* (1999) | 135 | 12 weeks | 0.6 |
| Mahler *et al* (2002) | 154 | 24 weeks | 0.5 |
| SFCA3007 | 176 | 24 weeks | 0.6# |
| Rennard *et al* | 132 | 12 weeks | Values not given, but p= ns vs placebo |
| 130/137 | 405 | 6 months | 0.7* |

| STUDY | n (Spiriva arm) | DURATION | Spiriva vs placebo mean TDI score |
|---|---|---|---|
| 130/137 | 402 | 6 months | 1.1† |
| Casaburi *et al* | 550 | 1 year | 1.1† |
| Huchon *et al* | 46 | 84 days | 1.3† |

*p<0.05 compared with placebo
# significance values not given
† exceeds clinical significance

The companies submitted that the results presented from the salmeterol trials with Spiriva were accurately reported and totally consistent with the available evidence regarding salmeterol. The companies did not accept that the claim was misleading or that insufficient explanation had been provided.

## COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its comments in points A1 and A2.

## APPEAL BOARD RULING

The Appeal Board noted that GlaxoSmithKline had criticised certain parts of the three comparisons. In ruling on these allegations the Panel had referred to its comments in points A2, A3 and A4.

With regard to the comparison of Spiriva with placebo, referenced to Casaburi *et al*, the Appeal Board considered that its comments on this study in point A3 above were relevant. The Appeal Board considered that the claim referring to health-related quality of life scores was too simplistic given the complexity of the use of SGRQ. There were statistically significant differences with placebo in relation to exacerbations and exacerbation-related hospitalisations. Boehringer Ingelheim and Pfizer had previously stated that the difference between placebo and Spiriva would mean that treating 1000 patients with Spiriva would result in 75 fewer hospitalisations per year (point A4).

The comparison with ipratropium, 'Significant improvement in lung function, and a statistically significant improvement in breathlessness scores and health-related quality of life scores, with a significant reduction in exacerbations' was referenced to Vincken *et al*. The Appeal Board noted that the differences between ipratropium and Spiriva were statistically significantly in favour of Spiriva, however they were less than one and hence did not achieve a clinically meaningful difference for that measure. The proportion of patients who achieved a clinically meaningful difference in TDI total score (improvement of ≥ 1 unit) was statistically significantly greater in the Spiriva group (31%) than in the ipratropium group (18%) (p=0.004). Similarly the difference between the products' SGRQ total scores was statistically significant in favour of Spiriva but was less than 4 units and hence did not achieve a clinically meaningful difference. More patients in the Spiriva group achieved a clinically meaningful improvement of 4 units (52% v 35% p< 0.01). The basis of the claim had not been made sufficiently clear. The Appeal Board noted previous comments regarding the SGRQ at point A3 above.

With regard to the comparison with salmeterol in relation to breathlessness score and health-related quality of life scores, the Appeal Board noted that the comparisons with salmeterol were not direct comparative claims. Each medicine had been compared with placebo. The claims appeared beneath the heading 'In a comparison with salmeterol, Spiriva delivered a: …'. The Appeal Board considered that in conjunction with the heading the claims would be read as direct comparisons between the two products.

The Appeal Board noted point A2 above regarding the claim 'Spiriva can make a life-changing difference in COPD'. The Appeal Board noted the submission from Boehringer Ingelheim and Pfizer that Spiriva could produce, for individual patients, differences that were life-changing. The claims in the detail aid, however, would be assumed to represent the expected response in most patients. The Appeal Board considered that given its comments above overall the implication that Spiriva could make a life-changing difference in COPD generally or in relation to all the parameters listed compared with placebo, ipratropium and salmeterol was misleading, could not be substantiated and was an exaggerated claim. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10 of the Code. The appeal was unsuccessful.

The Appeal Board considered that the claim that in a comparison with salmeterol, Spiriva delivered a 'Clinically significant difference in breathlessness score (1.1 units) after 6 months compared with placebo, whereas salmeterol did not (0.7 units) …' was consistent with the findings of Witek *et al*. It was not sufficiently clear given that there was data to show that the numbers of patients who responded ie achieved a one unit or greater improvement for TDI for Spiriva compared to salmeterol was not statistically different (the primary endpoint in the study), Donohoe and data on file.

The Appeal Board considered that the claim was misleading as it had not been put into the context of

the other results and it appeared that salmeterol did not produce a clinically significant difference in breathlessness score. Insufficient explanation had been provided. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

### 8 Claim 'Efficacy vs. ipratropium'

This claim was the heading to page 16 which compared Spiriva with ipratropium and stated that 'In a comparison with ipratropium, Spiriva delivered a:

Significant improvement in lung function
Sustained improvement in lung function
Statistically significant improvement in breathlessness scores…'.

The claims were referenced to Vincken *et al*.

#### COMPLAINT

GlaxoSmithKline stated that although statistically significant, the improvement over ipratropium in breathlessness (TDI focal score) was 0.9 which did not reach the clinically relevant difference of 1 unit for this instrument. As discussed under point A2, this outcome measure had a validated threshold for a clinically relevant difference of 1 unit, and there was no mention of this.

GlaxoSmithKline accepted that not all measures in clinical studies had validated levels of clinical significance. However, for a measure that did have such a validated threshold of clinical significance, it was misleading not to make this clear. TDI was relatively unfamiliar to most UK health professionals and they could not be expected to know that 0.9 was not a clinically relevant difference. Since it appeared on a page which concluded with the claim 'Spiriva can make a life-changing difference in COPD', the implication was that there was a difference that would be noticed by patients. A breach of Clause 7.2 of the Code was alleged.

#### RESPONSE

Boehringer Ingelheim and Pfizer stated that this allegation had been covered in the response to point A7. The companies did not accept that the claim that 'In a comparison with ipratropium, Spiriva delivered a: Statistically significant improvement in breathlessness scores' was misleading. It was a correct finding of the study.

The reference to the strapline had been covered in response to point A2.

#### PANEL RULING

The Panel noted its comments in points A2 and A7 above. The difference between breathlessness scores was statistically significant but had not achieved a clinically meaningful difference. The Panel ruled that the claim with regard to breathlessness, in conjunction with the strapline 'Spiriva can make a life-changing difference in COPD' was misleading in breach of Clause 7.2 of the Code.

#### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer appealed the Panel's rulings for the reasons given in points A2 and A7 above.

#### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

#### APPEAL BOARD RULING

The Appeal Board noted comments in points A2 and A7 above. The difference between breathlessness scores was statistically significant but had not achieved a clinically meaningful difference. The Appeal Board ruled that the claim with regard to breathlessness, in conjunction with the strapline 'Spiriva can make a life-changing difference in COPD', was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

### 9 Claim 'Statistically significant improvement in health-related quality of life scores'

This claim was also on page 16 and introduced with the statement 'In a comparison with ipratropium, Spiriva delivered a: ...'. The claim was referenced to Vincken *et al*.

#### COMPLAINT

GlaxoSmithKline stated that the difference in terms of SGRQ total score was less than 4 units between Spiriva and ipratropium; although statistically significant it was not clinically meaningful. There was no mention on this page of the level at which a change in SGRQ achieved clinical relevance. As discussed above for breathlessness scores (point A8), it should not be assumed that health professionals would know that a mean 4-unit difference was required for clinical significance. The claim implied there was a difference that would be noticed by patients – however the improvement with tiotropium over ipratropium did not reach the validated threshold for a clinically meaningful difference.

GlaxoSmithKline alleged that the claim was misleading in breach of Clause 7.2 of the Code.

#### RESPONSE

Boehringer Ingelheim and Pfizer stated that this allegation was covered by its response to point A7 above.

The companies did not accept that the claim that 'In a comparison with ipratropium, Spiriva delivered a: Statistically significant improvement in health-related quality of life scores' was misleading. (GlaxoSmithKline omitted the word 'scores' in its complaint). It was a correct finding of the study (Vincken *et al* 2002) and the use of the word 'scores' emphasised the numeric nature of the measure.

Boehringer Ingelheim and Pfizer therefore considered

that the claim was not in breach of Clause 7.2 of the Code.

### PANEL RULING

The Panel noted its comments in A7 and A8 above. The Panel considered that the claim, in the context in which it was used, was misleading. Insufficient explanation had been provided. The Panel ruled a breach of Clause 7.2 of the Code.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer noted the Panel's ruling in A7 that 'the difference between the products' SGRQ total scores was statistically significant in favour of Spiriva but was less than 4 units and hence did not achieve a clinically meaningful difference. More patients in the Spiriva group achieved a meaningful improvement of 4 units'.

Boehringer Ingelheim and Pfizer submitted that this significant response for Spiriva on health-related quality of life scores in comparison with ipratropium was clear and meaningful. Full details of a study did not need to be given in a summary page such as this and no further explanation was needed. As this was a detail aid for a presentation by a representative, discussion could take place if further information was sought.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

### APPEAL BOARD RULING

The Appeal Board noted comments in A7 and A8 above. The Appeal Board considered that the claim, in the context in which it was used, was misleading. Insufficient explanation had been provided. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

## 10 Claim 'In a comparison with salmeterol: ... Spiriva showed no evidence of tachyphylaxis'

This claim referenced to Donohue *et al* appeared on page 18 which was headed 'Efficacy vs. salmeterol'.

### COMPLAINT

GlaxoSmithKline alleged that the apposition of the claim implied that salmeterol showed tachyphylaxis, especially as it was set within the context of a double page spread comparing tiotropium with salmeterol. Boehringer Ingelheim had stated that this was simply a statement about Spiriva and there was no conclusion drawn with respect to whether salmeterol showed tachyphylaxis or not. However the question must therefore be raised as to why it was included on this page at all, if the intention was not to imply, by omission, that salmeterol caused tachyphylaxis.

The balance of evidence from a range of clinical studies was that salmeterol showed a sustained bronchodilator effect vs placebo in studies of 6 months to 1 year with no evidence of tachyphylaxis (Knobil *et al* 2002, Calverley *et al* 2002 and Stockley *et al* 2002).

GlaxoSmithKline alleged that in this context, the claim was misleading as it did not reflect the balance of evidence in breach of Clause 7.2 of the Code.

### RESPONSE

Boehringer Ingelheim and Pfizer stated that the claim was an accurate conclusion from the study results (Donohue *et al* 2002). Spiriva did not show evidence of tachyphylaxis (tolerance or loss of effect). No claim was made about salmeterol nor was one implied as the claim referred to 'in a comparison with salmeterol' not 'in comparison with salmeterol'. The claim appeared on the page headed 'Efficacy vs. salmeterol' as it came from efficacy studies comparing the two. It was a positive statement about Spiriva that did not need the response on salmeterol in order to make its point. The company did not accept that the claim was misleading and therefore there was no breach of Clause 7.2 of the Code.

### PANEL RULING

The Panel considered that given that the claim that 'Spiriva showed no evidence of tachyphylaxis' appeared on a page headed 'Efficacy vs. salmeterol' the failure to give any information about salmeterol and tachyphylaxis gave the impression that salmeterol caused tachyphylaxis. In the Panel's view the claim, in the context in which it was used, was misleading and a breach of Clause 7.2 was ruled.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer noted that the heading to the page was consistent with the introductory question on page 3 in which there was reference to 'Efficacy vs. salmeterol'. The reference was to the clinical evaluation of efficacy comparing Spiriva with salmeterol.

This evaluation included the observation concerning Spiriva and tachyphylaxis and was a consistent finding with Spiriva. Both Donohue *et al* (2002) and the Spiriva SPC agreed that 'The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance'.

Tolerance and tachyphylaxis could be used interchangeably in this context.

Boehringer Ingelheim and Pfizer submitted that no misleading statements as to the properties of salmeterol had been made. The claim accurately reflected the data for Spiriva, without passing any judgment on the issue for salmeterol. Boehringer Ingelheim and Pfizer did not accept that the omission of information on salmeterol could be regarded as misleading.

**COMMENTS FROM GLAXOSMITHKLINE**

GlaxoSmithKline referred to its response in point A1.

**APPEAL BOARD RULING**

The Appeal Board considered that given the context of the claim 'Spiriva showed no evidence of tachyphylaxis' the failure to give any information about salmeterol and tachyphylaxis gave the impression that salmeterol caused tachyphylaxis. The Appeal Board considered that the claim was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

**11 Claim 'In a comparison with salmeterol: … Spiriva patients achieved a clinically significant difference in breathlessness score (1.1 units) at 6 months compared with placebo whereas salmeterol did not (0.7 units)'**

This claim was referenced to Witek and appeared on page 18.

**COMPLAINT**

GlaxoSmithKline referred to point A7 above and alleged that this was a selective use of a secondary endpoint for breathlessness, where the primary endpoint showed a different result. The page also carried the strapline 'Spiriva can make a life-changing difference in COPD'.

GlaxoSmithKline alleged that the claim did not reflect the balance of evidence, was misleading in breach of Clause 7.2 of the Code.

**RESPONSE**

Boehringer Ingelheim and Pfizer stated that this allegation was covered in points A1 and A7. The companies did not consider that the claim was misleading and therefore there was no breach of Clause 7.2 of the Code.

**PANEL RULING**

The Panel noted its comments in points A1 and A7 above. The Panel considered that its ruling in A7 also applied here and therefore a breach of Clause 7.2 of the Code was ruled.

**APPEAL BY BOEHRINGER INGELHEIM AND PFIZER**

Boehringer Ingelheim and Pfizer referred to the relevant part of the appeal in point A7.

Boehringer Ingelheim and Pfizer considered that the results presented from the salmeterol trials with Spiriva were accurately reported and totally consistent with the available evidence regarding salmeterol. Boehringer Ingelheim did not accept that the claim was misleading or that insufficient explanation had been provided.

**COMMENTS FROM GLAXOSMITHKLINE**

GlaxoSmithKline referred to its response in point A1.

**APPEAL BOARD RULING**

The Appeal Board noted comments in points A1 and A7 above. The Appeal Board considered that its ruling in A7 also applied here and therefore upheld the Panel's ruling of breach of Clause 7.2 of the Code. The appeal was unsuccessful.

**12 Claim 'In a comparison with placebo, Spiriva significantly reduced the number of exacerbations† while salmeterol did not'**

This claim appeared on page 19 which was headed 'Efficacy vs. salmeterol'. The explanation of the obelus (†) was 'An exacerbation detected through monitoring of adverse events, was defined as a complex of respiratory events (ie cough, wheezing, dyspnoea or sputum production) lasting ≥ 3 days'.

**COMPLAINT**

GlaxoSmithKline alleged that the claim implied that salmeterol had no effect on exacerbations compared with placebo. This was selective use of the available data, and did not reflect the balance of evidence from other clinical trials. Boehringer Ingelheim had stated that as the claim was 'in a comparison' rather than 'in comparison with' it was justified in making the claim. It also stated that differences in study design meant that other studies did not need to be taken into account. However, the Code stated that claims must be based on an up-to-date comparison of all the evidence and reflect that evidence clearly.

Data were available from two large studies to show that, over one year, salmeterol reduced exacerbations by around 19-21% compared with placebo (Calverley *et al* 2002, Pauwels *et al* 2002 and Stockley *et al* 2002). Combining the results of these one-year studies (which involved over 1300 patients with poorly reversible COPD) showed that salmeterol was associated with a mean reduction of 19% in exacerbation rate ($p<0.001$ vs placebo). These data had been provided to Boehringer Ingelheim.

Although the definition of exacerbations was different in these studies compared to that used in the tiotropium studies, they were part of the evidence base, and should be taken into consideration when a claim was made against salmeterol. The claim did not take into account all the evidence, and for example should be more specific regarding length of study, patient type and definition of exacerbations.

GlaxoSmithKline alleged that the claim was misleading, did not reflect the balance of evidence in breach of Clause 7.2 of the Code.

**RESPONSE**

Boehringer Ingelheim and Pfizer stated that the claim was an accurate reflection of the results from studies 130 and 137 (data on file). The difference between salmeterol and placebo did not reach the level of statistical significance.

It was not appropriate to make direct comparisons between studies carried out at different times with different protocols, including patient selection and numbers and disease definitions. In this instance GlaxoSmithKline acknowledged that the definition of exacerbations was different in these studies compared to that used in the tiotropium studies.

Boehringer Ingelheim and Pfizer believed that the requirement of the Code for an up-to-date evaluation of all the evidence referred to comparisons of like with like. If other studies of Spiriva with salmeterol had come to differing conclusions, such differences would need to be taken into account in making claims. In this instance like was not being compared with like.

The fact that in the Spiriva study salmeterol showed a non-significant difference from placebo was not inconsistent with GlaxoSmithKline's salmeterol studies (where the differences were found to be statistically significant) as there were marked differences in study design and concomitant medications used that would contribute to the different results. To help illustrate this, Boehringer Ingelheim and Pfizer referred to the inclusion criteria of the two GlaxoSmithKline studies and the Boehringer Ingelheim studies in question:

> Stockley *et al* – Patients had to have had 2 exacerbations of COPD requiring treatment with steroids in the past year
>
> Calverley *et al* – Documented history of COPD exacerbations (including ≥ in the last year requiring oral corticosteroids and or antibiotics)
>
> 205.130 and 205.137 – Patients not required to have a history of exacerbations.

In addition, the definition of a COPD exacerbation was different in the Boehringer Ingelheim to the GlaxoSmithKline studies, as was the method of data collection.

This meant that the results of these 3 studies, with such different populations and using different definitions of an exacerbation, could not be directly compared.

Boehringer Ingelheim and Pfizer therefore submitted that the representation of the exacerbation data for tiotropium, salmeterol and placebo, was the most accurate way to show the evidence from the only study to date directly comparing the two active treatments.

At the time of preparation of the detail aid, Boehringer Ingelheim and Pfizer were not aware (and could not have been expected to have been aware) of the existence of the unpublished data on file SCOPD62002, and therefore could not have been expected to include these data in the overall available evidence even if it had been deemed appropriate.

The companies did not accept that the claim was misleading and therefore it was not in breach of Clause 7.2.

## PANEL RULING

The Panel noted that GlaxoSmithKline had data from two large studies to show that salmeterol was associated with a mean reduction in exacerbation rate compared to placebo.

The Panel noted that Boehringer Ingelheim and Pfizer were referring to the only study comparing Spiriva and salmeterol (data on file SP102-2). The exacerbation rate was determined from adverse event monitoring. No information was given in the detail aid about the nature of the exacerbations. The Panel accepted that it was not necessarily appropriate to compare results from different studies. Nonetheless the Panel considered that the claim implied that the balance of the data was such that salmeterol was no different to placebo with regard to reductions in numbers of exacerbations and this was not so.

The claim was misleading and the Panel ruled a breach of Clause 7.2 of the Code as alleged.

## APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer stated that the Panel was wrong to state 'No information was given in the detail aid about the nature of the exacerbations.' The obelus adjacent to the word 'exacerbations' referred to the statement that 'An exacerbation, detected through monitoring adverse events, was defined as a complex of respiratory events (i.e. cough, wheezing, dyspnoea or sputum production) lasting ≥ 3 days'. This definition also appeared on page 7 of the detail aid.

Boehringer Ingelheim and Pfizer noted that the Panel acknowledged 'that it was not necessarily appropriate to compare results from different studies' and then went on to indicate that it should have been done in this instance.

Boehringer Ingelheim and Pfizer contended that it was very rarely acceptable to compare results from different studies conducted with very different protocols and very different definitions and it was not appropriate in this instance.

Boehringer Ingelheim and Pfizer noted the study inclusion criteria of the trials presented by GlaxoSmithKline were very different from those of the Spiriva vs. salmeterol studies. Furthermore, the results of the GlaxoSmithKline studies were not available at the time the detail aid was prepared. The definition of an exacerbation was also different across these studies:

In contrast to the definition concerning Spiriva, GlaxoSmithKline (data on file SMS40026 and Calverley *et al* (2002)) defined an exacerbation as an incident requiring treatment with oral corticosteroids and/or antibiotics.

Boehringer Ingelheim and Pfizer submitted that it was reasonable and appropriate to quote the outcome of the only direct comparison of Spiriva with salmeterol where conditions and definitions were uniform (Friedman *et al*). In conclusion, the presentation of this evidence was a balanced and accurate assessment of data from specified comparative clinical trials, and did not mislead.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1 above.

### APPEAL BOARD RULING

The Appeal Board noted that GlaxoSmithKline had data to show that salmeterol was associated with a mean reduction in exacerbation rate compared to placebo. There was only one study directly comparing Spiriva and salmeterol. It was not necessarily appropriate to compare results from different studies. Nonetheless the Appeal Board considered that the claim implied that the balance of the data was such that salmeterol was no different to placebo with regard to reductions in numbers of exacerbations and this was not so. The claim was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

## B Leavepiece (ref SPI 066/SPV 35)

The leavepiece was entitled 'Introducing Spiriva'.

### 1 Claim 'Spiriva can make a life-changing difference on COPD'

The claim was followed by four comparisons between Spiriva and placebo.

### COMPLAINT

GlaxoSmithKline alleged that as detailed above the claim was misleading, not capable of substantiation and exaggerated in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

### RESPONSE

Boehringer Ingelheim and Pfizer referred to its response in point A7 above. It did not accept that the claim was misleading, nor capable of substantiation or exaggerated as alleged and it was thus not in breach of the Code.

### PANEL RULING

The Panel noted its rulings in points A2 and A7 above. The Panel considered its ruling at point A2 was particularly relevant here. The Panel considered the claim was exaggerated, misleading and not capable of substantiation. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

The Panel had referred to point A2 as being particularly relevant to this item. Boehringer Ingelheim and Pfizer agreed with this, because this was an example of the strapline being used as an overall general statement covering the collected potential benefits of Spiriva. The companies also agreed with the Panel that the reference to item A7 was relevant. Boehringer Ingelheim and Pfizer stated that their response to item A7 provided its substantiation for this strapline.

The companies did not accept that this claim was exaggerated, misleading and not capable of substantiation.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

### APPEAL BOARD RULING

The Appeal Board noted its rulings in points A2 and A7. The Appeal Board considered the claim was exaggerated as alleged and upheld the Panel's ruling of breaches of Clauses 7.2, 7.4 and 7.10 of the Code. The appeal was unsuccessful.

### 2 Claim 'Spiriva delivered via the HandiHaler encourages good compliance'

### COMPLAINT

GlaxoSmithKline alleged that as detailed above the claim was misleading, not supported by the evidence in breach of Clauses 7.2 and 7.4 of the Code.

### RESPONSE

Boehringer Ingelheim referred to its response in point A5 above. It did not accept that the claim was misleading or unsupported. It was thus not in breach of Clauses 7.2 or 7.4 of the Code.

### PANEL RULING

The Panel considered that its ruling of breaches of Clauses 7.2 and 7.4 in point A5 applied here. It therefore ruled breaches of Clauses 7.2 and 7.4.

### APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer referred to its response to point A5.

Boehringer Ingelheim and Pfizer submitted that the claim 'Spiriva delivered via the HandiHaler encourages good compliance' was a statement of fact substantiated by the study by Kesten *et al* and was not misleading.

### COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

### APPEAL BOARD RULING

The Appeal Board considered that its ruling at point A5 applied here. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4 of the Code. The appeal was unsuccessful.

## C Spiriva journal advertisements (SPI/SPV 267, SPI/SPV 346 and SPI/SPV 347)

### Claim 'Introducing Spiriva Open up to a new world of COPD management'

### COMPLAINT

GlaxoSmithKline alleged that the claim was exaggerated. The implication was of a major step forward compared with existing therapy for COPD management (ie anticholinergics such as ipratropium bromide and long acting ß2 agonists such as salmeterol). Such a claim was not supported by the data.

GlaxoSmithKline pointed out that tiotropium was not a new class of medicine – anticholinergics had been well established for many years; they worked by blocking the muscarinic receptors of the parasympathetic nervous system, preventing bronchoconstriction. Essentially, tiotropium and ipratropium bromide had the same mode of action, although tiotropium bound to the $M_3$ receptor for longer to give a longer duration of action. Tiotropium was taken once daily – but there was no evidence that once daily dosing regimens improved compliance compared with twice daily. Compared with ipratropium, there was little evidence of clinically relevant improvements in breathlessness scores or health-related quality of life (Total SGRQ) and no difference in hospitalisations for exacerbation. Compared with salmeterol there was little evidence of clinically relevant differences for lung function, and no statistical or clinical differences with regard to breathlessness (either in terms of the primary analysis – percentage responders or secondary endpoint – mean scores), total SGRQ, or exacerbations.

GlaxoSmithKline referred to the table it had provided in relation to point A1 summarising the results of the studies comparing salmeterol with tiotropium. It could be clearly seen that there was little difference of clinical significance between the two products.

GlaxoSmithKline alleged that the claim 'Open up to a new world of COPD management' was therefore exaggerated and all embracing, not substantiated by the available evidence in breach of Clause 7.10 of the Code.

### RESPONSE

Boehringer Ingelheim and Pfizer stated that in their opinion and that of respiratory clinicians involved with the development of Spiriva, there was no doubt that its introduction into clinical medicine was an important factor in the management of COPD. It was worth noting that Spiriva was the only product available that was licensed 'as a bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease'. Others were licensed for the treatment of reversible airways obstruction in COPD.

COPD had a reputation for being very difficult to treat effectively and was a condition where the patient showed a steady deterioration leading to death. Cholinergic tone was a major cause of impaired lung function in COPD and its relief with anticholinergics was recognised in national and international guidelines for the management of COPD. The most commonly used anticholinergic had been ipratropium but this had to be given up to 4 times daily.

While Spiriva was not a new class of medicine in the broadest sense, it had properties were not shared by others in the class. This was confirmed by the statement in Section 5.1 of the SPC.

> 'In the airways, tiotropium bromide competitively and reversibly antagonises the $M_3$ receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. The long duration is probably due to the very slow dissociation from the $M_3$ receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur. The bronchodilation is primarily a local effect (on the airways), not a systemic one.
>
> Dissociation from $M_2$-receptors is faster than from $M_3$, which in functional *in vitro* studies, elicited (kinetically controlled) receptor subtype selectivity of $M_3$ over $M_2$. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.'

Boehringer Ingelheim and Pfizer stated that they had shown in point A1 the additional benefits that could be obtained from Spiriva compared particularly with placebo or ipratropium. As an anticholinergic, Spiriva should be a very effective treatment in COPD as noted by the independent opinion in point A1 and its advantages over salmeterol had also been referred to in that section.

The introduction of Spiriva opened up new opportunities in the management of COPD. The prolonged efficacy of single daily dosage with an anticholinergic that reduced the incidence of exacerbations had been shown to be a clearly better treatment than the existing ipratropium and in some instances (and patients) superior to salmeterol. Thus, the introduction of Spiriva provided clinicians with a new and effective treatment for COPD which had long been a difficult condition to treat effectively and the companies submitted that this justified the claim 'Open up to a new world of COPD management'.

Boehringer Ingelheim and Pfizer did not accept that the claim was exaggerated, all embracing or incapable of substantiation. It was not in breach of Clause 7.10 of the Code.

### PANEL RULING

The Panel noted that before Spiriva was launched there were medicines available for use in COPD. The Panel noted that there were differences between the indication for Spiriva compared to previously available products ipratropium and salmeterol. Spiriva was not a new class of medicine but it had additional properties to other medicines. For example Spiriva was long-acting and therefore only needed to be given once a

day compared to ipratropium and salmeterol. The Panel considered that the claim was a broad claim and although Spiriva was different to other medicines it was not sufficiently different to justify the claim 'Open up to a new world of COPD management'. The Panel decided that the claim was exaggerated as alleged and ruled a breach of Clause 7.10 of the Code.

## APPEAL BY BOEHRINGER INGELHEIM AND PFIZER

Boehringer Ingelheim and Pfizer submitted that Spiriva was sufficiently different and to help reach this conclusion it was important to review the current management of COPD prior to the introduction of Spiriva. The background information on COPD as set out in point A7 also provided supporting evidence.

Bronchodilators were central in the treatment of COPD (Pauwels *et al* 2001). Several agents were available, acting either as beta receptor agonists, anticholinergics or xanthine derivatives. The most convenient and widely used bronchodilators were administered via an inhaler.

When deciding which bronchodilator to use, the current BTS guidelines advised that:

'[short acting] beta agonists used 'as required' can be tried first in view of their more rapid symptom relief. If [short acting] beta agonists do not control symptoms or if a regular maintenance therapy is desired, an anticholinergic can be added or substituted.'

Thus, the anticholinergic bronchodilators, of which ipratropium was by far the most widely used in COPD, were the main recommendation for long-term management of COPD. Evidence on comparisons of Spiriva with ipratropium had been given in the detail aid and referred to in this submission and included 'significant improvement in lung function, and a statistically significant improvement in breathlessness scores and health-related quality of life scores, with a significant reduction in exacerbations'. These significant advantages for Spiriva over ipratropium (Vincken *et al* 2002), confirmed a marked change in the therapeutic expectations for COPD with the introduction of Spiriva.

Boehringer Ingelheim and Pfizer stated that the Spiriva clinical trial programme measured efficacy in COPD using the standard primary endpoint of measurable lung function, $FEV_1$. In addition, secondary markers of efficacy were used to assess the effect of Spiriva on patient-reported outcomes, namely breathlessness, quality of life and rate of exacerbations. As had already been discussed in this submission, Spiriva had been shown to be at least as effective, if not superior to salmeterol in all of these variables.

Spiriva therefore was: the first new COPD treatment licensed in the UK for 4 years; the only once-daily inhaled maintenance therapy for COPD; the first medicine with selective $M_3$ receptor dissociation kinetics; an anticholinergic therapy as recommended by the BTS for maintenance treatment of COPD; a superior anticholinergic to the currently most widely prescribed one, ipratropium; superior to salmeterol in improving lung function in COPD; available in an inhaler device with features suitable for COPD patients; the first COPD treatment to have dyspnoea specifically included in its SPC.

Spiriva could therefore be justly claimed to be a significant new treatment for COPD and as such could be regarded as opening up a new world of COPD management.

As further support the companies referred to published statements on Spiriva:

'Current data indicate that once daily treatment with tiotropium in COPD is a major advance, and the drug is likely to become the standard anticholinergic maintenance therapy' (Van Noord, 2002).

'Tiotropium bromide (Ba 679) which has the unique property of kinetic selectivity, with rapid dissociation from $M_2$-receptors and very slow dissociation from $M_1$ and $M_3$-receptors' (Barnes 1999).

'Tiotropium has the advantage of a prolonged action and relative selectivity since it dissociates more quickly from muscarinic $(M)_2$ receptors than from $M_1$ or $M_3$ receptors. In contrast ipratropium is nonselective, blocking $M_1$, $M_2$ and $M_3$ receptors' (Rees 2002).

'Tiotropium has a prolonged duration of action and is the first inhaled bronchodilator demonstrated to be suitable for once-daily use' (Casaburi 2002).

'In clinical trials it demonstrated superior efficacy to other medicines in improving lung function ($FEV_1$)' (Scottish Medicines Consortium).

Boehringer Ingelheim and Pfizer did not accept that the claim 'Open up to a new world of COPD management' was exaggerated, being fully substantiated by the available evidence.

## COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response in point A1.

## APPEAL BOARD RULING

The Appeal Board considered that the claim was a broad claim and although there were differences between Spiriva and other medicines these were not sufficient to justify the claim 'Open up to a new world of COPD management'. The Appeal Board decided that the claim was exaggerated as alleged and upheld the Panel's ruling of a breach of Clause 7.10 of the Code. The appeal was unsuccessful.

**Complaint received** **31 October 2002**

**Case completed** **20 March 2003**

**CASE AUTH/1389/11/02**

# HOSPITAL DOCTOR v LUNDBECK

## Promotion of Cipralex

**A hospital doctor complained about the promotion of Cipralex (escitalopram) by Lundbeck. Cipralex was the S-isomer of the racemic compound, citalopram (Lundbeck's product Cipramil) which consisted of two enantiomers S- and R-citalopram. Escitalopram was the isomer responsible for citalopram's activity as a selective serotonin reuptake inhibitor (SSRI).**

**The complainant provided a partially anonymised copy of an email dated 11 June headed 'Cipralex – new antidepressant' which read 'GP trialists have been very enthusiastic at the prospect of having a new antidepressant that works after just one week and has far fewer side effects'. The complainant stated that the claim that Cipralex had 'far fewer side effects' was not justified by the research, which showed that in direct comparisons with equivalent doses of citalopram there was no statistically significant difference in the incidence of side-effects overall, drop-outs due to side-effects or the incidence of any of the twelve commonest side-effects.**

**The Panel noted Lundbeck's submission that the author of the email was a freelance journalist who was not an employee of the company or its public relation agency. The author had been sent a copy of Lundbeck's press briefing materials. The press briefing materials comprised a covering email and press release which announced the launch of Cipralex, made comparative efficacy claims with citalopram and discussed the incidence of depression. The only reference to side-effects appeared at the end of the press release in a section headed 'Notes for Editors' and read 'Like all medicines, SSRIs do have some side effects, which may cause the patient to stop taking the drug, but in the studies patients taking Cipralex (escitalopram) were no more likely to stop taking the drug than those taking placebo (dummy pills)'.**

**The Panel noted that Lundbeck's press materials did not include the disputed claim. The Panel noted that Section 4.8 of the Cipralex summary of product characteristics (SPC), 'Undesirable effects', listed eight classes of adverse events which had occurred more frequently with Cipralex than with placebo in clinical trials. The Panel considered that the sentence in Lundbeck's press release about side-effects gave the impression that the side-effect profile of Cipralex was comparable to placebo and that was not so. It was misleading in this regard and the Panel thus ruled a breach of the Code.**

**The complainant noted that the Cipralex marketing authorization was granted on 10 June and the email at issue was sent on 11 June. The complainant alleged a breach of the Code as the introduction of a new medicine must not be made known to the general public until reasonable steps had been taken to inform the medical and pharmaceutical professions of its availability.**

**The Panel noted that the press release was embargoed from use until 17 June. The Panel noted Lundbeck's arrangements to inform the medical and pharmaceutical professions about Cipralex before 17 June and considered that Lundbeck had satisfied the requirements of the Code on this point and no breach was ruled.**

**The complainant referred to the claim 'Cipralex is significantly more effective than Cipramil in treating depression' which appeared in a leaflet on a page headed 'Cipralex Superior efficacy and early symptom relief' above a graph comparing the change from baseline of Montgomery Asberg Depression Rating Scale (MADRS) scores of Cipralex, Cipramil and placebo. The data was referenced to Gorman *et al* (2002). The graph showed that Cipralex produced a statistically significant reduction in MADRS scores at weeks 1 and 8 compared to Cipramil ($p<0.05$).**

**Gorman *et al* was a meta-analysis of three studies comparing the efficacy of escitalopram with that of citalopram and placebo. The primary efficacy analysis in at least two of the three studies was change from baseline in MADRS total score at final assessment last observation carried forward (LOCF); Burke *et al* (2002) and Reines *et al* (2002). The complainant assumed that the third study was likely to have had the same primary efficacy measure. The meta-analysis showed no statistically significant difference between citalopram and escitalopram on the primary efficacy measure, which was consistent with the results of the individual studies.**

**Study MD-02 (the third study included in the meta-analysis) was described in the Cipralex product monograph as 'failed' as no statistically significant difference between placebo and escitalopram was demonstrated on the primary efficacy measure. The complainant stated that if a study aiming to show a difference between Cipralex and placebo had 'failed' if no significant difference in primary outcome measure emerged, any attempt to demonstrate a difference between Cipralex and citalopram must also have 'failed' if no statistically significant difference in primary outcome measure was found. The claim at issue was supported by an observed cases (OC) analysis where there was a statistically significant difference between MADRS scores at end-point. The meta-analysis showed no significant difference in the proportion of responders between escitalopram and citalopram. No significant difference was found in improvements on the other main measure in the studies, the Clinicians Global Impression of Improvement (CGI-I). No other measure of the whole study population showed any significant difference at end-point. Apparently significant differences quoted in the individual studies had therefore been demonstrated to be misleading when more powerful statistical methods were applied.**

**The complainant noted that four independent scientific bodies had reviewed the research comparing the efficacy of citalopram and escitalopram and all had concluded that there was no significant difference. The complainant was not aware of any independent review of this research**

**that had concluded that Cipralex was significantly more effective than citalopram.**

**The Panel noted that the claim at issue appeared beneath the heading 'Cipralex Superior efficacy and early symptom relief' and above a graph depicting reduction in MADRS scores over an eight week period. Although not stated on the graph it was clear that it had been adapted from Figure 1 of Gorman *et al* to show only the OC scores.**

**The Panel noted that Gorman *et al* was a meta analysis of three studies which determined whether escitalopram (10-20mg/day, n=520) represented an improved treatment for depression relative to citalopram (20-40mg/day, n=403). The study authors stated that the three studies were of similar design which allowed for the pooling of data to provide a sample size adequate for statistical comparisons between the two active treatment groups.**

**The efficacy analyses in Gorman *et al* were based on pooled intent to treat (ITT) population and were conducted using both LOCF and OC data. Cipralex was statistically significantly superior to citalopram treatment in improving MADRS scores at week 1 in both LOCF and OC analyses and week 6 in LOCF analysis and week 8 in OC analysis with trends in favour of Cipralex at weeks 4 and 6. In relation to CG-I Cipralex produced statistically significant improvements compared with citalopram at weeks 4 and 6 using OC analysis. Gorman *et al* concluded '… these findings suggest that escitalopram may be superior to citalopram in terms of both speed of onset and magnitude of its clinical effects'; 'these data … suggest escitalopram may have a faster onset and greater overall magnitude of effect than citalopram in improving symptoms of depression and anxiety …'. The authors also stated that 'This pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect'. Reference was also made to the 'observation of comparable antidepressant efficacy between 10mg Cipralex and 40mg citalopram'.**

**The Panel considered that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was a strong, unequivocal claim and as such was not a fair reflection of the data. The Panel considered the claim misleading in this regard and ruled a breach of the Code.**

**Upon appeal by Lundbeck, the Appeal Board noted the cautious conclusions of Gorman *et al*. Gorman *et al* had also stated 'This pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect'. The Appeal Board noted the more cautious views expressed by a number of independent bodies which had reviewed the comparative efficacy data of Cipralex and Cipramil as submitted by the complainant.**

**The Appeal Board considered that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was a strong, unequivocal claim and as such was not a fair reflection of the data. At week 8 the mean change from baseline in MADRS scores showed a statistically significant benefit for Cipralex compared with Cipramil (OC values) but no difference between the two if LOCF data was used. The Appeal Board considered the claim thus misleading and upheld the Panel's ruling of a breach of the Code.**

**The complainant noted that a graph which compared the change from baseline MADRS over eight weeks for Cipralex, Cipramil and placebo had appeared beneath the claim at issue above. The graph was partially reproduced from Gorman *et al* which showed results of an OC analysis, the original graph included the results at end-point on LOCF analysis, which was defined as the primary efficacy measure in at least two of the three studies analysed. The complainant stated that the main result of the meta-analysis should then be the LOCF analysis which had been omitted from the graph for no clear reason. The impression given was that Gorman *et al* clearly demonstrated the superiority of Cipralex, while the main (and more statistically sound) result showed no superiority. This gave an unbalanced impression of the results.**

**The Panel noted that the graph showed a statistically significant difference at 8 weeks in the reduction in the MADRS scores between Cipralex and Cipramil ($p<0.05$). No information was provided to indicate whether the graph referred to LOCF or OC analyses. The footnote to the graph stated that it showed pooled data (ITT) from '… 3 multi-centre, placebo-controlled, randomised double-blind, eight week trials'. Information about dosage, patient numbers and statistically significant differences was given. The Panel noted that Figure 1 in Gorman *et al* from which the graph at issue was adapted was labelled to indicate that the results were OC values by visit (weeks 1-8) and that LOCF values were given at endpoint (8 weeks). The LOCF analysis showed no statistically significant difference between Cipramil and Cipralex.**

**The Panel considered that the graph was not a fair reflection of the outcome of Gorman *et al* in relation to MADRS scores. It was misleading to omit the non-statistically significant LOCF values from the graph and include only OC values which had shown some statistically significant differences. A breach of the Code was ruled.**

**Upon appeal by Lundbeck the Appeal Board considered that in principle the OC analysis was a legitimate way to present comparative data. However, the Appeal Board noted the caveats in Gorman *et al* with regard to the comparative efficacy of Cipramil and Cipralex which were in contrast to the overall impression given by the graph in combination with the heading 'Cipralex is significantly more effective than Cipramil in treating depression'. The Appeal Board considered that the graph gave a misleading impression as to the relative efficacy of Cipralex and Cipramil. The Appeal Board upheld the Panel's ruling of a breach of the Code.**

**The complainant stated that the graph was described as representing an intention to treat analysis (ITT) analysis. This denoted an analysis whereby all patients for whom there had been an intention to**

**treat were included in the analysis, not just those who continued in the study. This was generally held to give more accurate results than analysis where drop-outs were disregarded. The graph presented showed results from OC analysis ie analysis of only those patients who had not dropped out. The claim that it was such an analysis was both incorrect and misleading, in that it gave a false impression of the rigour of the analysis.**

**The Panel considered that it was extremely important to ensure that readers were aware of the precise nature of the ITT analysis; to describe it as ITT without further explanation that patients had had at least one post-baseline assessment was inadequate. The artwork did not give a fair, balanced view and a breach of the Code was ruled.**

**The complainant noted that the results of Gorman *et al* had been presented in a poster format and later as a published paper; the results seemed different in each. In the poster the primary efficacy analysis (LOCF at end-point) showed no statistically significant difference but numerically greater efficacy for citalopram. When the paper was published in May 2002, fourteen patients had been excluded from the analysis. No reason was given. The primary efficacy analysis now showed a numerically greater efficacy for Cipralex. These two sets of figures could not both be accurate reports of the trial results and cast doubt on the reliability of the data.**

**The Panel noted Lundbeck's submission that the reason for the differences in the study and the poster was that there was a printing error in some copies of the poster. Lundbeck in the UK had not been responsible for the error and there was no evidence that Lundbeck's medical information department had supplied an incorrect version of the poster. Taking all the circumstances into account the Panel ruled no breach of the Code.**

**The complainant stated that on the Cipralex promotional website it was claimed that 'There is, for instance, a weak interaction between R-citalopram and the histamine $H_1$ receptor. This could mean that removal of R-citalopram would generate a slightly less sedating compound'.**

**The complainant stated that on the citalopram website it was claimed that citalopram (which was 50% R-citalopram) had 'negligible affinity' for the $H_1$ receptor and a 'lack of significant secondary receptor activity'. These statements must therefore also be true for R-citalopram.**

**It was simultaneously being claimed, in promotional campaigns for different medicines, that R-citalopram had a pharmacological effect that could cause side-effects, and that it had a lack of any significant effect. It was difficult to see how both of these claims could be 'accurate, balanced, fair, objective and unambiguous' at the same time.**

**The Panel noted that the claim 'There is for instance, a weak interaction between R-citalopram and the histamine $H_1$ receptor. This could mean that removal of R-citalopram would generate a slightly less sedating compound' appeared on a website with secure access to health professionals. The Panel did not accept Lundbeck's submission that the statements could not be construed as promotional claims. The material from the Cipralex website provided to the Panel comprised product specific material for health professionals on a company website and as such had to comply with the Code.**

**The Panel noted that enantiomers might differ in pharmacological effect which might result in demonstrable clinical differences. The Panel noted the evidence submitted by Lundbeck in relation to differences between the affinity of Cipralex, R-citalopram and citalopram for various receptors. The Panel noted that the Cipralex SPC included in Section 4.8, Undesirable effects, a list of adverse reactions which had 'occurred more frequently with Cipralex than with placebo'. This list included 'somnolence' which was classified as 'common' ie an incidence of between 1% and 10% – not placebo corrected. In Section 5.1, Mechanism of action, it stated 'Escitalopram has no or low affinity for a number of receptors including … histamine $H_1$'. Section 4.8 of the Cipramil SPC, Undesirable events, stated that the most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were, *inter alia*, somnolence. The incidence in excess over placebo was low (<10%). Under Pharmacological Properties, it stated 'citalopram has no or very low affinity for a series of receptors including … histamine $H_1$ …. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as … sedation … . In humans citalopram … has no or minimal sedative properties'.**

**Although it was not possible to make a direct comparison of incidence of somnolence between the two products on the basis of the statements in the SPCs, the Panel noted that there did not appear to be a significant clinical difference between them on this point.**

**The Panel noted that whilst the statement at issue was posed as a theoretical possibility it appeared beneath a question which began 'Why would one expect fewer side-effects …' which in the opinion of the Panel implied that it was nonetheless of clinical importance.**

**The Panel considered that given the medicines' respective SPCs it was difficult to see how given that citalopram had 'no or minimal sedative properties' it was possible to have a lower degree of sedative properties which was clinically meaningful. The Panel considered that the statement at issue was misleading and a breach of the Code was ruled.**

A hospital doctor complained about the promotion of Cipralex (escitalopram) by Lundbeck Ltd. Cipralex was the S-iomer of the racemic compound, citalopram (Lundbeck's product Cipramil) which consisted of two enantiomers S- and R-citalopram. Escitalopram was the isomer responsible for citalopram's activity as a selective serotonin reuptake inhibitor (SSRI).

### 1 Claim '… far fewer side effects'

The complainant provided a partially anonymised

copy of an email dated 11 June headed 'Cipralex – new antidepressant'. The email read 'GP trialists have been very enthusiastic at the prospect of having a new antidepressant that works after just one week and has far fewer side effects'. The author, a journalist, stated that medical experts were available to discuss the product. A quotation from Depression Alliance and a case study could be arranged.

### COMPLAINT

The complainant stated that on 11 June 2002 emails were sent to a number of national newspapers announcing the launch of Cipralex. These contained the claim that 'GP trialists have been very enthusiastic at the prospect of having a new antidepressant that works after just one week and has far fewer side effects'. The complainant stated that this would seem to come under the definition of promotion as defined in Clause 1.2 of the Code as 'the provision of information to the general public either directly or indirectly'. The claim that Cipralex had 'far fewer side effects' was not justified by the research, which showed that in direct comparisons with equivalent doses of citalopram there was no statistically significant difference in the incidence of side-effects overall, drop-outs due to side-effects or the incidence of any of the twelve commonest side-effects. The claim would not seem to meet the requirements of Clause 20.2 in that information made available to the general public must be factual and presented in a balanced way. The complainant stated that this was the responsibility of Lundbeck under Clause 20.5.

### RESPONSE

Lundbeck stated that the author of the email in question which was sent to national newspapers was a freelance journalist, who was sent a copy of Lundbeck's approved press briefing materials by its public relations agency. The covering email from the agency clearly stated that the press material was embargoed until 17 June 2002. Both the email and the material were factual and balanced and did not contain the claim '…has far fewer side effects'. The author of the email provided by the complainant was not an employee of Lundbeck or its public relations agency and Lundbeck could not be held responsible for the actions of the author of the email.

### PANEL RULING

The Panel noted Lundbeck's submission that the author of the email was a freelance journalist who was not an employee of Lundbeck or its public relations agency. The author had been sent a copy of Lundbeck's approved press briefing materials. The Panel was concerned that the email gave the impression that it was sent on behalf of Lundbeck.

The Panel noted that complaints about articles in the media or material produced by independent journalists were judged on the information provided by the pharmaceutical company or its agent to the journalists; such information was considered in relation to the requirements of Clause 20 of the Code. The Panel noted that Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of a product. Clause 20.5 stated that companies were responsible for information about their products which was issued by their public relations agencies.

The Panel examined the press briefing materials which comprised a covering email and press release. The press materials announced the launch of Cipralex, made comparative efficacy claims with citalopram and discussed the incidence of depression. The only reference to side-effects appeared at the end of the press release in a section headed 'Notes for Editors' and read 'Like all medicines, SSRIs do have some side effects, which may cause the patient to stop taking the drug, but in the studies patients taking Cipralex (escitalopram) were no more likely to stop taking the drug than those taking placebo (dummy pills)'.

The Panel noted that Lundbeck's press materials did not include the disputed claim. A general claim was made about side-effects and the class of medicine and a specific claim about the number of patients on Cipralex who stopped taking it compared to placebo in clinical trials. The Panel noted that Section 4.8 of the Cipralex summary of product characteristics (SPC), 'Undesirable effects', listed eight classes of adverse events which had occurred more frequently with Cipralex than with placebo in clinical trials. The frequencies listed in the SPC had not been placebo-corrected.

The Panel considered that the sentence in Lundbeck's press release about side-effects linked the incidence of side-effects with patients stopping medication in clinical trials and gave the impression that the side-effect profile of Cipralex was comparable to placebo; that was not so. The Panel considered that the press release gave a misleading impression about the side-effect profile of Cipralex and thus ruled a breach of Clause 20.2 of the Code.

## 2 Alleged breach of Clause 20.4

### COMPLAINT

The complainant noted that the Cipralex marketing authorization was granted on 10 June and the email at issue in point 1 above was sent on 11 June. The complainant alleged a breach of Clause 20.4 which required that the introduction of a new medicine must not be made known to the general public until reasonable steps had been taken to inform the medical and pharmaceutical professions of its availability.

### RESPONSE

Lundbeck stated that the marketing authorization for Cipralex was granted on 10 June 2002, a date that was anticipated within the company. Its sales force was already trained on the product and received a message informing them of the approval and launch of Cipralex at around 3pm on 10 June. The first calls to inform doctors and pharmacists of the availability of Cipralex were completed later the same day.

Details of the number of customers seen during the weeks beginning 10 and 17 June were provided. A letter to inform doctors and pharmacists of the availability of Cipralex was sent on 11/12 June and advertisements for Cipralex appeared in the medical press from 17 June onwards. All press material was embargoed from use until 17 June. Lundbeck submitted these activities constituted reasonable steps to inform medical and pharmaceutical professionals of the availability of Cipralex following its launch.

**PANEL RULING**

The Panel noted that the marketing authorization for Cipralex was granted on 10 June 2002. The press release sent by Lundbeck's agency to the author of the email in question on 11 June was embargoed from use until 17 June; a clear statement to this effect appeared in the first paragraph of the covering email and as a subheading to the press release. The Panel noted Lundbeck's submission about its activities to inform the medical and pharmaceutical professions about Cipralex before 17 June when the embargo on the press materials would be lifted. The Panel considered that Lundbeck had satisfied the requirements of Clause 20.4 and thus no breach of that clause was ruled.

**3 Claim 'Cipralex is significantly more effective than Cipramil in treating depression'**

The complainant stated that promotional materials had included the claim that 'Cipralex is significantly more effective than Cipramil in treating depression'. A 6 page gate folded leaflet (ref 0502/ESC/511/005(821)M) was provided. Page 2 of the leaflet featured the claim at issue on a page headed 'Cipralex superior efficacy and early symptom relief' above a graph which compared the change from baseline of Montgomery Asberg Depression Rating Scale (MADRS) scores of Cipralex, Cipramil and placebo. The data was referenced to Gorman *et al* (2002). The graph showed that Cipralex produced a statistically significant reduction in MADRS scores at weeks 1 and 8 compared to Cipramil ($p<0.05$).

**COMPLAINT**

The complainant noted that Gorman *et al* (2002) were consultants to or employees of Lundbeck or Forest Pharmaceuticals (a US partner of Lundbeck involved in developing and marketing Cipralex in the US) and was published in a supplement to CNS Spectrums, a journal edited by Gorman.

The complainant noted that Gorman *et al* was a meta-analysis of three studies comparing the efficacy of escitalopram with that of citalopram and placebo. The primary efficacy analysis in at least two of the three studies was change from baseline in MADRS total score at final assessment last observation carried forward (LOCF); Burke *et al* (2002) and Reines *et al* (2002). As the three studies were described in a Lundbeck product monograph as being part of an overall initial development programme, run concurrently, the complainant assumed that the third study was likely to have had the same primary efficacy measure. The meta-analysis showed no statistically significant difference between citalopram and escitalopram on the primary efficacy measure, which was consistent with the results of the individual studies.

Study MD-02 (the third study included in the meta-analysis) was described in the Cipralex product monograph as 'failed' as no statistically significant difference between placebo and escitalopram was demonstrated on the primary efficacy measure. If a study aiming to show a difference between Cipralex and placebo had 'failed' if no significant difference in primary outcome measure emerged, any attempt to demonstrate a difference between Cipralex and citalopram must also have 'failed' if no statistically significant difference in primary outcome measure was found. This was the case for all such comparative studies, as well as the meta-analysis.

The claim at issue was supported by an observed cases (OC) analysis where there was a statistically significant difference between MADRS scores at end-point. Although figures were not given, the difference appeared to be about one point on the 60 point MADRS scale. To understand what this difference represented in practice, one could imagine two hypothetical patients whose depression after treatment differed by the smallest amounts measured on the MADRS, a scale specifically designed to be sensitive to changes in depression. Their degree of depression was the same on nine out of the ten measures of the MADRS, but on the tenth measure there was a difference represented by the difference between the statements 'difficulties in starting activities' and 'difficulties in starting simple routine activities which are carried out with effort'. They differed in MADRS score by two points. The complainant stated that the 'significant increase in efficacy' claimed for Cipralex was about half that difference and only on the most generous interpretation possible of the statistics.

The meta-analysis showed no significant difference in the proportion of responders between escitalopram and citalopram. No significant difference was found in improvements on the other main measure in the studies, the Clinicians Global Impression of Improvement (CGI-I). No other measure of the whole study population showed any significant difference at end-point. Apparently significant differences quoted in the individual studies had been therefore demonstrated to be misleading when more powerful statistical methods were applied.

The complainant noted that four independent scientific bodies had reviewed the research comparing the efficacy of citalopram and escitalopram and all had concluded that there was no significant difference. The Danish Agency for Evaluation of Medicinal Products, the Stockholm Medical Council and Micromedex in the US all explicitly stated that they believed there was no significant difference. The Food and Drugs Administration (FDA) in the US was reported to have 'cautioned that [Cipralex] hasn't been proved superior to any antidepressant'.

The complainant was not aware of any independent review of this research that had concluded that

Cipralex was significantly more effective than citalopram. In view of the particular advice in the Code about emerging clinical or scientific opinion, the complainant alleged a breach of Clause 7.2.

## RESPONSE

Lundbeck noted that the complainant was correct to state that the primary measure of efficacy in the individual studies contributing to the pooled analysis by Gorman was the change from baseline in MADRS score at final assessment using the last observation carried forward (LOCF) method of analysis. For patients who dropped out of a study, this analysis involved carrying forward their last observation prior to dropping out and including this in an end-point analysis. Regulatory authorities required that account be taken of missing values in any clinical trial. Unfortunately, no universally applicable method of handling missing values was recommended by the authorities. One such statistical method was LOCF, and this was chosen as the individual Cipralex studies were conducted for regulatory purposes. In reality, however, the clinical relevance of the LOCF analysis had been questioned by leading statistical authorities who had stated that the usefulness of the LOCF approach was limited since it made very unlikely assumptions about the data, for example, that the unobserved post drop-out response remained frozen at the last observed value. Observed case (OC) analysis, on the other hand, reflected data from patients who actually attended the clinic visits and so, it could be argued, provided a more accurate and clinically relevant picture of treatment response at these visits. OC analysis was particularly appropriate for studies which had a balanced withdrawal profile between the different treatment arms. This was the case for the individual escitalopram studies contributing to the pooled analysis. Consequently both analyses appeared in Lundbeck's regulatory submissions and published studies.

The individual regulatory studies were designed and powered to detect differences between Cipralex and placebo, with citalopram included as a reference arm to validate the studies as the placebo response in depression studies could be very large.

The Gorman pooled analysis allowed clinicians to evaluate the data for themselves by presenting both the LOCF and OC data with equal prominence for key outcome parameters from each of the three contributing studies – change in MADRS score for patients overall and those who were severely depressed (MADRS score at study entry ≥ 30 points) and CGI-I. The pooled analysis did not specify a primary measure of efficacy and therefore it was not correct to state there were no statistically significant differences between Cipralex and citalopram for the efficacy measures. The following statistically significant ($p<0.05$) differences between Cipralex and citalopram were clearly apparent:

| | LOCF | OC |
|---|---|---|
| MADRS change from baseline | Weeks 1 and 6 | Weeks 1 and 8 |
| MADRS change from baseline – severe patients | Weeks 1, 6 and 8 | Weeks 1, 6 and 8 |
| CGI-I | | Weeks 4 and 6 |

Study MD 02 was considered a failed study because neither escitalopram nor the reference medicine (citalopram) showed significant separation from placebo for the primary measure of efficacy (MADRS change from baseline to week 8 using LOCF). The OC analysis for this measure, however, showed significant differences over placebo in favour of escitalopram and citalopram for this parameter. This study included a large number of centres each entering a small number of patients. There was a particularly large placebo response and it was likely that the variability associated with the small centres contributed to the result. When results from the two most deviant small centres were excluded, the study showed positive results for Cipralex compared to placebo for all the efficacy parameters using LOCF in spite of the particularly large placebo response. It was widely acknowledged that the placebo response in depression studies was large and varied. Up to 50% of patients could be expected to respond to placebo and in one-third to two-thirds of trials, in which an active control was used as a third arm, the effect of the active control could not be distinguished from that of placebo. The complainant was therefore wrong to claim that the individual studies and the pooled analysis had failed because they did not detect significant differences between Cipralex and citalopram. As stated previously, the individual studies were not primarily powered to do so and multiple statistically significant differences in favour of escitalopram were found in the pooled analysis.

The complainant implied that the pooled analysis was flawed and Lundbeck's presentation disingenuous. This was certainly not the case. Pooled analysis or meta-analysis of randomised controlled trials was considered to be the premier category of evidence when developing guidelines and CNS Spectrums, which published the pooled analysis, was a peer-reviewed publication.

A common criticism of pooled analysis was the selective inclusion of positive studies. This pooled analysis could not be criticised as selective as all studies which had compared Cipralex, citalopram and placebo were included, including a 'failed' study.

The complainant questioned the clinical relevance of the difference between escitalopram and citalopram on the MADRS score and speculated about the size of the actual difference and related this to hypothetical patients. Contrary to the hypothetical situation, escitalopram treated patients showed improvement across the range of items in the MADRS score. The clinical interpretation of changes in rating scale scores in clinical trials designed for registration had long been the subject of debate, not just in depression studies. Alternative parameters had therefore been

developed to aid clinical interpretation. In depression studies the proportion of baseline patients considered to be responders to treatment (≥ 50% decrease in baseline MADRS score) was often used. This was undertaken in the pooled analysis where 59.3%, 53.4% and 41.2% of escitalopram, citalopram and placebo-treated patients respectively were considered to be responders. Although both escitalopram and citalopram were significantly better than placebo ($p<0.001$) for this parameter, the complainant pointed out that the difference between escitalopram and citalopram was not significant. In reality, only the differences compared to placebo were presented in the paper. Escitalopram did in fact produce significantly more responders to treatment than citalopram ($p<0.05$).

It was also not correct to state that no significant difference was found for the other main measure on the analysis (CGI-I). Escitalopram was significantly superior to citalopram for this parameter at weeks 4 and 6 ($p<0.05$ OC).

The robust methods of the pooled analysis confirmed statistically (both LOCF and OC) the superiority trends for escitalopram compared to citalopram which were apparent in two of the studies which individually were not powered to detect significant differences between the two compounds for changes in the MADRS score. This was in complete contradiction to the complainant's statement that differences in individual studies had proved to be misleading when more powerful statistical methods were applied.

The opinions of four independent bodies referred to by the complainant were based on press releases. However, it was not clear what evidence they had evaluated and some had the stated intention to promote the use of cheaper generic treatment alternatives. One of these agencies, the Danish Medicines Agency, had since reviewed data comparing Cipralex and venlafaxine and confirmed that patients treated with escitalopram achieved sustained remission significantly faster than patients treated with venlafaxine. What could not be argued was that in a pooled analysis of all studies which had compared escitalopram, citalopram and placebo, published in a peer-reviewed journal, there were differences in favour of escitalopram over citalopram which were both statistically significant for several outcome measures at multiple time points and clinically relevant eg responder rates.

Lundbeck stated that far from contradicting this, the emerging scientific data supported the contention that Cipralex might, in addition, be superior to antidepressants other than citalopram. Montgomery *et al* (2002), cited by the Danish Medicines Agency, showed significant benefits for escitalopram compared with venlafaxine in a number of secondary efficacy parameters considered to be clinically relevant (proportion of responders and remitters ie those whose MADRS score fell to 12 or below), a superior tolerability profile and fewer discontinuation symptoms following the cessation of treatment.

Lundbeck stated that the complaint contained a number of errors and inaccuracies. Pooled analysis of randomised controlled trials was a valid and widely accepted technique used to further evaluate clinical effects and was the preferred source of evidence for guideline development groups. Gorman *et al* had been published in a peer-reviewed journal. The analysis was comprehensive and included all studies which had compared escitalopram, citalopram and placebo, including one 'failed study'. Individually the contributing studies were designed and powered to detect differences between escitalopram and placebo with citalopram being included as a reference compound. To comply with regulatory requirements, the LOCF analysis was applied to the individual studies. Lundbeck believed the OC analysis to be equally valid and more relevant to prescribing clinicians, hence its use in Lundbeck's material. The pooled analysis presented both the OC and LOCF analysis with equal prominence and there were significant differences (MADRS, all patients) in favour of escitalopram over citalopram at week 1 in both and at week 6 (LOCF) and at week 8 (OC). By presenting the OC analysis Lundbeck did not accept it was providing an unbalanced view of Cipralex and consequently it refuted all of the alleged breaches of the Code.

## PANEL RULING

The Panel noted that the claim at issue appeared beneath the heading 'Cipralex Superior efficacy and early symptom relief' and above a graph depicting reduction in MADRS scores over an eight week period. Although not stated on the graph it was clear that it had been adapted from Figure 1 of Gorman *et al* to show only the OC scores.

The Panel noted that the data was referenced to Gorman *et al*, a meta analysis of three studies which determined whether escitalopram (10-20mg/day, n=520) represented an improved treatment for depression relative to citalopram (20-40mg/day, n=403). The study authors stated that the three studies were of similar design which allowed for the pooling of data to provide a sample size adequate for statistical comparisons between the two active treatment groups.

The Panel noted that the studies examined in Gorman *et al* were Burke *et al* (2002), Reines *et al* (2002) and study MD 02. Burke *et al* was a placebo-controlled trial which examined the efficacy and tolerability of Cipralex; citalopram was an active treatment control. The primary outcome measure was the change from baseline in the MADRS total score at week 8 and the statistical analysis used was LOCF. The study authors noted that the 'results suggested that escitalopram within the doses studied may be more potent and better tolerated … than … citalopram'. The study was not designed to test the differences between active treatments and the authors stated that it was thus not possible to draw firm conclusions about such differences. Reines *et al* compared Cipralex with placebo; citalopram was used as the reference treatment. The primary efficacy analysis was based on the change from baseline in the MADRS total score at final assessment using LOCF. Secondary efficacy analyses were based on responders, remitters, CGI-S, CGI-I. There were no differences between Cipralex

and citalopram in the MADRS, CGI-S, CGI-I but there was a statistically significant difference in terms of remitters and responders. A copy of the third study (MD02) was not provided but according to Gorman *et al* it was a flexible dose study, similar in design to Reines *et al*.

The efficacy analyses in Gorman *et al* were based on pooled intent to treat (ITT) population and were conducted using both LOCF and OC data. Cipralex was statistically significantly superior to citalopram treatment in improving MADRS scores at week 1 in both LOCF and OC analyses and week 6 in LOCF analysis and week 8 in OC analysis with trends in favour of Cipralex at weeks 4 and 6. In relation to CG-I Cipralex produced statistically significant improvements compared with citalopram at weeks 4 and 6 using OC analysis. Gorman *et al* noted that its methodology was similar to that utilized by several authors. The Panel noted the complainant's criticism that the meta analysis included a 'failed' study and noted Lundbeck's submission on this point. Gorman *et al* stated that data represented all patients to date that had participated in completed placebo-controlled acute (up to 8 weeks) trials of major depression that included both Cipralex and citalopram treatment groups and therefore was as comprehensive as possible.

The Panel noted that both OC and LOCF data were presented in Gorman *et al*. The Panel noted the comments from both parties about the use of OC and LOCF analyses. Gorman *et al* concluded '… these findings suggest that escitalopram may be superior to citalopram in terms of both speed of onset and magnitude of its clinical effects'; 'these data … suggest escitalopram may have a faster onset and greater overall magnitude of effect than citalopram in improving symptoms of depression and anxiety …'. The authors also stated that 'This pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect'. Reference was also made to the 'observation of comparable antidepressant efficacy between 10mg Cipralex and 40mg citalopram'.

The Panel considered that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was a strong, unequivocal claim and as such was not a fair reflection of the data. The Panel considered the claim misleading in this regard and ruled a breach of Clause 7.2.

## APPEAL BY LUNDBECK

Lundbeck stated that Cipramil was a racemic mixture of two identical mirror-image molecules (S-citalopram and R-citalopram). The activity of citalopram to inhibit serotonin reuptake resided exclusively in the S-citalopram, whereas the R-citalopram appeared to have some negative effect. Cipralex was the active S-enantiomer (escitalopram) only, that had now been licensed for the treatment of depression and panic disorder. Lundbeck submitted that the claim, 'Cipralex is significantly more effective than Cipramil in treating depression' was substantiated by the pooled-analysis by Gorman *et al* (2002) published in CNS Spectrums, the official journal of the International Neuropsychiatric Association. CNS Spectrums was a peer-reviewed journal indexed in the internationally recognised bibliographic databases – Index Medicus, EMBASE and Excerpta Medica. Lundbeck stated that it worked with a number of well-respected independent researchers, many of whom were also editors or members of editorial panels of various journals. It was important to understand that all peer-reviewed journals had well recognised peer review processes that could not be superseded or bypassed even by members of the editorial panels. Professor Gorman was the winner of the 2001 American Psychiatric Association Research Prize and had authored more than 350 journal articles and textbook chapters.

Lundbeck stated that the three contributing studies were conducted for regulatory purposes and were designed and powered to show differences between escitalopram and placebo. Citalopram was included as a reference arm to validate the studies. This was in line with recommendations by the Committee for Proprietary Medicinal Products (CPMP). The placebo response in depression studies could be very large (up to 50% of patients responding); therefore it was important to have a compound with known antidepressant activity as a benchmark. For regulatory and clinical purposes predefined analyses were used, an OC analysis evaluated data for all patients completing a treatment course as well as an LOCF analysis, which was one of a series of analyses that could be performed to account for missing data. For the approval of new medicines both LOCF and OC data was presented to the regulatory authorities. The depression rating scale used was the recommended MADRS. The recommended global assessment scale CGI-I Clinical Global Impression of Improvement was also used.

Lundbeck stated that across the three studies, at the 8-week end point, numerical superiority of escitalopram was shown over citalopram in 5 out of 6 analyses (LOCF and OC for mean change in MADRS total score from baseline, the primary measure of efficacy in each of the studies, ITT analysis). There was statistical significance compared to placebo for escitalopram in all three studies in 5 out of 6 analyses. Lundbeck noted in the 'failed study'(MD02), no significant difference was found for escitalopram or citalopram over placebo in one analysis (LOCF), although when normal predictive tests and analyses for centre variations were performed it was clear that escitalopram was also significantly different from placebo in LOCF (in addition to the OC analysis).

Lundbeck stated that in order to assess if the consistent differences observed in the studies were significant and to permit sub-analysis requiring a larger sample size from similar studies, the findings were entered into a pooled-analysis. This was considered to be a well-respected methodology for analysing such data. Pooled-analysis or meta-analysis was a legitimate technique to further evaluate differences between two active agents. Such analyses were typically done where large samples were needed either for primary endpoints or sub-analysis of clinically relevant questions. Lundbeck noted that this type of analysis of randomised controlled trials, if properly conducted, was considered to be the top

category of evidence (Category 1a) by bodies such as the National Institute for Clinical Excellence (NICE Clinical Guidelines) and was recommended to guideline development groups (Shekelle *et al* 1999).

Lundbeck stated that the pooled-analysis in question did not state LOCF as an 'a priori' primary measure of efficacy, but analysed both OC and LOCF. The LOCF and OC data were therefore presented, with equal prominence, for key outcome parameters from the three contributing studies – change in MADRS score both for patients overall, those who were severely depressed, and CGI-I. Lundbeck submitted that in studies with a low and similar dropout rate in treatment arms (as in the escitalopram studies) many would consider OC as the best measure, as it actually described what happened at a particular time point, rather than making assumptions as the LOCF analysis did. Lundbeck noted that concerning the mean change in MADRS total score from baseline shown in the table below, escitalopram was more frequently significantly superior to placebo than citalopram and there was numerical superiority for escitalopram over citalopram at every study assessment point (LOCF and OC). These differences were statistically significant in favour of escitalopram at weeks 1 and 6 (LOCF) and weeks 1 and 8 (OC).

**Mean change in MADRS total score from baseline (ITT) – pooled analysis (Gorman *et al* 1999)**

| | | Study Week | | | | |
|---|---|---|---|---|---|---|
| | | **1** | **2** | **4** | **6** | **8** |
| Placebo | LOCF | –3.8 | –6.6 | –9.4 | –10.3 | –11.2 |
| | OC[1] | –3.9 | –7.0 | –9.9 | –11.0 | –12.0 |
| Escitalopram | LOCF | –4.7*+ | –7.8* | –11.0* | –13.0*+ | –13.8* |
| | OC[1] | –4.9*+ | –8.0* | –11.7* | –14.2* | –15.3*+ |
| Citalopram | LOCF | –3.7 | –7.2 | –10.2 | –12.0* | –13.1* |
| | OC[1] | –3.9 | –7.6 | –10.8 | –13.2* | –14.3* |

* $p < 0.05$ for mean change difference versus placebo
+ $p < 0.05$ for mean change difference versus citalopram
[1] additional data to supplement those presented in graphical form in Gorman *et al* 2000

Lundbeck noted that to aid the clinical interpretation of changes in the MADRS score, the proportion of patients considered to be treatment responders (≥ 50% decrease in baseline MADRS score) was used. In the pooled-analysis 59.3%, 53.4% and 41.2% of escitalopram, citalopram and placebo-treated patients respectively were considered to be responders. Lundbeck stated that although only the significance values compared to placebo were included in the publication of the pooled-analysis, escitalopram was also statistically significant as compared to citalopram for this parameter ($p<0.05$), data on file. The responder rate analysis confirmed findings in the study by Reines *et al* (2002).

Lundbeck noted that concerning the additional parameters of MADRS change for severely depressed patients and CGI-I for all patients again escitalopram was more frequently significantly superior to placebo than citalopram. For MADRS change in severely depressed patients, there was numerical superiority for escitalopram over citalopram at every study assessment point (LOCF and OC) that was statistically significant at weeks 1, 6 and 8 (LOCF and OC). For CGI-I for all patients, escitalopram was numerically superior at weeks 1, 2, 4 and 6 (LOCF and OC) and was statistically significant at weeks 4 and 6 (OC).

Lundbeck noted that the Panel quoted from Gorman *et al* (2002) regarding the interpretation of the study results to support its ruling. It was not unusual for authors to state that their results were 'suggestive' of a particular finding and that further research was needed for substantiation. Lundbeck noted, however, that Gorman *et al* (2002) stated clearly in the final paragraph that the pooled-analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect and that further research should be carried out to determine whether escitalopram would show similar advantages over other SSRIs.

Lundbeck submitted that the emerging scientific data on escitalopram supported the contention that escitalopram might indeed be superior to antidepressants other than citalopram. The study by Montgomery *et al* (2002) showed significant benefits for escitalopram compared with an antidepressant from a different class, venlafaxine (a serotonin and noradrenaline reuptake inhibitor – SNRI), in a number of parameters considered to be clinically relevant (proportion of responders and remitters, ie those whose MADRS score fell to 12 or below). Lundbeck noted in addition, that escitalopram had a superior tolerability profile and fewer discontinuation symptoms following treatment cessation.

Lundbeck submitted that extensive pre-clinical research had revealed a pharmacological rationale that might explain the above clinical findings with escitalopram (Mørk *et al* 2002). Escitalopram produced almost twice the levels of serotonin (5 HT) in the brains of laboratory animals when given alone compared with the same amount of escitalopram given together with R-citalopram as the parent compound citalopram. Lundbeck submitted that the R-citalopram appeared to be inhibiting the effect of escitalopram in some way. The ability to increase brain serotonin levels was the pharmacological property underlying the antidepressant activity of compounds like escitalopram. Lundbeck submitted that with this animal model it had biological evidence supporting the superior clinical efficacy and earlier symptomatic relief of escitalopram compared to citalopram seen in the Gorman *et al* (2002) pooled-analysis.

Lundbeck concluded that: individual studies powered to detect superiority over placebo consistently showed trends in favour of escitalopram over citalopram; a pooled-analysis of all relevant studies, published in a peer-reviewed journal, showed consistent superiority for escitalopram over citalopram for all parameters; the differences in favour of escitalopram over citalopram were statistically significant at multiple time points, across different outcome parameters and analyses (LOCF and OC); significantly more patients responded to treatment with escitalopram compared with citalopram; no study had demonstrated citalopram to have a statistically significant treatment effect over escitalopram; evidence was emerging that escitalopram might be superior to antidepressants other than citalopram; escitalopram produced higher

levels of serotonin in laboratory animals when given alone (as compared to a combination with R-citalopram) which might explain the clinical findings of superior efficacy.

Lundbeck submitted that there was clear and consistent evidence from the individual studies indicating escitalopram to be superior to citalopram (5 out of 6 analyses). This was confirmed in a rigorously inclusive pooled-analysis, conducted according to currently accepted methodological standards, which showed statistically significant differences in favour of escitalopram over citalopram using both the 'gold standard' MADRS depression rating scale score, and the clinically meaningful responder rates. In the presence of statistically significant and clinically relevant outcomes from properly conducted clinical studies and robust analytical methodologies, Lundbeck considered the claim to be substantiated.

Lundbeck further noted that advertising bearing the claim 'In depression……Cipralex offers significantly greater efficacy than Cipramil', was reviewed by the Medicines Control Agency (MCA) [now the Medicines and Healthcare products Regulatory Agency (MHRA)] in September 2002 and was not found to breach any regulations. The Medicines (Advertising) Regulations 1994 (SI 1994/1932 as amended), section 3A referred to advertising having to be presented objectively, without exaggeration and not to be misleading. Lundbeck submitted that the claim of superiority of Cipralex to Cipramil was considered to represent the data objectively, without exaggeration and not to be misleading.

Lundbeck stated that it had provided evidence from the highest level currently recognised by the scientific community (NICE Clinical Guidelines, Shekelle *et al* (1999)) showing consistent differences in favour of escitalopram compared to citalopram. Consequently, it considered that the claim in question reflected the data fairly.

## COMMENTS FROM THE COMPLAINANT

The complainant noted that Lundbeck had presented a wealth of statistical data along with an interpretation of its significance. The issue here was whether that interpretation was 'accurate, fair, objective and unambiguous'.

The complainant noted that it was implied that the interpretation of the data in Gorman *et al* was 'independent'. However a paper written by two employees of the company together with an academic who had declared a conflict of interest in terms of financial connection to the company, would not be seen to be entirely independent.

The complainant noted that there were however assessments of the significance of the data from a variety of groups in several different countries.

The UK Medicines Information Pharmacists Group: 'The evidence to support the claim that escitalopram has improved efficacy and a faster onset of action than citalopram in the treatment of depression is not compelling'; the Scottish Medicines Consortium: '… no clear benefits are demonstrated over the parent product'; the NHS Northern and Yorkshire Regional Drug and Therapeutics Centre: 'There is no compelling evidence to support claims that escitalopram is more effective, or has a faster onset of action, than citalopram'; the United States Department of Defense Pharmacoeconomic Center: 'The Council concluded that escitalopram does not offer significant clinical advantages over citalopram or other SSRIs …'; FDA: '[Cipralex] hasn't been proved superior to any antidepressant'; Micromedex: 'Available data do not suggest a significant advantage of this agent over citalopram or other SSRIs'; the Canadian Co-ordinating Office for Health Technology Assessment: '… concrete data is lacking demonstrating the benefits of this new antidepressant over others currently marketed, including the racemic parent'; the Danish Agency for Evaluation of Medicinal Products: 'no evident advantages' and the Stockholm Medical Council: escitalopram 'assessed not to be better than Cipramil'.

The complainant noted that, despite several independent sources being quoted in the original complaint supporting the view that the claim was misleading, Lundbeck had not quoted any independent source which supported its argument in any of its submissions, responses or in its appeal.

The complainant contended that the validity of the claim rested on the interpretation of the data. It could not be said that the issue of whether escitalopram was significantly more effective than citalopram in the treatment of depression had '… been resolved in favour of one generally accepted viewpoint'. To satisfy the terms of Clause 7.2 in these circumstances, 'particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. The complainant alleged that it was hard to see how a self-evidently 'strong, unequivocal claim' could be a balanced treatment of the issue, nor 'accurate, fair, objective and unambiguous'.

The complainant stated that escitalopram could only be significantly more effective than citalopram in the treatment of depression if R-citalopram had some pharmacological effect relevant to depression. The complainant alleged that it had been shown not to have any effect on the pharmacokinetics of escitalopram (Mørk *et al* 2002). It had also been shown, again in Lundbeck's own research, to demonstrate 'a lack of affinity for a very large number of receptors and binding sites'. The complainant noted that the only activity that had been suggested as having any potential to affect antidepressant activity was its effect on histamine $H_1$ receptors. The complainant noted, however, that the commonly prescribed and effective antidepressant mirtazapine was over 3000 times as potent in this regard, with many other antidepressants (eg doxepin, amitriptyline, imipramine, nefazodone, amoxapine, clomipramine and desipramine) having higher potency than R-citalopram (Richelson 2001). The complainant stated that it was extremely difficult to see how this small change in effect on $H_1$ receptors could significantly alter efficacy, when many other antidepressants had much greater range of effects on $H_1$ receptors with no significant difference in efficacy between them. The complainant noted that no other

relevant effect of R-citalopram at any binding site had been identified.

The complainant noted that Lundbeck had claimed that the removal of an essentially inert substance caused a significant increase in efficacy. This view was not shared by at least nine separate bodies in five different countries. The pre-defined main outcome of efficacy studies showed no significant difference in efficacy at end-point. The complainant alleged that the claim did not seem to be within the requirements of Clause 7.2.

## APPEAL BOARD RULING

The Appeal Board noted that Gorman *et al* had concluded that '… these findings suggest that escitalopram may be superior to citalopram in terms of both speed of onset and magnitude of its clinical effects'; 'these data … suggest escitalopram may have a faster onset and greater overall magnitude of effect than citalopram in improving symptoms of depression and anxiety …'. The Appeal Board considered that these were cautious statements. Gorman *et al* had also stated 'This pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect'. The Appeal Board noted the more cautious views expressed by a number of independent bodies which had reviewed the comparative efficacy data of Cipralex and Cipramil as submitted by the complainant.

The Appeal Board considered that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was a strong, unequivocal claim and as such was not a fair reflection of the data. At week 8 the mean change from baseline in MADRS scores showed a statistically significant benefit for Cipralex compared with Cipramil (OC values) but no difference between the two if LOCF data was used. The Appeal Board considered the claim thus misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful on this point.

### 4 Graph

The graph compared the change from baseline MADRS over eight weeks for Cipralex, Cipramil and placebo. The graph appeared beneath the claim at issue in point 3.

## COMPLAINT

The complainant noted that the graph was a partially reproduced graph from Gorman *et al* which showed results on an OC analysis. The original graph in Gorman *et al* included the results at end-point on LOCF analysis, which was defined as the primary efficacy measure in at least two of the three studies analysed. The complainant stated that the main result of the meta-analysis should then be the LOCF analysis which had been omitted from the graph for no clear reason. The impression given was that Gorman *et al* clearly demonstrated the superiority of Cipralex, while the main (and more statistically sound) result showed no superiority. This gave an unbalanced impression of the results, contravening Clause 7.8 of the Code.

## RESPONSE

Lundbeck stated that Gorman *et al* did not specify a main or primary analysis but presented both the LOCF and OC analyses with equal prominence. For the reasons stated at point 3 above, Lundbeck submitted that the OC analysis was more relevant to prescribers. It was not correct to say that the LOCF was 'more statistically sound', with comparable discontinuation rates in the individual studies, both were applicable and the OC approach provided a more representative impression of treatment response from patients who actually attended each individual visit. The LOCF analysis was also statistically significantly in favour of Cipralex over citalopram at weeks 1 and 6 for MADRS change from baseline. Lundbeck submitted that it was not presenting an unbalanced impression of the pooled analysis results.

## PANEL RULING

The Panel noted that the graph at issue was adapted from Figure 1 of Gorman *et al*. The Panel considered that its comments on Gorman *et al* at point 3 were relevant here.

The Panel noted that the graph at issue showed a statistically significant difference at 8 weeks in the reduction in the MADRS scores between Cipralex and Cipramil ($p<0.05$). No information was provided to indicate whether the graph referred LOCF or OC analyses. The footnote to the graph stated that it showed pooled data (ITT) from '… 3 multi-centre, placebo-controlled, randomised double-blind, eight week trials'. Information about dosage, patient numbers and statistically significant differences was given. The Panel noted Figure 1 in Gorman *et al* was labelled to indicate that the results were OC values by visit (weeks 1-8) and that LOCF values were given at endpoint (8 weeks). The LOCF analysis showed no statistically significant difference between Cipramil and Cipralex.

The Panel also noted that the graph at issue was not in accordance with the supplementary information to Clause 7.8 which stated that graphs which were taken from a published paper but not reproduced in their entirety should be clearly labelled as having been adapted from the paper in question.

The Panel considered that the graph was not a fair reflection of the outcome of Gorman *et al* in relation to MADRS scores. In the Panel's view insufficient information had been given about the results of Gorman *et al*. It was misleading to omit the non-statistically significant LOCF values from the graph and include only OC values which had shown some statistically significant differences. A breach of Clause 7.8 was ruled.

## APPEAL BY LUNDBECK

Lundbeck submitted that Gorman *et al* (2002) had presented the LOCF and OC data with, at least, equal

prominence. Lundbeck noted that the LOCF data were tabulated and the OC data were presented graphically. LOCF data were represented on the graph but only at a single time point compared with the five OC data points. Lundbeck submitted that the values for mean change in MADRS total score from baseline on escitalopram were numerically superior to their equivalent on citalopram at every study assessment point for both the LOCF and OC analysis and were statistically significantly superior at two time points in each analysis (LOCF weeks 1 and 6, OC weeks 1 and 8).

Lundbeck submitted that the LOCF and OC analysis showed the same consistent picture of superiority of escitalopram over citalopram and that presenting the OC data alone gave a fair reflection of the outcome of Gorman *et al* (2002) and was consequently not misleading.

### COMMENTS FROM THE COMPLAINANT

The complainant contended that that the issue here was whether the graph gave a 'clear, fair, balanced view' of the matters with which it dealt; a distinction must be drawn between the data and its interpretation.

The complainant noted that in the three studies which compared escitalopram with citalopram, the primary outcome measures were defined prior to examination of the results. For all three studies the primary outcome was reduction of MADRS score on LOCF analysis at week 8; this corresponded to the 'full analysis set' as defined in the European Agency for the Evaluation of Medicinal Products notes for guidance on statistical principles for clinical trials. OC analysis used, by definition, only those adhering to the trial protocol, the 'per protocol set'. The guidelines stated that 'In superiority trials the full analysis set was used in the primary analysis (except in exceptional circumstances) because it tended to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis …'. The complainant contended that the LOCF analysis was therefore the more appropriate analysis.

The complainant noted that the three sets of results were then combined. In the reasons given for the appeal, Lundbeck clearly stated that it considered the emphasis on the results was changed in the meta-analysis. The complainant contended that there was no reason why this should occur, and given that this change of emphasis distracted attention from the clear result that the primary outcome measure showed no significant difference between escitalopram and citalopram, this supposed change of emphasis was very concerning. The complainant alleged that there was nothing in Gorman *et al* to indicate OC analysis was more relevant than LOCF analysis, and indeed LOCF results were quoted in much more detail.

The complainant alleged that to quote this change of emphasis as a way of demonstrating that a 'clear, fair, balanced view' had been given was perplexing, when there was no scientific reason to change the importance attached to different results, and every reason to do so in order to provide a selectively favourable impression.

### APPEAL BOARD RULING

The Appeal Board considered that in principle the OC analysis was a legitimate way to present comparative data. However, the Appeal Board noted the caveats in Gorman *et al* with regard to the comparative efficacy of Cipramil and Cipralex which were in contrast to the overall impression given by the graph in combination with the heading 'Cipralex is significantly more effective than Cipramil in treating depression'. For all variables, the data in Gorman *et al* were analysed using both LOCF and OC data. The graph in question showed only the OC values (which demonstrated a statistically significant difference in favour of Cipralex compared with Cipramil) and not the LOCF data which showed no statistically significant difference between the two. The Appeal Board considered that the graph gave a misleading impression as to the relative efficacy of Cipralex and Cipramil. The Appeal Board also noted that although the graph at issue was taken from Gorman *et al*, it was not clearly labelled as having been adapted from the paper as required by the supplementary information to Clause 7.8. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8 of the Code. The appeal on this point was unsuccessful.

## 5 The intention to treat analysis

### COMPLAINT

The complainant stated that the graph was described as representing an intention to treat analysis (ITT) analysis. This denoted an analysis whereby all patients for whom there had been an intention to treat were included in the analysis, not just those who continued in the study. This was generally held to give more accurate results than analysis where drop-outs were disregarded. The graph presented showed results from OC analysis ie analysis of only those patients who had not dropped out. This was not, by definition, an ITT analysis. The claim that it was such an analysis was both incorrect and misleading, in that it gave a false impression of the rigour of the analysis. It was an important inaccuracy as the true ITT analysis showed a quite different result. A breach of Clause 7.8 was alleged.

### RESPONSE

Lundbeck stated that the ITT population was defined in the statistical analysis section of Gorman *et al* as '…comprising all patients from the three contributing studies who received at least one dose of double-blind study medication and had at least one post-baseline MADRS assessment'. This definition applied to both the OC and LOCF data presented. The graph in question was an OC analysis based on patients complying with the above ITT definition. The complainant was mistaken to contend that an OC analysis could not be applied to an ITT population. The ITT definition simply described the patient population which was then subject to the LOCF or OC analysis. Lundbeck did not accept that this presentation of the data was misleading.

**PANEL RULING**

The Panel considered that its comments at point 4 above were relevant here. The Panel noted that the supplementary information to Clause 7.8 required graphs or tables to be adequately labelled so that the information presented could be readily understood. The Panel noted that Gorman *et al* defined the ITT population as all patients from the three studies who received at least one dose of double-blind study medication and had at least one post-baseline MADRS assessment. The Panel queried whether this would be understood by readers who might assume that ITT meant analysing patients according to the treatment intended for them or all patients who received at least one dose of medication.

The Panel noted the parties' submission about the differences between OC and LOCF analysis. The Panel considered that it was extremely important to ensure that readers were aware of the precise nature of the analysis; to describe the analysis as ITT without further explanation was inadequate. The artwork did not give a fair, balanced view and a breach of Clause 7.8 was ruled.

### 6 Presentation of two versions of the meta-analysis

**COMPLAINT**

The complainant noted that the results of Gorman *et al* had been presented in a poster format and later as a published paper; the results seemed different in each. In the poster 403 patients on placebo, 524 on Cipralex and 408 on citalopram were said to have been the basis of the efficacy analyses. The primary efficacy analysis (LOCF at end-point) showed no statistically significant difference but numerically greater efficacy for citalopram.

When the paper was published in May 2002, the numbers of patients in the efficacy analysis were quoted as 398 on placebo, 520 on Cipralex and 403 on citalopram. Fourteen patients had been excluded from the analysis. No reason was given. The primary efficacy analysis now showed a numerically greater efficacy for Cipralex.

These two sets of figures could not both be accurate reports of the trial results, and cast doubt on the reliability of the data. What was behind this apparent change in reported results, giving a slightly more favourable impression of Cipralex, was unclear. It would seem that at the least the reporting had been inaccurate, contravening Clause 7.2.

**RESPONSE**

Lundbeck stated that there appeared to be an error in the reference from the complainant (Gorman poster American Psychiatric Association (APA) Meeting, May 2001). The actual poster presented confirmed numerical superiority for Cipralex over citalopram for MADRS change from baseline at week 8 (LOCF). Lundbeck had looked into how the complainant's copy of this poster could have this finding reversed. Unfortunately a printing error resulted in the Cipralex and Cipramil data points being reversed in some copies of the APA poster which were distributed. Now that this had been brought to its attention Lundbeck had taken steps to correct this error.

The discrepancy in the patient numbers between the publication of the poster and the full manuscript was because the larger patient population in the poster was based on all patients who received at least one dose of study medication. The slightly smaller population in the full paper was based in all patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment (see earlier definition of ITT population).

Both populations gave superiority for Cipralex over citalopram at week 8 (LOCF and OC) and the complainant's interpretation of the data had been compounded by a printing error in some poster copies for which Lundbeck apologised.

**FURTHER RESPONSE FROM LUNDBECK**

In response to a request for further information Lundbeck stated that the poster presentation by Gorman *et al* was made at the APA meeting, New Orleans, on 5-10 May 2001. The full paper was published in CNS Spectrums in 2002. There was no error in the patient numbers, the discrepancy was because the larger patient population in the poster was based on all patients who received at least one dose of study medication and the slightly smaller patient population in the poster was based on all patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment.

In the complainant's copy of the poster (a handout prepared for the APA meeting) the LOCF week 8 values for MADRS mean change from baseline for escitalopram and citalopram (figure 1) had inadvertently been reversed. The true situation was that escitalopram was numerically superior for LOCF at week 8 and this was reflected in the actual poster that was presented at the meeting. Lundbeck noted that figure 1 was primarily presenting the OC data (which was for all time points), with the LOCF data presented for a single time point ie week 8. The five assessment points on which the OC data was presented in figure 1 were correct. It seemed that a printing error in the copies of the poster handed out at the APA meeting had resulted in the escitalopram and citalopram LOCF points being reversed for the single assessment. The author, Gorman, and Lundbeck's co-partners in the USA, Forest Laboratories, were responsible for preparing the poster and the handout copies.

The erroneous poster handout was available to Lundbeck's Medical Information Department; however at launch of escitalopram in June 2002, the full paper was published. The full paper was made available to those requesting information on the compound. Copies of the poster might have been made available to those who specifically requested it, however, these were likely to have been small in number.

## PANEL RULING

The Panel noted Lundbeck's submission about the reasons for the differences in the ITT population and the week 8 LOCF data between the study and the poster. The Panel noted that the poster had been prepared by the author, Gorman, and Lundbeck's co-partners in the USA, Forest Laboratories, for distribution in the USA. Copies were made available to Lundbeck's UK Medical Information Department. Lundbeck stated that copies might have been made available to those specifically requesting the poster. Lundbeck stated that it had taken steps to correct the printing error in some poster copies. It was unclear how the complainant had received his copy of the poster. The Panel noted that Lundbeck in the UK had not been responsible for the printing error and there was no evidence before the Panel that Lundbeck's medical information department had supplied an incorrect version of the poster. The Panel noted that the data at issue in the leaflet was correctly referenced to the full paper. Taking all the circumstances into account the Panel ruled no breach of Clause 7.2 of the Code.

### 7 Activity of R-citalopram

A page of the Cipralex website headed 'Questions and Answers' addressed the question 'Why would one expect fewer side-effects by removing the inactive half of the molecules?' and stated that theoretically, fewer side-effects could be expected by the elimination of an unwanted activity connected with the enantiomer that had been removed and mentioned the possibility that the removal of R-citalopram would generate a slightly less sedating compound. The data was referenced to Sanchez *et al* (2002).

A page in the preclinical pharmacology section of the Cipramil website beneath the heading 'Effects on other receptor systems, citalopram selectivity' stated '*In vitro* receptor binding studies indicate negligible affinity for … histamine H 1'. Reference was also made to a 'lack of significant secondary receptor activity'. Under a heading of 'General pharmacology' it was stated that citalopram did not potentiate barbiturate-induced sleeping time indicating the 'absence of sedation'.

## COMPLAINT

The complainant stated that Cipralex was a derivative of citalopram, which was a mixture of equal parts of escitalopram (S-citalopram) and R-citalopram. They differed only in the presence or absence of R-citalopram. On the Cipralex promotional website it was claimed that 'There is, for instance, a weak interaction between R-citalopram and the histamine $H_1$ receptor. This could mean that removal of R-citalopram would generate a slightly less sedating compound'.

On the citalopram promotional website it was claimed that citalopram (which was 50% R-citalopram) had 'negligible affinity' for the $H_1$ receptor and a 'lack of significant secondary receptor activity'. These statements must therefore also be true for R-citalopram.

It was simultaneously being claimed, in promotional campaigns for different medicines, that R-citalopram had a pharmacological effect that could cause side-effects, and that it had a lack of any significant effect. It was difficult to see how both of these claims could be 'accurate, balanced, fair, objective and unambiguous' at the same time. A breach of Clause 7.2 was alleged.

## RESPONSE

Lundbeck stated that the complainant had pointed out apparent pharmacological inconsistencies relating to statements concerning the behaviour of citalopram (a racemic mixture of two enantiometers – escitalopram (S-citalopram) and R-citalopram) and R-citalopram when used alone. Lundbeck noted that both sites referred to by the complainant as 'promotional sites', were password protected and available only to physicians who had registered to access them. The sites had been developed, corporately, only in order to provide scientific product information for health professionals.

R-citalopram had a greater affinity for $H_1$ receptors compared to citalopram and Cipralex respectively. The comment relating to the role of R-citalopram on the website could best be described as a scientific hypothesis and was designed to contribute to the debate on enantiomeric differences. It clearly stated that 'theoretically' removal of R-citalopram 'could' result in a less sedating compound. In this context the statements were not intended and could not be construed as promotional claims.

In relation to pharmacological behaviour it could not simply be assumed that what was true for citalopram was true for the individual enantiomers as the complainant claimed. The enantiomers did not have identical pharmacological activities to the parent compound when they were separated and evaluated individually. The above reference illustrated this as did Lundbeck's extensive pre-clinical research. In addition a poster by Mørk *et al* (2002) illustrated the point very well. Cipralex produced almost twice the levels of serotonin (5HT) in the brains of laboratory animals when given alone compared with the same amount of Cipralex given together with R-citalopram as the parent compound citalopram. The R-citalopram appeared to be modulating the effect of the Cipralex in some way. The ability to increase brain serotonin levels was the pharmacological property underlying the antidepressant activity of compounds like Cipralex. In this animal model Lundbeck therefore had biological evidence supporting the superior clinical efficacy and earlier symptomatic relief of Cipralex compared to citalopram (Gorman *et al* pooled analysis). Lundbeck therefore submitted that the information presented for both compounds was accurate and balanced.

## PANEL RULING

The Panel noted that the claim 'There is for instance, a weak interaction between R-citalopram and the histamine $H_1$ receptor. This could mean that removal of R-citalopram would generate a slightly less

sedating compound' appeared on a website with secure access to health professionals.

The Panel did not accept Lundbeck's submission that the statements could not be construed as promotional claims. The material from the Cipralex website provided to the Panel comprised product specific material for health professionals on a company website and as such had to comply with the Code.

The Panel noted that enantiomers might differ in pharmacological effect which might result in demonstrable clinical differences. The Panel noted the evidence submitted by Lundbeck in relation to differences between the affinity of Cipralex, R-citalopram and citalopram for various receptors. Owen *et al* (2001) showed that Cipralex was 10-fold (1,973±152) less potent than its racemate R-citalopram (181±5) at the $H_1$ receptor. It was on this basis that Lundbeck suggested that removing R-citalopram would generate a slightly less sedating compound. Mørk *et al* which examined the *in vitro* and *in vivo* 5-HT uptake inhibitory activity of Cipralex illustrated differing effects of Cipralex, R-citalopram and citalopram upon serotonin levels and concluded that the biological data supported the notion of a superior clinical efficacy and earlier time to effects of Cipralex compared to citalopram.

The Panel noted that the Cipralex SPC included in Section 4.8, Undesirable effects, a list of adverse reactions which had 'occurred more frequently with Cipralex than with placebo'. This list included 'somnolence' which was classified as 'common' ie an incidence of between 1% and 10% – not placebo corrected. In Section 5.1, Mechanism of action, it stated 'Escitalopram has no or low affinity for a number of receptors including … histamine $H_1$'.

Section 4.8 of the Cipramil SPC, Undesirable events, stated that the most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were, *inter alia*, somnolence. The incidence in excess over placebo was low (<10%). Under Pharmacological Properties, it stated 'citalopram has no or very low affinity for a series of receptors including … histamine $H_1$ …. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as … sedation … . In humans citalopram … has no or minimal sedative properties'.

Although it was not possible to make a direct comparison of incidence of somnolence between the two products, on the basis of the statements in the SPCs the Panel noted that there did not appear to be a significant clinical difference between them on this point.

The Panel noted that whilst the statement at issue was posed as a theoretical possibility it appeared beneath a question which began 'Why would one expect fewer side-effects …' which in the opinion of the Panel implied that it was nonetheless of clinical importance.

The Panel considered that given the medicines' respective SPCs it was difficult to see how given citalopram had 'no or minimal sedative properties' it was possible to have a lower degree of sedative properties which was clinically meaningful. The Panel considered that the statement at issue was misleading and a breach of Clause 7.2 was ruled.

**Complaint received** **18 November 2002**

**Case completed** **7 May 2003**

**CASE AUTH/1392/11/02**

# GLAXOSMITHKLINE v JANSSEN-CILAG

## Topamax journal advertisements

**GlaxoSmithKline complained about two journal advertisements for Topamax (topiramate) issued by Janssen-Cilag. Topamax was indicated as adjunctive therapy for adults and children over two years of age with epilepsy. The phrase 'Top Class' appeared in both advertisements and was followed in each by the brand logo which incorporated the statement 'As add-on therapy' and the claim 'Because life without seizures is so much better'.**

**GlaxoSmithKline alleged that the phrase 'Top Class' implied that Topamax had special merit as the top brand in the class of antiepileptic medicines. Not only was this all-embracing claim highly contentious, it was also misleading and incapable of substantiation.**

**The Panel considered that the phrase 'Top Class' was ambiguous; it might be read as implying that Topamax had a special merit compared to other antiepileptic medicines or that it was simply one amongst many top class medicines. The claim was thus misleading and not capable of substantiation. The Panel considered that the phrase 'Top Class' would be associated with the claim 'Because life without seizures is so much better'. The Panel noted its rulings below and considered that on balance the phrase 'Top Class' was also exaggerated as alleged. Breaches of the Code were ruled.**

**Upon appeal by Janssen-Cilag, the Appeal Board considered that the phrase 'Top Class' was ambiguous, on its own it could be read as simply referring to one amongst a number of top class medicines. However, in the context of an advertisement which referred to 'Topamax As add-on therapy' and included the claim 'Because life without seizures is so much better', it could also imply that Topamax had a special merit compared to other antiepileptic medicines. In this regard the Appeal Board did not consider that the comparative efficacy data was sufficiently robust to support such a strong claim. The Appeal Board considered that the phrase 'Top Class' was misleading, exaggerated and not capable of substantiation. The Panel's ruling of breaches of the Code was upheld.**

**GlaxoSmithKline alleged that the claim 'Because life without seizures is so much better' was a hanging comparison, since no reference was made to any other medicine against which Topamax was compared. This claim was also misleading and incapable of substantiation since it implied that all patients receiving Topamax achieved seizure freedom which was not the case. In a prospective observational study of 170 patients with epilepsy (Stephen *et al* 2000), only 23% receiving Topamax adjunctive therapy became seizure-free for six months or more. These data did not support the claim.**

**The Panel did not accept that the claim 'Because life without seizures is so much better' was a hanging comparison as alleged; life without seizures was being compared to life with seizures, as submitted by Janssen-Cilag. No breach of the Code was ruled on this narrow point.**

**The Panel considered that in the context of an advertisement for Topamax the claim implied that patients receiving Topamax achieved freedom from seizures and that was not so. Stephen *et al* reported that only 23% of patients became seizure-free and some of these were on monotherapy which was not consistent with the product's summary of product characteristics (SPC). The Panel considered that the claim was misleading and could not be substantiated; a breach of the Code was ruled.**

**Upon appeal by Janssen-Cilag, the Appeal Board noted that the two advertisements differed significantly. The first advertisement was a double page spread and apart from the prescribing information the only text included was 'Top Class', below which was the Topamax product logo and the strapline 'Because life without seizures is so much better'. The second advertisement contained more detail. Beneath the heading 'Topamax is a logical first choice add-on for your patients uncontrolled on monotherapy' were five stab points, the first of which was '23% of refractory patients become seizure free when adding in Topamax'. Below the five stab points were the product logo and the strapline 'Because life without seizures is so much better'.**

**The Appeal Board considered that in the first advertisement the claim 'Because life without seizures is so much better' implied that patients receiving Topamax achieved freedom from seizures and that was not so. There was no additional data to put the claim into context. The Appeal Board considered that the claim was misleading and could not be substantiated and upheld the Panel's ruling of a breach of the Code.**

**The Appeal Board noted that in the second advertisement the claim at issue was qualified by the bullet point '23% of refractory patients become seizure free when adding in Topamax', which was referenced to Stephen *et al*. The Appeal Board considered that in this context the claim was not misleading and had been substantiated and ruled no breach of the Code.**

**One of the advertisements featured a photograph of a young woman in the driving seat of a car tearing up an L-plate and being congratulated by a young man. A smaller picture of the same scene appeared on the second page of the other advertisement.**

**GlaxoSmithKline stated that the artwork implied that the young woman, who presumably had epilepsy, had just passed her driving test. In order to hold a UK driving licence a person with epilepsy needed to be seizure-free for at least 12 months. The artwork was alleged to be misleading as it implied that all patients receiving Topamax would be seizure-free for at least 12 months, whereas in Tartara *et al* 1996 only 1 patient out of 15 was seizure-free for over 12 months. GlaxoSmithKline stated that further evidence taken from 84 patients**

**who received Topamax during a consecutive period of twelve months or more without interruption showed that only 7 (8.3%) were seizure-free for a consecutive period of 12 months or more (Janssen-Cilag's data on file).**

**The Panel noted GlaxoSmithKline's submission that to hold a driving licence in the UK one needed to be seizure-free for at least 12 months. The Panel noted Tartara *et al* and Janssen-Cilag data on file. The Panel considered that the photograph was misleading given the 12 month seizure-free data. The photograph would be seen as depicting a common event. A breach of the Code was ruled.**

**Upon appeal by Janssen-Cilag, the Appeal Board considered that the photographs promoted the false hope that gaining a driving licence was an achievable event for patients on Topamax. The Appeal Board considered that based on the 12-month seizure-free data this would be an extremely unlikely occurrence. The Appeal Board considered that the photograph was misleading; it would be seen as depicting a common event. The Appeal Board upheld the Panel's ruling of a breach of the Code.**

GlaxoSmithKline UK Limited complained about two journal advertisements (refs 02161 and 02153) for Topamax (topiramate) issued by Janssen-Cilag Ltd which appeared in Seizure (June 2002) and Journal of Neurology, Neurosurgery and Psychiatry (April 2002) respectively.

Topamax was indicated as adjunctive therapy for adults and children over two years of age who were inadequately controlled on conventional first line antiepileptic medicines for partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

### 1 Claim 'Top Class'

This phrase appeared in both advertisements. The phrase was followed in each advertisement by the brand logo which incorporated the statement 'As add-on therapy' and the claim 'Because life without seizures is so much better'.

### COMPLAINT

GlaxoSmithKline alleged that the phrase 'Top Class' implied that Topamax had special merit as the top brand in the class of antiepileptic medicines. Not only was this all-embracing claim highly contentious it was also misleading and incapable of substantiation. GlaxoSmithKline alleged breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

### RESPONSE

Janssen-Cilag stated that 'Top Class' was a colloquial term, which was in widespread general use and was not an all-embracing term or a superlative; for example, there were many top class chefs and many top class pupils. Topamax was one of the class of antiepileptic medicines used as adjunctive treatment for epilepsy. Each of the medicines used for epilepsy had specific properties and many of them were top class medicines. The UK regulatory process was well known for the rigour with which it reviewed products. There was nothing in the advertisement that suggested that Topamax was **THE** top class or the top brand as alleged. As no claim had been made that Topamax was the top brand no substantiation for this was required.

Janssen-Cilag noted that it was using poetic licence in playing on the 'Top' part of the product name.

Janssen-Cilag submitted that the use of the phrase 'Top Class' did not imply special merit and was not misleading. As no claim had been made, or implied that Topamax was 'the top brand' the claim was not in breach of Clauses 7.2, 7.4 or 7.10 of the Code.

### PANEL RULING

The Panel considered that the phrase 'Top Class' was ambiguous; it might be read by some as implying that Topamax had a special merit compared to other antiepileptic medicines or that it was simply one amongst many top class medicines. The claim was thus misleading and not capable of substantiation. The Panel considered that the phrase 'Top Class' would be associated with the claim 'Because life without seizures is so much better'. The Panel noted its rulings at point 2 below and considered that on balance the phrase 'Top Class' was also exaggerated as alleged. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

### APPEAL BY JANSSEN-CILAG

Janssen-Cilag did not consider that the phrase 'Top Class' was misleading, exaggerated, all-embracing or ambiguous. The phrase was applicable to Topamax and could be substantiated. Janssen-Cilag denied breaches of Clauses 7.2, 7.4 and 7.10 and referred to its response to the Panel.

Janssen-Cilag considered that as no head-to-head, double-blind, randomized-controlled trials of antiepileptic medicines had been performed, the only available method for comparing their efficacy was a meta-analysis. A table provided by Janssen-Cilag appears on the next page.

Janssen-Cilag submitted that Topamax was consistently associated with the highest odds for treatment response (odds ratio) and the lowest number of patients that needed to be treated (NNT) to gain one treatment responder. Both of these were measures of therapeutic efficiency. As confidence intervals overlapped, a conservative interpretation of these data was that topiramate was at least as effective as other newer antiepileptic medicines as an adjunctive therapy for partial onset seizures.

Janssen-Cilag noted van Rijckevorsel *et al* presented data from 'number needed to treat' (NNT) analyses of various newer antiepileptic medicines. In this analysis, topiramate was associated with the lowest number of patients that needed to be treated to gain one extra responder in addition to placebo (3.25 [range: 2.67 – 4.16]). Levetiracetam was associated

**Odds ratio for response: Meta-analyses of clinical trials of newer antiepileptic medicines as adjunctive therapy for refractory partial onset seizures, with or without secondary generalization.**

| | OR for response (95% CI) | | NNT (range) |
|---|---|---|---|
| | **Chadwick *et al* (1996)** | **Marson *et al* (1997)** | **van Rijckevorsel *et al* (2001)** |
| Topiramate | 4.27 (2.84, 6.43) | 4.07 (2.87, 5.78) | 3.25 (2.67 – 4.16) |
| Levetiracetam | – | – | 3.92 (3.28 – 4.88) |
| Vigabatrin | 3.68 (2.45, 5.51) | 3.67 (2.44, 5.51) | 3.76 (2.94 – 5.19) |
| Oxcarbazepine | – | – | 4.37 (3.51 – 5.79) |
| Tiagabine | 3.01 (1.99, 4.55) | 3.03 (2.01, 4.58) | 6.7 (5.12 – 9.66) |
| Lamotrigine | 2.24 (1.42, 3.53) | 2.32 (1.47, 3.68) | 8.87 (5.93 – 17.56) |
| Gabapentin | 2.31 (1.54, 3.45) | 2.29 (1.53, 3.43) | 9.10 (6.27 – 16.61) |

OR = odds ratio
NNT = number needed to treat;
– = value not reported

with an NNT of 3.92 (3.28 – 4.88), the figure for lamotrigine was 8.87 (5.93 – 17.56) and for gabapentin it was 9.10 (6.27 – 16.61).

Janssen-Cilag maintained that no claim had been made that Topamax was the top brand, but considered that there was adequate substantiation that Topamax was among the top class of newer antiepileptic medicines.

## COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline did not make any specific comments on this particular point. Commenting on Janssen-Cilag's appeal as a whole, GlaxoSmithKline did not consider that it subtracted from the Panel's ruling. The additional data did nothing to reassure GlaxoSmithKline with regard to the Topamax advertising, which the company maintained was misleading, all-embracing and incapable of substantiation.

## APPEAL BOARD RULING

The Appeal Board considered that the phrase 'Top Class' was ambiguous, on its own it could be read as simply referring to one amongst a number of top class medicines. However, in the context of an advertisement which referred to 'Topamax As add-on therapy' and included the claim 'Because life without seizures is so much better', it could also imply that Topamax had a special merit compared to other antiepileptic medicines. In this regard the Appeal Board did not consider that the comparative efficacy data was sufficiently robust to support such a strong claim. The Appeal Board considered that the phrase 'Top Class' was misleading, exaggerated and not capable of substantiation. The Panel's ruling of breaches of Clauses 7.2, 7.4 and 7.10 was upheld. The appeal on this point was unsuccessful.

### 2 Claim 'Because life without seizures is so much better'

This claim appeared on each advertisement beneath the product logo.

## COMPLAINT

GlaxoSmithKline alleged that the claim 'Because life without seizures is so much better' was a hanging comparison, since no reference was made to any other medicine against which Topamax was compared. This claim was also misleading and incapable of substantiation since it implied that all patients receiving Topamax achieved seizure freedom which was not the case. In a prospective observational study of 170 patients with epilepsy (Stephen *et al* 2000), only 23% receiving Topamax adjunctive therapy became seizure-free for six months or more. Clearly these data did not support the claim, which GlaxoSmithKline alleged was in breach of Clauses 7.2 and 7.4 of the Code.

## RESPONSE

Janssen-Cilag stated that one of the key goals during treatment of epilepsy was to reduce seizure frequency, and if possible to achieve long periods without seizures. To the patient, each day without seizures could be important, and there was evidence that the quality of life was improved in patients who had no seizures compared to having seizures.

The claim 'Because life without seizures is so much better' simply reflected one of the key aims of patients with epilepsy – ie to achieve significant periods of time without seizures. The claim clearly implied that life without seizures was better than life with seizures. There had been no hanging comparison whereby Topamax was described as being better or stronger or suchlike.

The claim was not linked to any specific claim for seizure freedom, however it was worth noting that in Stephen *et al* up to 23% of patients taking Topamax as adjunctive treatment for epilepsy were seizure-free for six months or more. This represented a very significant proportion of patients being without seizures, within a group of patients suffering from refractory epilepsy. In addition Janssen-Cilag had shown that 8.3% of patients treated with Topamax as adjunctive therapy for epilepsy in a tertiary referral centre were seizure-free for more that 12 consecutive months (data on file).

Janssen-Cilag submitted that the claim was a general statement about epilepsy, was not a hanging comparison, and was supported by published data and, therefore, was not in breach of Clauses 7.2 and 7.4 of the Code.

## PANEL RULING

The Panel did not accept that the claim 'Because life without seizures is so much better' was a hanging comparison as alleged; the Panel considered that life without seizures was being compared to life with seizures, as submitted by Janssen-Cilag. No breach of Clause 7.2 was ruled on this narrow point. This ruling was not appealed.

The Panel noted that Stephen *et al* was a prospective observational study which assessed the efficacy and tolerability of Topamax in refractory epilepsy. Overall the results showed that the addition of Topamax to the regimens of 170 patients resulted in 70% reporting a mean ≥ 50% reduction in seizure frequency compared with a 3-month prospective baseline on unchanged dosage; 23% were seizure-free for at least 6 months. The authors noted that this response rate was substantially higher than that reported in artificial placebo controlled, fixed-dose regulatory trials using a patient population with more severe epilepsy. 47% of patients had a useful therapeutic response. Eight of the 39 seizure-free patients and 3 of the 80 responders were on Topamax monotherapy. Topamax was discontinued in 30% of patients; in 12 it was withdrawn because of worsening seizures, a phenomenon occasionally seen with the introduction of most antiepileptic medicines.

The Panel considered that in the context of an advertisement for Topamax the claim implied that patients receiving Topamax achieved freedom from seizures and that was not so. Stephen *et al* reported that only 23% of patients became seizure-free and some of these were on monotherapy which was not consistent with the product's summary of product characteristics (SPC). The Panel considered that the claim was misleading and could not be substantiated; breaches of Clauses 7.2 and 7.4 were ruled. These rulings were appealed.

## APPEAL BY JANSSEN-CILAG

Janssen-Cilag considered that the claim 'Because life without seizures is so much better' was capable of substantiation, was not misleading and was used appropriately in the context of the advertisement and so not in breach of Clauses 7.2 and 7.4.

Janssen-Cilag considered that one of the key goals of treating epilepsy was to reduce the seizure frequency, and if possible to achieve long periods without seizures. To the patient each day without seizures could be important, and there was evidence that the quality of life was improved in those patients who had no seizures compared to those with seizures.

Janssen-Cilag noted that Jacoby *et al* (1998) had shown that higher seizure frequency was consistently associated with impaired daily functioning and higher levels of anxiety and depression. Patients with higher seizure frequency also reported higher levels of stigmatisation. The joint impact of depression, anxiety and stigma meant that these patients had problems achieving their personal goals and scored low on the personal fulfilment scale. Baker *et al* (1997) showed similar results, with the relationship between seizure frequency being closely associated with poorer outcomes with respect to cost of illness, quality of life and mortality. Selai *et al* (2002) showed that patients treated with Topamax had significantly higher health status (QoL) after six months compared to their baseline score. Patients started on other newer antiepileptic medicines had similar or worse health status after six months.

Janssen-Cilag considered that these studies supported the value to the patient of achieving seizure freedom. Patients who became free of seizures had significantly higher quality of life scores than patients who failed to have a 50% reduction in seizure frequency. Topamax offered a chance of achieving seizure freedom and had also been shown to improve quality of life. This supported the use of the phrase 'Because life without seizures is so much better' and also its use in an advertisement for Topamax.

Janssen-Cilag considered the statement 'Because life without seizures is so much better' simply reflected one of the key aims of patients – to achieve significant periods of time without seizures and was not linked to a claim for seizure freedom with Topamax. However, Topamax was associated with seizure freedom in an important proportion of patients used within the current licensed indication. In Stephen *et al*, a study of 170 patients started on adjunctive Topamax therapy in line with the licensed indication, 23% of patients were seizure free for six months or more. In the context of refractory epilepsy this represented a significant proportion of patients without seizures. Janssen-Cilag noted that in Stephen *et al* concomitant antiepileptic medicines were withdrawn in some patients either at their request or in an attempt to alleviate side-effects with only a small number remaining on single agent therapy at the end of the study. Janssen-Cilag did not consider that this altered the validity of the study.

Janssen-Cilag noted in addition it had shown that 8.3% of patients treated with Topamax as adjunctive therapy for epilepsy in a tertiary referral centre were seizure free for more than twelve months (data on file).

## COMMENTS FROM GLAXOSMITHKLINE

See point 1 above.

## APPEAL BOARD RULING

The Appeal Board noted that the two advertisements differed significantly. Advertisement 02153 was a double page spread and apart from the prescribing information the only text included was 'Top Class' below which was the Topamax product logo and the strapline 'Because life without seizures is so much better'. Advertisement 02161 contained more detail. Beneath the heading 'Topamax is a logical first choice add-on for your patients uncontrolled on monotherapy' were five stab points the first of which was '23% of refractory patients become seizure free when adding in Topamax'. Below the five stab points was the product logo and the strapline 'Because life without seizures is so much better'.

The Appeal Board considered that in advertisement 02153 the claim 'Because life without seizures is so

much better' implied that patients receiving Topamax achieved freedom from seizures and that was not so. There was no additional data to put the claim into context. The Appeal Board considered that the claim was misleading and could not be substantiated and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted that in advertisement 02161 the claim at issue was qualified by the bullet point '23% of refractory patients become seizure free when adding in Topamax' which was referenced to Stephen *et al*. The Appeal Board considered that in this context the claim was not misleading and had been substantiated and ruled no breach of Clauses 7.2 and 7.4. The appeal on this point was successful.

During its consideration of this matter the Appeal Board was concerned to note that the data cited in support of the claim '23% of refractory patients become seizure free when adding in Topamax' related to a specific time period of only at least 6 months. The Appeal Board considered that given the nature of the condition it was important to give details of the time period. Some readers would assume that the data related to a longer time period and asked that Janssen-Cilag be advised of its concerns in that regard.

### 3 Photograph of a young woman in a car

Advertisement 02153 featured a photograph of a young woman in the driving seat of a car tearing up an L- plate and being congratulated by a young man. A smaller picture of the same scene appeared on the second page of the other advertisement.

#### COMPLAINT

GlaxoSmithKline stated that the artwork implied that the young woman, who presumably had epilepsy, had just passed her driving test. In order to hold a driving licence in the UK a person with epilepsy needed to be seizure-free for at least 12 months. The artwork was alleged to be misleading as it implied that all patients receiving Topamax would be seizure-free for at least 12 months, whereas in a published long-term prospective trial of Topamax adjunctive therapy (Tartara *et al* 1996) only 1 patient out of 15 was seizure-free for over 12 months. GlaxoSmithKline stated that further evidence supporting its concern came from Janssen-Cilag's data on file. These data were taken from a total of 84 patients who received Topamax during a consecutive period of twelve months or more without interruption. Of these only 7 (8.3%) were seizure-free for a consecutive period of 12 months or more. A breach of Clause 7.8 of the Code was alleged.

#### RESPONSE

Janssen-Cilag stated that for any treatment in any therapy area it was well understood by clinicians that not all patients responded to the treatment. Clinicians who treated patients with epilepsy were well aware of the difficulty in treating patients with refractory epilepsy, and achieving seizure freedom for more than 12 months was an important outcome for any patient requiring adjunctive therapy for epilepsy. The visual was consistent with evidence that some patients taking Topamax as adjunctive therapy might have prolonged periods without seizures. It did not suggest that **all** patients receiving Topamax would be seizure-free for 12 months, or that **all** patients receiving Topamax achieved seizure freedom.

Published data supported the belief that some patients on adjunctive Topamax treatment might become seizure-free for prolonged periods of greater than 12 months, and clinicians had reported individual cases of patients who had had their driving licence restored. In addition, in a retrospective single-centre review of patients using an electronic database 8.3% were seizure-free for a consecutive period of 12 months or more and so could be a holder of a driving licence.

Janssen-Cilag submitted that the visual was not misleading, adhered to the letter and spirit of the Code, and so was not in breach of Clause 7.8.

#### PANEL RULING

The Panel noted that both advertisements featured a photograph of a young woman sitting in the driving seat of a car tearing up an L-plate. The Panel noted GlaxoSmithKline's submission that to hold a driving licence in the UK one needed to be seizure-free for at least 12 months. The Panel noted that Tartara *et al* demonstrated that 1 patient (out of 15 patients in the study with drug refractory partial epilepsy or Lennox Gastaut Syndrome) was seizure-free for 19 months. The Panel noted the Janssen-Cilag data on file. The Panel considered that the photograph was misleading given the 12 month seizure-free data. The photograph would be seen as depicting a common event. The Panel ruled a breach of Clause 7.8 of the Code. This ruling was appealed.

During its consideration of this case the Panel noted that the supplementary information to Clause 7.8, Artwork, Illustrations, Graphs and Tables, stated that 'Care must be taken to ensure that artwork does not…… detract from any warnings or contraindications'. The Panel noted that Section 4.7 of the Topamax SPC, 'Effects on ability to drive and use machines', stated 'As with all antiepileptic drugs, Topamax may produce central nervous system related adverse events. Drowsiness is likely and Topamax may be more sedating than other antiepileptic drugs. These adverse events could potentially be dangerous in patients driving a vehicle … particularly until such time as the individual patient's experience with the drug is established'. The Panel considered that the photograph of a young woman sitting in the driver's seat being congratulated on passing her test detracted from the warning in the SPC and requested that the company be advised of its concerns.

#### APPEAL BY JANSSEN-CILAG

Janssen-Cilag did not consider that the advertisement suggested that all patients would become seizure free, but as some patients might become seizure free and hence be allowed to resume driving, it did not

consider that this visual was misleading and therefore was not in breach of Clause 7.8 of the Code.

Janssen-Cilag considered that the photograph was a reasonable one and did not consider that all patients would need to be rendered seizure-free with treatment for at least one year to justify its use. For any treatment in any therapy area it was well understood by clinicians that not all patients would respond fully but the aspirational goal for the patient was worth remembering – seizure freedom was the aspirational goal in epilepsy as normotension would be for a patient with hypertension.

Janssen-Cilag considered that clinicians who treated patients with epilepsy were well aware of the difficulty in treating patients with refractory epilepsy, and achieving seizure freedom for more than 12 months was an important outcome for any patient requiring adjunctive therapy. The visual acknowledged that some patients might have prolonged periods without seizures but did not suggest that all patients receiving Topamax would be seizure-free for twelve months, nor suggest that all patients receiving Topamax achieved seizure freedom.

Janssen-Cilag noted that Topamax had been shown repeatedly to allow some patients to achieve seizure freedom in short and medium term clinical trials (Guberman *et al* 2002, Sharief *et al* 1996 and Abou-Khalil *et al* 2000).

Janssen-Cilag noted that Tartara *et al* (1996) also supported the belief that some patients on adjunctive Topamax treatment might become seizure-free for prolonged periods of greater than twelve months, and clinicians had reported to Janssen-Cilag individual cases of patients who had had their driver's licences restored. In addition in a retrospective single-centre review of patients using an electronic database 8.3% were seizure-free for a consecutive period of twelve months or more (data on file) and so could be a holder of a driver's licence.

Janssen-Cilag noted that the SPC for Topamax contained a warning about driving:

'Drowsiness is likely and Topamax may be more sedating than other antiepileptic drugs. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.'

However if a patient had been established on Topamax and was seizure-free there would have been considerable discussion between the treating physician and the patient about restoration of their driver's licence. Janssen-Cilag did not believe that this should prevent this image from being used in a Topamax advertisement.

### COMMENTS FROM GLAXOSMITHKLINE

See point 1 above.

### APPEAL BOARD RULING

The Appeal Board considered that the photograph in each advertisement promoted the false hope that gaining a driving licence was an achievable event for patients on Topamax. The Appeal Board considered that based on the 12-month seizure-free data this would be an extremely unlikely occurrence. The Appeal Board considered that the photograph was misleading; it would be seen as depicting a common event. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8 of the Code. The appeal on this point was unsuccessful.

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| **Complaint received** | **20 November 2002** |
| **Case completed** | **18 March 2003** |

CASE AUTH/1398/12/02

# LEO v GALDERMA

## Silkis journal advertisement

Leo complained about a Silkis (calcitriol) journal advertisement, issued by Galderma, headed 'Revealing the confident new face of psoriasis', beneath which appeared three head and shoulder photographs of a woman. In the first shot the woman's face was out of focus, in the second it was less out of focus and in the third the woman's face was in focus. Beneath the brand logo in the bottom right-hand corner of the advertisement was the claim 'New confidence in psoriasis'. The top left hand corner featured the claim 'May be used in sensitive areas of the body such as the face' in a highlighted yellow box.

Leo alleged that the prominent and repeated use of the word 'confident', the picture of the face and the highlighted advice to use Silkis on the face, misled the reader as to the caution and care that must be used when applying the product to sensitive areas. The Silkis summary of product characteristics (SPC) had a special warning that Silkis '…can be applied to the face with caution, as there is an increased risk of irritation in this area'.

The Panel considered that the combination of the claims 'Revealing the confident new face of psoriasis', 'May be used on sensitive areas of the body such as the face' and the photographs were such that the advertisement was designed to encourage use of Silkis on the face. According to its SPC Silkis could be applied to the face with caution as there was an increased risk of irritation. The Panel noted that the prescribing information included a reference that Silkis could be used with caution on the face. The Panel considered that the advertisement gave the overall impression that Silkis could be used on the face without any further consideration, which was misleading. A breach of the Code was ruled.

Upon appeal by Galderma the Appeal Board considered that the overall impression of the advertisement was misleading for the same reasons as the Panel. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The claim 'New Silkis ointment is an effective yet well tolerated treatment for psoriasis' was referenced to a cumulative irritancy study in which healthy volunteers applied calcitriol, calcipotriol (Leo's product Dovonex), tacalcitol and one vehicle under occlusion (Queille-Roussel *et al* 2001). None of the products was licensed for use under occlusion.

Each product was applied once daily from Monday to Friday of each week for three weeks; calcitriol and calcipotriol were not licensed for once daily use. Leo doubted whether any of the applications were to the face and so given this, and the fact that healthy volunteers used the products in ways inconsistent with their marketing authorizations, Leo questioned the suitability of the data to substantiate the claims in question. The study showed that the mean cumulative irritancy of calcitriol was 300% greater than the vehicle and so in comparison it was not well tolerated. The study had also evaluated the phototoxicity and potential for photosentisitization of the products.

Although the advertisement included no direct comparison between Silkis and other products the reader was directed to Queille-Roussel *et al* from which they would conclude that Silkis had superior qualities compared to tacalcitol or calcipotriol in the clinic. This was not substantiated by the reference.

The Panel noted that the claim at issue related only to Silkis. The advertisement made no direct or implied comparison between Silkis, calcipotriol and tacalcitol. Queille-Roussel *et al* had reported on the results of four separate studies designed to evaluate cumulative irritancy, cutaneous contact sensitization, potential photoallergic contact sensitization and phototoxicity of calcitriol. The report concluded that calcitriol was a well tolerated treatment for stable plaque-type psoriasis. When tested in healthy volunteers it did not give rise to any cumulative irritancy or sensitizing. Calcitriol compared to its vehicle and white petrolatum was neither phototoxic nor did it show any potential for photosensistization. It was stated that the findings were consistent with the findings of the clinical trial programme where no major adverse events had been observed even after therapy of up to 78 weeks. The SPC stated that a low incidence of skin irritation (reddening, itching) had been reported following the use of Silkis which was usually temporary. If sensitivity or severe irritation occurred treatment should be discontinued temporarily or altogether.

The Panel noted Leo's comments about the methods used in the studies reported by Queille-Roussel *et al* and Galderma's submission on these points. The use of Silkis was not consistent with the details in the SPC. Queille-Roussel *et al* referred to the results of the Silkis clinical trials. Taking all the data into account the Panel did not consider that the claim was misleading nor incapable of substantiation as alleged; there was no comparison in the advertisement. The Panel ruled no breaches of the Code.

Leo noted that the prescribing information in the advertisement stated 'Use in restricted amounts during pregnancy if considered essential by the physician'. However, the SPC stated 'Silkis should only be used in pregnancy in restricted amounts when clearly necessary'. Leo alleged that the prescribing information was not consistent with the SPC.

The Panel noted the wording in the SPC that 'There are no adequate data from the use of Silkis in pregnant women. Studies in animals have shown developmental toxicity at doses which caused maternal toxicity (see section 5.3). The potential risk for humans is unknown. Silkis should only be used during pregnancy in restricted amounts when clearly necessary. Calcium levels should be monitored'. The prescribing information stated 'Pregnancy and Lactation: Not to be used during breast-feeding. Use in restricted amounts during

**pregnancy if considered essential by the physician. Calcium levels should be monitored'. The Panel considered that the prescribing information was consistent with the SPC with regard to use in pregnancy and ruled no breach of the Code.**

Leo Pharmaceuticals complained about a Silkis (calcitriol) advertisement (ref SILK/60/0702) issued by Galderma (UK) Limited, which had appeared in Prescriber, November 2002.

Leo marketed Dovonex (calcipotriol).

### 1 Use on face

The advertisement was headed 'Revealing the confident new face of psoriasis' beneath which appeared three head and shoulder photographs of a woman. In the first shot the woman's face was out of focus, in the second shot the woman's face was less out of focus and in the third shot the woman's face was in focus. Beneath the brand logo in the bottom right-hand corner of the advertisement was the claim 'New confidence in psoriasis'. The top left hand corner featured the claim 'May be used in sensitive areas of the body such as the face' in a highlighted yellow box.

### COMPLAINT

Leo alleged that the prominent and repeated use of the word 'confident', the picture of the face and the highlighted advice to use Silkis on the face of patients misled the reader as to the caution and care that must be used when applying the product to sensitive areas. The Silkis summary of product characteristics (SPC) had a special warning that Silkis '…can be applied to the face with caution, as there is an increased risk of irritation in this area'.

Leo alleged that the overall tone of the advertisement and highlighting of use on the face was misleading as Silkis had a special warning with regard to possible adverse effects when used on sensitive areas; readers were not warned of the caution they must exercise when using Silkis. A breach of Clause 7.2 of the Code was alleged.

### RESPONSE

Galderma stated that the original SPC (2001) for Silkis carried the warning that 'the ointment should not be applied to the face, because there is an increased risk of irritation in this area'. Following the submission of clinical data to the European authorities they were all satisfied that the product was safe for application on the face and hence the warning on the SPC (2002) was changed to propose the following advice 'the ointment can be applied to the face with caution, as there is an increased risk of irritation in this area'.

The advertisement clearly identified that Silkis '**may** be used on **sensitive areas** of the body such as the face…' as opposed to the information appearing in the SPC ie 'can be used on the face …'.

Furthermore, the prescribing information clearly identified that Silkis 'can be applied to the face with caution, as there is an increased risk of irritation in this area'. This cautionary advice was not different to many topical products applied to sensitive parts of the body. Galderma therefore did not see how the advertisement would be claimed to be in breach of the Clause 7.2, when the Silkis SPC clearly advised that the product could be used on the face and the cautions for use were clearly highlighted in the prescribing information.

### PANEL RULING

The Panel considered that the combination of the claims 'Revealing the confident new face of psoriasis', 'May be used on sensitive areas of the body such as the face' and the photographs were such that the advertisement was designed to encourage use of Silkis on the face. According to its SPC Silkis could be applied to the face with caution as there was an increased risk of irritation.

The Panel noted that the prescribing information included a reference that Silkis could be used with caution on the face. It was an established principle under the Code that an otherwise misleading claim or impression could not be qualified by the prescribing information. The Panel considered that the advertisement gave the overall impression that Silkis could be used on the face without any further consideration which was misleading. A breach of Clause 7.2 was ruled.

### APPEAL BY GALDERMA

Galderma submitted that the photograph did not represent an exhortation to prescribe solely for the face. The wording on the advertisement was consistent with the SPC. Facial use was not contraindicated. The wording was chosen deliberately not to over emphasise facial use but to alert prescribers to the fact that the Silkis SPC had been amended to allow use on the face.

Galderma noted that the established principle under the Code that an otherwise misleading claim or impression could not be qualified by the prescribing information was not disputed though it did not consider this to be relevant in this particular case. Galderma submitted that the Panel had misinterpreted the statement on the Silkis SPC, '… with caution as there is an increased risk of irritation in this area', and argued that this statement could be applicable to the use of any topical medicine on the face, and was therefore a simple statement of fact. Due to their basic knowledge of facial skin structure, prescribers would not refrain from prescribing Silkis for use on the face if the additional fact, that there was 'an increased risk of irritation in this area', was incorporated within the body of the advertisement.

Galderma submitted that the Panel's ruling would be a dangerous precedent to set and could precipitate a flood of speculative complaints. Galderma referred to a number of advertisements including an advertisement for a proton pump inhibitor with a specific caution in the prescribing information for use in the elderly, yet the advertisement had depicted photographs of the elderly; an advertisement for a

topical steroid with a specific warning for use near the eyes and long-term continuous use in children had depicted a large photograph of a child's face and used the word 'eyes' in a very prominent strapline; an advertisement for an NSAID which had a caution for use in the elderly yet the advertisement had a picture of an elderly lady.

Galderma submitted that the SPC for Silkis allowed use on the face but sensibly advised caution, since the face was a sensitive area. The claim was not overstated, exaggerated or misleading. The words '… May be used on sensitive areas of the body such as the face …' were selected deliberately so as not to overemphasise Galderma's claim. Galderma submitted that the Panel's ruling meant that any product that carried any warning in its use must list this as a heading or qualifying note on its advertising. This had never been custom or practice and Galderma did not believe that this requirement was contained anywhere in the Code and was certainly not specified in Clause 7.2, or its supplementary information.

### COMMENTS FROM LEO

Leo stated that the overall impact on the reader to use Silkis on the face must take into account the use of only the head and shoulders photograph of a patient plus the heading 'Revealing the confident new face …', and the lines 'new confidence' and 'may be used … such as the face'. Leo alleged that this clearly encouraged the reader to prescribe Silkis for use on the face.

Leo noted that Galderma had stated in its appeal that the wording was chosen to 'alert prescribers … allow use on the face'; the prominent and repeated use of the word 'confident' in conjunction with 'face' was inconsistent with this claim. Leo reiterated its original complaint that the use of the word 'confident' misled the reader as to the care and caution that must be used when prescribing Silkis for use on the face.

Leo alleged that Galderma's claim that the SPC had been misinterpreted and that the MCA or other regulators used this as a standard statement was not true; the SPC was based upon the data submitted by the applicant. If Galderma had submitted sufficient data to demonstrate no increased risk of irritation on the face, then the SPC would reflect this. Galderma had implied that it was not worth its while in adding a warning regarding facial use to the advertisement because prescribers had a 'basic knowledge of skin structure'. Leo argued that if a marketing authorization holder was unsure or doubtful of the knowledge level and experience of the target audience then it had an even greater responsibility to point out the risks involved in applying medicines to the face.

Leo stated that it was difficult to follow Galderma's argument that this ruling set a 'dangerous precedent'. Leo understood that the Panel's ruling was based on the Code and individual case decisions. Leo stated that it did not see how using examples of current practice was relevant to this case.

### APPEAL BOARD RULING

The Appeal Board considered that the claims 'Revealing the confident new face of psoriasis', 'May be used on sensitive areas of the body such as the face' and the photographs gave the impression that Silkis could be used on the face without further consideration and that was not so. The Appeal Board noted that the Silkis SPC stated that Silkis could be applied to the face with caution as there was an increased risk of irritation. The Appeal Board considered that the overall impression of the advertisement was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

## 2 Claim 'New Silkis ointment is an effective yet well tolerated treatment for psoriasis'

The claim was referenced to Queille-Roussel *et al* (2001).

### COMPLAINT

Leo noted that there was only one reference cited to support the claim which it alleged was misleading and did not make a fair comparison between calcitriol, calcipotriol nor tacalcitol. Therefore Leo alleged that the claim had not been substantiated.

In particular:

- Cumulative irritancy study was performed with three products and one vehicle under occlusion. None of the products was licensed for use under occlusion. The application was for five days, with a weekend break for three weeks. The application was once a day only which was not within the marketing authorization for calcitriol and calcipotriol. The study was performed in healthy volunteers. Leo referred to the supplementary information to Clause 7.2. It was doubtful whether any of the applications were to the face and brought the ability of the data to substantiate the claims into question.
- Similarly the sensitisation study was performed with volunteers and under occlusive patches. The mean cumulative irritancy of calcitriol was 300% greater than the vehicle (table II); and so in comparison calcitriol was not well tolerated at all. The phototoxicity and the photoallergenic contact parts of this study were also completed in ways outside the Silkis SPC and in healthy volunteers not patients.

Although no direct comparison was made between Silkis and other products in the advertisement the reader was directed to only one reference; within this the less observant would conclude that Silkis had superior qualities compared to tacalcitol or calcipotriol in the clinical setting. This was not substantiated by the reference and therefore the piece did not substantiate the comparison that was made. Leo alleged breaches of Clauses 7.2, 7.3 and 7.4.

### RESPONSE

Galderma noted that Queille-Roussel *et al* reviewed the results of four separate studies designed to evaluate specific local safety parameters. The only claim made in the advertisement was 'New Silkis ointment is an effective, yet well tolerated treatment for psoriasis'.

There was no shortage of evidence available to show that Silkis was 'effective' and 'well tolerated' for the treatment of psoriasis, indeed the grant of the marketing authorization would have been based on the provision of such clinical evidence. Absolutely no direct or indirect reference was made to comparator products. Galderma failed therefore, to understand how the reference could be claimed to be misleading, not make a fair comparison between comparator products and therefore not be substantiated.

With regard to the points raised by Leo, Galderma submitted that occlusive-patch application (Finn chambers) was a validated and accepted method of maximising exposure to a potential irritant, thereby providing an accurate indication of the potential for irritation. This fact was clearly highlighted in the materials and methods section of the reference. Since this scientifically validated method was used in order to determine the potential for irritation Galderma did not see how the licensed use of the product was relevant. The authors clearly discussed the similarities between their findings and those observed within the clinical trials.

With regard to the use of healthy volunteers, Galderma noted that the supplementary information to Clause 7.2 of the Code stipulated that '…care must be taken with the use of such data (derived from healthy volunteers) as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance'. Galderma submitted that the skin around a psoriasis plaque was 'normal skin' and it was on these peri-lesional areas that irritation usually occurred. The authors openly discussed the similarities between their findings, and those observed within the clinical situation. Studies in healthy volunteers were of relevance and significance and did not mislead.

Galderma noted that the Silkis SPC clearly stated that the product 'can be applied to the face', hence referring to this in the advertisement was not considered as a claim, but to be in compliance with the SPC, and consequently did not require substantiation by the inclusion of a reference. The licensing authorities had been provided with, and satisfied by, the substantiating clinical evidence in support of the use of Silkis on the face. Furthermore, the claim in question made no reference to the fact that any application was made to the face.

Galderma explained that the mean cumulative irritation index scores (CII) with regard to erythema, were 0.03 for calcitriol and 0.01 for calcitriol vehicle. The five point grading system defined 0=no reaction, 0.5=erythema barely visible, 1=mild erythema through to 3=severe erythema. The mean CII scores observed in this study were barely above grade 0 (no reaction), and thus the above product could be considered as being well tolerated. The difference between the scores for calcitriol (0.03) and calcitriol vehicle (0.01) was clinically insignificant.

Galderma stated that no reference whether direct or indirect was made to phototoxicity or photoallergic contact sensitization in the advertisement and therefore the deficiencies in this regard as claimed by Leo were irrelevant. Galderma did not understand how it could be alleged that a promotional piece was in breach of Clauses 7.2, 7.3 and 7.4 when no reference was made to phototoxicity or photoallergic contact sensitization.

Galderma stated that it was extraordinary that Leo had made the allegations stating that 'although no direct comparison was made between Silkis and other products in the piece…', and then further on state that '…the piece does not substantiate the comparison made'. The only claim made was that the product was effective and well tolerated; the tolerability of the product was clearly discussed and substantiated by Queille-Roussel *et al*. Galderma submitted that it could not be held responsible for the conclusions drawn by the 'less observant' as claimed by Leo, other than to reiterate the balanced results presented and reviewed in the cited reference.

### PANEL RULING

The Panel noted that the claim at issue related only to Silkis. The advertisement made no direct or implied comparison between Silkis, calcipotriol and tacalcitol.

Queille-Roussel *et al* had reported on the results of four separate studies designed to evaluate specific local-safety parameters of calcitriol in terms of cumulative irritancy, cutaneous contact sensitization, potential photoallergic contact sensitization and phototoxicity. The report concluded that calcitriol was a well tolerated treatment for stable plaque-type psoriasis. When tested in healthy volunteers it did not give rise to any cumulative irritancy or sensitizing. Calcitriol compared to its vehicle and white petrolatum was neither phototoxic nor did it show any potential for photosensitization. It was stated that the findings were consistent with the findings of the clinical trial programme where no major adverse events had been observed even after therapy duration of up to 78 weeks. The SPC stated that a low incidence of skin irritation (reddening, itching) had been reported following the use of Silkis and such irritation was usually of a temporary nature. If sensitivity or severe irritation occurred treatment should be discontinued temporarily or altogether.

The Panel noted Leo's comments about the methods used in the studies reported by Queille-Roussel *et al* and Galderma's submission on these points. The use of the product was not entirely consistent with the details in the SPC. Some of the sensitivity tests had been performed on healthy volunteers using the product once daily for five days with a two day break. Queille-Roussel *et al* referred to the results of the Silkis clinical trials. Taking all the data into account the Panel did not consider that the claim was misleading nor incapable of substantiation as alleged; there was no comparison in the advertisement. The Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code.

## 3 Prescribing information

### COMPLAINT

Leo pointed out that the prescribing information in the advertisement stated that in pregnancy: 'Use in

restricted amounts during pregnancy if considered essential by the physician'. However, the SPC stated 'Silkis should only be used in pregnancy in restricted amounts when clearly necessary'. Leo stated that the prescribing information had been altered and was not consistent with the SPC. A breach of Clause 4.1 of the Code was alleged.

## RESPONSE

Galderma stated that Clause 4.1 required that prescribing information be provided in a clear and legible manner in all promotional material for a medicine except for abbreviated advertisements. The prescribing information was clearly presented and therefore there was no breach of Clause 4.1.

With regard to the concern that the prescribing information had been altered and was not consistent with the SPC, Galderma stated that no restriction prevented the alteration of the prescribing information, in fact the Code encouraged 'the substance of the relevant information in the SPC' to appear in abbreviated form in the prescribing information. The actual wording in the SPC was 'should only be used in pregnancy in restricted amounts when clearly necessary' whilst the prescribing information stated 'use in restricted amounts during pregnancy if considered essential by the physician'. Silkis was a prescription only medicine and therefore the decision as to whether the product was used during pregnancy lay with the prescribing physician. Galderma submitted that the term used in the prescribing information (considered essential by the physician) was much stronger and clearer advice about the use of Silkis than the SPC (when clearly necessary).

Galderma denied a breach of Clause 4.1 of the Code.

## PANEL RULING

The Panel noted that Clause 4.1 required that the prescribing information listed in Clause 4.2 be provided in a clear and legible manner. The supplementary information stated that the prescribing information must be consistent with the SPC. Clause 4.2 required prescribing information to contain, *inter alia*, a succinct statement of the side-effects, precautions and contraindications relevant to the indications in the advertisement, giving in an abbreviated form the substance of the relevant information in the SPC.

The Panel noted the wording in the SPC that 'There are no adequate data from the use of Silkis in pregnant women. Studies in animals have shown developmental toxicity at doses which caused maternal toxicity (see section 5.3). The potential risk for humans is unknown. Silkis should only be used during pregnancy in restricted amounts when clearly necessary. Calcium levels should be monitored'. The prescribing information stated 'Pregnancy and Lactation: Not to be used during breast-feeding. Use in restricted amounts during pregnancy if considered essential by the physician. Calcium levels should be monitored'. The Panel considered that the prescribing information was consistent with the SPC with regard to use in pregnancy and ruled no breach of Clause 4.1 of the Code.

**Complaint received** **11 December 2002**

**Case completed** **8 April 2003**

CASE AUTH/1399/12/02

# ROCHE v ORTHO BIOTECH

## Promotion of Eprex

**Roche complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech in relation to recent safety concerns about the product involving anti-erythropoietin antibodies and pure red cell aplasia (PRCA). Roche marketed NeoRecormon (epoetin beta).**

**Eprex was indicated for the treatment of anaemia associated with chronic renal failure (CRF) in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis. It was also indicated for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis. Eprex was also indicated for the treatment of anaemia in adult patients receiving chemotherapy.**

**The five items at issue were letters to health professionals dated 19 November 2001, 17 July 2002 and 2 August 2002, a company statement dated 2 August 2002 which accompanied the letter of the same date and a supplement to a journal.**

**Roche alleged that the materials disparaged other epoetins, provided misleading and inaccurate information about the changes to the Eprex summary of product characteristics (SPC), attributed some of these misleading claims to health authorities, inferred that similar warnings and changes would be imposed on other epoetins and omitted crucial information about causality that was provided to financial analysts in USA.**

**Roche noted that the 'Dear Healthcare Professional' letter dated 19 November 2001 described changes to the Eprex SPC following 40 reports of PRCA. Roche understood that European regulatory authorities had requested such a letter to be sent in all EU countries in view of the SPC amendments. Similar requests had not been made to Roche or companies marketing other epoetins.**

**The letter was sent to inform the reader of important safety information for Eprex. It was clear therefore that the letter was about Eprex, not other epoetins. However, Roche considered that reference to 'other erythropoietins' in the second paragraph 'Very rare cases of PRCA have been reported from post-marketing experience in patients with chronic renal failure, most of them being treated with Eprex or other erythropoietins' fundamentally changed the tone, message and nature of the letter. As it was about Eprex the letter should have only referred to the post-marketing experience of Eprex. Ortho Biotech was not in any position to know or comment on the whole post-marketing experience for all erythropoietins. There was no correspondence or consultation with Roche.**

**Roche noted that the relevant European regulatory authorities had requested Ortho Biotech to inform the profession that most cases of PRCA were as a result of treatment with Eprex. Reference to 'other erythropoietins' deliberately misled and created confusion. The statement was ambiguous, exaggerated and could not be substantiated. Finally, Roche alleged that the statement disparaged NeoRecorman as it suggested that PRCA was at least as common with other erythropoietins.**

**Roche noted that 'Dear Doctor' letters were normally considered non-promotional because they involved important safety announcements, which were clear and unambiguous and non-promotional (Clause 1.2) and did not therefore require prescribing information. This letter was deliberately misleading and disparaging and was intended to promote Eprex in comparison with other products; it should have included prescribing information.**

**The Panel noted that this was a difficult matter; this was the first time that a letter giving safety information, drawn up in consultation with the regulatory authorities, had come before it for consideration under the Code. Clause 1.2 of the Code stated that 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they include no product claims' were exempt from the definition of promotion. The 'Dear Healthcare Professional' letter in question had been issued in co-operation with European regulatory authorities, the letter clearly related to an adverse-reaction warning for Eprex.**

**The letter referred to the product's licensed indication. The Panel considered that the second paragraph 'Very rare cases of pure red cell aplasia (PRCA) have been reported from the post-marketing experience in patients with [chronic renal failure], most of them being treated with Eprex or other erythropoietins', was ambiguous in that it implied that the incidence of PRCA with Eprex was no more than that seen with other erythropoietins. The letter included details about the incidence for Eprex but no comparable information was given with regard to other erythropoietins. The data showed that most of the cases of PRCA had occurred in Eprex-treated patients with very few cases occurring in patients treated with other erythropoietins. This was not made clear in the letter. The Panel considered that the statement constituted an inaccurate comparative claim for Eprex and thus brought the letter within the scope of the Code. The Panel considered that the claim was ambiguous, misleading and could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that the claim was exaggerated or that it disparaged NeoRecormon and no breach was ruled. As no prescribing information was included the Panel also ruled a breach of the Code.**

**Upon appeal by Ortho Biotech, the Appeal Board considered that this was a very difficult area. The Appeal Board noted the exemptions to the term 'promotion' in Clause 1.2 of the Code, as referred to by the Panel.**

**The Appeal Board noted that the letters dated 19 November 2001 and 17 July 2002 were safety warning letters which Ortho Biotech had been required to send by the regulatory authorities. It appeared that each letter was subjected to a regulatory approval process.**

**The Appeal Board considered that in principle safety warning letters required by the regulatory authorities were potentially subject to the Code. Companies should thus bear in mind the requirements of the Code. A safety warning letter required by the regulatory authorities would be exempt from the Code if it met the exemption given in Clause 1.2 of the Code as outlined above. The Appeal Board considered that in such circumstances mention of a product indication would not necessarily be seen as a product claim. Each case would have to be decided on its merits.**

**The letter dated 19 November had been issued in cooperation with the European regulatory authorities and clearly related to an adverse reaction warning for Eprex. At the time the letter was sent the Eprex SPC (dated 9 November 2001) stated (section 4.8, undesirable effects) that 'Pure red cell aplasia (erythroblastopenia) has very rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins'. The Appeal Board noted both parties' submissions about the incidence of PRCA but considered that given the statement in the SPC the reference to '…other erythropoietins' in the letter was not inconsistent with the SPC. The Appeal Board did not consider that the statement in the letter was ambiguous, misleading, inaccurate and incapable of substantiation as ruled by the Panel. As a consequence the Panel's rulings of breaches of the Code were overturned by the Appeal Board.**

**The Appeal Board considered that the letter was a factual announcement relating to an adverse reaction warning which was exempt from the definition of promotion as set out in Clause 1.2 of the Code and was thus not subject to the Code. It did not need prescribing information.**

**Roche referred to a second 'Dear Healthcare Professional' letter sent on 17 July 2002 following an urgent safety restriction from the European regulators which recommended major restrictions on the use of subcutaneous Eprex. This resulted in a major change to the Eprex SPC. The letter recommended that Eprex should be administered intravenously (IV) in chronic renal failure (CRF) patients where feasible. However the letter did not state that the SPC had been changed more radically than this for haemodialysis patients such that they should now only receive Eprex IV. Roche alleged that this omission was misleading. In addition, although the letter stated that the product should be stored and handled according to the SPC it did not state why this was important. Ortho Biotech had not informed the profession that a major change to the formulation of Eprex took place in 1998 and that the majority of cases of PRCA had occurred since that time. Speculation that this reformulation might have affected the stability of the product had been published in the New England Journal of Medicine and clearly it was particularly important that a potentially less stable product should be handled according to the cold chain instructions. To omit this information from a letter about safety was misleading, particularly as this information was provided later to financial analysts in USA.**

**The Panel noted its comments above about such letters and their position with regard to the Code. The 'Dear Healthcare Professional' letter now at issue had also been issued in co-operation with the European regulatory authorities and related to an adverse-reaction warning for Eprex.**

**The letter stated that most cases of PRCA had occurred following the subcutaneous use of Eprex and only in patients with CRF and that, as a result, 'the product should be administered by intravenous (IV) route in CRF patients where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient'. The letter then referred to changes to the SPC.**

**The Eprex SPC had been revised to include the statement that in adult haemodialysis patients the product should be administered by the intravenous route. This was not mentioned in the letter at issue. The SPC had previously stated that in adult haemodialysis patients subcutaneous administration should be preferred over IV use. The Panel considered that the information given in the 'Dear Healthcare Professional' letter was incomplete with regard to amended advice on route of administration. In that regard the letter was inaccurate and inconsistent with the particulars listed in the Eprex SPC. The letter thus came within the scope of the Code. Breaches were ruled. The Panel did not consider that the letter was misleading with regard to the side-effects of Eprex. No breach was ruled. Although information about the formulation change was not irrelevant the Panel did not consider that omitting such information from the letter in question was misleading *per se*. The Panel ruled no breach in that regard.**

**Upon appeal by Ortho Biotech, the Appeal Board noted that the letter dated 17 July had been issued in cooperation with the European regulatory authorities and clearly related to an adverse reaction warning for Eprex. The letter stated that most cases of PRCA had occurred following the subcutaneous use of Eprex and only in patients with CRF and that, as a result, 'the product should be administered by intravenous (IV) route in CRF patients where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient'. The letter then referred to changes to the SPC.**

**The Appeal Board considered that the letter was factually correct with regard to CRF patients. It did not consider that in the context of the letter as a whole the omission of information about the route of administration for adult haemodialysis patients meant that the letter was inaccurate and inconsistent with the Eprex SPC as ruled by the Panel. As a consequence the Panel's rulings of breaches of the Code were overturned by the Appeal Board.**

**The Appeal Board considered that the letter was a factual announcement relating to an adverse reaction warning which was exempt from the definition of promotion as set out in Clause 1.2 of the Code and was thus not subject to the Code. The appeal was successful.**

**Roche noted that a subsequent letter dated 2 August was sent to offer clarification on matters raised in the letter of 17 July. The letter dated 2 August was entitled 'Eprex Immunogenicity in Perspective' with a sub-heading of 'PRCA – the facts to date' and should have included prescribing information. Roche alleged that the references to regulatory authorities, including the French Agency and the European Agency (repeated also in the accompanying 'Company Statement') were in breach of the Code. Roche alleged that the reader was misled into believing that although restrictions had only been placed on Eprex, a 'new assessment currently on-going' was likely to result in restrictions on other epoetins. The assessment had been completed and the Eprex SPC had been changed. This myth of an ongoing assessment (over and above routine surveillance) was tantamount to disparagement of NeoRecormon in breach of the Code. Roche alleged that to deliberately use the reputation and status of the regulatory authorities as a vehicle for this sort of misleading correspondence brought the pharmaceutical industry into disrepute in breach of Clause 2.**

**Roche alleged that the final bullet point of the letter was misleading. It included unqualified advice that clinicians could 'maintain the existing regimen of subcutaneous Eprex' for CRF patients. Roche referred to section 4.2 of the revised SPC which stated 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible'. Beneath this general statement was more detailed instruction for specific patient groups. To promote the maintenance of the existing regimen was not consistent with either the SPC or the advice of the European regulators' urgent safety warning.**

**In addition, although the letter was sub-headed 'the facts to date', no mention was made of the change to the formulation of Eprex even though this was cited as a possible cause. The effect of all these breaches was to bring the industry into disrepute. A breach of Clause 2 was alleged.**

**The Panel did not accept Ortho Biotech's submission that the letter was outside the scope of the Code. The letter had accompanied a promotional mailing and so had been used in a promotional setting. It was subject to the Code. A breach of the Code was ruled as prescribing information had not been included.**

**The Panel considered that the reference to a new assessment of the erythropoietins currently ongoing was misleading as this had already taken place. Breaches of the Code were ruled which were upheld on appeal by Ortho Biotech. The Panel ruled no breach of the Code with regard to the allegations that the statement was a misleading comparison, that it was misleading with regard to the side effects of Eprex or that it disparaged NeoRecormon.**

**The final bullet point stated that in patients with chronic renal failure, already taking Eprex by subcutaneous injection, clinicians had three prescribing options. The Panel considered that the three prescribing options had been presented with equal weight. It was not clear that the second option to maintain SC administration should only be followed where the first, a change to IV therapy, was not feasible. The Panel noted that advice given in the SPC for subcutaneous use of Eprex in adult patients with renal insufficiency not yet undergoing dialysis and in adult peritoneal dialysis patients, referred to considering the risk/benefit for each patient. The Panel considered that the statement in the letter regarding route of administration was inconsistent with the Eprex SPC and that it was misleading and could not be substantiated. Breaches of the Code were ruled which were upheld on appeal by Ortho Biotech. The Panel did not consider that the statement was misleading with regard to the side effects of Eprex. No breach was ruled.**

**The Panel noted that under the sub-heading 'PRCA – the facts to date', there was no mention of the possible role played by the change in the Eprex formulation. The Panel considered that on balance, by not addressing the issue of formulation change, the letter was misleading; it was not presenting 'the facts to date'. A breach of the Code was ruled which was upheld on appeal by Ortho Biotech. The Panel did not, however, consider that the omission of information about the formulation change misled the reader with regard to the side effects of Eprex. No breach was ruled.**

**The Panel noted its comments and rulings above and considered that, on balance, the letter was such as to reduce confidence in the industry and to bring it into disrepute. A breach of Clause 2 was ruled. This ruling was upheld on appeal by Ortho Biotech.**

**Roche alleged that a 'Company Statement' which accompanied the letter of 2 August 2002 and which was supposed to 'highlight key aspects of the revised [SPC] and current scientific literature', was selective, erroneous, incomplete, misleading and failed to include prescribing information. The statement included a reference to the French regulatory authority acting as the reference member state for Eprex. No mention was made of the change in Eprex formulation.**

**Although no direct reference was made to NeoRecormon Roche stated that there was an inevitable inference that the product was being commented upon each time 'the erythropoietins as a whole' were mentioned. There was no mandate for Ortho Biotech to be offering comment on anything other than its own product, unless it was clearly pointing out that the incidence of PRCA was lower with other products than with Eprex. It was clear from discussions that Roche had had with clinicians that statements pertaining to 'erythropoietins as a whole' had had the effect of disparaging NeoRecormon and could be regarded as knocking copy.**

**The Panel noted that the Company Statement referred to the Medicines Control Agency (MCA)**

**and its approval of the 'Dear Doctor' letter dated July 2002 and the revised SPC. Promotional material must not include, *inter alia*, any reference to the MCA and a breach was ruled.**

**The Company Statement referred to the 'heightened awareness of reports of increased immunogenicity and [PRCA] in association with Eprex and other erythropoietins'. It was also stated that 'all exogenous recombinant proteins … have been associated with immunogenic phenomena and antibody production'. The Panel considered that these statements failed to convey that Eprex was associated with a greater incidence of PRCA than any other erythropoietin; it appeared that all were equal in this regard. The Panel considered that this was a misleading comparison which could not be substantiated. Breaches of the Code were ruled. This ruling was upheld on appeal by Ortho Biotech. The Panel did not consider that the statements disparaged NeoRecormon. No breach of the Code was ruled. A further breach was ruled as prescribing information had not been included.**

**Roche alleged that the statement that change to IV administration was 'not mandatory', was over simplistic and misleading. Comments about feasibility of subcutaneous administration were married to recommendations of undertaking a risk benefit evaluation of usage in patients not yet undergoing dialysis. Therefore the assertion in the Company Statement that 'Section 4.3 of the revised SPC does not contra-indicate SC administration of Eprex for any patient group' was misleading and did not represent the SPC in its entirety as this was not the case for haemodialysis patients. Roche noted that this section of the Company Statement also made reference to the potential increased dose required if patients changed to IV administration. This included the statement 'Ortho Biotech will work with individual units … to ensure that no funding issues compromise this change'. This appeared to be a disguised financial inducement to persuade clinicians from taking an obvious alternative action, which was to switch to another epoetin so as to continue with the SC route.**

**The Panel noted that the Company Statement noted that PRCA was mainly associated with subcutaneous administration and that a change to IV therapy might lessen the risk. It was stated 'Although not mandatory, the revised SPC … recommends a change to IV administration for particular patients where feasible'. The revised SPC, however, stated that in adult haemodialysis patients Eprex should be administered by the IV route – the previous SPC had stated that the subcutaneous route was preferred in such patients. The Panel considered that there were patient groups for whom IV administration of Eprex was mandatory. The Panel considered that the Company Statement was not consistent with the particulars listed in the SPC in this regard. A breach of the Code was ruled. This ruling was upheld on appeal by Ortho Biotech.**

**With regard to subcutaneous administration the Company Statement also stated 'Section 4.3 of the revised SPC does not contraindicate SC administration of Eprex for particular patients and the wording of Sections 4.2 and 4.4 confirms that a change to IV administration for Chronic Renal Failure patients is not mandatory'. The Panel noted its comments above. Although it was true that Section 4.3, Contra-indications, of the Eprex SPC did not refer to subcutaneous administration the Panel nonetheless considered that the Company Statement was misleading in that it played down the need to change to IV Eprex and the limited circumstances for SC use. The Panel considered that the Statement was not consistent with the particulars listed in the SPC and a breach was ruled. This ruling was upheld on appeal by Ortho Biotech.**

**The Panel noted that financial discounts were common in the industry and were outside the scope of the code. There was no reason why a company could not decide to allow a discount on a product or decide to withdraw a discount previously given. The Panel ruled that there had been no breach of the Code in this regard.**

**Roche alleged that a section of the Company Statement made no mention of the requirement for IV administration in haemodialysis and gave no information about the risk benefit. It implied that certain patients would remain on SC administration and stated that the SPC did not contraindicate SC administration, which was alleged to be misleading because no mention was made of the fact that essentially SC use was not indicated in haemodialysis.**

**The Panel noted its comments regarding the change from subcutaneous to IV administration above. The section of the Company Statement in question stated that SC administration was not contraindicated in any patient group and that it was not mandatory to change patients to IV therapy. The Panel considered that in this regard the Company Statement was misleading and inconsistent with the particulars listed in the SPC. Breaches were ruled. The Panel did not consider, however, that in this regard the Company Statement was a misleading comparison, misleading with regard to side effects or exaggerated. No breaches were ruled.**

**Roche had also alleged a breach with regard to the mention of the European Agency. The Panel noted its previous comments in this regard and ruled no breach of the Code in this regard.**

**With regard to the allegations relating to the statement that the European Agency was currently reviewing erythropoietins as a whole, the Panel considered that its rulings of breaches made above also applied here. Further breaches were thus ruled. This ruling was upheld on appeal by Ortho Biotech.**

**Roche noted that the section of the Company Statement under the sub-heading 'Continuing with SC administration with a change to a different erythropoietin' stated that '… the revised SPC does not contra-indicate SC administration of Eprex for any patient group….'. This statement was clearly designed to dissuade clinicians from the need to change to an alternative product. It was false and misleading. The Company Statement then added unsubstantiated information which was contrary to**

**the safety warning issued by the European Pharmacovigilance Working Party by suggesting that if the patient had been treated for 'months to years' a switch was not required in view of the 'assessment of all erythropoietins' and the nebulous 'ongoing research being conducted by others'. No evidence was presented to justify the assertion that PRCA was unlikely after prolonged treatment. The claim was apparently justified by referring to a regulatory authority, misquoting that authority (as detailed above) and finally giving no details about ongoing research. This statement contradicted the recommendation of the SPC.**

**In relation to the claim in the Company Statement that Section 4.3 of the revised SPC did not contraindicate SC administration of Eprex for any patient group, the Panel considered that its rulings above were relevant. The Panel noted that the Company Statement implied that the longer that patients with chronic renal failure were on Eprex the less of a risk PRCA became. The Panel considered that although referred to in the SPC, the phrase '… [cases of PRCA] have rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins …', within the context in which it appeared in the Company Statement, played down the need to change patients to IV therapy and thus was misleading and inconsistent with the SPC. Breaches of the Code were ruled. This ruling was upheld on appeal by Ortho Biotech.**

**The Panel considered its rulings made above with regard to the European Agency's ongoing review of the erythropoietins applied here. Breaches were thus ruled. This ruling was upheld on appeal by Ortho Biotech.**

**The Panel considered that the impression was given that PRCA was as common with Eprex as with the other erythropoietins and this was not so. A breach of the Code was ruled. This ruling was upheld on appeal by Ortho Biotech. The Panel did not consider that the section was misleading about the side effects of Eprex or exaggerated and ruled no breach of the Code. The Panel considered that, with regard to the reference to the European Agency, its ruling above concerning the reference to the French regulatory authority was relevant. No breach of the Code was ruled.**

**The Panel noted that Roche alleged that a regulatory authority had been misquoted; the Company Statement did not contain any quotations and so no breach was ruled.**

**The final paragraph of the Company Statement headed 'Going Forward' stated that Ortho Biotech would 'closely monitor the emerging scientific and medical literature in relation to these issues and will update the UK renal community as this further data becomes available'. Roche alleged that Ortho Biotech had not updated the community on even the current literature. Roche noted that Ortho Biotech had stated that the product should be handled according to the SPC without explaining why this was so important. Roche alleged that the Company Statement failed to recognise the special nature of medicines and did not maintain high standards in breach of the Code. A breach of Clause 2 was also alleged.**

**The Panel considered that Ortho Biotech had been selective with regard to the references it had cited in its Company Statement. The company had not kept the renal community up-to-date with the relevant literature. The Panel considered that high standards had not been maintained. A breach was ruled. This ruling was upheld on appeal by Ortho Biotech.**

**The Panel noted its rulings and considered that, on balance, the Company Statement was such as to reduce confidence in the industry and to bring it into disrepute. A breach of Clause 2 was ruled. This ruling was upheld on appeal by Ortho Biotech.**

**Roche alleged that an article in a journal supplement illustrated how Ortho Biotech had sought to inform about Eprex safety in a disguised way. This supplement was supported by Ortho Biotech and mostly contained sound advice from independent authors about how to handle products which required a cold chain. The supplement did not explain at any point why this was important, why Ortho Biotech had commissioned it or its relevance to the current safety issue.**

**Roche noted that the section headed 'The Manufacturer' made several claims about Eprex and numbers of patients who had benefited. It then explained the company's values and beliefs encompassed in a document called Credo. Roche noted that the key part of Credo was the company's responsibility to the profession, patients and all who used its products. The item was clearly promotional and should have included prescribing information.**

**The Panel considered that the chapter headed 'The Manufacturer' promoted Eprex and as prescribing information was not included a breach of the Code was ruled. The aim of the supplement was to address the pharmaceutical implications of cold chain management, not the clinical consequences relating to individual products. The Panel, therefore, did not accept that the chapter headed 'The Manufacturer', even though written by employees of Ortho Biotech, needed to address in any detail the clinical implications of not maintaining the cold chain with regard to Eprex. In that regard the Panel did not consider that the chapter was misleading. Nor did the Panel consider it either misleading or disparaging to illustrate one point in the chapter with a reference to interferon alpha. The Panel ruled no breaches of the Code.**

**The Panel did not accept that the whole supplement was disguised promotion of Eprex. The supplement addressed general pharmaceutical issues of cold chain management. No breach of the Code was ruled.**

**The Panel did not consider that reference to Ortho Biotech's Credo meant that high standards had not been maintained or that it brought discredit upon or reduced confidence in the industry. No breaches of the Code, including Clause 2, were ruled.**

**Roche alleged that in addition to the breaches of the clauses mentioned above, the effect of Ortho**

**Biotech's activities, exemplified in the five items at issue, was to bring the industry into disrepute in breach of Clause 2.**

**The Panel noted that PRCA, although a rare complication of therapy, was a serious condition. In the Panel's view it was essential that clinicians were clearly informed of all the issues so that they could minimise the risk to their patients. The Panel noted its comments and rulings above in particular those with regard to the need to change patients to IV therapy. The Panel considered that by not stressing that subcutaneous injections should not be given to some patients and that the maintenance of subcutaneous administration in others was only second choice to switching to IV and not a choice in itself, patient safety had been compromised. The Panel considered that overall such advertising brought discredit upon, and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.**

**Upon appeal by Ortho Biotech, the Appeal Board noted that the Panel's ruling of a breach of Clause 2 applied to the three letters to health professionals and the Company Statement. The Appeal Board noted that two of the letters at issue had been ruled not to be within the scope of the Code. The Appeal Board had upheld the Panel's rulings of breaches of Clause 2. With regard to the letter dated 2 August and the Company Statement the Appeal Board therefore decided that the circumstances did not warrant a further ruling of a breach of Clause 2 and ruled accordingly. The appeal on this point was successful.**

Roche Products Limited complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech in relation to recent safety concerns about the product involving anti-erythropoietin antibodies and pure red cell aplasia (PRCA). Roche marketed NeoRecormon (epoetin beta).

Eprex was indicated for the treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis. It was also indicated for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis. Eprex was also indicated for the treatment of anaemia in adult patients receiving chemotherapy.

## GENERAL COMMENTS FROM ROCHE

Roche alleged that through a broad range of activities Ortho Biotech had misled the medical community with regard to the incidence of PRCA with Eprex relative to other epoetins including NeoRecormon. Ortho Biotech had not restricted its comments and information to Eprex but had consistently sought to imply equal problems with other epoetins. In addition, communications about this serious unexpected adverse reaction, including changes to the summary of product characteristics (SPC) recommended by regulatory authorities, which should also have reflected the emerging scientific knowledge and the current literature, were selective, misleading, and made claims which were not capable of substantiation. Many of these claims, particularly those about other epoetins, were supported only by reference to regulatory authorities which made investigation and confirmation of the claims extremely difficult. Other claims were clearly inconsistent with the changes to the licence for Eprex which were the cause of the communications.

Roche noted that much of this activity had been through one-to-one verbal communications from Ortho Biotech representatives to health professionals. In addition Roche referred to five items.

Roche explained that epoetin alfa (Eprex), and epoetin beta (NeoRecormon) stimulated red blood cell production and were licensed for the treatment of anaemia secondary to chronic renal dysfunction and cancer chemotherapy. Although the active compounds were similar, they were formulated differently.

PRCA was a rare haematogical condition where the bone marrow failed to produce red blood cells. Anti-erythropoietin antibodies were a newly described cause of this condition. This was a serious safety issue, as the patient must stop epoetin therapy and thereafter might have to be on regular blood transfusions indefinitely. Prior to 1998 epoetins were not associated with PRCA and no reference was made to it in the SPCs.

Casadevall *et al* (1999) reported cases of anti-erythropoietin antibodies associated with PRCA in renal dialysis patients treated with epoetins to the French health authority, the Agence Francaise de Securite Sanitaire Des Produits de Sante (AFSSPS). Accordingly in March 2001 the SPC for NeoRecormon was changed to include the following statement: 'In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red-cell aplasia (PRCA) occurred during rHuEPO therapy' even though this was not a specific epoetin beta effect. No change was made to the Eprex SPC.

In November 2001, Roche understood that Ortho Biotech was directed by the Committee for Proprietary Medicinal Products (CPMP) to change the Eprex SPC and inform the health profession about the change via a 'Dear Doctor' letter. According to the letter there were then 40 cases of confirmed or suspected PRCA mostly occurring after 1998.

Casadevall *et al* was published in the New England Journal of Medicine in February 2002 with a follow up letter in April. Of 39 patients studied, 36 were receiving Eprex at the time of anaemia onset.

In July 2002 the European Pharmacovigilance Working Party of the CPMP considered a growing number of reports of PRCA associated with Eprex. This led to an urgent safety restriction for Eprex and a further change to its SPC advising against its subcutaneous (SC) use in haemodialysis patients and only where intravenous (IV) administration was not feasible in other renal patients. Another 'Dear Doctor' letter communicated this information to health professionals. No such changes were made to the SPC of NeoRecormon or other epoetins marketed in Europe.

The ruling noted at that time:-

'Although a few cases of [PRCA] have also been observed with other marketed erythropoietins (less than about ten cases throughout the world), the great majority of these cases were reported with Eprex.' Other erythropoietins would include Epogen, Procrit, NeoRecormon and darbepoetin.

Roche stated that the reason for the increase in PRCA cases was the subject of debate. However in any review of 'emerging clinical or scientific opinion' (supplementary information to Clause 7.2 of the Code) certain recent publications should be cited as highly relevant. Firstly, the original paper and subsequent follow up letter by Casadevall *et al* showed that the majority of reported cases were associated with Eprex. Secondly the editorial of the same edition of the New England Journal of Medicine speculated that one of the reasons for the appearance of this problem was a change in the manufacture of Eprex in 1998 when human serum albumin was removed as the stabiliser.

No comment on these publications or on the speculation about formulation change had been provided by Ortho Biotech in the UK. However Dr Per Peterson, Chairman of Research and Development, Johnson & Johnson, cited the change of formulation of Eprex as one of the three major causes of the problem when presenting this issue to financial analysts in USA. In addition communication from one regulatory authority included information about the change in formulation among other possible causes of the problem.

Roche considered therefore that the communications from Ortho Biotech in the UK had ignored this important information as part of a campaign to lead physicians to believe that this problem applied equally to all epoetins. The UK profession had therefore not been informed of important research findings which had nonetheless been presented to financial analysts in the USA.

In summary Roche alleged that the communications detailed below; disparaged other epoetins, provided misleading and inaccurate information about the changes to the Eprex SPC, attributed some of these misleading claims to health authorities, inferred that similar warnings and changes to the Eprex SPC would be imposed on other epoetins as a result of 'new ongoing assessments by Health Authorities' etc and omitted crucial information about causality that was nonetheless provided to financial analysts in USA.

## GENERAL COMMENTS FROM ORTHO BIOTECH

Ortho Biotech noted that the two 'Dear Doctor' letters at issue in points A and B below were regulatory communications that had been subjected to formal approval by the European regulators. They therefore did not constitute 'promotion' as defined in the Code. Clause 1.2 of the Code stated that the term 'promotion' meant 'any activity undertaken by a pharmaceutical company or with its authority that promotes the prescription, supply, sale or administration of its medicines'. Specifically excluded were 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse reaction warnings …'. Indeed, it was difficult to see how there could be a promotional motive behind a 'Dear Doctor' letter intended to inform physicians about safety concerns with a product. As an explanation of the basis for, and the nature of, 'Dear Doctor' letters in question, Ortho Biotech outlined the relevant regulatory processes to which it had adhered.

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### A 'Dear Healthcare Professional' letter: 'Important Safety Information Eprex: reports of pure red cell aplasia"

#### COMPLAINT

Roche noted that this 'Dear Healthcare Professional' letter dated 19 November 2001, which was sent to health professionals, described changes to the Eprex SPC following 40 reports of PRCA. Roche understood that regulatory authorities in Europe had requested such a letter to be sent in all EU countries in view of the SPC amendments. Similar requests had not been made to Roche or companies marketing other epoetins. Although the letter referred to 'other erythropoietins' and to 'post-marketing experience' Ortho Biotech did not consult Roche prior to sending this letter.

The first paragraph of the letter stated that it was sent to inform the health professional of important safety information for Eprex. It was clear therefore that the letter was about Eprex, not other epoetins. However the second paragraph stated that 'Very rare cases of PRCA have been reported from post-marketing experience in patients with chronic renal failure, most of them being treated with Eprex or other erythropoietins'.

Roche considered that including the words 'or other erythropoietins' fundamentally changed the tone, message and nature of the letter. It exemplified the distortion of informing clinicians on a safety issue in the execution of a covert marketing campaign.

The letter was about Eprex and should therefore have confined itself to the post-marketing experience of Eprex. Ortho Biotech was not in any position to know or comment on the whole post-marketing experience for all erythropoietins. There was no correspondence or consultation with Roche. Thus the phrase 'post-marketing experience' in the context of this letter should relate to Eprex.

Roche believed that the relevant regulatory authorities in Europe requested Ortho Biotech to inform the profession that most cases of PRCA were as a result of treatment with Eprex. By adding the phrase 'or other erythropoietins' in this context Roche alleged that Ortho Biotech had deliberately misled and created confusion between its product and other epoetins with regard to a claim about side effects in breach of Clauses 7.2, 7.3 and 7.9. The statement was ambiguous and exaggerated in breach of Clauses 7.2 and 7.10. Roche alleged that the statement was in breach of Clause 7.4 as it could not be substantiated.

Finally, as it suggested that PRCA was as common (or possibly more common) with other erythropoietins (depending on how one interpreted the sentence) it disparaged NeoRecormon in breach of Clause 8.1.

Whatever the meaning of the statement it differed from other letters sent out by Ortho Biotech affiliates in Europe. In the Netherlands the format of the letter was almost identical to that in the UK except for the statement in question. The translation read 'From post-marketing data, it was noted that in patients with chronic kidney insufficiency some rare cases of PRCA appeared. Most patients were treated with Eprex and some with other erythropoietins'. This was clear, unambiguous and represented the facts at the time.

Roche noted that 'Dear Doctor' letters were normally considered non-promotional because they involved important safety announcements, which were clear and unambiguous and non-promotional (Clause 1.2). They did not therefore require prescribing information. In this case the letter was deliberately misleading, and attempted to include other products in the statement without prior consultation and thereby disparaged them. As such the letter was intended to promote Eprex in comparison with other products; it therefore should have included prescribing information (Clause 4.1).

## RESPONSE

Ortho Biotech noted that contrary to Roche's suggestion, the CPMP played no part in the variation of marketing authorisations for products that were not centrally-approved, unless there was a need for it to resolve disagreements between the national authorities. The relevant change in the Eprex SPC was introduced by Ortho Biotech, in consultation with the French agency and the other national authorities.

Ortho Biotech stated that the letter in question was a regulatory communication following an urgent safety restriction. Following intensive discussions between the French agency and Ortho Biotech regarding the relevant documentation, the 24-hour consultation period for this urgent safety restriction occurred between 8/9 November 2001. During the process, the text for the letter was agreed by each of the concerned member states and disseminated by the reference member state. Having received the agreed text of the letter, the Pharmacovigilance Group in the Medicine Control Agency's (MCA's [now known as the Medicines and Healthcare products Regulatory Agency MHRA]) Post Licensing Division telephoned Ortho Biotech to initiate discussions regarding the necessity of further amendments to the planned letter on 9 November 2001. On 13 November 2001, Ortho Biotech provided the MCA with the suggested text of the letter and SPC for the UK. On 14/15 November Ortho Biotech had discussions with the MCA in order to finalise the text of these documents, and the wording of an MCA website announcement. On 15 November the MCA confirmed its approval of the text of the SPC and letter with very minor changes.

Ortho Biotech noted that Roche had alleged that certain wording in the letter was misleading and thus in breach of the Code. However, Ortho Biotech maintained its position that this document could not be treated as promotional. It was a regulatory communication and, as such, its wording had been reviewed and approved by numerous regulatory authorities, including the French agency and the MCA. The Code should not therefore be used as a basis to regulate its content or any attachments that might accompany it.

Ortho Biotech also noted that contrary to Roche's assertion, it was the Dutch version which was different (in the relevant section) from the text agreed during the consultation period of 8/9 November 2001 rather than the UK version. The relevant wording agreed by the member states was: 'Very rare cases of pure red blood cell aplasia (PRCA) have been reported from the post-marketing experience in patients with CRF, most of them being treated with Eprex or other erythropoietins.'

This wording was approved unchanged by the MCA. It was therefore the Dutch version which showed slight variation. In any event, the fact that the language required by an authority in another member state might differ slightly from the centrally agreed wording did not suggest that Ortho Biotech UK had misled the intended recipients of the letter. If anything, it demonstrated that the regulatory approval processes could occasionally result in variations in wording from country to country. Ortho Biotech stated that if Roche had concerns about the approved wording of the letter, it was difficult to see why it needed to air its grievances before the Authority; it should have raised them with the regulators at the time the letter was issued.

Ortho Biotech reiterated that the letter was not an advertisement and therefore did not need to be accompanied by prescribing information. The MCA expressly agreed that the letter could refer readers to the company's website where the revised SPC was available or offer to provide a copy of the SPC directly on request.

Ortho Biotech noted that, in contrast to these regulatory, approved communications, Roche had not restricted its own discussions with the medical community to its own product. Instead, it denigrated Eprex and misrepresented its own position. Roche's activities had been the subject of a recent complaint (Case AUTH/1366/10/02) in which the company was ruled in breach of numerous aspects of the Code, and in one occasion was deemed to have brought the industry into disrepute.

Ortho Biotech denied that it had breached Clauses 4.1, 7.2, 7.3, 7.4, 7.9, 7.10 and 8.1 of the Code.

## PANEL RULING

The Panel noted that this was a difficult matter; this was the first time that a 'Dear Healthcare Professional' letter giving safety information, drawn up in consultation with the regulatory authorities, had come before it for consideration under the Code. Clause 1.2 of the Code stated that 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse-reaction warnings, trade catalogues

and price lists, provided they include no product claims' were exempt from the definition of promotion. The 'Dear Healthcare Professional' letter in question had been issued in co-operation with European regulatory authorities, the letter clearly related to an adverse-reaction warning for Eprex.

The first paragraph of the letter referred to the product's licensed indication. The second paragraph stated 'Very rare cases of pure red cell aplasia (PRCA) have been reported from the post-marketing experience in patients with [chronic renal failure], most of them being treated with Eprex or other erythropoietins'. The Panel considered that this statement was ambiguous in that it implied that the incidence of PRCA with Eprex was no more than that seen with other erythropoietins. The letter included details about the incidence for Eprex. No information was given about the data or incidence for the other erythropoietins. The data showed that most of the cases of PRCA had occurred in patients being treated with Eprex with very few cases occurring in patients treated with other erythropoietins. This was not made clear in the letter. The Panel considered that the statement constituted an inaccurate comparative claim for Eprex, ie that it was no more likely to cause PRCA than other erythropoietins, and thus brought the letter within the scope of the Code. The Panel considered that the claim was ambiguous, misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code were ruled. The Panel did not consider that the claim was exaggerated or that it disparaged NeoRecormon; no breach of Clauses 7.10 and 8.1 was ruled.

The Panel considered that as the letter was not exempt from the definition of promotion it thus followed that it was required to include prescribing information. As no prescribing information was included the Panel ruled a breach of Clause 4.1 of the Code.

## APPEAL BY ORTHO BIOTECH

### General Comments

Ortho Biotech submitted that it had never claimed that the numbers of cases of PRCA with Eprex and other erythropoietins were equal; it had always stated that Eprex had been associated with more cases. However, in making its allegations, Roche repeatedly stated, or implied, both that PRCA was not associated with its product and that it had not been associated with any increase in reports of PRCA. For the reasons set out below, this was untrue and misleading.

Ortho Biotech stated that regulatory authorities had taken the position that PRCA was a phenomenon associated with Eprex and other recombinant erythropoietin products. It was also true that NeoRecormon was linked to a number of reports of PRCA associated with its clinical use in chronic renal failure (CRF) patients.

Ortho Biotech submitted that in Roche promotional pieces that had already been the subject of a complaint in Case AUTH/1366/10/02, Roche had repeatedly asserted either that NeoRecormon was not linked to cases of PRCA or that the only one reported case of PRCA with it could be discounted on the basis of the relevant patient's clinical predisposition.

Ortho Biotech submitted that at the Appeal Board hearing for Case AUTH/1366/10/02 held on 19 March 2003, representatives from Roche stated that there were only two cases of PRCA where the patient was treated exclusively with NeoRecormon.

Ortho Biotech noted that just after the Appeal Board hearing, Swissmedic, the Swiss medicines regulator, published on its website an update on a 'New rare and severe undesirable affect of recombinant erythropoietin'. Ortho Biotech submitted that according to the figures there were eight reports of patients treated exclusively with NeoRecormon who had developed antibody-positive PRCA. In addition, there were thirteen patients with antibody-positive PRCA who had received NeoRecorman and other erythropoietins prior to a loss of clinical effect. Ortho Biotech submitted that Roche, immediately before this publication [of Swissmedic] had continued to assert that it was aware of only two cases of confirmed PRCA that were exclusively associated with its product. The dossier submitted to the Swiss regulators in respect of known PRCA cases associated with NeoRecormon as of 31 December 2002 contradicted the information presented to the Appeal Board by Roche on 19 March. Ortho Biotech was surprised and concerned by this.

Ortho Biotech was also concerned by Roche's continuous citing of Casadevall *et al* (2002) which reported thirteen cases of PRCA associated with identifiable anti-erthyropoietin antibodies within the patients' sera. Of these cases, twelve were associated with Eprex and one with NeoRecormon. Roche had been critical of Ortho Biotech in not consistently quoting this article. However, all the cases reported within this article had been reported openly to the medical community and regulatory authorities, as well as all other confirmed or suspected cases well in advance of the publication. Roche had consistently quoted this article as if it were the entirety of the data. It represented less than a tenth of the cases quoted in communications from Ortho Biotech, and further, Roche had attempted to disassociate the single case associated with its product within this article by discounting a link on the basis of the patient's clinical disposition. Of even greater concern was that Roche had cited this article as evidence of the greater safety profile for its own product compared to Eprex in a manner which was totally inconsistent with the principles of pharmacovigilance reporting and safety comparisons.

Ortho Biotech submitted that in addition, Roche had expounded within its promotional claims that an increase in PRCA reported with Eprex was in relation to manufacturing problems, a notion derived from the speculative comment within Casadevall *et al*.

Ortho Biotech noted that all aspects of the manufacture of Eprex had been investigated, and to date no identifiable problem had been discovered. Furthermore, in respect of manufacturing, the FDA and the French authorities (on behalf of the European regulatory agencies) had investigated the manufacturing sites for Eprex and had drawn similar

conclusions. Additionally, Eprex remained within its release specifications and had done so throughout the entire period during which reports of PRCA had occurred.

Ortho Biotech submitted that Roche had also directed its speculative commentary towards the formulation of Eprex, since there was a temporal association between increased reports of PRCA and a major formulation change ie removal of human serum albumin (HSA) as a stabiliser, and addition of polysorbate 80 as an alternative stabiliser. Whilst this was indeed a major reformulation, Ortho Biotech had informed health professionals in its communications. In contrast Roche had misled that its own product had not undergone a major formulation change. This, as debated at the Appeal hearing on 19 March, was untrue, in that NeoRecormon was granted a marketing authorization in 1998 for a major change in formulation from a powder to a liquid 'ready for injection'. Such a change according to authoritative sources represented a change similar in magnitude to removal of HSA.

Ortho Biotech submitted that the implication of the formulation changes in respect of Eprex and reports of PRCA were unclear and remained speculative.

Ortho Biotech noted that Roche also complained that it had not sufficiently informed the medical community with respect to the handling of Eprex and the implications this might have had towards the increased number of suspected cases of PRCA reported. Roche had implied that as a result of its reformulation Eprex was inherently unstable.

Ortho Biotech submitted that Roche's comments had been made without knowledge of the stability data submitted to the appropriate regulatory authorities, and ignored further the considerable steps taken by Ortho Biotech to assure the integrity of Eprex within the cold supply chain. Ortho Biotech submitted that the significance of its cold chain integrity initiatives was not in respect of inherent instability, but to ensure compliance with the storage and handling instructions within section 6.4 of the Eprex SPC which stated 'Store at 2 to 8 C. The cold chain should be closely maintained until administration to the patient. Do not freeze or shake and protect from light'.

Ortho Biotech noted that the important point in this respect was that if the product was not handled in a controlled way then there was no guarantee that the product was stored in a manner as instructed within the SPC. Eprex was stable when stored at room temperatures for prolonged periods, but once in the community there was no way of knowing at what temperature it was exposed to, should it not be maintained within a controlled environment; hence Ortho Biotech's initiatives to assist correct handling of the product in accordance with the SPC. These activities fully supported the broader initiatives of the MCA in respect of advice to pharmacists regarding handling of biopharmaceuticals.

Ortho Biotech submitted that Roche's commentary in respect of reports of PRCA associated with Eprex had been based upon speculative marketing rather than science. This was not the approach undertaken by Ortho Biotech, which had alluded to emerging science and knowledge. Indeed opinion as to the cause of the association between PRCA and epoetins differed between regulatory authorities. The latest commentary from the Swiss authorities also suggested that the hypotheses expounded by Roche were unproven.

The first sentence within the paragraph taken from the Swissmedic website statement (translated into English) made it clear that any hypotheses remained unproven;

'It is as yet unclear why the above problem [PRCA] in the treatment of renal anaemia with recombinant erythropoietin did not occur or was not recognised until 10 years after its launch in the market. At the same time, it is not yet known to what extent other indications which are treated with recombinant erythropoietin may be affected. Another puzzle is the visibly higher incidence of PRCA in Europe as compared to the US. The change in the route of application from intravenous to primarily subcutaneous in the last years might be a key. So might other explanations of a more technical nature, such as improper storage, a modification of excipients or as yet unidentified accompanying factors.'

Ortho Biotech noted that the strongest association between reports of PRCA in CRF patients and clinical use of Eprex was that all cases had been associated with the subcutaneous route of administration, hence the guidance and advice issued to health professionals within the [regulatory] approved letter of 17 July (point B of the appeal) to use the intravenous route of administration where feasible. At this time, despite the fact that there were no cases of PRCA associated with Eprex when used exclusively intravenously, this advice was not accepted by all the nephrology community, with the Canadian Nephrology Society in particular stating that there was insufficient evidence available to advise a change in route of administration, suggesting that such a change might cause more problems than the rare cases of PRCA the advice sought to reduce. Other agencies eg the Israeli Nephrology and Hypertension Society however emphatically stated that the IV route was preferred and further, that this change should occur with all erthyropoietins.

Ortho Biotech noted that notwithstanding these public disagreements between agencies a 'Health Care Professional' letter was formally approved via the appropriate regulatory route which was subsequently issued in the UK by Ortho Biotech on 11 December 2002. This letter removed any option with regard to the route of administration for Eprex, by contra-indicating the subcutaneous route of administration (in CRF patients only). The accompanying changes within the SPC included appropriate changes.

Ortho Biotech noted that Roche had also repeatedly asserted that regulatory attention had focussed exclusively on Eprex, and that there had been no ongoing assessment of the safety of other erythropoietins either at the EMEA Pharmacovigilance Working Party (PhVWP) level or elsewhere. This was untrue, and contradicted the statement on the French Medicines Agency's own website.

Ortho Biotech noted that there had been ongoing meetings within the European agencies, and in particular a meeting was convened by the French authorities to which representatives of the principal companies which manufactured and marketed epoetins and similar molecules were invited. The minutes indicated that representatives from Roche attended and that that the purpose of the meeting was 'to discuss and explore the feasibility of a common programme to monitor PRCA incidents on patients receiving erythropoietins'. The PhVWP made clear that it considered PRCA was an issue for patients receiving all erythropoietins and expressed the CPMP's consensus that a risk management plan should be put in place for every erythropoietin in order to monitor the issue and estimate the true incidence of PRCA.

At this meeting all the parties agreed that there was a need to prospectively monitor the incidence of PRCA among CRF patients receiving erythropoietin therapies. The study was to be conducted in accordance with the case definitions for PRCA, suspected PRCA and antibody-mediated PRCA as developed and used by Ortho Biotech and in accordance with a common anti-erythropoietin antibody testing methodology agreed between the parties. Moreover, the PhVWP proposed that the study would be conducted in accordance with a single protocol for all marketing authorization holders under the supervision of an independent scientific co-ordinating centre.

Ortho Biotech found it difficult in the light of the above to understand how Roche argued that PRCA was not linked to its product and that it was an issue only for Eprex and that there was no ongoing assessment of all erythropoietin therapies.

### Background to the appeal

Ortho Biotech submitted that the background to the appeal could be divided into two main elements, the first dealt with the Panel's ruling in respect of Clause 1.2 of the Code. Ortho Biotech submitted that communications to health professionals regarding safety of a particular product, the contents of which were formally approved via the appropriate regulatory mechanism, and which it was mandated to send to health professionals (who were also nominated by the regulatory process under European Directives) should be exempt from the Code.

Ortho Biotech submitted that to view such formally approved (by regulatory authorities) communications (points A and B) as promotional and therefore subject to the Code created enormous difficulty for companies. In the event that the contents of those letters were ruled to be in breach of the Code, the company might be unable to give the undertaking and assurance in accordance with the Constitution and Procedure, that such communication could or would not be used again, since this might be a requirement of a regulatory authority and as such mandated to a company to so use, in accordance with European Directives.

Ortho Biotech submitted that this obvious conflict in following due regulatory procedure, which then might inadvertently bring a company in breach of the Code, was an important element of this case which required resolution under, or amendment of, Clause 1.2, exempting mandated regulatory communications such as formally approved 'Dear Healthcare Professional' letters from review under the Code.

Ortho Biotech noted that in respect of these two letters (points A and B) and also other items within this case, the nature of the appeal could be clarified by division of the argument into three principal areas: promotion in relation to Clauses 7, 3 and 2 and 9.1.

### Background in relation to Clause 7: Information, claims and comparisons.

Ortho Biotech submitted that there were two principal elements, firstly the use of spontaneously reported adverse events as an inappropriate basis for comparison of incidence (of an event) or safety of one product over another. Secondly, and related to the first point, any comparisons must use the similar nomenclature. Ortho Biotech outlined its processes for investigating reports of PRCA which had a bearing on this case.

### Use of spontaneously reported adverse events as an inappropriate basis for comparative safety and event incidence between products.

Ortho Biotech submitted that these complex issues were the subject of extensive ongoing clinical research, scientific investigation and regulatory review and described the conditions associated with PRCA which was a rare condition characterised by selective failure in the proliferation of red blood cell precursors in the bone marrow resulting in a profound anaemia. PRCA had been associated with autoimmune, viral, neoplastic disease, as well as multiple drug treatments, and more recently with immune-mediated anti-erythropoietin antibodies. The pathophysiology and clinical course of the immune-mediated PRCA was not fully understood and was the subject of intense and continued investigations.

Ortho Biotech noted that immune-mediated PRCA was also associated with other erythropoietins although, numerically not to the same degree as associated with Eprex. Simple comparison of numerical differences to determine the relative incidence of these reports to each different epoietin was however not straightforward. Ortho Biotech had never denied however that it had the majority of reported cases associated with Eprex nor had it ever implied numerical equivalence with other erythropoietins and in particular NeoRecormon.

The full extent to which PRCA was associated with all epoietin products and its cause(s) had yet to be fully determined. In the absence of comparative clinical or suitable epidemiological data, any comparisons in relation to reports of PRCA appeared to be based solely on a numerical comparison of spontaneous adverse event reported data. Such comparisons, however, had many flaws and were not appropriate for such comparisons.

Ortho Biotech submitted that a review of reputable texts on adverse drug reactions highlighted the

numerous possible confounding factors and biases that affected the validity of spontaneous reporting data and highlighted the problems with their meaningful interpretation.

Ortho Biotech noted that spontaneous reporting had significant limitations because it depended on voluntary reporting by doctors of suspected reactions encountered during regular clinical practice, which inevitably might lead to bias. Reporting was often incomplete, potentially distorted by media attention, and also declined with time following awareness of a particular event. Disease could also alter in terms of its natural history and in itself might be complex (ie PRCA) making diagnosis and identification of cases difficult or inaccurate. For these and other reasons, spontaneous reporting schemes were generally considered to be useful only for identification of new hazards, ie as an early warning system of side effects that might occur, but not as a basis for comparing incidence between medicines of the same class. Spontaneous reporting schemes were not considered to be a realistic basis for estimating the relative safety of medicines within the same therapeutic class nor were they a useful basis for determining the incidence of adverse drug reaction (report of CIOMS working group 1999). This was because neither the numerator nor the denominator could be accurately determined and there was no way of knowing what proportion of suspected adverse events had been reported.

### Background to the methodology for investigation of a nomenclature relating to reporting of PRCA

Ortho Biotech stated that in consultation with regulatory authorities worldwide Johnson & Johnson continued to conduct a comprehensive scientific investigation into the increased number of post marketing reports of loss of (therapeutic) effect where PRCA was suspected in patients treated with Eprex, particularly occurring post 1998.

Ortho Biotech submitted that analysis of its data presented to regulatory authorities and healthcare professionals included any report of a patient who had been administered Eprex or any other epoietin therapy, and who had experienced a loss of therapeutic effect which was suspected to be related to PRCA, regardless of availability of bone marrow examination results or evidence of anti-erythropoietin antibodies. Ortho Biotech submitted that it was important that it did not exclude from its reports cases where treatment had included multiple epoietin products was reported, ie if any patient had received Eprex at any time, the event was reported as associated with Eprex.

Ortho Biotech submitted that, consequently, its investigations and reports to the regulatory authorities and health professionals were thorough and open. Ortho Biotech therefore refuted allegations that it attempted to mislead the medical community in respect of PRCA and its association with Eprex and also within its reporting did not imply in any way that there was numerical equivalence or similar incidence of PRCA cases with other erythropoietins.

### Diagnosis of PRCA

Ortho Biotech stated that the definitive diagnosis of PRCA required a bone marrow biopsy in which there was a reduction exclusively of the erythroid precursor cell line, with other elements of the bone marrow being essentially normal. In many patients with chronic disease, such as CRF patients however such a bone marrow picture might not be so distinct. Emerging knowledge had also indicated for example that in myelodysplastic syndromes (MDS) it was now accepted that red cell aplasia might be a presenting feature of the disease with a mixed morphological picture within the bone marrow. Other factors made the diagnosis of PRCA (and associative cause) difficult and details were provided. So as not to inadvertently miss cases, it was decided to construct a database along the following definitions.

**Suspected PRCA:** These included cases with an apparent loss of (therapeutic) effect and were subsequently reported as either a bone marrow positive (for PRCA), or bone marrow not performed (or result not known).

**Bone Marrow Confirmed PRCA:** These were reported cases in patients with a loss of effect (reduction in haemoglobin or profound anaemia) whilst being treated with Eprex and with a bone marrow biopsy characterised by a virtual absence of the red blood cell precursors (< 0.5% erythroblasts) and also by decreased reticulocyte count in the peripheral blood smear (<1%).

**Antibody Mediated PRCA:** These were cases of suspected PRCA (with or without bone marrow confirmation) in which the presence of anti-EPO antibodies had been detected in a patient's serum, regardless of the antibody assay used. Ortho Biotech submitted that the type of antibody assay methodology used was important in that there were two principal types of assay that varied in sensitivity. Johnson & Johnson set up, validated, and used a central laboratory to investigate the serum samples obtained from patients anywhere in the world, who had been reported to it of having suspected PRCA. Given that many cases were reported retrospectively, often with very little clinical data available, this was not always possible, hence the antibody status of these patients were listed on the database as unknown.

Ortho Biotech stated that in addition, many cases with bone marrow biopsies had also been reported retrospectively and in very few cases had it been able to review the histology of the bone marrow or even have access to the report on the biopsy. Nevertheless, if they were reported to Ortho Biotech as being likely to be a case of PRCA this had gone on its database as a bone marrow positive case.

### Background in respect of Clause 3.2 ie promotion of Eprex in a manner which was consistent with its marketing authorization.

Ortho Biotech stated that Roche's suggestion that in haemodialysis patients the intravenous administration of Eprex was mandatory, was based on a misunderstanding of the meaning of the SPC for Eprex at the time the second 'Dear Healthcare Professional letter' dated 17 July 2002 was sent to health professionals and also to the changes in the SPC which occurred at that time as a result of due

regulatory process. The revised SPC for July 2002 under Section 4.2, 'Posology and Method of Administration', stated 'in patients with chronic renal failure, the product [Eprex] should be administered by the intravenous route where feasible'. This was not a contraindication of the SC route. The wording allowed for, but did not define, circumstances where Eprex might be administered to patients with chronic renal failure via the subcutaneous route.

Ortho Biotech noted that under a further subheading to this section the revised SPC stated, 'in patients on haemodialysis, the product should be administered by the intravenous route'. Following this and the previous sentence from the SPC was a statement referring the reader to Section 4.4 of the SPC to give greater clarity as to the rationale for this amended advice on route of administration. Section 4.4 stated 'As the PRCA cases are mainly associated with the subcutaneous route of administration, Eprex should be administered to chronic renal failure patients by the intravenous route where feasible'.

Ortho Biotech submitted that the use of the words 'feasible' and 'should' within the revised SPC dated July 2002 were not words of contraindication. Indeed, there was no revision to Section 4.3 of the SPC; 'contraindications'. Guidance from the European Commission regarding the SPC made clear that Section 4.3 of the SPC should contain only contraindications and therefore was limited to 'situations where the medicinal product must not be given for safety reasons, i.e. absolute contraindications'. Section 4.3 of the SPC for Eprex (July 2002) did not contraindicate the subcutaneous route of administration for Eprex in any subgroup of patients (as implied by Roche). Furthermore, the 'Dear Healthcare Professional' letter dated 17 July 2002 (point B) advising clinicians in respect of the route of administration was headed by the phrase 'Amended advice on route of administration'. The word 'advice' and the revisions of the SPC discussed in the letter were not the result of oversight, but were specific phrases and amendments following an extensive consultative process involving all the regulatory authorities within member states.

Ortho Biotech submitted that the company intent and requirement following the amendments to the SPC in July of 2002 was clearly to advise clinicians to use the intravenous route of administration in CRF patients, which in practice was limited to haemodialysis patients who had a readily available intravenous portal of access. The situation in reality was however not as simple as might appear, and some clinicians made a judgement not to administer Eprex via the intravenous route in spite of the amended advice from Ortho Biotech as per the letter of the 17 July 2002. Under these circumstances, the SPC allowed for a clinician to administer Eprex subcutaneously since the judgement of feasibility for the use of the IV route was a matter for that individual clinician and, at that time, the SPC for Eprex did not contraindicate the subcutaneous route of administration.

**Background comments in respect of the status of 'Dear Doctor' letters formally approved via the regulatory process.**

Ortho Biotech again noted the legal and regulatory status of such communications, which were approved via the appropriate regulatory processes, and which companies were required to send to nominated health professionals. Details were provided.

**Specifics of the appeal**

**A 'Dear Healthcare Professional' letter; 'Important Safety information Eprex:reports of pure red cell aplasia'**

Ortho Biotech submitted that the 'Dear Healthcare' letter had been reviewed, commented on and approved by the regulators on no less than three occasions, ie at a minimum, prior to the initiation of the urgent safety restriction procedure, during the 24 hour period for comment and prior to the final release of the communication to nominated health professionals within their jurisdictions. Of the 15 EU medicines regulators only the Dutch chose to modify the language of the letter, as prepared and approved by the French acting as reference member state, prior to its release within the country of their jurisdiction.

Ortho Biotech noted that the reason that all the regulatory authorities approved the content of the 'Dear Healthcare Professional' letter was that its contents were factual, informative and not misleading. Indeed, it was inconceivable that misleading statements regarding Eprex or other erythropoietin products would have found their way through this review and approval process.

Ortho Biotech noted that Roche appeared to object primarily to a statement that appeared in the second paragraph of the letter that 'very rare cases of pure red cell aplasia (PRCA) have been reported from the post-marketing experience in patients with [chronic renal failure], most of them being treated with Eprex or other erythropoietins' and alleged that this statement was misleading and/or ambiguous because it suggested that PRCA was also associated with NeoRecormon. Post-marketing safety data clearly showed that PRCA was associated with NeoRecormon. Further reference to PRCA and its association with erthyropoietins was made within the SPC for NeoRecormon.

Ortho Biotech noted that Roche had complained also that the statement implied direct comparison of incidence (of PRCA) between Eprex and other erthyropoietins. The letter did not. Ortho Biotech referred to its comments above as to why this would not be appropriate; regulatory authorities were well aware of the limitations of comparisons in respect to safety and incidence derived from adverse events which had been spontaneously reported.

Ortho Biotech noted that the Panel had previously also found comparative safety claims based only on spontaneous adverse event reporting data to be misleading and details were provided.

Ortho Biotech submitted that examples cited of made clear that comparisons based upon spontaneously reported events were misleading. The regulatory authorities that played a role in the development of the 'Dear Healthcare Professional' letter [point A] also

understood that such comparisons were inherently flawed and hence were not contained within a regulatory communication.

Ortho Biotech noted the Panel commented that this was the first occasion that such a 'Dear Healthcare Professional' letter giving safety information, had been considered under the Code. Ortho Biotech submitted that the letter was factual, accurate, non-promotional and hence came within the provisions of Clause 1.2 of the Code since they were 'factual, accurate, informative announcements … concerning licensed medicines and relating … to … adverse reaction warnings.' As such the letter was exempt from consideration under the Code.

Ortho Biotech referred to its previous comments regarding having been obliged by regulatory authorities to issue a 'Dear Healthcare Professional' letter, which if found to be in breach of the Code might create difficulties for a company to give an undertaking to cease use of such materials forthwith. For example, a company might be legally obliged to circulate such communications as part of world-wide periodic safety update reports which must include details of all safety-related, including urgent safety restrictions, the reasons for these actions, including all relevant documentation and any communication with the health professionals (eg 'Dear Healthcare Professional' letters) as a result of such action.

Ortho Biotech noted that in addition, regulatory authorities might use approved 'Dear Healthcare Professional' letters as the means by which they communicated safety information of this kind to the relevant professional groups. The reason for this was that the 'Dear Healthcare Professional' letter was the sole legal and regulatory mechanism for regulators and marketing authorization holders to communicate important safety information to physicians.

Ortho Biotech further noted that the importance of 'Dear Healthcare Professional' letters in this respect was set to increase. An EMEA document made clear that they were the main channel of communication between regulators and doctors. Indeed, the document expressed concern that the device was not being used as effectively as it might. It proposed that the 'Dear Healthcare Professional' letters for all products, whether approved nationally, by the mutual recognition procedure or the centralised procedure, should all be placed on a central EMEA Web site.

Ortho Biotech submitted that in light of all the above, it appealed against the Panel's determination that this 'Dear Healthcare Professional' letter was in breach of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code. Ortho Biotech also considered that it did not fall within the definition of promotion, but fell within the remit of Clause 1.2 and therefore was not subject to review under the Code. Consequently Ortho Biotech also denied a breach of Clause 4.1 of the Code.

## COMMENTS FROM ROCHE

Roche alleged that the matter was a simple one. Following a regulatory requirement to inform health professionals that Eprex had PRCA safety concerns (and preceding the subsequent requirement to withdraw the subcutaneous route suspected of being a contributing factor), Ortho Biotech sought to minimise the commercial impact and in so doing created promotional items, subject to the Code, that misled the target audience as to the scale of the problems with Eprex, and to the importance of the changes to the recommended route of administration of Eprex. Roche noted that in the following observations all comments to Eprex and PRCA related only to patients with renal anaemia.

## GENERAL COMMENTS

Roche stated that it had not misled the Appeal Board nor had it submitted inaccurate and incomplete safety data. The fact that Ortho Biotech had misled on a matter of patient safety was the serious matter at hand.

Roche noted that in its appeal that 'Ortho Biotech had never claimed that the numbers of cases of PRCA with Eprex and other erythropoietins were equal. [Ortho Biotech] had always stated that Eprex had been associated with more cases'. Never? Always? Referring to point A, the 'Dear Healthcare Professional' letter (19 November 2001) 'Important Safety Information Eprex: reports of pure red cell aplasia', this letter plainly stated that 'Very rare cases of pure red cell aplasia (PRCA) had been reported from post-marketing experience in patients with CRF, most of them being treated with EPREX or other erythropoietins'. There remained the clear inference that incidence of PRCA was the same for all members of the class. There was no mention of the fact that there were more cases with Eprex. In this context, the Ortho Biotech appeal statement that 'it had never sought to play down the number of associated cases' did not appear credible. Throughout Ortho Biotech's communications these differences had been minimised to an extent of putting patient safety at risk by attempting to qualify PRCA as a wholly class effect. The Panel's rulings of breaches of Clauses 4.1, 7.2, 7.3, 7.4, and 7.9 therefore seemed appropriate.

Roche noted that Ortho Biotech's appeal claimed that 'Roche repeatedly stated, or implied, both that PRCA was not associated with its product and that it had not been associated with any increase in reports of PRCA'. Again, this was not true. It contradicted the Roche SPC for NeoRecormon, which stated non-specifically: 'In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO therapy'. Also, it did not reflect the evidence presented to the Panel by Roche. The facts were that Roche was proactive in adding this very rare adverse event to its marketing authorization; Ortho Biotech presumably chose not to do so and were subject to a regulatory requirement to send a 'Dear Healthcare Professional' letter (warning about Eprex and PRCA). Roche noted that in the UK about 90% of NeoRecormon was given subcutaneously and Roche had never been asked or required to send any safety letters on PRCA. Periodic Safety Updates Reports had all been routine, with the most recent in February 2003.

Roche noted in the appeal Ortho Biotech claimed 'support for units and its determination to assist in a

move to the use of the IV route of administration' from subcutaneous. Ortho Biotech seemed to have failed in facilitating this move. Roche speculated that, due to the continued subcutaneous use endorsed by Ortho Biotech in point C, the marketing authorization was then withdrawn for the Eprex subcutaneous route in December 2002.

Roche alleged that the letter sent out by Ortho Biotech on 2 August 2002 (point C), sought to minimise the Eprex subcutaneous safety issues, formerly raised in the 'Dear Healthcare Professional' letter sent on 17 July 2002 (point B). The impact of the 2 August letter (point C) was to raise prescriber concern and confusion, which resulted in a number of enquiries to Roche. Roche had tried to reassure enquirers that the decisions of the regulatory bodies in Europe mandating changes to the SPC for Eprex did not apply to NeoRecormon and that there was no other on-going assessment that might lead to similar restrictions for NeoRecormon. This was still the case some nine months later.

Roche noted that Ortho Biotech's appeal referred to Case AUTH/1366/10/02 and stated 'Roche had repeatedly asserted either that NeoRecormon was not linked to cases of PRCA or that the only one reported case of PRCA with its product could be discounted on the basis of the relevant patient's clinical predisposition'. Again, this was totally false. In addition the French regulatory authority which was responsible for the Eprex safety issue stated on its website that the majority of cases were due to Eprex and some (about ten worldwide) were associated with other epoetins. This was in line with Roche's own reporting of cases with NeoRecormon.

Roche noted that Ortho Biotech had stated that '…Roche expound within [its] promotional claims that an increase in PRCA reported with Eprex is in relation to manufacturing problems'. Roche had looked hard for evidence to back up this assertion but had, thus far, not found any reference in its promotion that manufacturing problems were inferred as the cause of this epidemic. Conversely Roche had commented that the cause could be due to changes to the formulation as cited in the New England Journal of Medicine, and in the Webcast by Ortho Biotech's parent company to which Roche had referred previously. Roche made a clear distinction between a deliberate formulation change and a manufacturing problem.

Roche stated that it was sympathetic with the Ortho Biotech uncertainty expressed in the appeal that 'the implication of the formulation changes in respect of Eprex and reports of PRCA were unclear…'. With biotech products, it was well known that any changes in production could impact on efficacy and safety. It was therefore logical to speculate that suspected cases of PRCA could be linked to fundamental formulation changes. Since Ortho Biotech now admitted being 'unclear' about such implications, it was a pity such uncertainties were not shared with healthcare professionals, although they were shared with the financial community in USA but not in the UK as Roche had previously pointed out. In addition the current website of Ortho Biotech's parent company had a statement referring to the formulation change. 'While studies confirm our HSA-free product meets the same stability requirements as its HSA containing predecessor under recommended storage conditions, the data also show a decline in stability under stress conditions with the HSA-free formulation… Inappropriate handling may lead to enhanced levels of aggregation, which generally promotes immunogenicity in proteins'.

**The legal basis and regulatory process for the issue of 'Dear Doctor' letters**

Roche alleged that it was an obvious legal side-step that Ortho Biotech wished to exempt misleading communications from the scrutiny of the Code. It was therefore of concern that Ortho Biotech seemed to advocate that a 'Dear Doctor letter' *per se* should not be subject to the Code. This could create a precedent and allow this communication route to automatically evade the breaches of the Code that were ruled by the Panel at points A and B.

Roche noted that whilst regulatory authorities might scrutinize such items for scientific accuracy it was the company's responsibility to ensure compliance with local codes of promotional practice. If the European Regulatory Authorities had drafted the 'Dear Doctor' letter and then insisted that no changes be made then Roche might accept the Ortho Biotech case. Roche stated that it was in its experience with 'Dear Doctor' letters that it was the company that drafted the original document and amendments were then negotiated with the regulatory authority. Roche considered whatever the circumstances it was still the responsibility of the company to ensure that any statements made were not misleading. It was interesting that Ortho Biotech did not defend the statement implicating 'other erythropoietins' (which suggests it accepted it breached the Code), but put the blame for it on the regulatory authorities. The question remained as to whether Ortho Biotech requested the regulatory authority to change this misleading statement and if so whether the request was rejected. Roche suggested that the regulatory authority did not propose the sentence in question because it bore no relationship to the information posted by the MCA on its website contemporaneously to the 'Dear Doctor' letter. Roche suggested that this was evidence to show that the UK regulatory authority did not implicate other epoetins in its safety warning which went contrary to Ortho Biotech position.

**Background in relation to methodology for investigation of nomenclature, diagnosis etc of PRCA**

Roche noted that Ortho Biotech was highly critical of the spontaneous adverse reporting system, and it disfavoured its product. It was disquieting that Ortho Biotech therefore seemed to place so little faith in systems like the Yellow Card Reporting System of the CSM. This was an essential part of the pharmacovigilance mechanism. If European agencies additionally wished to instigate epidemiological studies, Roche welcomed this.

Roche noted that Ortho Biotech also criticized the definitions and diagnosis of PRCA whilst the

definitions it provided were speculative. However, the Panel had rightly ruled on current definitions and evidence.

### Specifics of the appeal – Points A, B, and C

Roche considered the Panel was correct to view the content of these items as promotional.

Roche alleged that Item A had inferred that Eprex had similar PRCA problems to other erythropoietins. It sought to give false confidence, was misleading, and put patients at risk.

Roche agreed that the Panel was right to acknowledge the subtleties in Item B. By being incomplete, and by emphasis, it gave the reader misleading advice about the route of administration and, hence, breached Clause 3.2.

Roche noted that for Item C, the ruling of the Panel was in March 2003. Roche alleged that Ortho Biotech up to that time was unable to substantiate the claim that the European agency was assessing erythropoietins as a whole. The fact that Ortho Biotech felt it could substantiate the claim after the Panel ruling did not alter the fact that this claim was not capable of substantiation at the time of the letter being sent on the 2 August 2002. It was important also that for the item in question Ortho Biotech stated that an assessment was on-going at the time of the letter. Ortho Biotech insisted that the PhVWP meeting in March 2003 substantiated its claim that, at the time of release of Item C, there was an ongoing assessment of all erythropoietins. This seemed irrelevant to the Panel's ruling. Ortho Biotech could not possibly have known that this meeting was to take place, back in August 2002. It remained the fact that Ortho Biotech referenced, in retrospect, a statement by the French regulators. Whilst it was true that all medicines were assessed in some respect on an ongoing basis, the Panel was correct to ask the question why Ortho Biotech had felt the need to reiterate this statement throughout its letter.

Roche alleged that with respect to the information given about the route of administration, the same comment was made for Item B. Ortho Biotech was incorrect in stating 'Its statements [for Eprex] were consistent with the SPC'.

Roche alleged that some of the confusion created here by Ortho Biotech's letter stemmed from references to certain regulatory agencies. The letter implied that assessments had occurred that had not. This could also have reduced the reader's confidence in UK regulatory process by the omission of references to the MCA, it being highly likely that the reader would be unaware of Clause 9.4. For the same sound reasons that the MCA could not be cited in promotion, and as the regulatory framework in Europe became harmonized, it was respectfully suggested that the ABPI considered reviewing Clause 9.4 and expand it to encompass 'any' licensing authority.

Roche noted that with regard to Point D, Ortho Biotech stated '…readers would have been fully aware that the numbers of cases associated with Eprex was greater than with other erythropoietins'. How? Then as now, there was no evidence that all readers were aware in August 2002 of the differences in erythropoietins. Ortho Biotech had not produced such evidence.

Roche noted that in addition, the impression given in the way the three administration options were presented unduly supported a subcutaneous route.

Finally, Roche noted that the criticism that the NEJM was 'in ignorance', underlined the selective nature of the information Ortho Biotech wished to provide.

### Breach of Clause 2

Roche noted that the fact that Ortho Biotech's appeal stated it 'had been diligent around advice and recommendations contained within the two Dear Doctor letters, and had successfully converted patients towards the IV route of administration' must be judged against the actual prescriber confusion that was created as a direct result of these two letters at that point in time, the risk to which patients might have been put, and the ultimate requirement to withdraw the marketing authorisation in the subcutaneous route for Eprex in December 2002.

Roche alleged that regarding its assertion that Ortho Biotech had undertaken a concerted campaign to play down the relevance of this safety issue to the medical profession, Roche noted that the Panel had recently found Ortho Biotech in further breach of a number of clauses of the Code in Case AUTH/1415/2/03 supporting this assertion.

Roche, in conclusion, endorsed the Panel's interpretation of the Code. Breaches of Clause 2 were reserved for cases of a serious nature. Roche was confident for the reasons stated above and in its original complaint that the Panel's concerns over Ortho Biotech's communications were well founded.

## APPEAL BOARD RULING

The Appeal Board considered that this was a very difficult area. The Appeal Board noted that Clause 1.2 of the Code stated that factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they included no product claims were exempt from the definition of the term 'promotion'.

The Appeal Board noted that the letters at issue in points A and B were safety warning letters which Ortho Biotech submitted that it had been required to send by the regulatory authorities. The Appeal Board noted the companies' comments on the arrangements for writing and approving the letters. It appeared that each letter was subjected to a regulatory approval process. The Appeal Board did not accept Ortho Biotech's submission that such letters should be exempt from the Code.

The Appeal Board considered that in principle safety warning letters required by the regulatory authorities were potentially subject to the Code. Companies should thus bear in mind the requirements of the Code. A safety warning letter required by the regulatory authorities would be exempt from the

Code if it met the exemption given in Clause 1.2 of the Code as outlined above. The Appeal Board considered that in such circumstances mention of a product indication would not necessarily be seen as a product claim. Each case would have to be decided on its merits.

The Appeal Board noted that the letter in question (point A) had been issued in cooperation with the European regulatory authorities and clearly related to an adverse reaction warning for Eprex. The first paragraph in question referred to the product's licensed indications. The second paragraph stated 'Very rare cases of pure red cell aplasia (PRCA) have been reported from the post-marketing experience in patients with CRF, most of them being treated with EPREX or other erythropoietins'.

The Appeal Board noted that at the time the letter in question (Point A) was sent (19 November 2001) the SPC for Eprex (dated 9 November 2001) stated (section 4.8, undesirable effects) that 'Pure red cell aplasia (erythroblastopenia) has very rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins'. The Appeal Board considered that the second paragraph in the letter was not inconsistent with the SPC on this point.

The Appeal Board noted both parties' submissions about the incidence of PRCA but considered that given the statement in the SPC the reference to '…other erythropoietins' in the letter was not inconsistent with the SPC. The Appeal Board did not consider that the statement in the letter was ambiguous, misleading, inaccurate and incapable of substantiation as ruled by the Panel. As a consequence the Panel's rulings of breaches of the Code (Clauses 7.2, 7.3, 7.4 and 7.9) were overturned by the Appeal Board.

The Appeal Board considered that the letter was a factual announcement relating to an adverse reaction warning which was exempt from the definition of promotion as set out in Clause 1.2 of the Code and was thus not subject to the Code. It did not need prescribing information.

The appeal was successful.

### B 'Dear Healthcare Professional' letter 'Amended advice on route of administration & reminder about storage conditions'

#### COMPLAINT

Roche noted that this second 'Dear Healthcare Professional' letter was sent to the profession on 17 July 2002 following an urgent safety restriction from the European Pharmacovigilance Working Party which recommended major restrictions on the use of subcutaneous Eprex. This resulted in a major change to the Eprex SPC. In this letter there was a boxed section which stated that 'Cases of PRCA have been reported with epoetin products marketed in the EU, the majority of which relate to Eprex administration mainly by the subcutaneous route and only in patients with CRF'. This statement was clear and unambiguous and suggested that the statement in the first 'Dear Doctor' letter (point A) was misleading and disparaged other epoetins.

The letter recommended that Eprex should be administered intravenously (IV) in chronic renal failure patients where feasible. However the letter did not state that the SPC had been changed more radically than this for patients undergoing haemodialysis such that they should now only receive Eprex IV. Roche alleged that this omission and misinformation was in breach of Clauses 3.2, 7.2 and 7.9.

In addition, although the letter stated that the product should be stored and handled according to the SPC it did not state why this was important. This was in line with other communications on this issue. Ortho Biotech had not informed the profession about a major change to the formulation of Eprex in 1998 (which might have led to instability of the product if not handled according to instructions in the SPC) and that the majority of cases of PRCA had occurred since that time. Speculation that this change in formulation might have affected the stability of the product had already been published in the New England Journal of Medicine and clearly it was particularly important that a potentially less stable product should be handled according to the cold chain instructions. Therefore not to include this information in a communication about safety was in breach of Clause 7.9 particularly as this information was provided later to financial analysts in USA.

Roche alleged that this letter misled the profession about the extent of the changes to the Eprex SPC and also omitted important information which would have helped the management of this issue in breach of Clauses 3.2, 7.2 and 7.9.

#### RESPONSE

Ortho Biotech stated that, contrary to Roche's submission, the European Pharmacovigilance Working Party within the EMEA did not issue urgent safety restrictions; its only potential role in this context was as a consensus-building venue for safety-related discussions by the member state authorities. The relevant change in the Eprex SPC was introduced by Ortho Biotech, in consultation with the French and other national authorities.

Ortho Biotech noted that the 24-hour consultation period for this urgent safety restriction occurred between 11/12 July 2002, with France acting as the reference member state. On 12 July, shortly after the completion of this consultation period, the MCA faxed its proposals for the letter to Ortho Biotech. On 15 July Ortho Biotech discussed the proposed wording of the SPC revisions and the second 'Dear Doctor' letter. On 16 July the MCA approved the wording of the letter.

Ortho Biotech repeated that it was important to note that this letter was subject to numerous and repeated approvals by the regulatory authorities, including the MCA. It was not advertising within the meaning of the Code and therefore should not be the subject of any complaint to the Authority.

Although this was the second letter on the subject of PRCA, any change in content did not necessarily mean that the previous letter issued eight months earlier was misleading. Each letter stood alone, and both were subject to appropriate regulatory scrutiny and approval.

Ortho Biotech stated that with regard to the revision of the SPC and amended advice on the route of administration for Eprex detailed within this letter, Roche had fundamentally misunderstood the context of this communication and implications of the changes. The SPC changes were not as radical as Roche implied.

It was unthinkable that such due process would produce a letter which did not accurately reflect the revisions of the SPC. Furthermore, the SPC did not contraindicate subcutaneous administration in haemodialysis patients as Roche had implied. The revised SPC of July 2001, under section 4.2, Posology and Method of Administration, stated 'In patients with chronic renal failure [Eprex] should be administered by the intravenous route where feasible'. This was not a contraindication of the subcutaneous route. The wording allowed for, but did not define, circumstances where Eprex might be administered subcutaneously to patients with chronic renal failure.

Under a further sub-heading to this section the revised SPC stated 'In patients on haemodialysis [Eprex] should be administered by the intravenous route'. Following this, and the previous sentence from the SPC, was a statement which referred prescribers to section 4.4 of the SPC to give greater clarity to the rationale for this amended advice on route of administration. Section 4.4 stated 'As the PRCA cases are mainly associated with the subcutaneous route of administration, Eprex should be administered to chronic renal failure patients by the intravenous route where feasible'.

Ortho Biotech stated that the use of the words, 'feasible', and 'should' in both statements were not words of contraindication. Indeed there was no revision to section 4.3 of the SPC; Contra-indications. Furthermore the heading of the letter stated 'Amended advice on route of administration'. The word 'advice' and the revisions of the SPC discussed in the letter were not the result of oversight, but were specific phrases and amendments following an extensive consultative process involving all the European regulatory authorities. The mandatory changes to the route of administration implied by Roche, and use of the word 'only' were entirely fictional.

Ortho Biotech noted that Roche had also alleged a breach of Clause 7.9 in respect of statements made about storage and handling of Eprex. This letter was a regulatory communication and was both accurate and factual. The statements about the correct handling and storage of Eprex were consistent with the SPC, and were considered and approved by the regulatory authorities. Their inclusion within the letter was deemed both appropriate and sufficient. Speculation by Roche on the rationale for inclusion, and comments about information later provided to financial analysts outside of the UK was neither appropriate nor relevant to the due regulatory process.

In summary, the 'Dear Doctor' letter was a regulatory communication and was entirely consistent with the central document agreed on 11/12 July. Ortho Biotech denied any breaches of Clauses 3.2, 7.2, and 7.9 of the Code.

## PANEL RULING

The Panel noted its comments in point A above about 'Dear Doctor' letters and their position with regard to the Code. The 'Dear Healthcare Professional' letter now at issue had been issued in co-operation with the European regulatory authorities and related to an adverse-reaction warning for Eprex.

The letter stated that most cases of PRCA had occurred following the subcutaneous use of Eprex and only in patients with CRF and that, as a result, 'the product should be administered by intravenous (IV) route in CRF patients where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient'. The letter then referred to changes to Sections 4.2, 4.3, 4.4 and 4.8 of the SPC.

The Panel examined the Eprex SPC as provided by Ortho Biotech. There had been a number of changes to Section 4.2 (Posology and method of administration). The reference to SC administration was no longer point a in the subsection headed 'method of administration' it now appeared after the instructions for IV administration as point b.

For CRF patients the SPC stated 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible (see Section 4.4 – Pure Red Cell Aplasia)'.

For adult haemodialysis patients the SPC stated 'In patients on haemodialysis the product should be administered by the intravenous route (see Section 4.4 – Pure Red Cell Aplasia)'.

For adult patients with renal insufficiency not yet undergoing dialysis the SPC stated that '… the product should be administered by the intravenous route where feasible (see Section 4.4 – Pure Red Cell Aplasia). If IV access is not feasible in a patient with renal insufficiency not yet undergoing dialysis, the risk/benefit of SC administration should be considered for each patient.

For adult peritoneal dialysis patients the SPC stated that '… the product should be administered by the intravenous route where feasible (see Section 4.4 – Pure Red Cell Aplasia). If IV access is not feasible in a peritoneal dialysis patient the risk/benefit of SC administration should be considered for each patient'.

Section 4.4 (Special warnings and precautions for use) of the SPC stated that 'As the PRCA cases are mainly associated with the subcutaneous route of administration, Eprex should be administered to chronic renal failure patients by the intravenous route where feasible'.

The Eprex SPC had been revised to include the statement that in adult haemodialysis patients the

product should be administered by the intravenous route. This was not mentioned in the letter at issue. The SPC had previously stated that in adult haemodialysis patients subcutaneous administration should be preferred over IV use. The Panel considered that the information given in the 'Dear Healthcare Professional' letter was incomplete with regard to amended advice on route of administration. In that regard the letter was inaccurate and inconsistent with the particulars listed in the Eprex SPC. The letter thus came within the scope of the Code. Breaches of Clauses 3.2 and 7.2 were ruled. The Panel did not consider that the letter was misleading with regard to the side-effects of Eprex. No breach of Clause 7.9 was ruled.

The Panel noted that the stated purpose of the letter was to provide the most recent information regarding the worldwide reported cases of PRCA in patients treated with Eprex as of 31 May, 2002. A table of data showed that reports of PRCA had increased since 1998. It was stated that no single trigger had been identified and that the company was examining all possible factors which could contribute to the immunogenicity of Eprex. There was no discussion regarding the possible impact of the formulation change upon the incidence of PRCA. Boxed text advised readers that Eprex should be handled and stored as described in its SPC and that in this regard patients should be referred to the patient information leaflet. Although information about the formulation change was not irrelevant the Panel did not consider that omitting such information from the letter in question was misleading *per se*. The Panel ruled no breach of Clause 7.9 in that regard.

## APPEAL BY ORTHO BIOTECH

Ortho Biotech repeated all the arguments raised in point A above.

Ortho Biotech noted that the letter advised health professionals that Eprex should only be administered by the IV route in CRF patients where feasible. It also reminded health professionals of the importance of correct handling of the product.

The purpose of the letter was to inform health professionals of important information relating to post-marketing reports of PRCA in patients with chronic renal failure, and to provide the most recent information regarding the world-wide reported cases of PRCA in patients treated with Eprex. The communication made clear that 'the majority of [cases] related to Eprex administered mainly by the subcutaneous route and only in CRF'. The letter was determined [by the regulatory process] to be accurate, succinct but complete.

Ortho Biotech submitted that with respect to amended advice on route of administration (which was within the title of the letter) the letter stated that '…..the product [Eprex] should be administered by the intravenous (IV) route in CRF patients where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient'. Changes made within the SPC for Eprex stated 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible'. For adult haemodialysis patients the SPC stated that 'In patients on haemodialysis the product should be administered by the IV route (see section 4.4 – Pure red cell aplasia).

Ortho Biotech noted that there were no changes to section 4.3 Contra-Indication ie the subcutaneous route of administration was not contra-indicated in any patient group. The words within the letter giving 'advice' on route of administration, the word 'should' rather than a word such as 'must' which would mandate the use of the IV route were not part of the communication within the 'Dear Healthcare professional' letter, ie contra-indication of the SC route was not the intended communication to the healthcare profession. This letter was clear in this point, and changes to the SPC reinforced this position, in particular there being no changes to section 4.3 ie no absolute contra-Indication.

Ortho Biotech noted that the information provided in respect of reports of PRCA was up to date, and the association with the SC route of administration was identified clearly, as was advice to use the IV route where feasible, and the label changes made were appropriate to this. Consequently, Ortho Biotech denied breaches of Clauses 3.2 and 7.2.

## COMMENTS FROM ROCHE

See point A above.

## APPEAL BOARD RULING

The Appeal Board noted its comments in point A concerning the safety warning letters required by regulatory authorities and their position with regard to the Code.

The Appeal Board noted that the letter in question (point B) had been issued in cooperation with the European regulatory authorities and clearly related to an adverse reaction warning for Eprex. The letter stated that most cases of PRCA had occurred following the subcutaneous use of Eprex and only in patients with CRF and that, as a result, 'the product should be administered by intravenous (IV) route in CRF patients where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient'. The letter then referred to changes to Sections 4.2, 4.3, 4.4 and 4.8 of the SPC.

The Eprex SPC had been revised to include the statement that in adult haemodialysis patients the product should be administered by the intravenous route. This was not mentioned in the letter at issue. The SPC had previously stated that in adult haemodialysis patients subcutaneous administration should be preferred over IV use.

The Appeal Board considered that the letter was factually correct with regard to CRF patients. It did not consider that in the context of the letter as a whole the omission of information about the route of administration for adult haemodialysis patients meant that the letter was inaccurate and inconsistent with the Eprex SPC as ruled by the Panel. As a consequence the Panel's rulings of breaches of the

Code (Clauses 3.2 and 7.2) were overturned by the Appeal Board.

The Appeal Board considered that the letter was a factual announcement relating to an adverse reaction warning which was exempt from the definition of promotion as set out in Clause 1.2 of the Code and was thus not subject to the Code. The appeal was successful.

### C Ortho Biotech letter to health professionals dated 2 August 2002. 'Eprex Immunogenicity in Perspective'

#### COMPLAINT

Roche noted that on 12 July 2002 the European Pharmacovigilance Working Party issued an urgent safety alert regarding Eprex and new guidelines recommending its administration by the intravenous route. This resulted in a change to the Eprex SPC which Ortho Biotech told health professionals about in a 'Dear Healthcare Professional' letter, dated 17 July (point B above). A subsequent letter signed by a business unit director and dated 2 August was sent to offer clarification on matters raised in the letter of 17 July. Roche considered that clarification was necessary because the previous letter had misled the profession by omission of the full change to the SPC (as outlined in point B above). The contents of this second letter entitled 'Eprex Immunogenicity in Perspective' with a sub-heading of 'PRCA – the facts to date' included additional breaches of Clauses 7.2 (on misleading information in respect to side-effects) in addition to other breaches as outlined below.

The second paragraph of this letter stated that the 'Dear Doctor' letter of 17 July had 'raised a number of questions and issues, which require further discussion'. The Medical Director signed the original letter to which this one referred so it was extraordinary, but relevant, that the clarification was signed by marketing. In addition the opportunity was taken to make several claims for the product, including comparisons with other products. Roche considered that the letter came within the definition of promotion outlined in Clause 1.2 of the Code and that it should therefore have included prescribing information (Clause 4.1). The letter should not be considered solely as factual information about adverse reactions.

Roche noted that the letter included several bullet points under the sub-heading 'PRCA – the facts to date'. Of particular concern were the references to regulatory authorities, including the French Agency and the European Agency in bullet points 3 and 4 (repeated also in the accompanying 'Company Statement' (point D)). France was the reference member state for Eprex under the mutual recognition procedure and as such acted as the licensing authority for Eprex and undertook all post-approval activities. The French Agency was cited as supporting the claim that all exogenous recombinant proteins could be immunogenic particularly if given subcutaneously. Roche alleged that the references to regulatory authorities were in breach of Clause 9.4.

The fourth bullet point (also repeated several times in the Company Statement (point D)) claimed that 'A new assessment of the erythropoietins as a whole is currently taking place at the European Agency'. This statement was misleading and out of context. Roche had checked with the French regulatory authority and with the rapporteur for NeoRecormon and had found no evidence that such an assessment over and above routine surveillance was on going at that time. It was difficult to get written statements to this effect for reasons that were implicit in the need for Clause 9.4. The statement was later referenced in the 'Company Statement ' (point D below) to a media release on the French regulatory authority's website which was dated 4 July and which referred to a new assessment. However the company believed that this 'new assessment' referred to the European assessment of 9/10 July which had already been completed before the date of the letter in question. The outcome of these meetings or 'assessments' was the changes to the Eprex licence described above. Roche provided confidential copies of correspondence with the relevant regulatory authorities.

Roche stated that Ortho Biotech used reference to this media release to persuade health professionals that another 'new assessment' was ongoing when in fact the assessment had been completed and action taken ie the Eprex SPC had been changed.

Roche alleged that these two bullet points misled the reader into believing that although restrictions had only been placed on Eprex, all such products were immunogenic and a 'new assessment currently on-going' was likely to result in restrictions on other epoetins. Roche considered that this claim was not substantiated, that reference to a regulatory authority made it difficult to substantiate and that it was a most serious breach of the Code involving Clauses 7.2, 7.3, 7.4, 7.9, 8.1 and 9.4. Roche noted that it had asked Ortho Biotech to confirm this statement but had not received a satisfactory response in breach of Clause 7.5.

This myth of an ongoing assessment (over and above routine surveillance) applicable to other erythropoietins was widely disseminated by this letter and Roche believed that Ortho Biotech's representatives continued to make similar statements. As such this was tantamount to disparagement of NeoRecormon in breach of Clause 8.1. Many clinicians had subsequently told Roche that they were waiting the outcome of this assessment before deciding how best to manage their patients on the basis that changing a patient to a different epoetin would be unwise if that product was the subject of an ongoing safety assessment that might subsequently result in similar restrictions to the epoetin the patient was currently taking.

Roche alleged that to deliberately use the reputation and status of the regulatory authorities as a vehicle for this sort of misleading correspondence not only breached the above clauses but brought the pharmaceutical industry into disrepute in breach of Clause 2.

Roche alleged that the final bullet point of this letter was also in breach of the Code. Through purporting to clarify the changes to the SPC the recommendations contained therein contradicted the

earlier 'Dear Healthcare Professional' letter and the SPC. It included unqualified advice that clinicians could 'maintain the existing regimen of subcutaneous Eprex' for patients with chronic renal failure. This was clearly misleading as section 4.2 of the revised SPC stated 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible'. Beneath this general statement was more detailed instruction for specific patient groups. The SPC also stated that: 'in patients on haemodialysis the product should be administered by the intravenous route' and 'In patients with renal insufficiently not yet undergoing dialysis, the product should be administered by the intravenous route where feasible' (section 4.4 SPC – Pure Red Cell Aplasia). To promote the maintenance of the existing regimen was not consistent with either the SPC or the advice of the European Pharmacovigilance Working Party's urgent safety warning. Roche alleged breaches of Clauses 3.2, 7.2, 7.4 and 7.9.

Roche considered that the letter, sent by marketing to clarify a 'Dear Healthcare Professional' letter issued by the medical department, was more misleading and erroneous on this important safety issue than its predecessor. It did not make clear that patients on haemodialysis should not be given Eprex subcutaneously, and that pre-dialysis patients should only receive it subcutaneously if the risk/benefit had been considered (Clauses 3.2, 7.2 etc). It misled the reader into believing the problem was shared with other epoetins, referred to regulatory authorities and alluded to ongoing assessments to discourage physicians from considering alternative epoetins. Finally it recommended unconditionally, ongoing subcutaneous administration as one of three treatment options, which was at odds with the original European Pharmacovigilance Working Party directive which it was supposed to reflect.

In addition for a communication with a sub-heading of 'the facts to date' no mention was made of the change to the formulation of Eprex even though this was cited as a possible cause in the editorial of the New England Journal of Medicine (Clauses 7.2, 7.9). The effect of all these breaches was to bring the industry into disrepute (Clause 2).

## RESPONSE

Ortho Biotech noted that this letter was not a regulatory communication as the two previous items in points A and B.

Ortho Biotech stated that in a letter of 28 August 2002 from Johnson & Johnson Europe to Roche in Basel, Switzerland, Johnson & Johnson had responded fully to an earlier Roche complaint about this letter. Johnson and Johnson's letter indicated that, on 8 August 2002, Ortho Biotech had already unilaterally decided not to use either this item or that at issue in point D below. Rather than being the result of any concerns regarding the content of these documents, Ortho Biotech's decision was part of a new policy not to make further statements to the UK medical community without prior consultation with the MCA. While urging Roche to take a similarly constructive approach, Ortho Biotech nevertheless provided Roche with an undertaking that this material would not be used again. Ortho Biotech therefore requested that this complaint was dismissed on the basis that the matter had been fully resolved between the companies, and that the complaint on this matter should not have been submitted to the Authority. Ortho Biotech nevertheless denied all Roche's alleged breaches of the Code.

Ortho Biotech stated that contrary to Roche's assertion, it could not see how this document could justifiably be used as a basis for arguing that an earlier regulatory communication was misleading. In respect of not providing prescribing information with this letter, Clause 1.2 of the Code allowed for exclusion of materials which were factual, accurate and informative announcements. Due to the nature of the letter, and the timing in respect of the recently issued 'Dear Healthcare Professional' letter (point B), Ortho Biotech considered that the letter now at issue and the Company Statement (point D) below fell within the context of exclusion as allowed by Clause 1.2, hence were not promotional and therefore did not require prescribing information.

The French Agency stated (via its websites) that exogenous recombinant proteins had been associated with immunogenic phenomena and antibody formation, particularly when administered subcutaneously. This was also consistent with the prescribing information for NeoRecormon, which stated in section 4.4, Special warnings and special precautions for use, that 'In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO therapy', and with the revised SPC for Eprex.

The letter in question did not include any reference to the Medicines Commission, the Committee on Safety of Medicines, the Medicines Control Agency or the licensing authority and was therefore not in breach of Clause 9.4. Ortho Biotech stated that it had quoted only public statements by the French Agency. As far as the company was aware, the purpose of Clause 9.4 of the Code must be to prevent companies from using undisclosed statements about products without the consent of the relevant regulators. In this case, the French Agency had made a public statement about Eprex and Ortho Biotech could see no possible objection to its references to this statement. Such references to regulatory statements and actions were a common feature of Roche's communications on this issue.

At the time of this letter, Ortho Biotech stated that the European Agency for the Evaluation of Medicinal Products (EMEA) had indicated that it was conducting an assessment of erythropoietins as a whole. Additionally, other regulatory authorities eg in Israel, Poland, Switzerland, Australia and Canada were undertaking reviews of all erythropoietins. From review of their statements it was clear that there was a variety of (independent) opinion in respect of the potential issues around PRCA and antibody formation, in particular with respect to the potential for other erythropoietins to be associated with this immunogenic phenomenon.

In relation to Clause 7.2, which governed discussion of emerging clinical or scientific opinion, particularly

when an issue was not resolved in favour of one generally accepted viewpoint, Ortho Biotech considered that an expression of the views of the different regulatory authorities beyond Europe was particularly meaningful.

The letter at issue did not deny that PRCA had been associated with Eprex, nor that there had been a recent label change. The comment that PRCA had been associated with other erthyropoietins was factual and consistent with the SPCs for both Eprex and NeoRecormon. Additionally no suggestion was made that any other epoetin would undergo a label change. The interpretation by Roche was an exaggerated view of what was actually written. The balanced approach taken within the letter differed from Roche's promotional material at the time which had already been the subject of Case AUTH/1366/10/02 and had been found to be in breach of numerous aspects of the Code. In particular the Panel in its ruling stated that Roche's material 'gave the impression that NeoRecormon was not associated with any risk of PRCA'. This was clearly not true, since it was within the SPC for NeoRecormon.

Clearly regulatory authorities had differing views in respect to the degree of risk. Bringing this to the attention of the nephrology community did not denigrate NeoRecormon. The aspect of risk was important for clinicians to appreciate especially when considering continued use of Eprex and/or switching patients to another product. In switching to another product a clinician would wish for a balanced view of any associated risk.

Also, on the basis of the same arguments put forward in point B above, patients could still continue to receive Eprex subcutaneously, and hence statements made in this letter and in the Company Statement at issue in point D below, were consistent with the Eprex SPC.

Ortho Biotech considered that this letter was factual and balanced and consistent with the Eprex SPC; it presented information in a balanced manner, it did not mislead the reader nor did it disparage NeoRecormon. The company denied all of the alleged breaches of the Code.

## PANEL RULING

The Panel noted Ortho Biotech's submission that as the letter at issue had already been withdrawn, as a result of intercompany dialogue, the complaint should be dismissed. Such a course of action was not within the Constitution and Procedure. The Panel noted that complaints could only be withdrawn by a complainant company with the consent of the respondent company up until such time as the respondent company's comments on the complaint had been received by the Authority, but not thereafter (Paragraph 15.1).

The Panel noted that Ortho Biotech considered that the letter was exempt from the definition of promotion. The Panel noted its comments in point A above with regard to the exception to the definition of promotion as stated in Clause 1.2 of the Code in relation to factual, accurate, informative announcements. The penultimate paragraph referred to 'the rare incidence of PRCA in relation to Eprex and indeed other erythropoietins'. The Panel considered that this was similar to the statement considered at point A above. It implied that Eprex was no more likely to cause PRCA than other erythropoietins. It was inaccurate in this regard and thus brought the letter within the scope of the Code. Further, the letter had been sent out with the Company Statement. The Company Statement contained the claim that 'Eprex offer[s] an improvement in the quality of life for the chronic renal failure patient …'. The letter had thus accompanied a promotional mailing and so had been used in a promotional setting. It was signed by the Business Unit Director – Eprex. The Panel considered that the letter was thus subject to the Code. The letter referred to Eprex and so should have included prescribing information for the product; none was provided. The Panel ruled a breach of Clause 4.1 of the Code.

The Panel noted that two of the bullet points at issue were 'However, in the recent French Regulatory Agency review of Eprex it has been acknowledged that almost all exogenous recombinant proteins, used as therapeutic agents, have been associated with immunogenic phenomena and antibody production, particularly when administered subcutaneously' and 'A new assessment of the erythropoietins as a whole is currently taking place at the European Agency'.

The Panel noted that Clause 9.4 of the Code stated 'Promotional material must not include any references to the Medicines Commission, the Committee on Safety of Medicines, the Medicines Control Agency or the licensing authority, unless this is specifically required by the licensing authority'. The Panel considered that the clause referred to UK regulatory mechanisms and not to those of other countries. The Panel thus ruled no breach of Clause 9.4 with regard to the reference to the French Regulatory Agency.

The Panel noted that the letter referred to a new assessment of the erythropoietins as a whole which was taking place at the European Agency. It appeared, however, that this assessment was the one that had already taken place and which had resulted in Ortho Biotech issuing its 'Dear Health Professional' letter of 17 July, the subject of point B above. Ortho Biotech had provided no information to show that there was a further new assessment taking place at the EMEA. The Panel considered that the reference to a new assessment of the erythropoietins was thus misleading and could not be substantiated. Ortho Biotech had not provided any substantiation. Breaches of Clauses 7.2, 7.4 and 7.5 were ruled. This ruling was appealed. The Panel did not, however, consider that the statement was a misleading comparison, that it was misleading with regard to the side effects of Eprex or that it disparaged NeoRecormon. No breach of Clauses 7.3, 7.9 and 8.1 was ruled.

The final bullet point stated that in patients with chronic renal failure, already taking Eprex by subcutaneous injection, clinicians had three prescribing options: 'To change to IV administration, where feasible – To maintain the existing regimen of

subcutaneous route of administration with Eprex – To continue with SC administration with a change to a different erythropoietin'. The Panel considered that the three prescribing options had been presented with equal weight. It was not clear that the second option should only be followed where the first, a change to IV therapy, was not feasible. The Eprex SPC stated that 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible'. The Panel noted that advice given in the SPC for subcutaneous use of Eprex in adult patients with renal insufficiency not yet undergoing dialysis and in adult peritoneal dialysis patients referred to considering the risk/benefit for each patient. The Panel considered that the statement in the letter regarding route of administration was inconsistent with the particulars listed in the Eprex SPC and that it was misleading in that regard and could not be substantiated. Breaches of Clauses 3.2, 7.2 and 7.4 of the Code were ruled. This ruling was appealed. The Panel did not consider that the statement was misleading with regard to the side effects of Eprex. No breach of Clause 7.9 was ruled.

The Panel noted that the letter was headed 'Eprex Immunogenicity in Perspective' and the introductory paragraphs referred to the company statement which was intended to highlight key aspects of, *inter alia*, current scientific literature. The Panel noted that in the next section, under the sub-heading 'PRCA – the facts to date', there was no mention of the possible role played by the change in the Eprex formulation; this had, some months earlier, been raised as a question in an editorial in the New England Journal of Medicine (February 2002). It was true that reports of PRCA with Eprex had increased since 1998 and that the formulation of the product in Europe had been changed in that year. The Panel considered that, on balance, by not addressing the issue of formulation change the letter was misleading; it was not presenting 'the facts to date'. The Panel ruled a breach of Clause 7.2 of the Code. This ruling was appealed. The Panel did not, however, consider that the omission of information about the formulation change misled the reader with regard to the side effects of Eprex. No breaches of Clauses 7.2 and 7.9 were ruled.

The Panel noted its comments and rulings above and considered that, on balance, the letter was such as to reduce confidence in the industry and to bring it into disrepute. A breach of Clause 2 was ruled. This ruling was appealed.

## APPEAL BY ORTHO BIOTECH

Ortho Biotech appealed the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.5 of the Code in respect of the reference to a 'new assessment of the erythropoietins as a whole which was taking place at the European Agency.' The French Medicines Agency had indicated that this assessment was ongoing in a public manner. In general their meetings (and minutes) were not made public, hence it was difficult to comment on the contents of earlier PhVWP working parties meetings. This had now changed. Prior to, and also subsequent to the date of the letter at issue in point C, the PhVWP had been and still was undertaking a review of all erythropoietins. This had culminated in a meeting attended by Roche and other manufacturers on 19 March 2003, at which the PhVWP stated that they had concern relating to PRCA, and wished for a formal prospective study as to its true incidence, and required all manufacturers to be involved to use the same protocols and also the same terminology and reporting methods. Ortho Biotech considered that these minutes provided incontrovertible evidence that the EMEA had, and continued to, conduct assessments of erythropoietins as a whole and their link to PRCA. Ortho Biotech therefore appealed Clauses 7.2, 7.4, and 7.5 in these respects.

Ortho Biotech also appealed the Panel's ruling of breach of Clauses 3.2, 7.2 and 7.4 that the statement in the letter regarding route of administration was inconsistent with the particulars listed in the Eprex SPC and that it was misleading in that regard and could not be substantiated.

Ortho Biotech stated that it had already commented in relation to the route of administration in point B. Ortho Biotech stated that notwithstanding its advice to administer Eprex via the IV route, where clinicians did not wish to change practice, for whatever reason, they were able to do without contravening the SPC amendments, since the SC route of administration had not been contra-indicated (despite Roche's assertions to the contrary). The reason a clinician had decided that the IV route was not 'feasible', or that they did not wish to change to another erythropoietin differed between clinicians, though was a choice that they were entitled to make. Ortho Biotech submitted that its statement reflected these choices.

Ortho Biotech submitted that it was also undertaking due diligence in assisting clinicians to move from the SC towards the IV route of administration, and overcoming considerable logistical and clinical barriers to achieve this.

Ortho Biotech submitted that its statements were consistent with the SPC, and were not misleading in this respect, and could be substantiated, hence it appealed the Panel's rulings in respect of Clauses 3.2, 7.2, and 7.4.

Ortho Biotech also appealed the Panel's ruling of a breach of Clause 7.2 of the Code in respect of its failure to address the issue of formulation change in the letter. Ortho Biotech disagreed with the Panel in its interpretation as to the importance of the formulation changes in relation to increased reports of PRCA. Neither Ortho Biotech, nor its parent Johnson & Johnson, nor any drug regulator world-wide had been able to make such a determination based on the available evidence. Any reflections as to the contribution of such a change to the issue would be entirely speculative; what was known was that the Eprex had (and continued to) remain within its release specifications, and that it was stable when handled in accordance with its SPC. Additionally stability data had been submitted to the appropriate authorities to the effect that it was in fact stable under storage conditions which were not consistent with its SPC, ie the formulation change might not be as important as Roche had speculated. Further, reports of PRCA had been associated with epoetin alfa in the

USA, where the stabiliser had remained consistent ie contained HSA. Roche interestingly also had not introduced the concept of a major formulation change of NeoRecormon (in fact it had denied any major formulation changes since 1998), and it too had been associated with reports of PRCA according to the SwissMedic statement.

Ortho Biotech noted that consequently, as no single theory as to the cause of increased reports of PRCA fitted the facts, authorities such as the Swiss Medic had not felt sufficiently confident to be drawn towards firm conclusions.

Ortho Biotech noted that additionally, new publications from Casadevall had also alluded to the problems of elucidation of the cause (of PRCA), and although possible effects of any formulation change were discussed, went on to state that a single cause would probably never be found. Given the speculative nature of the possible role (or otherwise) of any formulation change in the increased reporting of PRCA, Ortho Biotech felt it not relevant to discussions within its communication, and appealed against the Panel's rulings of breaches of Clauses 7.2.

Ortho Biotech appealed the Panel's ruling of a breach of Clause 2 of the Code in respect of the entirety of this letter. Ortho Biotech did not consider that it had committed any breach of the Code, in respect of Clause 7 nor importantly Clause 3.2, It therefore could not see any basis for a determination that its letter was such as to reduce confidence in the industry and to bring it into disrepute.

**COMMENTS FROM ROCHE**

See point A above.

**APPEAL BOARD RULING**

The Appeal Board noted that bullet point 4 of the letter referred to a new assessment of the erythropoietins as a whole which was taking place at the European Agency. The Appeal Board noted Ortho Biotech's assertions that this was supported by evidence on the European regulatory authority's website which stated that 'A new assessment of the erythropoietins as a whole is currently taking place at the European Agency'. However, the Appeal Board further noted Roche's submission that this new assessment was referred to in a press release from the French Agency for the safety of health products as being concluded at a meeting of the European Pharmacovigilance group, which met on 9 and 10 July 2002.

The Appeal Board noted that this meeting occurred before the letter in question was issued on 2 August 2002. The Appeal Board did not consider that there was any evidence to indicate that at the time the letter was sent a new assessment of erythropoietins, over and above routine continuing assessment, was taking place at the European Agency as submitted by Ortho Biotech. The reference to the new assessment was thus misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.5. The appeal on this point was unsuccessful.

The Appeal Board noted that the final bullet point which stated that clinicians had three prescribing options: 'To change to IV administration, where feasible – To maintain the existing regimen of subcutaneous route of administration with Eprex – To continue with SC administration with a change to a different erythropoietin' had been presented with equal weight. It was not clear that the second option should only be followed where the first, a change to IV therapy, was not feasible. The Eprex SPC stated that 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible'. The Appeal Board noted that advice given in the SPC for the subcutaneous use of Eprex in adult patients with renal insufficiency not yet undergoing dialysis and in adult peritoneal dialysis patients referred to considering the risk/benefit for each patient. The Appeal Board considered that the statement in the letter regarding route of administration was inconsistent with the particulars listed in the Eprex SPC and that it was misleading in that regard and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 3.2, 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted that the letter was headed 'Eprex Immunogenicity in Perspective' and the introductory paragraphs referred to the company statement which was intended to highlight key aspects of, *inter alia*, current scientific literature. The Appeal Board noted that in the next section, under the sub-heading 'PRCA – the facts to date', there was no mention of the possible role played by the change in the Eprex formulation. The Appeal Board considered that by not addressing the issue of formulation change the letter was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above. The Appeal Board considered that the letter did not give a fair impression of the seriousness of the matter. The Appeal Board considered that the letter was such as to reduce confidence in the industry and to bring it into disrepute. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

During its consideration the Appeal Board noted that the letter did not include the generic name immediately adjacent to the most prominent display of the brand name as required by Clause 4.3 of the Code. The Appeal Board requested that Ortho Biotech be so advised.

**D Ortho Biotech company statement dated 2 August 2002**

**1 'Eprex Immunogenicity in Perspective'**

**COMPLAINT**

Roche noted that a 'Company Statement' accompanied the letter of 2 August 2002 (point C). Roche alleged that this statement, which was supposed to 'highlight key aspects of the revised [SPC] and current scientific literature', was selective, erroneous, incomplete and misleading. The company also considered that this was a promotional item for

the reasons given above and should have contained prescribing information (Clause 4.1).

Roche noted that below the sub-heading 'Eprex Immunogenicity in Perspective' attention was drawn to 13 years of market exposure of Eprex but this was largely irrelevant as the upsurge in the phenomenon of PRCA with antibodies had only been observed since 1998 (which happened to follow the change to the manufacturing of Eprex). Roche considered that the perspective being offered here was a confusing one.

The statement included yet again a reference to the French regulatory authority acting as the reference member state for Eprex in breach of Clause 9.4. In addition it included a reference to Porter (2001) which stated 'The lack of detectable anti-erythropoietins antibodies has been reported in several studies. Nonetheless, several papers exist that report the development of assays for anti-erythropoetin antibodies, suggesting that they can occur. In addition, several publications have reported sporadic, infrequent observations of anti-erythropoietin antibodies'. Thus this article reflected the position prior to the recent upsurge in cases with Eprex. Therefore citing it in this context was misleading as, although this comment was undoubtedly true in principle, it did not enhance understanding of the current situation where the problem of an upsurge in immunogenicity was not seen with 'all exogenous recombinant proteins' but only with Eprex. In addition no reference was made in this or any other part of the company statement to the publications in the New England Journal of Medicine by Casadevall *et al* nor to the FDA follow-up letter which showed differences between epoetins in respect to PRCA or to the New England Journal of Medicine editorial which raised the issue of manufacturing change in Europe.

These were major omissions in a statement purporting to highlight key aspects of current literature, which also made comparisons with other products. Such information should be accurate, balanced, fair etc and based on up-to-date evaluation of all evidence. Yet again no mention was made of the change in Eprex formulation even though this was crucial evidence from the literature (supplementary information to Clause 7.2 – emerging clinical or scientific opinion). Roche alleged that this first section of the statement detailed above was in breach of Clauses 7.2, 7.3, 7.4 and 7.9.

Although no direct reference was made to NeoRecormon in this piece there was an inevitable inference that the product was being commented upon each time 'the erythropoietins as a whole' were mentioned. There was no mandate for Ortho Biotech to be offering comment on anything other than its own product, unless it was clearly pointing out that the incidence of PRCA was lower with other products than with Eprex.

Regardless of how Ortho Biotech justified including these statements pertaining to 'the erythropoietins as a whole', it was clear from discussions that Roche had had with clinicians that they had had the effect of disparaging NeoRecormon and could subsequently be regarded as knocking copy, in breach of Clause 8.1.

The profession was entitled to expect Ortho Biotech's views on the publications concerning formulation theories and possible aetiologies particularly in a company statement purporting to reflect current scientific literature. Instead Ortho Biotech offered suggestions that all epoetins were equally associated with PRCA quoting regulatory authorities in this regard.

In summary Roche considered that the Company Statement was promotional, and misleading in relation to a serious side effect and thus breached Clauses 4.1, 7.2, 7.3, 7.4, 7.9, 8.1 and 9.4.

## RESPONSE

Ortho Biotech repeated that following a unilateral decision to submit all company communications on PRCA and its association with Eprex and other erythropoetin products to the regulators prior to their evaluation, it had already provided Roche with an undertaking that it would not reuse this statement. The company thus did not consider that this complaint was appropriate under these circumstances.

The Company Statement was nevertheless not misleading and complied with the Code.

Ortho Biotech stated that for the reasons set out above and also given within the response to point C above, the company did not consider that a reference to a statement by the French authority was misleading in breach of Clause 9.4 of the Code.

Ortho Biotech noted that it did not state that the upsurge in reports of PRCA was associated with all erythropoietin products. Rather, it emphasised that, despite the heightened awareness of the issue, the side effect remained rare and was associated with treatment with all recombinant exogenous proteins. All these claims were factual, not misleading and consistent with the prescribing information for both Eprex and NeoRecormon.

The citation of the paper by Porter was entirely justified; it was the only paper that the French Agency and the member states required to be cited in the 'Dear Doctor' letter text they had approved.

As indicated above, and as conceded by Roche, the precise cause of PRCA had yet to be determined. Ortho Biotech considered that pointing to the association suggested by Roche would have been inconsistent with the supplementary information to Clause 7.2 of the Code, which required special care when discussing clinical or scientific issues that had not been resolved in favour of one generally accepted viewpoint. Ortho Biotech also noted the same arguments put forward under point C above in respect of its response to the complaints in point D. The company therefore denied breaches of Clauses 4.1, 7.2, 7.3, 7.4, 7.9 and 8.1 of the Code.

## PANEL RULING

The Panel noted its comments in point C above with regard to the withdrawal of complaints.

The Company Statement referred to the MCA and its approval of the 'Dear Doctor' letter (July 2002) and the revised SPC. Clause 9.4 stated that promotional material must not include, *inter alia*, any reference to the MCA. A breach of Clause 9.4 was ruled.

The Company Statement referred to the 'heightened awareness of reports of increased immunogenicity and [PRCA] in association with Eprex and other erythropoietins'. It was also stated that 'all exogenous recombinant proteins … have been associated with immunogenic phenomena and antibody production'. The Panel considered that these statements failed to convey to readers that Eprex was associated with a greater incidence of PRCA than any other erythropoietin; it appeared that all of the compounds were equal in this regard. The Panel considered that this was a misleading comparison which could not be substantiated. Breaches of Clauses 7.2, 7.3, 7.4 and 7.9 were ruled. This ruling was appealed. The Panel did not consider that the statements disparaged NeoRecormon. No breach of Clause 8.1 was ruled.

The Company Statement did not include any prescribing information for Eprex. A breach of Clause 4.1 was ruled.

### APPEAL BY ORTHO BIOTECH

Ortho Biotech maintained that as this was sent to the same health professionals who had received the two previous letters (points A and B) and with whom Ortho Biotech had had extensive communication, readers would have been fully aware that the numbers of cases associated with Eprex was greater than with other erythropoietins. The Panel had however found within its ruling that Ortho Biotech had not made it clear that Eprex was associated with a greater incidence. As detailed previously, spontaneously reported adverse events were an inappropriate basis for comparison of incidence and Ortho Biotech referred to its comments at point A above. Ortho Biotech submitted that its comments regarding reports of PRCA with other erythropoietins, and that antibodies were associated with all exogenously administered proteins could be fully substantiated and were not misleading. Consequently Ortho Biotech appealed the rulings of breaches of Clauses 7.2, 7.3, 7.4, and 7.9.

### COMMENTS FROM ROCHE

See point A above.

### APPEAL BOARD RULING

The Appeal Board considered that the Company Statement failed to convey to readers that Eprex was associated with a greater incidence of PRCA than any other erythropoietin; it gave the impression that all the products were equal in this regard and that was not so. The Appeal Board considered that this was a misleading comparison which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3, 7.4 and 7.9. The appeal on this point was unsuccessful.

## 2 'Changing to IV administration'

### COMPLAINT

Roche considered that the statement under this sub-heading of the Company Statement, that change to IV administration was 'not mandatory', was over simplistic and misleading in a situation where total clarity was necessary.

Whilst the SPC suggested that there might be circumstances where changing to IV might not be feasible it clearly divided patients into those undergoing dialysis and those with chronic renal failure not yet undergoing dialysis (SPC section 4.2) and made different recommendations for each group. With regard to patients undergoing dialysis, section 4.2 of the revised Eprex SPC stated 'in patients on haemodialysis the product should be administered by the intravenous route'; this was clearly mandatory. Therefore Ortho Biotech had made a claim which was not consistent with the SPC in breach of Clause 3.2.

Comments about feasibility of subcutaneous administration were married to recommendations of undertaking a risk benefit evaluation of usage in patients not yet undergoing dialysis. Therefore the assertion in Ortho Biotech's Company Statement that 'Section 4.3 of the revised SPC does not contra-indicate SC administration of Eprex for any patient group' was misleading and did not represent the SPC in its entirety as this was not the case for haemodialysis patients (the largest group, incidentally). Therefore the Company Statement was also in breach of Clause 3.2 both specifically and in the general message of the piece.

Roche noted that this section of the Company Statement also made reference to the potential increased dose required if patients changed to IV administration. This included the statement 'Ortho Biotech will work with individual units … to ensure that no funding issues compromise this change'. This appeared to be a disguised financial inducement to persuade clinicians from taking an obvious alternative action, which was to switch to another epoetin so as to continue with the SC route (the route recommended by the European Guidelines). Roche noted that the European Guidelines were sponsored by Ortho Biotech and yet in this statement the company seemed to be promoting a route of administration which was not recommended whilst stating that it was 'ensuring that current standards are maintained.' Clearly a change to IV administration increased the total daily dose of Eprex which had financial implications. There was thus an additional reason for the unit to consider switching to an alternative therapy. Roche alleged that the allusion to financial assistance in this Company Statement was an inducement to prescribe in breach of Clause 18.1.

### RESPONSE

Ortho Biotech noted that Roche had alleged that a change to IV administration was mandatory. This, as argued previously, was untrue and Ortho Biotech therefore denied a breach of Clause 3.2 of the Code.

The supplementary information to Clause 18.1 made clear that '[m]easures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 are outside the scope of the Code … and are excluded from the provisions of this clause'. A review of previous complaints on this

issue confirmed that 'simple' discounts, ie those that were purely financial, were acceptable. The offering of discounts of the kind envisaged by Ortho Biotech therefore did not constitute an inducement to prescribe and was consistent with the Code.

## PANEL RULING

The Company Statement noted that PRCA was mainly associated with subcutaneous administration and that a change to IV therapy might lessen the risk. It was stated 'Although not mandatory, the revised SPC … recommends a change to IV administration for particular patients where feasible'. The revised SPC, however, stated that in adult haemodialysis patients Eprex should be administered by the IV route – the previous SPC had stated that the subcutaneous route was preferred in such patients. The Panel considered that there were patient groups for whom IV administration of Eprex was mandatory. The Panel considered that the Company Statement was not consistent with the particulars listed in the SPC in this regard. A breach of Clause 3.2 was ruled. This ruling was appealed.

With regard to subcutaneous administration the Company Statement also stated 'Section 4.3 of the revised SPC does not contraindicate SC administration of Eprex for particular patients and the wording of Sections 4.2 and 4.4 confirms that a change to IV administration for Chronic Renal Failure patients is not mandatory'. The Panel noted its comments above. Although it was true that Section 4.3, Contra-indications, of the Eprex SPC did not refer to subcutaneous administration the Panel nonetheless considered that the Company Statement was misleading in that it played down the need to change to IV Eprex and the limited circumstances for SC use. The Panel considered that the Statement was not consistent with the particulars listed in the SPC and a further breach of Clause 3.2 was ruled. This ruling was appealed.

The Company Statement stated that Ortho Biotech would 'work with individual units to minimise the impact of the change [from subcutaneous Eprex to IV] and to ensure that no funding issues compromise this change'. The Panel noted that under Clause 1.2 of the Code the term promotion did not include measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. The supplementary information to Clause 18.1 gave further information in this regard stating that 'Measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 are outside the scope of the Code (see Clause 1.2) and are excluded from the provisions of this clause. Other trade practices are subject to the Code. The terms 'prices', 'margins' and 'discounts' are primarily financial terms'. The Panel noted that the discount offered by Ortho Biotech was as a result of a change of use of a product from SC to IV as a result of a change in the SPC. The Panel noted that financial discounts were common in the industry and had been in regular use prior to 1 January 1993. There was no reason why a company could not decide to allow a discount on a product or decide to withdraw a discount previously given. It was true that the arrangements might amount to an inducement to continue to use Eprex. This was however not unacceptable. Although inducements to prescribe were in general not permitted under the Code, financial discounts having that effect were allowed if they came within the exemption for discounts in Clause 1.2 of the Code, as set out above. This exemption was included in the Code in conformity with UK and European law. Further the discount appeared to be offered to hospitals and not to individuals. It might be argued that the prohibition in Clause 18.1 on inducements to health professionals or administrative staff did not apply to this situation. The Panel noted its rulings about the Company Statement. Nevertheless it decided that there had been no breach of Clause 18.1 of the Code and ruled accordingly.

## APPEAL BY ORTHO BIOTECH

Ortho Biotech noted that the Panel had ruled that for haemodialysis the IV route was mandatory, yet no changes had been made to the appropriate section within the SPC ie 4.3 Contra-Indications, hence the revised SPC allowed for haemodialysis patients to receive Eprex SC, when a clinician considered that it was not feasible to use the IV route, though did speculate under what circumstances this might occur.

Ortho Biotech also appealed the Panel's ruling that the statement played down the need to change to the IV route. Ortho Biotech considered that the Panel had not taken sufficient notice of the complex clinical circumstances around the provision of anaemia management and funding for Eprex (and other erythropoietins) in that there was a considerable mix of shared care and other complex funding arrangements which were well known to the nephrology community, and which would make any changes to practice initially difficult, and not manageable within short time-frames. Additionally, the statement made it clear to the healthcare professional that Ortho Biotech was committed to working with individuals (clinicians and nephrology units). The Panel had indeed noted the phrase that Ortho Biotech would 'work with individual units to minimise the impact of the change [from subcutaneous Eprex to IV] and to ensure that no funding issues compromised this change'. Ortho Biotech submitted that this open promise reinforced its support for units and its determination to assist in a move to the use of the IV route of administration. This did not play down the need to change towards the IV route. Ortho Biotech denied a breach of Clause 3.2 in this respect.

## COMMENTS FROM ROCHE

See point A above.

## APPEAL BOARD RULING

The Appeal Board considered that there were patient groups for whom IV administration of Eprex was mandatory. The Appeal Board considered that the Company Statement was not consistent with the

particulars listed in the SPC in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

Although it was true that Section 4.3, Contra-indications, of the Eprex SPC did not refer to subcutaneous administration, the Appeal Board nonetheless considered that the Company Statement was misleading in that it played down the need to change to IV Eprex and the limited circumstances for SC use. The Appeal Board considered that the Company Statement was not consistent with the particulars listed in the SPC and upheld the Panel's ruling of a further breach of Clause 3.2. The appeal on this point was unsuccessful.

### 3 'Maintaining SC route of administration with current Eprex treatment'

#### COMPLAINT

Roche alleged that under this sub-heading of the Company Statement, Ortho Biotech had repeated misinformation. As stated above, the changes to the Eprex SPC made it clear that the SC route of administration was not recommended in haemodialysis. In predialysis Eprex should only be used if IV was not feasible and then if the risk benefit had been taken into account. However, this section of the Company Statement made no mention of the requirement for IV administration in haemodialysis and gave no information about the risk benefit. Indeed the statement implied that certain patients would remain on SC administration and cited emerging scientific and medical data, (clearly an all embracing claim) the misleading review of the European Agency, and unspecified ongoing research (again all embracing) being conducted by others. No details of this research were provided. Indeed the whole sentence was meaningless and intended merely to obfuscate. It was then stated that the SPC did not contraindicate SC administration which was misleading because no mention was made of the fact that essentially SC use was not indicated in haemodialysis. Roche alleged that this section of the Company Statement was in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10 and 9.4.

#### RESPONSE

Ortho Biotech repeated that the subcutaneous administration was permitted under the revised SPC. Consequently, the company denied a breach of Clause 3.2 of the Code.

Ortho Biotech stated that its Company Statement made clear the changes to the SPC, and importantly that a switch to alternative products was one possible outcome of clinicians' assessments of the risk of PRCA to their patients. In making such assessments clinicians would seek further information from all companies and independent bodies such as regulatory authorities. Consequently advising clinicians of the emerging debate regarding relative risk was both informative and factual, did not mislead with respect to Eprex, and did not denigrate other erthyropoietins in general, nor NeoRecormon in particular. Ortho Biotech therefore denied any breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10 and 9.4 of the Code.

#### PANEL RULING

The Panel noted its comments regarding the change from subcutaneous to IV administration in points B and D2 above. The section of the Company Statement in question stated that subcutaneous administration was not contraindicated in any patient group and that it was not mandatory to change patients to IV therapy. The Panel considered that the sub-heading 'Maintaining SC route of administration with current Eprex treatment' added to the impression that maintenance of subcutaneous therapy was as much an option as changing to IV and that was not so. In the Panel's view maintenance of SC therapy was only a second line option ie where IV therapy was not feasible in certain patients. The Panel considered that in this regard the Company Statement was misleading and inconsistent with the particulars listed in the SPC. Breaches of Clauses 3.2, 7.2 and 7.4 were ruled. The Panel did not consider, however, that in this regard the Company Statement was a misleading comparison, misleading with regard to side effects or exaggerated. No breaches of Clauses 7.3, 7.4 and 7.10 were ruled.

Roche had also alleged a breach of Clause 9.4 with regard to the mention of the European Agency. The Panel noted its comments at point C above. No breach of the Code was ruled. (The Panel noted that in point D1 above it had already ruled a breach of Clause 9.4 with regard to the reference to the MCA).

With regard to the allegations relating to the statement that the European Agency was currently reviewing erythropoietins as a whole, the Panel noted its comments in point C above and considered that its rulings of breaches of Clause 7.2 and 7.4 applied here too. Further breaches of those clauses were thus ruled. This ruling was appealed.

#### APPEAL BY ORTHO BIOTECH

Ortho Biotech appealed the breaches of Clauses 7.2 and 7.4 in respect of the statements made regarding the European Agency review of all erythropoietins, and referred to its response to point C above.

#### COMMENTS FROM ROCHE

See point A above.

#### APPEAL BOARD RULING

The Appeal Board considered that its comments and rulings at point C above regarding the statement that the European Agency was currently reviewing erythropoietins as a whole were relevant here and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

### 4 'Continuing with SC administration with a change to a different erythropoietin'

#### COMPLAINT

Roche considered that the section of the Company

Statement under this sub-heading dealt with one of the major questions raised by the profession, which this company statement was supposed to address. However instead of addressing the safety issue in a balanced, fair and objective way the first sentence of this section stated that '… the revised SPC does not contra-indicate SC administration of Eprex for any patient group…'. This statement was clearly designed to dissuade clinicians from the need to change to an alternative product and was false, and misleading for all the reasons stated above.

The Company Statement then added unsubstantiated information which was contrary to the safety warning issued by the European Pharmacovigilance Working Party by suggesting that if the patient had been treated for 'months to years' (note the misleading way that the 'number' of months or years was omitted) that a switch was not required in view of the 'assessment of all erythropoietins' and the nebulous 'ongoing research being conducted by others'. No evidence was presented to justify the assertion that PRCA was unlikely after prolonged treatment. The claim was apparently justified by referring to a regulatory authority, misquoting that authority (as detailed above) and finally giving no details about ongoing research. This statement contradicted the recommendation of the SPC and was inconsistent with it (Clause 3.2). It also breached Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 9.4 and 11.2.

Roche emphasised how misleading and irresponsible this statement was:

- By continually referring to this new/ongoing assessment of all erythropoietins this deliberately led the clinician, who might consider switching to an alternative product which had not been the subject of an urgent safety restriction, to delay this conversion. In doing so the clinician might, unknowingly expose the patient to an increased risk of this serious side effect.
- This statement had been responsible for very many queries to Roche's medical department, most of which were to ask when the similar restriction for NeoRecormon would be announced.
- Understandably clinicians did not wish to change to another therapy which might have an imminent restriction imposed upon it.

## RESPONSE

Ortho Biotech stated that for reasons already put forward it denied breaches of Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 9.4 and 11.2 of the Code.

## PANEL RULING

In relation to the claim that Section 4.3 of the revised SPC did not contraindicate SC administration of Eprex for any patient group the Panel considered that its rulings at points D2 and D3 were relevant. The Panel noted that the Company Statement implied that the longer that patients with chronic renal failure were on Eprex the less of a risk PRCA became. Section 4.4 of the Eprex SPC stated that '[PRCA] has rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins'. The Panel considered that although referred to in the SPC, the phrase '… [cases of PRCA] have rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins …' within the context in which it appeared in the Company Statement played down the need to change patients to IV therapy. The Panel considered that the discussion of Sections 4.3 and 4.4 of the SPC were misleading and inconsistent with the SPC in this regard. Breaches of Clauses 3.2, 7.2 and 7.4 were ruled.

The section at issue in the Company Statement referred to the European Agency's ongoing review of the erythropoietins and the Panel noted its comments in point C above about this. The Panel considered its rulings made in point C applied here. Breaches of Clauses 7.2 and 7.4 were thus ruled. This ruling was appealed.

The Panel noted that the section at issue in the Company Statement referred to PRCA having been rarely reported following treatment 'with Eprex or other erythropoietins'. The Panel considered that its comments at point D1 in relation to the claim '… reports of increased immunogenicity and [PRCA] in association with Eprex and other erythropoietins' was relevant here. The Panel considered that the claim at issue gave the impression that PRCA was as common with Eprex as with the other erythropoietins which was not so. The Panel considered that this was a misleading comparison and ruled a breach of Clause 7.3 of the Code. This ruling was appealed. The Panel did not consider that the section was misleading about the side effects of Eprex or exaggerated and ruled no breach of Clauses 7.9, 7.10. The Panel considered that, with regard to the reference to the European Agency, its ruling in point C above concerning the reference to the French regulatory authority was relevant. No breach of Clause 9.4 of the Code was ruled.

The Panel noted that it was alleged that a regulatory authority had been misquoted. The Company Statement did not contain any quotations and so there could be no misquotation. No breach of Clause 11.2 was ruled.

## APPEAL BY ORTHO BIOTECH

Ortho Biotech submitted with respect to references to the European Agency's ongoing review of erythropoietins that it appealed breaches of clauses 7.2, and 7.4 for the same reasons put forward under point C and also point D.3 immediately above.

Ortho Biotech also appealed a breach of clause 7.3 in that the statement referring to reports of PRCA following treatment with Eprex and other erythropoietins was not misleading, and could be fully substantiated for reasons previously stated within this document under points A and B. Additionally, as stated previously within this document, it was not possible to compare incidence of events reported when relying on spontaneously reported adverse events.

## COMMENTS FROM ROCHE

See point A above.

### APPEAL BOARD RULING

The Appeal Board considered that its rulings and comments at point C regarding the European Agency's ongoing review of the erythropoietins applied here. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board considered that its comments and rulings at point D1 were relevant here; the claim at issue gave the impression that PRCA was as common with Eprex as with the other erythropoietins which was not so. The Appeal Board considered that this was a misleading comparison and upheld the Panel's ruling of a breach of Clause 7.3 of the Code. The appeal on this point was unsuccessful.

## 5 'Going Forward'

### COMPLAINT

In the final paragraph of the Company Statement headed 'Going Forward' Ortho Biotech stated that it would 'closely monitor the emerging scientific and medical literature in relation to these issues and will update the UK renal community as this further data becomes available'. Despite this being a statement professing to be specifically for that purpose, Ortho Biotech had not updated the community on even the current literature. The community had not been informed that a leading physician in this field speculated in the New England Journal of Medicine that the increases in the incidence of PRCA since 1998 could be due to a change in the manufacture. Ortho Biotech had not informed the community that its affiliate company in Singapore had issued a statement from that country's regulatory authority that speculated on the change in formulation, the handling conditions and other possible explanations. In addition no mention was made of data subsequently presented to financial journalists in New York in which the chairman of research and development for the parent company speculated on these changes as causes of PRCA.

Roche noted that Ortho Biotech had reminded the community to handle the product according to the SPC without explaining why this was so important. Doing so would draw attention to the differences in manufacture and stability between its product and other epoetins. With such disclosures it would become apparent that it was not the epoetin part of the product but its formulation that caused this problem, therefore more stable epoetin products might exist, representing a safer alternative.

In summary this Company Statement, produced by the marketing department to clarify a medical communication which was itself misleading, compounded these errors and then added many more misleading claims of its own. Roche considered that overall this piece was in breach of multiple clauses of the Code as outlined above. In addition Roche alleged that this piece as a whole failed to recognise the special nature of medicines etc. and did not maintain high standards in breach of Clause 9.1. Roche alleged that overall it also breached Clause 2.

### RESPONSE

Ortho Biotech stated that it would, in consultation with the appropriate regulators, continue to investigate the cause(s) of PRCA and evaluate the extent that it was associated with erythropoietin therapy. Until the cause(s) of PRCA were known, neither the regulators nor Ortho Biotech considered that it was appropriate to speculate publicly regarding such issues. The company sought only to remind physicians to prescribe Eprex in accordance with its prescribing information; it was always mindful of the special nature of medicines and considered that its actions and statements complied with the Code. The company denied breaches of Clauses 9.1 and 2 of the Code.

### PANEL RULING

The Company Statement referred to Ortho Biotech's commitment to further the understanding of PRCA associated with erythropoietins and that the company would closely monitor the relevant emerging scientific and medical literature and keep the UK renal community updated in this regard. The Company Statement was intended to highlight key aspects of the revised SPC and current scientific literature. The Company Statement had, however, been distributed in July 2002 but it made no mention of the paper by Casadevall *et al* and the accompanying editorial comment which had been published in the New England Journal of Medicine in February 2002. The Panel considered that Ortho Biotech had thus been selective with regard to the references it had cited in its Company Statement. The company had not kept the renal community up-to-date with the relevant literature. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed.

The Panel noted its comments and rulings in the points above and considered that, on balance, the Company Statement was such as to reduce confidence in the industry and to bring it into disrepute. A breach of Clause 2 was ruled. This ruling was appealed.

### APPEAL BY ORTHO BIOTECH

Ortho Biotech submitted that it had consistently communicated to health professionals updates in relation to reports of PRCA and continued to do so. Ortho Biotech did not fail to refer to the NEJM editorial comment that accompanied the Casadevall New England Journal of Medicine paper, but chose not to refer to it. The two meanings were different. For the reasons previously outlined above, there could be no justification for highlighting the reformulation of Eprex as the likely or probable cause of the PRCA phenomenon with Eprex. Neither Ortho Biotech nor any regulatory body had felt that it could draw any firm conclusions regarding the likely causes of PRCA having reviewed all the available evidence. The NEJM editorial was speculative and was made in ignorance of the extensive investigations into the issue of PRCA, which to this day had not elucidated definitive causes for the problem.

Ortho Biotech stated that the PhVWP had made it clear that it considered PRCA a concern across all

erythropoietins, and further publications from Casadevall, though speculating on any role that a reformulation might have, conceded that probably the cause might never be known.

Ortho Biotech further noted that all the cases within the NEJM article had been reported to the medical community and were included within the two formally approved 'Dear Healthcare Professional' letters that were part of the appeal (A and B). The article consisted of a small fraction of known cases, and was speculative, without giving any specific details, as to how a formulation change could contribute to PRCA. Ortho Biotech considered reference to this article for this limited purpose (ie discussion of formulation change) was not relevant to the broader issues in respect of route of administration which its Company Statement and the two 'Dear Healthcare Professional' letters principally addressed. Ortho Biotech had cited the Casadevall article extensively when discussing methodology for testing antibodies, and also for discussion of the target sites for the neutralising antibodies. For the above reasons Ortho Biotech denied a breach of Clause 9.1.

### COMMENTS FROM ROCHE

See point A above.

### APPEAL BOARD RULING

The Appeal Board considered that Ortho Biotech had been selective with regard to the references it had cited in its Company Statement. No mention was made of the paper by Casadevall *et al*. The company had not kept the renal community up-to-date with the relevant literature. The Appeal Board considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings in the points above and considered that, on balance, the Company Statement was such as to reduce confidence in the industry and to bring it into disrepute. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

## E Medicines Management and the cold chain. Pharmacy Management Supplement October 2002.

### COMPLAINT

Roche stated that this item illustrated how Ortho Biotech had sought to inform about Eprex safety in a disguised way. This supplement was supported by Ortho Biotech and mostly contained sound advice from independent authors about how to handle products which required a cold chain. But the supplement did not explain at any point why this was important, why Ortho Biotech had commissioned it or its relevance to the current safety issue.

Roche noted that the section headed 'The Manufacturer' made several claims about Eprex including its indication and numbers of patients who had benefited. It then explained the company's values and beliefs encompassed in a document called Credo. Roche noted that the key part of Credo was the company's responsibility to the profession, patients and all who used its products. The item was clearly promotional and should have included prescribing information (Clause 4.1).

The third paragraph discussed antibodies in a very generic way never once mentioning the current problem associated with Eprex. The article was clearly relevant to Eprex and included the statement that such adverse reactions due to antibody formation might lead to serious clinical consequences. As such one might have expected some discussion of PRCA and how this might be attributable to an unstable formulation if stored outside the cold chain recommendations. No mention was made of this in the text, only a reference to the first publication of Casadevall *et al*. The title of Casadevall's paper was provided in the reference list but this referred only to 'erythropoietin' and not to Eprex or Epo alfa. Thus from the text of the article the reader would not be aware of the particular problem of PRCA with Eprex. Indeed the paragraph which dealt with possible outcomes of poor cold chain handling did not list PRCA as an example but stated only that observed adverse events secondary to antibody formation included anaphylactoid reactions, delayed hypersensitivity, irreversible thrombocytopenia and aplasia. There was no such condition as 'aplasia' *per se*. It meant no growth. It was a term used to qualify a medical condition such as 'aplastic anaemia' or PRCA. The authors had deliberately used this term in a misleading way so as not to associate PRCA with Eprex.

In addition none of the recent relevant data or publications were discussed in this article. Thus there was no mention of the follow up letter by Casadevall *et al* to the New England Journal of Medicine or the letter from the FDA or the editorial detailing the manufacturing issue which might have led to the instability of Eprex. These were crucial recent data relevant for an article about handling the cold chain of a product. Roche considered these data were ignored because they implicated Eprex in this problem. As such this article, which was clearly promotional and provided claims on side-effects, did not reflect available evidence nor was it balanced, fair etc (Clauses 7.2, 7.9).

This paragraph also contained a sentence about storage temperature, which could be implicated as a contributor to enhanced immunogenicity. This was highly topical and relevant to Eprex but the authors ignored this and chose to illustrate it by reference to a different product, Roche's interferon alpha-2a. This was a 1997 reference thus ignoring recent information described above and Ortho Biotech's own company statements to the financial press in the USA. This paragraph was therefore misleading, not balanced, fair, or objective in breach of Clause 7.2. It was not based on an up-to-date evaluation of all the evidence, reflecting that evidence clearly, in breach of Clause 7.3. As it dealt with side effects, it also breached Clause 7.9. The reference to interferon alfa rather than to Eprex to illustrate a problem with cold chain products was misleading and disparaging in breach of Clauses 7.3 and 8.1.

Roche noted that the supplement was clearly labelled as supported by a grant from Ortho Biotech.

However this section made product claims and dealt with adverse events in a misleading manner. It was produced in October, within three months of two 'Dear Doctor' letters dealing with major changes to the Eprex SPC in relation to a serious side effect that could be the result of formulation change and poor handling. It appeared several weeks after the chairman of research and development for the company had made significant statements about the likely cause of PRCA, which included instability of the product since formulation change. Roche considered that this piece should have included such important information especially that relating to the SPC change and, as a minimum, should have included prescribing information alongside this article (Clause 4.1).

Thus the whole supplement which purported to deal with cold chain management was in fact disguised promotion of Eprex in breach of Clause 10.1. Ortho Biotech was attempting to ensure correct handling of the product because of the risk of PRCA without providing reasons for why this was so important at this current time. PRCA was a serious adverse event and therefore warranted clear unambiguous information not something dressed up as general advice about cold chain handling. The section on Eprex should have made clear the nature of the problem and the consequences of poor handling rather than general, generic statements referenced to an old paper on a completely different competitor's product and only to one of the many recent publications.

Roche noted that 'Credo' meant 'I believe' in Latin and referred to a confession of faith. Roche did not consider this piece reflected the meaning of Credo given by the authors, indeed its use in this context was a cynical attempt to mislead the reader into thinking the company only had the patients' welfare at heart. This type of claim was clearly not appropriate for a document, which although purporting to advise health professionals on the pitfalls of breaking the cold chain, disguised the current relevance to Eprex. It ignored the special nature of medicines and the professional audience to which the material was directed. It fell well short of the high standards expected by the medical community in breach of Clause 9.1 and, for all the other breaches outlined above, Clause 2.

## RESPONSE

Ortho Biotech stated that this article provided a general discussion of a manufacturer's responsibility to ensure correct cold chain distribution of its products. This was in response to new guidelines on storage and handling of biological products being compiled by the MCA. Indeed, Ortho Biotech worked closely with the MCA in respect of these guidelines. As the company was also reviewing storage and handling procedures for Eprex it was not unreasonable to use Eprex as an example. It would be unreasonable to expect a company to contribute such an article without any reference to its own products and its practical experience with them. Other examples using different products were also used.

Within the article there were a wide range of views expressed, with respect to the handling of biological products, from hospital and community pharmacists, pharmacy technicians, a foreword from a member of the MCA. It was therefore not unreasonable to put a manufacturer's point of view.

This message in the piece was necessarily simple and general; it was that the Johnson & Johnson Group of companies had significant experience with the development and commercialisation of biotechnology products, and sold numerous biotech products. One of the most important of these was Eprex. All manufacturers had a duty to patients and prescribers, and in Johnson & Johnson's case this was reflected in the company's Credo. The consequences of failure to ensure correct cold chain handling and delivery of recombinant protein therapies might compromise their integrity, and the company had therefore taken the proactive decision to review and update its procedures for cold chain maintenance.

The article was therefore not an advertisement. It was factual, accurate, informative reference material concerning licensed medicines that highlighted the importance of maintaining adequate cold chain distribution of certain types of medicine, including erythropoietins like Eprex. It contained no product claims.

Both the Code and the advertising regulations and associated MCA guidelines on the advertising and promotion of medicines in the UK distinguished between advertising and 'reference material, factual informative statements or announcements … provided they did not contain a product claim'. The MCA guidelines defined a product claim as 'written or spoken words intended to encourage prescription or supply by health professionals and use of medicines by the general public, generally by means of highlighting the qualities of a medicine'. Ortho Biotech could not identify any such claim in this article.

Ortho Biotech noted that, as in Case AUTH/401/2/96, references to a product name did not necessarily imply a product claim. What was important was that the material was presented in a factual and balanced way. Ortho Biotech considered this to be the case here since the references to Eprex in this piece were not excessive. Moreover, the piece would not encourage physicians to prescribe Eprex.

Contrary to Roche's assertion, the piece was not intended to inform prescribers of changes in the prescribing information for Eprex. Ortho Biotech could not identify any particular element of this article that could be interpreted as doing so. It arose from a genuine concern that poor storage and distribution of biotechnology products raised potential safety concerns and a desire to ensure that the cold chain was better controlled.

Johnson & Johnson's Credo was an important element of its business practices. Company employees all participated in periodic surveys and evaluations of the company's performance of its Credo responsibilities. These assessments were then fed back to the senior management and corrective action was promptly taken to remedy any shortcomings.

Rather than being 'a cynical attempt to mislead', Ortho Biotech considered that the existence of the Credo and the steps taken by the company's senior management to ensure that it was complied with could only be of benefit to patients and doctors. Reference to the company's Credo within this article emphasised how important Ortho Biotech and Johnson & Johnson took patient safety. This aspect had been constant in all of the company's contacts with regulatory authorities and the UK (and other) medical communities. Ortho Biotech found Roche's dislike of such expressions of good intent rather perplexing.

In respect of referring to its company code of conduct (the Credo) Ortho Biotech denied a beach of Clause 2. For all the reasons set out above, it also denied breaches of Clauses 4.1, 7.2, 7.3, 7.9 and 8.1 of the Code.

**PANEL RULING**

'Medicines Management and the Cold Chain' was published as a supplement to 'Pharmacy Management'. Maintenance of the cold chain was important in ensuring the safe and effective transportation and storage of vaccines and biological products. The supplement addressed issues regarding this aspect of medicines management which were relevant to pharmacists as they were responsible for ensuring the quality of the medicines which they dispensed. The final chapter of the supplement, entitled 'The Manufacturer', was written by two Ortho Biotech employees. Eprex was referred to three times; each mention of the product name was in capital letters. It was stated that Eprex was Ortho Biotech's leading product and that it was used for the prevention and treatment of anaemia in renal disease, cancer, HIV and critical care and that to date over 3 million patients had benefited from treatment. The Panel considered that the final chapter of the supplement thus promoted Eprex. The supplement therefore should have included prescribing information. As no prescribing information was included the Panel ruled a breach of Clause 4.1 of the Code.

The Panel considered that the aim of the supplement was to address the pharmaceutical implications of cold chain management, not the clinical consequences relating to individual products. The Panel, therefore, did not accept that the chapter headed 'The Manufacturer', even though written by employees of Ortho Biotech, needed to address in any detail the clinical implications of not maintaining the cold chain with regard to Eprex. In that regard the Panel did not consider that the chapter was misleading. Nor did the Panel consider it either misleading or disparaging to illustrate one point in the chapter with a reference to interferon alpha. The Panel ruled no breaches of Clauses 7.2, 7.3, 7.9 and 8.1.

The Panel did not accept that the whole supplement was disguised promotion of Eprex. The supplement addressed general pharmaceutical issues of cold chain management. No breach of Clause 10.1 was ruled.

The Panel did not consider that reference to Ortho Biotech's Credo meant that high standards had not been maintained or that it brought discredit upon or reduced confidence in the industry. No breach of Clauses 9.1 and 2 was ruled.

**F Breach of Clause 2**

**COMPLAINT**

Roche considered that the above items had not been produced in isolation but reflected other modes of promotion including representative activity. As such they formed part of a concerted campaign of subterfuge and misinformation. Roche considered that briefing materials over the last year or so might well confirm its complaint on this score.

The written evidence presented suggested widespread breaches of the Code, intended by Ortho Biotech to ameliorate the effect of changes to the Eprex SPC concerning safety that might result in the prescribing of alternative epoetins. The communications were designed to make the health professional believe that a) the problem of antibodies and PRCA was of the same frequency with all epoetins, b) that although major changes had been made to the SPC these were not necessarily to be followed and c) that an ongoing assessment and research by others was likely to lead to similar restrictions on all epoetins.

Thus the above items claimed three times that PRCA occurred with other epoetins; mentioned the French or European Agency five times and the Medicines Control Agency twice to substantiate misleading statements; mentioned 'a new ongoing assessment of all epoetins' on four occasions and claimed that the change to IV was not mandatory on three occasions.

Roche considered that Ortho Biotech had taken advantage of the clinicians' limited understanding of the complex EU regulatory and pharmacovigilance environment to deliberately mislead them about this issue. The company had implied that the restriction on its label was self-imposed, leaving the clinician wondering why the other manufacturers had not followed suit. Ortho Biotech had implied, and continued to insinuate, that assessment of other epoetins was imminent with the confusion that this resulted in. The company had been less than open about the nature of the restriction, not pointing out that the clear differences in recommended routes of administration of Eprex and NeoRecormon had been endorsed by the European agencies.

Roche stated that in addition it was aware that Ortho Biotech representatives had continued to play down the significance of the problem reiterating what was stated in the letter of August. That was to say that they had been verbally endorsing the fact that the new Eprex SPC still permitted the SC route in all patients.

Roche considered that in addition to the breaches of the clauses mentioned above the effect of Ortho Biotech's activities, exemplified in these 5 items, was to bring the industry into disrepute in breach of Clause 2. Roche considered that Ortho Biotech should publicly retract these misleading and damaging claims and statements. This should involve clear communication to the health profession that statements about 'new assessments of the

erythropoietins as a whole' were out of context and misleading and that statements which had disparaged other epoetins were misleading. Clearly there was need for clarification about the SPC changes for Eprex with regard to IV and SC use. In addition health professionals who had received the pharmacy management supplement should be informed more comprehensively about the true nature of the problem and the disguised version should be withdrawn.

## RESPONSE

Ortho Biotech stated that its overriding impression was that Roche was seeking to take retaliatory action against it in response to the findings made in respect of its advertising for NeoRecormon. Roche seemed determined to complain about every communication from Ortho Biotech since November 1991, irrespective of the merits of the complaints. Three of the items it identified as having breached the Code were not even promotional pieces. Two were approved regulatory communications and one was a general, factual and balanced article about the importance of ensuring sound cold chain distribution of biotech products.

Ortho Biotech noted that Roche had bought the other two items of its complaint to its attention in August last year. Although the company considered that many of the concerns Roche raised were baseless, it had already taken the decision to submit all communications regarding Eprex and PRCA to the regulators prior to their circulation and therefore had no difficulty in providing Roche with an undertaking that it would also not use the relevant materials again.

Ortho Biotech considered that Roche's complaints were ill-conceived and misplaced, based upon a restrictive view of available data and inappropriate interpretation of the revisions to the SPC for Eprex.

## PANEL RULING

The Panel noted that PRCA, although a rare complication of therapy, was a serious condition. In the Panel's view it was essential that clinicians were clearly informed of all the issues so that they could minimise the risk to their patients. The Panel noted its comments and rulings above in particular those with regard to the need to change patients to IV therapy. The Panel considered that by not stressing that subcutaneous injections should not be given to some patients and that the maintenance of subcutaneous administration in others was only second choice to switching to IV and not a choice in itself, patient safety had been compromised. The Panel noted its ruling of a breach of Clause 2 at point D5. The Panel considered that overall such advertising brought discredit upon, and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

## APPEAL BY ORTHO BIOTECH

Ortho Biotech stated that it had been diligent around the advice and recommendations contained within the two 'Dear Doctor' letters (points A and B), and had successfully converted many patients towards the IV route of administration.

Ortho Biotech additionally submitted that it had communicated the rare reports of PRCA associated with Eprex in a fully open way, and had sought to appraise the medical community as to the reasons behind the increased reporting. The evidence continued to emerge, principally as a result of ongoing investigations by Ortho Biotech and its company's research capabilities. As evidence unfolded, it was clear that the European agencies also viewed PRCA as a concern across all erythropoietins, and were instigating prospective epidemiological studies as a result.

Ortho Biotech noted that recent reports published by the Swiss regulatory agency had confirmed cases of PRCA associated exclusively with epoetin beta, in addition to other mixed cases where the patient had received epoetin beta as well as other epoetins before the loss of efficacy associated with PRCA occurred.

Ortho Biotech submitted that statements it had made in respect of PRCA had never denied that there was an association with Eprex, and it had never sought to play down the number of associate cases. This was not the position taken by all manufacturers of epoetins products.

Ortho Biotech stated that it had not sought to mislead the medical community in areas where there was, in particular, emerging science and data (related to Clause 7), nor had it undertaken not to convert clinicians towards the IV route of administration following changes to the SPC (related to Clause 3.2). Ortho Biotech submitted that although the Panel had ruled breaches of the Code in some areas which it had accepted, on balance its activities were such that it had remained within the spirit of the Code such that it had not brought the Industry into disrepute. Ortho Biotech therefore denied an overall breach of Clause 2.

## COMMENTS FROM ROCHE

See point A above.

## APPEAL BOARD RULING

The Appeal Board noted that the Panel's ruling of a breach of Clause 2 applied to the materials at issue in points A, B, C and D. The Appeal Board noted that the letters at issue in points A and B had been ruled not to be within the scope of the Code. The Appeal Board had upheld the Panel's rulings of breaches of Clause 2 at points C and D. The Appeal Board therefore decided that the circumstances did not warrant a further ruling of a breach of Clause 2 and ruled accordingly. The appeal on this point was successful.

**Complaint received** **16 December 2002**

**Case completed** **17 June 2003**

CASE AUTH/1401/12/02

# PHARMACIA/DIRECTOR v GLAXOSMITHKLINE CONSUMER HEALTHCARE

## NiQuitin CQ Clear Patch journal advertisement

**Pharmacia complained about a NiQuitin CQ Clear Patch (transdermal nicotine) journal advertisement issued by GlaxoSmithKline Consumer Healthcare and published in GP. As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.**

**The advertisement was headed 'Make sure they're covered in the morning' and stated 'When smokers are trying to quit, mornings can catch them unawares. Once they've been without nicotine for 6-8 hours, cravings can be intense and hard to resist, which is why many smokers get more cravings in the morning than the rest of the day. Indeed, two out of three smokers light up within 30 minutes of waking. *NiQuitin CQ* patches provide nicotine continuously over a 24-hour period, reducing morning cravings compared with a 16-hour patch, for these heavily dependent smokers. Don't let increased morning cravings increase their risk of relapse. Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go'.**

**Pharmacia supplied Nicorette Patch, a 16-hour transdermal nicotine patch.**

**With regard to the heading, 'Make sure they're covered in the morning', and the claim, 'When smokers are trying to quit, mornings can catch them unawares', Pharmacia was unaware of any published data which showed that the mornings were a more difficult time than any other for those trying to quit smoking. Shiffman *et al* (1996) showed that for those trying to quit, the urge to smoke was greater toward the end of the day, rather than in the morning. The same author (Shiffman *et al*, 2000) confirmed that there was little difference in craving scores between 'morning hours' and 'all day' and that the temptation to relapse was much lower in the 'morning hours' than 'all day'. The claim also inferred that mornings could be a time of acute craving and that the NiQuitin CQ Patch was of particular use in these instances. However, Shiffman *et al* (2002) discussed the merits of various nicotine replacement therapy (NRT) formulations and advocated that the use of acute administration of nicotine had potential advantages over nicotine patches, notably in allowing the smoker to control the amount and timing of the dosing and to use acute dosing as a rescue medication to combat acute episodes of craving. Pharmacia alleged that the claim was misleading.**

**The Panel noted that Shiffman *et al* (1996) assessed data of first smoking lapses from ex-smokers who recorded lapse and temptation episodes. The participants did not receive any NRT. The results showed a distinct excess of lapses at night; 37% of lapses occurred between 8pm and 12am although only 21.6% of cases of craving occurred at this time. 24% of cases of craving occurred between 8am-12pm but only 19.4% of lapses. The authors noted that the relative paucity of lapses in the morning when the most addicted smokers reported the greatest craving was notable. With regard to urge to smoke the authors noted that participants generally reported intense urges and cravings during first lapses; the fact that a substantial minority relapsed with no urge experience demonstrated that subjective craving was not a necessary condition for smoking lapsing.**

**Shiffman *et al* (2000) compared the efficacy of a 24-hour patch [NiQuitin] and a 16-hour patch [Nicorette] for relief of morning craving in smokers (n=244) who suffered morning cravings and smoked their first cigarette within 30 minutes of waking. The results showed superior relief of craving and withdrawal symptom relief was obtained from the 24-hour patch, compared with the 16-hour patch, during the first two weeks of abstinence when symptoms were at their peak. The data further showed that participants on the 24-hour patch showed statistically significantly lower craving on waking at all post-quit time intervals than those on the 16-hour patch ($p < 0.001$). In each treatment group craving scores were greater during the morning hours than all day. The statistical significance of the differences was not stated. The study authors noted that their results applied to a particular population of smokers and that generalisation of the results to all smokers had not been established. The Panel queried whether the results were thus applicable to the general population of smokers who were trying to quit.**

**The Panel noted that the claim 'When smokers are trying to quit, mornings can catch them unawares' would be considered within the context of the advertisement as a whole. The prominent heading 'Make sure they're covered in the morning' was a bold unequivocal claim which set the tone for the advertisement as a whole; it would establish the morning hours, in the minds of readers, as being the time when most smokers were most at risk of craving and therefore possible relapse. Subsequent text discussed the NiQuitin 24-hour patch in the context of morning craving and an increased risk of relapse. Whilst the Panel noted that subsequent text was more cautious 'mornings *can* catch them unawares' and 'cravings *can* be intense' (emphasis added), it nonetheless did not negate the initial impression created by the heading.**

**Overall the Panel considered that within the context of the advertisement, the claim 'When smokers are trying to quit, mornings can catch them unawares' gave a misleading impression about the significance of morning cravings compared with those experienced at other times of the day. A breach of the Code was ruled.**

**Upon appeal by GlaxoSmithKline Consumer Healthcare, the Appeal Board noted that NiQuitin CQ Clear was indicated for the relief of nicotine**

withdrawal symptoms including cravings associated with smoking cessation. The summary of product characteristics (SPC) also stated that 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. Given the data and the statement in the SPC that use for 24 hours was recommended to optimise effect against morning cravings, the Appeal Board did not consider that the claim 'When smokers are trying to quit, mornings can catch them unawares' and the heading 'Make sure they're covered in the morning' were unreasonable. No breach of the Code was ruled.

Pharmacia stated that the claim 'Once they've been without nicotine for 6-8 hours, cravings can be intense and hard to resist, which is why many smokers get more cravings in the morning than the rest of the day. Indeed, two out of three smokers light up within 30 minutes of waking' referred to many smokers from the general currently smoking population, not the quitting population. Pharmacia's view that the first sentence referred to the general smoking population and not the quitting population was reinforced by the second sentence concerning the habits of current smokers who might light up within 30 minutes of waking. Indeed, data presented by Shiffman *et al* (1996) suggested that smokers trying to quit found the opposite end of the day [8pm-12am] most difficult. Pharmacia referred to its comments above and alleged that the claim was misleading.

The Panel noted that the claim at issue was preceded by the claim considered above which introduced the paragraph 'When smokers are trying to quit, mornings can catch them unawares'. The claim at issue began 'Once they've been without nicotine …' and in the opinion of the Panel would be read as referring to the patient population identified in the preceding sentence ie smokers who were trying to quit. The Panel did not accept that the claim referred to the general smoking population and thus ruled no breach of the Code on this narrow point.

Pharmacia noted that the claim '*NiQuitin CQ* patches provide nicotine continuously over a 24-hour period, reducing morning cravings compared with a 16-hour patch, for these heavily dependent smokers' followed that at issue above and was referenced to Shiffman *et al* (2000). The advertisement clearly discussed quitting in the general smoking population. The advertisement wording implied that 'these heavily dependent smokers' were the same population as the general smoking population and that most smokers trying to quit had morning cravings. Shiffman *et al* (2000) had studied a very specific group of highly dependent quitting smokers ie those with morning cravings and who smoked their first cigarette within 30 minutes of waking. Indeed the authors acknowledged that the generalisation of their results to all smokers was not established.

Although Pharmacia was unhappy with the general tone of the advertisement given the undertaking made by GlaxoSmithKline Consumer Healthcare, it believed that this was a specific breach of the undertaking given in Case AUTH/1253/11/01: 'A reader would assume that the claims at issue would refer to the general smoking population rather than the subgroup examined in Shiffman *et al* and that was not so'. Breaches of the Code were alleged including a breach of Clause 2.

The Panel noted that in Case AUTH/1253/11/01 it had considered that the claim, referenced to Shiffman *et al* (2000), 'NiQuitin CQ patches have the advantage of offering constant 24-hour nicotine replacement, significantly reducing morning cravings' in an advertisement was misleading in breach of the Code. The Panel had noted that the advertisement discussed NiQuitin in relation to successful quitting in the general smoking population. A reader would assume that the claims at issue related to the general smoking population rather than the subgroup of smokers who smoked within 30 minutes of waking and who experienced morning cravings examined in Shiffman *et al* (2000) and that was not so. An explanatory footnote was insufficient to negate this impression.

Turning to the present case, Case AUTH/1401/12/02, the Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its comments above on Shiffman *et al* (2000) and the patient population therein. The Panel noted that the claim at issue was different to that previously considered in Case AUTH/1253/11/01 and did not rely upon a footnote to define the patient population; it described the patient group as 'smokers who were trying to quit' and as 'heavily dependent smokers'. It would not be read as applying to the general smoking population. The preceding sentence referred to smokers who lit up within 30 minutes of waking. The Panel therefore considered that the claim at issue was not caught by the undertaking given in Case AUTH/1253/11/01 and no breaches of the Code were ruled including a ruling of no breach of Clause 2.

In relation to the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go', Pharmacia stated that it was not known if the treatment of morning cravings led to better long-term cessation rates. Morning cravings had not been shown to be a cause of relapse. Pharmacia also referred to its comments regarding the most common times of day for cravings/temptation.

Overall the advertisement implied that 24-hour patches had greater efficacy in achieving smoking cessation than 16-hour patches. Direct comparative trials of 24-hour vs 16-hour patches with an endpoint of cessation did not exist. However, the Cochrane Collaboration had conducted a meta-analysis of all the published studies of nicotine patches and concluded there was no evidence of a difference in clinical effectiveness of 16-hour compared to 24-hour patch.

**One placebo-controlled study comparing the same nicotine patch when used for 24 or 16 hours did not show any statistically significant difference between the two for quit rates or tobacco withdrawal symptoms (Daughton *et al*, 1991). The study showed that those who used the patch for only 16 hours had a lower rate of relapse than those on the 24-hour regimen. Another more recent study of the NiQuitin CQ Patch compared treatment efficacy between subjects who elected to use the patch for 24 hours vs 16-hour use (Shiffman *et al* 2002). Outcomes did not differ between these self-selected groups and analyses of treatment efficacy were unchanged when self-selected 24-hour vs 16-hour use was included as a co-variant.**

**Pharmacia alleged that this claim was misleading. The claim did not reflect the current body of evidence but inferred a greater likelihood of success with a 24-hour patch than a 16-hour patch.**

**The Panel did not accept that the advertisement compared NiQuitin CQ patches with the 16-hour patch solely in relation to morning cravings, as suggested by GlaxoSmithKline Consumer Healthcare. The final paragraph linked the increased morning cravings with an increased risk of relapse and concluded 'Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go'. The Panel considered that a reader would assume that the stated reduction in morning cravings achieved with the 24-hour patches was such that NiQuitin CQ had greater efficacy in achieving smoking cessation compared to the 16-hour patch.**

**The Panel noted that the Cochrane Report on NRT for smoking cessation (2002) reviewed the efficacy of different forms of NRT in achieving abstinence or a sustained reduction in the amount smoked. The report concluded, *inter alia*, that wearing the patch only during waking hours (16 hours/day) was as effective as wearing it for 24 hours/day. The report authors stated that further research was required in relation to direct comparisons between the various forms of NRT and between different doses and durations of treatment. The Cochrane report only analysed randomized trials in which NRT was compared to placebo or no treatment or where different doses of NRT were compared. It excluded trials which did not report cessation rates and those with follow-up of less than six months. Shiffman *et al* (2000) was thus excluded as it was a comparison of 24- and 16-hour patches and assessed craving and abstinence only over two weeks.**

**The Panel noted its comments on Shiffman *et al* (2000) above. Whilst not examined in the Cochrane report it was nonetheless relevant. However given the findings of the Cochrane Report the Panel did not consider that Shiffman *et al* (2000) alone was sufficient to substantiate the overall impression that NiQuitin CQ was more efficacious in achieving smoking cessation than the 16-hour patch. Shiffman *et al* (2000) examined abstinence and cravings only. There was no direct comparative data on overall efficacy. The Panel thus considered that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go' overstated the data and within the context of the advertisement was misleading about the relative efficacy of the 24-hour and 16-hour patch as alleged. A breach of the Code was ruled.**

**Upon appeal by GlaxoSmithKline Consumer Healthcare, the Appeal Board noted that the Panel had considered that a reader would assume that the stated reduction in morning cravings achieved with 24-hour patches was such that NiQuitin CQ had greater efficacy in achieving smoking cessation compared to the 16-hour patch. The Panel had then referred to the data to support this impression. The Appeal Board noted that smoking cessation was not the licensed indication for NiQuitin CQ; the product was licensed for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation, not for smoking cessation *per se*.**

**The Appeal Board noted that the final paragraph of the advertisement 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' gave the impression that because NiQuitin CQ was effective in relieving morning cravings it would also be effective in long-term smoking cessation. The Appeal Board considered that the phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches which were referred to in the preceding paragraph.**

**The Appeal Board considered that the claim gave the impression that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of the Code.**

Pharmacia Limited complained about a NiQuitin CQ Patch (transdermal nicotine) journal advertisement (ref NCQ/PWT/O802/003F) issued by GlaxoSmithKline Consumer Healthcare and published in GP 21 October 2002. As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

The advertisement was headed 'Make sure they're covered in the morning' which was followed by:

'When smokers are trying to quit, mornings can catch them unawares. Once they've been without nicotine for 6-8 hours, cravings can be intense and hard to resist, which is why many smokers get more cravings in the morning than the rest of the day. Indeed, two out of three smokers light up within 30 minutes of waking.

*NiQuitin CQ* patches provide nicotine continuously over a 24-hour period, reducing morning cravings compared with a 16-hour patch, for these heavily dependent smokers.

Don't let increased morning cravings increase their risk of relapse. Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go.'

Pharmacia supplied Nicorette Patch, a 16-hour transdermal nicotine patch.

**1 Heading 'Make sure they're covered in the morning'. Claim 'When smokers are trying to quit, mornings can catch them unawares'**

**COMPLAINT**

Pharmacia stated that neither the heading nor the claim was referenced. Pharmacia was unaware of any published data which showed that the mornings were a more difficult time than any other for those trying to quit smoking. Shiffman *et al* (1996) published a table which showed that for those trying to quit, the urge to smoke was greater toward the end of the day, rather than in the morning. Shiffman *et al*, 2000 confirmed that there was little difference in average baseline adjusted craving scores between 'morning hours' and 'all day' (not further defined) for the patches tested and that the temptation to relapse was much lower in the 'morning hours' than 'all day' (not further defined).

This claim also inferred that mornings could be a time of acute craving and that the NiQuitin CQ Patch was of particular use in these instances. However, Shiffman *et al* (2002) discussed the merits of various nicotine replacement therapy (NRT) formulations and advocated that the use of acute administration forms of nicotine had potential advantages over nicotine patches, notably in allowing the smoker to control the amount and timing of the dosing and to use acute dosing as a rescue medication to combat acute episodes of craving.

Pharmacia alleged that the claim was misleading in breach of Clause 7.2 of the Code.

**RESPONSE**

GlaxoSmithKline Consumer Healthcare stated that there was no requirement for every statement made in an advertisement to be referenced as long as they were capable of substantiation (Clause 7.4 of the Code). Pharmacia might be unaware of any published data which showed that mornings were a more difficult time than any other for those trying to quit smoking, but the advertisement made no claim to such effect and therefore, Pharmacia's comments were irrelevant. The opening sentences of the advertisement used the modal verb 'can' to qualify the statements so that no absolute claim was made. The phrase '…mornings can catch them unawares' did not in its language or effect preclude the possibility that some patients might not be caught unawares in the morning and similarly it did not preclude the possibility of patients being caught unawares at other times of the day.

GlaxoSmithKline Consumer Healthcare noted that Pharmacia alleged that the use of the term 'caught unawares' meant that relapse would occur at the time identified. To be caught unaware was to be surprised, usually with negative connotations. GlaxoSmithKline Consumer Healthcare had used it to convey that this might be a time of day that smokers trying to quit found uncomfortable because of cravings, a symptom health professionals would be well aware of and relief of which was covered by the indications of NiQuitin CQ Patch. The subsequent sentence went on to discuss cravings further. This language did not automatically infer, or cause the reader to assume, that the patient would relapse at that moment. GlaxoSmithKline Consumer Healthcare noted that although actual relapses were not disproportionately common in the morning, elevated morning craving was related to later relapse risk (Shiffman *et al* 1997) and so control of morning craving might not simply make things more comfortable for the patient (and thus provide an immediate clinical benefit in the form of symptom relief), but might also be an important element in promoting longer term success (Shiffman *et al* 2000).

GlaxoSmithKline Consumer Healthcare noted that Pharmacia asserted that Shiffman *et al* (1996) supported its position that the urge to smoke was greater towards the end of the day. The table Pharmacia referred to showed the time of day smoking lapses occurred, not cravings or urges. GlaxoSmithKline Consumer Healthcare submitted that an equally intense urge or craving might or might not lead to relapse depending on a multiplicity of factors including the patient's coping mechanisms. Accepted scientific practice did not therefore allow conclusions about the relative intensity of cravings at different times of the day based on lapse data. The table also reported temptations (an acute rise in the urge to smoke or an occasion where they came to the brink of smoking even though they did not have an acute rise in urge) and it could be seen that slightly more temptations occurred in the morning (8am-12pm) than the evening (8pm-12am). Indeed, the authors of the study concluded that 'Lapses may cluster at night as a result of the cumulative effects of stress or smoke exposure throughout the day, or because of the clustering of relevant events (eg socialising, alcohol drinking) during this time'.

Pharmacia's assertion that Shiffman *et al* (2000) confirmed that there was little difference… between 'morning hours' and 'all day' for the patches tested was inaccurate for several reasons. Firstly, comparing the tally of total temptations for a two hour 'morning' time period with the tally of total temptations of a seventeen hour 'all day' time period was misleading because the total number of temptations in a seventeen hour period would necessarily be greater than the total number of temptations in a two-hour subset of that period. The data actually showed that, numerically, 16-hour Nicotrol/Nicorette patch users experienced higher craving for cigarettes in the morning than during the entire day (which included the morning and later periods in the day, thus diluting the comparison between the morning and the rest of the day).

Pharmacia's assertion that Shiffman *et al* (2000) data showed quite clearly that the temptation to relapse was much lower in the 'morning hours' than 'all day' again underscored Pharmacia's misunderstanding of the study: morning cravings were not the same as the temptations to smoke reported. Craving was a physiological symptom of abstinence that varied continuously in intensity and might occur without provocation, while 'temptation to smoke' referred to peak urges typically invoked by environmental stimuli associated with smoking.

The data in Shiffman *et al* (2000) tallied the number of episodes of temptation; it did not, as Pharmacia

suggested, measure the relative intensity of cravings throughout the day. The data cited did not support either the assertion that there was little difference in morning and all day cravings or the assertions made about increased craving occurring later in the day.

Pharmacia had argued that the advertisement also inferred that mornings could be a time of acute craving. As explained above, the true language and/or implication of the advertisement was that at least some smokers experienced morning cravings. The craving intensity data in Shiffman *et al* (2000) showed this claim to be true. Pharmacia's proposition that the use of acute administration forms of nicotine had potential advantages over nicotine patches and its citation of Shiffman *et al* (2002) as support for that position appeared to be irrelevant to the issues at hand. The advertisement did not compare NiQuitin CQ patch with all the various formulations of nicotine replacement therapy (NRT). It focused solely on a direct comparison of 24-hour versus 16-hour patch.

In any event a finding that acute NRT forms might have some advantages over nicotine patches did not mean that nicotine patches such as NiQuitin CQ (or Nicorette, for that matter) had no efficacy at the specific time in question. The utility of, and even the need for, acute forms of NRT as rescue medications was not inconsistent with efficacy for the NiQuitin CQ patch. In fact, if a patch was able to maintain nicotine dosing overnight, the therapeutic levels achieved in the morning might well prevent acute craving episodes from occurring, thus obviating the need for 'rescue'.

The United States Food and Drug Administration (FDA) recognised such potential benefit of the 24-hour patch, evidenced by the FDA-approved labelling for NicoDerm CQ (the brand name for NiQuitin CQ in the US): 'if you crave cigarettes when you wake up, wear the patch for 24 hours'. The UK summary of product characteristics (SPC) stated 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. The patient information leaflet read 'However, removing the patch after 16 hours will reduce its effectiveness in relieving the urge to smoke felt by some smokers upon waking'.

GlaxoSmithKline Consumer Healthcare submitted that accordingly, there was no breach of the Code as alleged.

## PANEL RULING

The Panel noted Pharmacia's comment that neither the headline nor claim were referenced. There was no allegation in this regard. Nevertheless the Panel noted that under Clause 7.6 of the Code, when promotional material referred to published studies clear references should be given. Neither the headline nor claim was referred to a published study and thus the references did not need to be cited. The material had to be capable of substantiation.

The Panel noted that Shiffman *et al* (1996) assessed Ecological Momentary Assessment (EMA) data of first smoking lapses from ex-smokers (n=108) who recorded lapse and temptation episodes on palm-top computers. The participants did not receive any NRT. The study authors noted that the results showed a distinct excess of lapses at night; 37% of lapses occurred between 8pm and 12am although only 21.6% of cases of craving occurred at this time. 24% of cases of craving occurred between 8am-12pm but only 19.4% of lapses. The authors noted that the relative paucity of lapses in the morning when the most addicted smokers reported the greatest craving was notable. With regard to urge to smoke the authors noted that participants generally reported intense urges and cravings during first lapses; the fact that a substantial minority relapsed with no urge experience demonstrated that subjective craving was not a necessary condition for smoking lapsing.

Shiffman *et al* (2000) compared the efficacy of a 24-hour patch [NiQuitin] and a 16-hour patch [Nicorette] for relief of morning craving in smokers (n=244) who suffered morning cravings and smoked their first cigarette within 30 minutes of waking. The results showed superior relief of craving and withdrawal symptom relief was obtained from the 24-hour patch, compared with the 16-hour patch during the first two weeks of abstinence when symptoms were at their peak. The data further showed that participants on the 24-hour patch showed statistically significantly lower craving on waking at all post-quit time intervals than those on the 16-hour patch ($p < 0.001$). The baseline-adjusted craving scores for all post-quit intervals for each time block showed that in each treatment group craving scores were greater during the morning hours than all day. The statistical significance of the differences was not stated. The study authors noted that their results applied to a particular population of smokers and that generalisation of the results to all smokers had not been established. The Panel queried whether the adjusted baseline craving scores were thus applicable to the general population of smokers who were trying to quit.

The Panel noted Pharmacia's reference to the discussion in the preamble to Shiffman *et al* (2002) about the potential advantages of acute administration of nicotine (orally or intra-nasally) to treat acute episodes of craving.

The Panel noted that the claim 'When smokers are trying to quit, mornings can catch them unawares' would be considered within the context of the advertisement as a whole. The prominent heading 'Make sure they're covered in the morning' was a bold unequivocal claim which set the tone for the advertisement as a whole; it would establish the morning hours, in the minds of readers, as being the time when most smokers were most at risk of craving and therefore possible relapse. Subsequent text discussed the NiQuitin 24-hour patch in the context of morning craving and an increased risk of relapse. Whilst the Panel noted that subsequent text was more cautious 'mornings **can** catch them unawares' and 'cravings **can** be intense' (emphasis added), it, nonetheless, did not negate the initial impression created by the heading.

Overall the Panel noted its comments about the data to support the claim in question and considered that within the context of the advertisement, the claim

'When smokers are trying to quit, mornings can catch them unawares' gave a misleading impression about the significance of morning cravings compared with those experienced at other times of the day. A breach of Clause 7.2 of the Code was ruled.

## APPEAL BY GLAXOSMITHKLINE CONSUMER HEALTHCARE

GlaxoSmithKline Consumer Healthcare submitted that the basis for appeal was to explain the clinical importance of morning cravings to prescribers and the patients seeking help to quit smoking. To reiterate that the UK indication for NiQuitin CQ patch was 'relief of withdrawal symptoms including cravings associated with smoking cessation' not abstinence *per se* and that efficacy in these areas was therefore a valid basis of claims. To make clear the link between morning cravings and relapse risk, and explain the apparent contradiction that cravings could be worse in the morning, even though this was not when most relapses occurred. To clarify the relevance of the findings of the Cochrane report and the only direct head-to-head study of the two products in question and to put them into context and thus to satisfy the Appeal Board that it had not given a misleading impression as to the significance of morning cravings or overstated the data concerning the relative efficacy of the 24-hour and 16-hour patch as ruled by the Panel.

GlaxoSmithKline Consumer Healthcare submitted that morning cravings were significant to prescribers because, for many patients, morning cravings were the worst of the day. Relief of cravings, including morning cravings, was recognised as being of clinical importance to prescribers and patients. The severity of morning cravings also predicted the risk of relapse later that same day. Whether a patient suffered morning cravings was the kind of question that a doctor asked the patient when assessing how best to help. Morning cravings and cravings at other times of the day were a well recognised symptom in those trying to quit and covered by the licensed indication of NiQuitin CQ patch.

GlaxoSmithKline Consumer Healthcare explained that nicotine addiction was a chronic, relapsing condition and was classified as a disease. Nicotine replacement therapy addressed the physical aspect of withdrawal and craving but did not address the behavioural and psychological modifications required for successful quitting. All treatments were only aids to ease the symptoms associated with quitting, they did not directly stop the person smoking. Nicotine replacement therapy eased the symptoms of withdrawal including craving, but did not 'cure smoking'. However, just as removing the pain of a toothache was a legitimate and recognised clinical endpoint for an analgesic, relief of cravings (like relief of wheezing or pain) was a clinical endpoint for nicotine replacement therapy, whatever the ultimate abstinence rate.

GlaxoSmithKline Consumer Healthcare stated that morning cravings (and the efficacy of 24-hour wear in minimising such cravings) were highlighted in the NiQuitin CQ patch SPC because morning cravings in particular were recognised as being of clinical importance: 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. GlaxoSmithKline Consumer Healthcare submitted that this statement which appeared in the posology section of the SPC was not limited to a highly selected group of patients, but applied to the whole general quitting population.

GlaxoSmithKline Consumer Healthcare stated that it was not, however, the mornings when most relapses occurred. On the face of it, this seemed to be contradictory. However, a craving of a particular intensity did not automatically lead to instant relapse as this depended on many other factors, such as the availability of cigarettes, the strength of the smoking cues confronting the individual, and the individual's ability to resist the craving. GlaxoSmithKline Consumer Healthcare questioned why relapse rates were higher later in the day and had considered that evenings presented many more smoking cues, such as drinking, relaxation, others smoking and more opportunity, created by proximity to other smokers and to cigarettes, and the removal of workplace smoking restrictions.

GlaxoSmithKline Consumer Healthcare stated that the timing of the moment of relapse did not diminish the importance of morning cravings, which set the scene for the day. Although it was well known that cravings in general were predictive of subsequent relapse to smoking, Shiffman *et al* (1997) showed that the severity of morning cravings specifically predicted risk of relapse later that same day. Hence control of morning cravings was important not only to relieve discomfort but also because morning cravings uniquely predicted the risk of relapse to smoking later that day.

GlaxoSmithKline Consumer Healthcare submitted that when a patient requested help in quitting smoking, the doctor must decide if treatment was necessary or appropriate. The majority of smokers attempting to quit made a number of attempts before final success, but each attempt was part of the cyclic process required to overcome an addiction that was on a par with addiction to heroin or cocaine. When the doctor made the decision to prescribe a nicotine replacement therapy, that decision would be based on the patient in front of them, who would be a current smoker. This would be a prescription for a course of treatment (prescribing by brand was recommended as different systems had different step-down processes) so would not be mid way through a long-term therapy. Nicotine replacement therapy was designed to replace some of the nicotine from smoking so that withdrawal and craving symptoms would be reduced. Nicotine replacement therapy was an aid to smoking cessation, not a cure. Indeed the licensed indication was not 'smoking cessation', but the relief of symptoms associated with it. These symptoms peaked during the first few weeks of cessation as the body readjusted to coping without cigarettes. It was in these initial weeks when relapse was highest.

GlaxoSmithKline Consumer Healthcare submitted that the doctor and patient must decide together which was the most suitable nicotine replacement therapy. The level of nicotine dependence would be a

relevant factor as it might affect the dose, and would alert the prescriber to cases where withdrawal symptoms were likely to be severe and the prognosis poor, indicating more intensive help might be required. Being able to anticipate likely problems that the smoker would face could help them be prepared. Identifying times of day they were more likely to smoke, or situations they associated with smoking, or factors that made them relapse last time could all be used to shape the treatment decisions. GlaxoSmithKline Consumer Healthcare submitted that morning cravings were clinically very relevant; the Fagerström Tolerance Questionnaire, the most widely accepted measure of nicotine dependence, specifically asked three questions which directly related to the need for a cigarette first thing in the morning. GlaxoSmithKline Consumer Healthcare stated that these were the kind of questions that the doctor asked the patient when assessing how best to help.

GlaxoSmithKline Consumer Healthcare submitted that even Pharmacia had recognised morning cravings to be of particular concern to GPs and patients; training documents from 2002 discussed how Pharmacia representatives should deal with GPs who were concerned about morning cravings. 'GPs could be of the opinion that 24 hour patches were more effective (or better) than 16 hour patches for a number of reasons; morning cravings – 'I've heard that NiQuitin CQ patches are better at dealing with morning cravings', 'most smokers complain of morning cravings, that's when they're going to need the most help quitting' and a separate document also discussed how Pharmacia products could be used to counter early morning cravings. 'To cover early morning cravings = heavily dependent smoker – use combination – either 4mg gum or 2 microtabs/hour…. Claim patch works within 15 – 20 minutes of applying'. GlaxoSmithKline Consumer Healthcare submitted that notwithstanding that these claims were outside the licensed details for Nicorette, they recognised the widely accepted importance of morning cravings for GPs and patients.

GlaxoSmithKline Consumer Healthcare submitted therefore that the headline 'Make sure they're covered in the morning' established the morning as one of the important times of day for most smokers, and one for which effective symptom reduction was available and recognised as useful by prescribers.

## COMMENTS FROM PHARMACIA

Pharmacia requested that the Appeal Board looked at the advertisement from an overall perspective as a prospective prescriber would reasonably be expected to do.

Pharmacia's view was that the message that the reader took away was that there was a clinically significant problem in the morning for quitters and that NiQuitin CQ could provide the solution. Pharmacia alleged that this gave a misleading impression about the significance of morning cravings compared with those experienced at other times of the day. Furthermore, when prescribing nicotine patches the goal for both doctor and patient was smoking cessation and not just to control cravings.

With regard to the importance of morning cravings Pharmacia noted that GlaxoSmithKline Consumer Healthcare had explained that morning cravings were the worst of the day for a substantial number of smokers and that this was discussed in its response to the complaint. Pharmacia disputed this and stated that in response to Pharmacia's assertion that it was unaware of any published data which showed that mornings were a more difficult time than any other for those trying to quit smoking, GlaxoSmithKline Consumer Healthcare stated 'that the advertisement made no such claim to such effect'. GlaxoSmithKline Consumer Healthcare also stated that 'The true language and/or implication of the advertisement was that at least **some** [emphasis added] smokers experienced morning cravings'.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had suggested that relief of cravings, including morning cravings, was itself recognised as being of clinical importance. Pharmacia stated that this was clearly true from the approved indication: 'relief of withdrawal symptoms including cravings associated with **smoking cessation**' [emphasis added]. The advertisement was also clear on this point by saying: 'When smokers are trying to **quit** [emphasis added], mornings can catch them unawares'. Pharmacia stated that the treatment goal was clearly to promote cessation and avoid relapse by treating craving and withdrawal symptoms.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had stated that relief of craving was a clinical endpoint for nicotine replacement therapy. Pharmacia stated that this was not correct. The use of nicotine replacement therapy for relief of craving, for example in situations where smoking was prohibited such as on public transport, was not at present an approved indication and although such use might be beneficial it could not be promoted under the current approved indication for smoking cessation. Pharmacia alleged that to avoid this pitfall, GlaxoSmithKline Consumer Healthcare had set the context for the advertisement with 'When smokers are trying to **quit**' [emphasis added].

Pharmacia stated that by quoting the SPC for NiQuitin CQ Patches, GlaxoSmithKline Consumer Healthcare tried to ascertain that morning cravings were of particular clinical importance. Pharmacia had never seen any data supporting this claim. Once a smoker had quit smoking his mind-set and psychological state was different and there was no consensus that craving in the morning was important for ex-smokers during the first smoke-free day, or any later day. Pharmacia noted that the main literature suggesting this had been published by Shiffman and his group, during the period in which he had been working as an exclusive consultant for GlaxoSmithKline Consumer Healthcare.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare then argued that the severity of morning cravings also predicted the risk of relapse later that same day.

Pharmacia noted that as GlaxoSmithKline Consumer Healthcare pointed out, the mornings, when quitters woke up full of determination to get through the day

ahead without a cigarette, were not the peak time for relapse. Pharmacia concurred with GlaxoSmithKline Consumer Healthcare's statement that relapse was more likely to occur in the evening. GlaxoSmithKline Consumer Healthcare tried to work itself around the problem that relapse typically occurred later in the day by suggesting that the control of morning cravings was important since their severity predicted the risk of relapse later that same day. The argument for this was fragile for several reasons. It was based on one paper, Shiffman *et al* 1997. The study, of untreated smokers, was evaluated using complicated statistics to conclude that morning cravings predicted relapse later in the day. It was not possible from the data given in the publication to reassess this. However accepting that this was correct, the conclusion would be to treat quitters with NRT during the period when they were at most risk for relapse ie during the afternoon/evening. Pharmacia noted that GlaxoSmithKline Consumer Healthcare had suggested instead that its putative predictor should be treated.

Pharmacia contended that the study did not show that morning cravings caused relapse, it only suggested that they predicted relapse later in the day. Neither did this or any other study show that treatment of morning cravings prevented later relapse; this was pure speculation. Pharmacia also noted that Shiffman *et al* 2003 stated that 'Acute cravings, often provoked by exposure to smoking cues, appear to be important triggers for smoking relapse. Relief of acute craving[*] may therefore be an important step in preventing relapse' (*Acute situational craving, as distinct from morning craving, Pharmacia insertion).

Pharmacia agreed with this statement, which contradicted GlaxoSmithKline Consumer Healthcare's position that acute cravings might be unrelated to relapse, and that treatment of morning cravings might prevent relapse at later occasions than the actual episode of craving.

Pharmacia noted that Daughton *et al* (1991) a randomized study comparing the use of the NiQuitin patch for 16 and 24 hours did not confirm that 24 hour use prevented relapse better than 16 hours. Although this early study did not follow the present dosage and treatment instructions it was designed to compare 16- and 24-hour use and would reveal the advantages with 24-hour patch use, if, as GlaxoSmithKline Consumer Healthcare claimed, they were real. Pharmacia stated that this was the only study it knew of where a fully controlled and blinded design compared the same patch used for 16 or 24 hours. No data from this study supported the idea that 24-hour treatment prevented relapse (or was better for any other reason) than 16-hour treatment.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had referred to the Fagerström Test for Nicotine Dependence (Heatheton *et al*, 1991) (misquoted as the Fagerström Tolerance Questionnaire in the GlaxoSmithKline Consumer Healthcare appeal) in relation to the importance of mornings cravings to both prescriber and patient. Pharmacia noted that this was a rating scale to measure tobacco dependence in current smokers, and several of the questions indicating high dependence focussed on the need for cigarettes in the morning (How soon after you wake do you smoke your first cigarette?; Which cigarette would you hate most to give up? and Do you smoke more frequently during the first hours after waking than during the rest of the day?). Pharmacia contended that clearly none of these questions had any relevance once a smoker had become an ex-smoker. Furthermore it was not a scale or measurement tool for the assessment or rating of cravings.

GlaxoSmithKline Consumer Healthcare had also inferred that Pharmacia had accepted the importance of morning cravings by citing training material that had been forwarded to it by a representative who formerly worked for Pharmacia's contracted sales force provided by Innovex. Pharmacia had made investigations as to the source of this material and had not been able to trace it. This document had not been produced by Pharmacia.

In Pharmacia's view morning cravings did not set the scene for the day: they occurred at a point when the smoker was determined to get through the day and could reasonably be expected to be pleased with themselves when they got past that point without failing.

Pharmacia alleged that the overall tone of the advertisement, with the prominent heading 'Make sure they're covered in the morning' followed by 'When smokers are trying to quit, mornings can catch them unawares', despite the subsequent text, gave a misleading impression about the clinical significance of morning cravings compared with other times of the day in the general quitting population.

### APPEAL BOARD RULING

The Appeal Board noted that NiQuitin CQ Clear was indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. The SPC also stated that 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'.

Given the data and the statement in the SPC that use for 24 hours was recommended to optimise effect against morning cravings, the Appeal Board did not consider that the claim 'When smokers are trying to quit, mornings can catch them unawares' and the heading 'Make sure they're covered in the morning' were unreasonable. The Appeal Board did not consider that the claim 'When smokers are trying to quit, mornings can catch them unawares' was misleading as alleged and ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

**2 Claim 'Once they've been without nicotine for 6-8 hours, cravings can be intense and hard to resist, which is why many smokers get more cravings in the morning than the rest of the day. Indeed, two out of three smokers light up within 30 minutes of waking'**

**COMPLAINT**

Pharmacia stated this unreferenced claim referred to many smokers from the general currently smoking population, not the quitting population. Pharmacia's view that the first sentence referred to the general smoking population and not the quitting population was reinforced by the second sentence concerning the habits of current smokers who might light up within 30 minutes of waking. Indeed, the data presented by Shiffman *et al* (1996) suggested that smokers trying to quit found the opposite end of the day (8pm-12am) most difficult. Pharmacia referred to its comments in point 1 above. This claim was alleged to be misleading, referring as it did to the general smoking population, and not to the quitting population in breach of Clause 7.2 of the Code.

**RESPONSE**

GlaxoSmithKline Consumer Health Care stated that the allegation was confusing in its focus on smoking and quitting populations as distinct groups. Pharmacia seemed to agree that smokers in general had more craving in the morning, but that those smokers who quitted or sought treatment had less craving in the morning, rendering the statement in the advertisement inaccurate. In reality the opposite was true: those who quitted, and especially those who elected to use NRT, were more likely to smoke within 30 minutes of waking than those people who did not attempt to quit. A survey of all smokers showed 66.7% of UK respondents smoked their first cigarette within 30 minutes of waking. In the same survey a significantly higher percentage of those who had used NRT in the past (and therefore by definition had a history of quitting and quitting with NRT) smoked 20+ cigarettes per day and smoked within 30 minutes of waking (61.3% vs. 46.6% p=0.0042), indicating the correlation between NRT selection and tobacco dependence. As discussed in point 1, the data showed that, numerically, both Nicorette and NiQuitin CQ patch users experienced higher craving for cigarettes in the morning than during the entire day (which included the morning and later periods in the day, thus diluting the comparison between the morning and the rest of the day) throughout the course of the study, providing further support for the notion that higher craving in the morning was very common in smokers trying to quit smoking.

Contrary to Pharmacia's assertion, the data presented in Shiffman *et al* (1996) did not suggest that smokers trying to quit found the opposite end of the day (8pm-12am) most difficult. These data showed only that more lapses to smoking occurred during the stated time period, not that that smokers generally found that time of day most difficult. More pertinently, the advertisement did not state that mornings were the most difficult time for all smokers trying to quit; it merely stated that 'many' smokers experienced more cravings within 30 minutes of waking. Both of these claims were substantiated, and both of these characteristics were inclusion criteria to the study cited in the advertisement, Shiffman *et al* (2000). It followed that the information presented reflected the available data and was fair and accurate.

GlaxoSmithKline Consumer Healthcare denied any breach of the Code.

**PANEL RULING**

The claim at issue was preceded by the claim considered at point 1 which introduced the paragraph 'When smokers are trying to quit, mornings can catch them unawares'. The claim at issue began 'Once they've been without nicotine …' and in the opinion of the Panel would be read as referring to the patient population identified in the preceding sentence ie smokers who were trying to quit. The Panel did not accept Pharmacia's allegation that the claim referred to the general smoking population and thus ruled no breach of Clause 7.2 of the Code on this narrow point.

During its consideration of this point the Panel was concerned that it was difficult to know to which population the first paragraph referred. The first two sentences, ie the claims considered in points 1 and 2, appeared to refer to those smokers trying to quit although it was impossible to tell if they were doing so with or without the help of NRT. The second sentence referred to the intensity of morning cravings and in that regard the Panel noted GlaxoSmithKline Consumer Healthcare's submission that intensity of morning cravings varied between different populations of smokers/quitters. The third sentence which stated that two out of three smokers light up within 30 minutes of waking appeared to relate to a survey of all UK smokers. The Panel noted from its consideration of point 1 above that it could not be assumed that results obtained in one population of smokers applied to all smokers. The Panel considered that in such circumstances it was important to be clear as to which group of smokers/quitters claims referred and asked that GlaxoSmithKline Consumer Healthcare be advised of its concerns in this regard.

**3 Alleged breach of undertaking**

**COMPLAINT**

Pharmacia noted that the claim '*NiQuitin CQ* patches provide nicotine continuously over a 24-hour period, reducing morning cravings compared with a 16-hour patch, for these heavily dependent smokers' followed that at issue in point 2 and was referenced to Shiffman *et al* (2000). Pharmacia stated that the advertisement clearly discussed quitting in the general smoking population. The advertisement wording implied that 'these heavily dependent smokers' were the same population as the general smoking population. GlaxoSmithKline Consumer Healthcare was implying that most smokers trying to quit had morning cravings. Shiffman *et al* (2000) had studied a very specific group of highly dependent quitting smokers ie those with morning cravings and who smoked their first cigarette within 30 minutes of waking. Indeed the authors acknowledged that the generalisation of their results to all smokers was not established. Pharmacia referred to its additional comments made in points 1 and 2 above.

Although Pharmacia was unhappy with the general tone of the advertisement given the undertaking made by GlaxoSmithKline Consumer Healthcare, it

alleged that this was a specific breach of the undertaking given in Case AUTH/1253/11/01: 'A reader would assume that the claims at issue would refer to the general smoking population rather than the subgroup examined in Shiffman *et al* and that was not so.'

When responding to the alleged breach of undertaking the Authority asked GlaxoSmithKline Consumer Healthcare to bear in mind Clauses 22, 9.1 and 2.

**RESPONSE**

GlaxoSmithKline Consumer Healthcare stated that in Case AUTH/1253/11/01, the Panel had found that 'the results [of Shiffman *et al* 2000] demonstrated that 24 hour wear of NiQuitin yielded consistently better relief of craving…', but that GlaxoSmithKline Consumer Healthcare had not been sufficiently clear about the population to whom these results applied. In the new advertisement, GlaxoSmithKline Consumer Healthcare had been explicit. The first two paragraphs elucidated the characteristics of the population studied in the trial mentioned in the third paragraph. It was plain from the presentation of the advertisement that the text of all three short paragraphs was to be read together and as such, this message was clear.

The reiteration of the phrase 'these heavily dependent smokers' did not, as Pharmacia complained, imply that the advertisement was discussing the general smoking population, it discussed and addressed heavily dependent smokers. Use of the phrase clearly and fairly drew attention to their being a specific type of smoker, not smokers in general, (although in the previous case, Case AUTH/1253/11/01, the Panel conceded that '…the characteristics of the sample matched those for most treatment studies.'). The term 'heavily dependent smokers' was chosen as the focus on morning craving and time to first cigarette was consistent with a core construct of the Fagerström Test for Nicotine Dependence (FTND) which was one of the most widely recognised and studied metrics for determining severity of tobacco dependence. Moreover, by stating 'these heavily dependent smokers,' the advertisement clearly referred back to the population described in the preceding paragraph. In the circumstances, Clause 22 had not been breached and high standards had been maintained in accordance with Clause 9.1. GlaxoSmithKline Consumer Healthcare had not brought the industry into disrepute through the content of the advertisement and the concerns raised in Case AUTH/1253/11/01 had been met.

GlaxoSmithKline Consumer Healthcare noted that Pharmacia went on to claim that GlaxoSmithKline Consumer Healthcare was implying that most smokers trying to quit had morning cravings. This was true. For example, as part of the screening process for two GlaxoSmithKline-sponsored studies evaluating morning craving, 62% of smokers who called to participate in these trials reported that their craving was worse in the morning than in the rest of the day. The advertisement stated that many, not all, smokers got more cravings in the morning than the rest of the day. It was therefore a fair, balanced and reasonable presentation of the available data.

**PANEL RULING**

The Panel noted that Case AUTH/1253/11/01 concerned, *inter alia*, the promotion of NiQuitin CQ patch by GlaxoSmithKline Consumer Healthcare. The Panel had considered that the claim, referenced to Shiffman *et al* (2000), 'NiQuitin CQ patches have the advantage of offering constant 24-hour nicotine replacement, significantly reducing morning cravings' in an advertisement was misleading in breach of Clause 7.3 of the Code. The Panel had noted that the advertisement discussed NiQuitin in relation to successful quitting in the general smoking population. A reader would assume that the claims at issue related to the general smoking population rather than the subgroup of smokers who smoked within 30 minutes of waking and who experienced morning cravings examined in Shiffman *et al* (2000) and that was not so. The footnote beneath the bar chart was insufficient to negate this impression.

Turning to the present case, Case AUTH/1401/12/02, the Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its comments above at points 1 and 2 on Shiffman *et al* (2000) and the patient population therein. The Panel noted that the claim at issue was different to that previously considered in Case AUTH/1253/11/01 and did not rely upon a footnote to define the patient population; it described the patient group as 'smokers who were trying to quit' and as 'heavily dependent smokers'. It would not be read as applying to the general smoking population. The preceding sentence referred to smokers who lit up within 30 minutes of waking. The Panel therefore considered that the claim at issue was not caught by the undertaking given in Case AUTH/1253/11/01. No breach of Clauses 22, 9.1 and 2 was ruled.

**4 Claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go'**

**COMPLAINT**

Pharmacia stated that this unreferenced claim followed the claim at issue in point 3 'NiQuitin CQ patches provide nicotine continuously over a 24-hour period, reducing morning cravings compared with a 16-hour patch, for these heavily dependent smokers'. It was simply not known if the treatment of morning cravings led to better long-term cessation rates. Morning cravings had not been shown to be a cause of relapse. Pharmacia also referred to its comments in point 1 regarding the most common times of day for cravings/temptation.

Overall the advertisement implied that 24-hour patches had greater efficacy in achieving smoking cessation than 16-hour patches. Direct comparative

trials of 24-hour vs 16-hour patches with an endpoint of cessation did not exist. However, the Cochrane Collaboration had conducted a meta-analysis of all the published studies of nicotine patches and concluded there was no evidence of a difference in clinical effectiveness of 16-hour compared to 24-hour patch.

One published placebo-controlled study comparing the same nicotine patch when used for 24 or 16 hours, did not show any statistically significant difference between the two treatment regimens for quit rates or tobacco withdrawal symptoms (Daughton *et al*, 1991). The study showed that those who used the patch for only 16 hours had a lower rate of relapse than those on the 24-hour regimen.

Another more recent study of the NiQuitin CQ Patch compared treatment efficacy between subjects who elected to use the patch for 24 hours vs 16-hour use (Shiffman *et al* 2002). Outcomes did not differ between these self-selected groups and analyses of treatment efficacy were unchanged when self-selected 24-hour vs 16-hour use was included as a co-variant.

Pharmacia alleged that this unreferenced claim was misleading in breach of Clause 7.3 of the Code. The claim did not reflect the current body of evidence but inferred a great likelihood of success with a 24-hour patch than a 16-hour patch.

## RESPONSE

GlaxoSmithKline Consumer Healthcare stated that Pharmacia argued that it was simply not known if treatment of morning cravings led to better long-term cessation rates'. In fact, the advertisement did not mention quit rates, better or otherwise; rather, it clearly and unambiguously stated that NiQuitin CQ reduced morning cravings more than a 16-hour patch in heavily dependent smokers. Craving relief was itself an important clinical benefit of NRT since a primary purpose of all NRT products was to relieve the symptoms of nicotine withdrawal, and was reflected in the licensed indication, 'for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation'.

Pharmacia then contended that morning cravings had not been shown to be a cause of relapse. However, a large and methodologically robust study had shown that morning cravings were a robust predicator of relapse, even when the relapse occurred later in the day (Shiffman *et al* 1997). Greater morning craving on waking predicted a greater risk of relapse. In their final summing up the authors stated 'Unexpectedly, urge intensity on waking proved to be the most robust dynamic predictor of subsequent smoking'. Hence the claim was not misleading.

The second sentence was simply a call to action for the doctor to prescribe NiQuitin CQ.

Pharmacia went on to contend that overall, the advertisement implied that 24-hour patches had greater efficacy in achieving smoking cessation than 16-hour patches. GlaxoSmithKline Consumer Healthcare did not imply this and the advertisement was clear in its discussion of reduced morning craving as the particular outcome on which GlaxoSmithKline Consumer Healthcare was comparing the products. The licence was for the relief of nicotine withdrawal symptoms including cravings. It was reasonable to use this as the basis of a claim or a measure of efficacy. Increased abstinence rates were not asserted in the advertisement although Shiffman *et al* (2000) showed that subjects using the 24-hour patch remained abstinent for significantly longer during the study period than those using the 16-hour patch ($p<0.016$). Direct head-to-head comparison of products was the gold standard measure of comparative efficacy. This was the only study that had directly compared NiQuitin CQ and Nicorette patches. The Cochrane collaboration did not include Shiffman *et al* (2000) in its meta-analysis but did note that there was significant heterogeneity in the results of the trials using a 16-hour patch which might reduce confidence in its findings.

Pharmacia cited a placebo-controlled study, Daughton *et al* (1991), showing that those who used the patch for only 16 hours had a lower rate of relapse than those on the 24-hour regimen. This study compared NiQuitin CQ patches worn for 16 and 24 hours, for a four week treatment period (hence outside the licence) and did not study the Nicorette 16-hour patch at all, thus it was difficult to see how it could be relevant to Pharmacia's complaint.

Pharmacia then referred to Shiffman *et al* (2002), which compared treatment efficacy between subjects who elected to use the patch for 24 hours vs 16-hour use and outcomes did not differ between these self-selected groups. GlaxoSmithKline Consumer Healthcare stated that Shiffman *et al* (2002) had no relevance to Nicorette, the 16-hour patch used in Shiffman *et al* 2000, as it was only a study of NiQuitin CQ which had a very different pharmacokinetic profile to Nicorette. Smokers themselves self-selected whether to engage in 16- or 24-hour wear, therefore the two groups could not be assumed to be similar. Indeed, the presumption was that the groups were different in important ways (eg the people who had little morning craving might have elected 16-hour wear). Thus, this was not a like for like comparison, and could not be used to judge the relative efficacy of the two regimens. Indeed, Pharmacia failed to quote the authors' conclusions, which suggested that self-selection might be exactly what made the quit rates comparable between the two regimens. It would also be inappropriate to extrapolate the results as a comparison of any 24-hour patch and any 16-hour patch as NiQuitin CQ was formulated as a 24-hour patch, however long it was worn for, so the study could only ever be a comparison of 24- or 16-hour wear of a 24-hour patch.

GlaxoSmithKline noted Pharmacia's allegation that the advertisement was misleading because it inferred a greater likelihood of success with a 24-hour patch than a 16-hour patch. GlaxoSmithKline Consumer Healthcare had been clear and concise in its claim for reduced morning cravings with no mention of comparative quit rates. Abstinence was not the only measure of clinical benefit applicable to nicotine patches and as the only direct comparison of NiQuitin CQ and Nicorette products had shown a significant reduction in morning cravings GlaxoSmithKline

Consumer Healthcare agreed that this represented a measure of greater success with a 24-hour patch than a 16-hour patch in the context of the licensed indication for these products. Accordingly there was no breach of Clause 7.3 of the Code.

In summary, GlaxoSmithKline Consumer Healthcare stated that each of the statements was fair and could be substantiated and it had made clear the population of smokers to whom the study referred.

Mornings could catch smokers unawares, as could other times of day. Morning cravings could be intense and many (not all) smokers got greater cravings in the mornings rather than the rest of the day. Even the study mentioned in the advertisement showed that participants had higher craving scores in the morning than the rest of the day throughout the duration of the study. Two out of three smokers lit up within 30 minutes of waking as verified by the UK sample from a pan-European survey, and two other surveys into study participants demonstrated that a majority of smokers seeking treatment to quit smoking had worse craving in the morning than in the rest of the day. Increased morning cravings were a robust predicator of subsequent relapse.

## PANEL RULING

The Panel did not accept that the advertisement compared NiQuitin CQ patches with the 16-hour patch solely in relation to morning cravings, as suggested by GlaxoSmithKline Consumer Healthcare. The final paragraph linked the increased morning cravings with an increased risk of relapse and concluded 'Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go'. The Panel considered that a reader would assume that the stated reduction in morning cravings achieved with the 24-hour patches was such that NiQuitin CQ had greater efficacy in achieving smoking cessation compared to the 16-hour patch.

The Panel noted that the Cochrane Report on NRT for smoking cessation (2002) reviewed the efficacy of different forms of NRT in achieving abstinence or a sustained reduction in the amount smoked. The report concluded, *inter alia*, that wearing the patch only during waking hours (16 hours/day) was as effective as wearing it for 24 hours/day. The report authors stated that further research was required in relation to direct comparisons between the various forms of NRT and between different doses and durations of treatment.

The Cochrane report only analysed randomized trials in which NRT was compared to placebo or no treatment or where different doses of NRT were compared. It excluded trials which did not report cessation rates and those with follow-up of less than six months. Shiffman *et al* (2000) was thus excluded as it was a comparison of 24- and 16-hour patches and assessed craving and abstinence only over two weeks.

The Panel noted its comments on Shiffman *et al* (2000) at point 1 above. Whilst not examined in the Cochrane report it was nonetheless relevant. However given the findings of the Cochrane Report the Panel did not consider that Shiffman *et al* (2000) alone was sufficient to substantiate the overall impression that NiQuitin CQ was more efficacious in achieving smoking cessation than the 16-hour patch. Shiffman *et al* (2000) examined abstinence and cravings only. There was no direct comparative data on overall efficacy. The Panel thus considered that the claim 'Don't let increased morning cravings increase their risk of relapse. Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go' overstated the data and within the context of the advertisement was misleading about the relative efficacy of the 24-hour and 16-hour patch as alleged. A breach of Clause 7.2 was ruled.

The Panel noted its concerns in point 2 in relation to the first paragraph of the advertisement. GlaxoSmithKline Consumer Healthcare had submitted in its response to point 1 above that the advertisement focused solely on a direct comparison of 24-hour versus 16-hour patch. The advertisement appeared to be about all smokers who were attempting to quit. The final sentence stated 'Prescribe *NiQuitin CQ* 24-hour patch and help smokers quit from the word go'. There was, however, only one direct comparison of Nicorette and NiQuitin CQ patches; Shiffman *et al* (2000) which was a short-term study in a highly selected group of quitters. The Panel was concerned that the advertisement appeared to refer to quitters in general and asked that GlaxoSmithKline Consumer Healthcare be advised of its concerns in this regard.

## APPEAL BY GLAXOSMITHKLINE CONSUMER HEALTHCARE

GlaxoSmithKline Consumer Healthcare submitted that the advertisement did not make any comparative claim between 24-hour use and 16-hour use of nicotine patches; the claim concerned only symptom control, not overall efficacy; the group selected by the Shiffman (2000) study were typical of smokers attending a doctor's clinic to request help to quit a compulsive addiction.

GlaxoSmithKline Consumer Healthcare submitted that the claim 'Don't let increased morning cravings increase their risk of relapse' was supported by a body of evidence discussed in point 1 above and in the response to the complaint. 'Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' did not make any comparative claim for superior long-term abstinence rates. It was a straightforward call to action to the doctor to prescribe the product in line with its licensed indication to help smokers quit. The use of the phrase 'from the word go' reinforced that this was the beginning of the quit process which was the time when smokers were most at risk of relapse. Doctors were well aware that quitting smoking was not a one-off event for most people and that getting through the initial couple of weeks was crucial. Withdrawal and craving symptoms were at their worst and relapse rates their highest. Protecting the patient from as much of the physical effects of nicotine withdrawal as possible was the benefit of nicotine replacement therapies and a parameter that doctors recognised as being relevant to the therapy area.

GlaxoSmithKline Consumer Healthcare noted that the Panel reported that 'Shiffman *et al* (2000) examined abstinence and cravings only. There was no direct comparative data on overall efficacy'. GlaxoSmithKline Consumer Healthcare noted that control of symptoms of smoking cessation (including relief of cravings) was a recognised benefit of nicotine replacement therapy and contended that the advertisement (and Shiffman *et al* 2000) focussed not on 'overall efficacy' but on symptom control during the early withdrawal phase of quitting smoking.

GlaxoSmithKline Consumer Healthcare submitted that there was therefore no reason for the Panel to consider the findings of the Cochrane report on nicotine replacement therapy as the explicit remit of Cochrane was to look only at long-term quit rates, not symptom control. GlaxoSmithKline Consumer Healthcare did not consider that the results of Cochrane were relevant as it had not made a claim for improved long-term abstinence rates.

GlaxoSmithKline Consumer Healthcare noted that in the advertisement, in an effort to be unambiguous and clear about the subjects in the study, it referred to 'these heavily dependent smokers' after having described the entry criteria for Shiffman *et al* (2000) in the advertisement. As the author himself stated, 'Generalisation of the results to all smokers was not established, although the characteristics of the sample match those of most treatment studies'. All studies must have inclusion and exclusion criteria and by definition a selected population. The criteria chosen by Shiffman *et al* (2000) matched the profile of the majority of smokers wishing to quit with nicotine replacement therapy. GlaxoSmithKline Consumer Healthcare stated that 62% of all the smokers applying to enter the trial not only had morning cravings, but also had more cravings in the morning than the rest of the day. GlaxoSmithKline Consumer Healthcare submitted that these findings reflected that far from being highly selective, the smokers in Shiffman *et al* (2000) represented the majority of the quitting population seen in clinic, although obviously not all.

GlaxoSmithKline Consumer Healthcare submitted that on review of a number of patch studies, some of which were used as the basis of licence applications, it could be seen that the majority of participants would be classified as 'heavily dependent' (based on their Fagerström Tolerance Questionnaire scores), smoking 20-30 per day and many smoking soon after waking (where recorded). GlaxoSmithKline Consumer Healthcare submitted that if these smokers were used as the basis for general licence applications, it was reasonable that they could also be used for making claims. GlaxoSmithKline Consumer Healthcare submitted that it was careful to identify the population in the studies, but they did not represent just a small subset of smokers. They were a typical smoker presenting to clinic requesting help to quit a compulsive addiction.

## COMMENTS FROM PHARMACIA

Pharmacia referred to its response to the appeal in point 1. Morning cravings had not been shown to be the cause of relapse later in the day and treatment in the morning had not been shown to prevent relapse at any later occasion.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had maintained that the claim now at issue concerned only symptom control and that no comparative claim of overall efficacy was made.

Pharmacia alleged that in the context of nicotine patch treatments available to the prescriber to aid smoking cessation, the claim implied greater efficacy in achieving smoking cessation for 24-hour patches than for 16-hour patches in a general quitting population. Pharmacia noted that its own 16-hour patch Nicorette, was licensed for use in smoking cessation.

Pharmacia noted that the claim on symptom control ie morning cravings was supported by Shiffman *et al* (2000) which enrolled 244 smokers who specifically suffered from morning cravings and smoked their first cigarette of the day within 30 minutes of waking. They were thus not reflective of the broad quitting population in which some quitters would have morning cravings.

Pharmacia noted that these quitters were randomly assigned to one of 2 regimes using either the 24-hour NiQuitin patch or the 16-hour Nicorette patch with imperfect blinding (the dummy patches were not identical to the active patches available on the market) using a double dummy design with labelled active patches and unlabelled placebo patches. Quitters had also received behavioural counselling. Pharmacia noted a number of important points about this study:

Abstinence was not required for the subjects to be included in the analyses; this was not a cessation study and so would not be included in meta-analyses of efficacy (such as the Cochrane review); there was no intention to make any objective comparison between different patch regimes; the results could not be extrapolated beyond this specific population as the author admitted.

The study did not look at the long-term outcome of cessation nor had the results been replicated elsewhere. The study had only lasted for 2 weeks and so it was impossible to state whether the 24-hour NiQuitin CQ Patch had helped smokers 'to quit from the word go'.

Pharmacia noted the Panel's findings that the results showed superior relief of craving and statistically significant relief of the withdrawal symptoms of anxiety and irritability. The remaining elements of nicotine withdrawal symptoms were not reduced by the 24-hour patch in a statistically significant way. However the subjects in this study were allowed to smoke up to 5 cigarettes per day but the timing of when these cigarettes were smoked was not known. Pharmacia stated that the results from this study were potentially confounded by this.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had stated that the advertisement (and Shiffman *et al* 2000) focussed not on overall efficacy but on symptom control during the early phase of quitting. GlaxoSmithKline Consumer Healthcare stated that it was not referring to abstinence, (quitting) at all but just cravings. Why then had

GlaxoSmithKline Consumer Healthcare set up the context of the advertisement with 'When smokers are trying to quit' and signed off with 'quit from the word go'? Pharmacia had not seen any riders on the advertisement to clarify this point.

Pharmacia noted that GlaxoSmithKline Consumer Healthcare had contended in its original response to the complaint that the advertisement focussed solely on a direct comparison of 24-hour versus 16-hour patch (Shiffman 2000) in a highly selected population. Pharmacia did not consider that the adjusted baseline craving scores reported in this study were applicable to the general population of smokers trying to quit – which was the overall impression given by the advertisement.

Pharmacia noted GlaxoSmithKline Consumer Healthcare's view that the study population was typical of the quitting population at large who attended 'a doctor's clinic to request help to quit a compulsive addiction'. GlaxoSmithKline Consumer Healthcare concluded this by only looking at the study populations of various published clinical trials, however this did not translate to the potential quitting population in the UK since only 37% of men and 25% of women smokers smoked more than 20 cigarettes per day (Office for National Statistics, 2001).

Pharmacia alleged that the overall tone of the advertisement was misleading as it suggested that the claims derived from a 2-week study in a specific and self-selected population with marked morning cravings related to all smokers trying to quit.

Pharmacia noted that whilst GlaxoSmithKline Consumer Healthcare had attempted to dismiss the findings of the Cochrane Collaboration (Silagy *et al* 2003), it had considered these to be highly relevant since the advertisement was clearly making a broader claim on overall efficacy – the meat of this review – and this data was the only source of any comparisons on cessation rates. Cochrane concluded that 'there was no evidence of a difference in clinical effectiveness for 16-hour compared to 24-hour patch'.

## APPEAL BOARD RULING

The Appeal Board noted that the Panel had considered that a reader would assume that the stated reduction in morning cravings achieved with 24-hour patches was such that NiQuitin CQ had greater efficacy in achieving smoking cessation compared to the 16-hour patch. The Panel had then referred to the data to support this impression. The Appeal Board noted that smoking cessation was not the licensed indication for NiQuitin CQ; the product was licensed for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation, not for smoking cessation *per se*.

The Appeal Board noted that the final paragraph of the advertisement 'Don't let increased morning cravings increase their risk of relapse. Prescribe NiQuitin CQ 24-hour patch and help smokers quit from the word go' gave the impression that because NiQuitin CQ was effective in relieving morning cravings it would also be effective in long-term smoking cessation. The Appeal Board considered that the phrase 'from the word go' appeared to differentiate NiQuitin CQ from the 16-hour patches which were referred to in the preceding paragraph.

The Appeal Board considered that the claim gave the impression that NiQuitin CQ 24-hour patch was more likely to help a patient to stop smoking than a 16-hour patch. The Appeal Board considered that the claim overstated the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

**Complaint received** **17 December 2002**

**Case completed** **7 May 2003**

CASE AUTH/1402/12/02

# GLAXOSMITHKLINE CONSUMER HEALTHCARE v PHARMACIA

## Promotion of Nicorette Patch

GlaxoSmithKline Consumer Healthcare complained about the promotion of Nicorette Patch (16 hour transdermal nicotine) by Pharmacia. The materials at issue as provided by Pharmacia were a detail aid (December 2001), a leavepiece (February 2002) and a Smoking Cessation Training Programme for health professionals. The detail aid and leavepiece were different to the materials supplied by GlaxoSmithKline Consumer Healthcare. The claims at issue were the same or similar in both leavepieces and both detail aids.

The claim 'Up to 4 times the success of placebo at 1 year' appeared in the leavepiece. The detail aid included a claim 'Up to 4 times the success of placebo* – abstinence rates at 1 year, p<0.001'. The claims were referenced to Tønnesen *et al* (1991). The explanation for the asterisk was given in a footnote as 'Across all clinical trials Nicorette Patch generally doubles the chance of success, however, in one large trial (289 smokers) it was shown to be over 4 times better than placebo at 12 months and up to 5 times better than placebo at 6 months'. GlaxoSmithKline Consumer Healthcare alleged that this was an unbalanced view of the data; cherry picking a particular study did not represent a fair and accurate picture of the likelihood of success compared with placebo. Of the eight published studies on the 16-hour patch, half had a success rate that was only double, or less, compared to placebo.

The Panel noted that Tønnesen *et al* had shown that at 52 weeks 17% of those in the nicotine patch group (n=145) and 4% of the placebo group (n=144) were abstinent (p<0.0001).

The Cochrane Review (Silagy *et al* 2002) concluded that all of the commercially available forms of nicotine replacement therapy (NRT) increased quit rates by 1.5 to 2 fold regardless of setting. The percentage of smokers abstinent after 12 months was 14% for patch users. When abstinence rates for all trials were pooled using the longest duration of follow-up available 17% of smokers allocated to receive NRT had successfully quit compared with 10% in the control group. The Panel noted that the footnote to the claim which appeared in the detail aid stated that across all clinical trials Nicorette Patch generally doubled the chance of success. There was no footnote to the claim in the leavepiece. The Panel considered that, irrespective of a qualifying footnote, the claims were thus not a fair, balanced evaluation of the data as alleged and each was ruled in breach of the Code.

A bar chart comparing the 16-hour and 24-hour patches in terms of the relapse rates after 6 months for successful short-term abstainers appeared in both the detail aid and the leavepiece. The relapse rate for 16-hour delivery was 10% compared with 45% for 24-hour delivery. The bar chart was referenced to Daughton *et al* (1991) and appeared beneath the heading referring to proven long-term success with 16-hour nicotine delivery. GlaxoSmithKline Consumer Healthcare alleged that the bar chart misled the reader into believing the 16-hour patches were superior to 24-hour patches because the relapse rates for 24-hour delivery were significantly higher than 16-hour delivery patches. There were three fundamental reasons why the claims breached the Code. Firstly Daughton *et al* was conducted using NiQuitin CQ used for either 24 or 16 hours – so it was misleading to represent that any findings from it related to the Nicorette patch. Secondly an unlicensed dosage regimen was used and thirdly it was not a fair reflection of the body of evidence.

No indications of initial success rates were given so a true reflection of efficacy could not be made. The explanatory footnote accompanying the bar chart described the short-term abstainers as 'smoke-free for the 4 weeks after initiating treatment' whereas Daughton *et al* stated that to qualify as smoke-free, participants needed to have abstained for only the final two weeks of the four week trial.

The bar chart implied that there was a significant difference between 16-hour delivery and 24-hour delivery, whereas a statistical comparison had not been made. The study authors repeatedly stated that no significant difference in quit rates between the two active treatments was seen at the time points measured.

GlaxoSmithKline Consumer Healthcare referred to the Nicorette Patch relapse figures from other studies used as reference for the material. Stapleton *et al* (1995) showed a relapse rate of 67% (from 38.3% abstinent at 3 weeks to 12.6% at 6 months). Tønnesen *et al* (1991) showed a similar relapse rate between 6 and 12 weeks, and even a 20% relapse between 6 and 2 weeks. GlaxoSmithKline Consumer Healthcare alleged that the bar chart did not reflect the body of evidence. The company noted that the pharmacist/nurse Training Programme did not include the bar chart, but conveyed the information relating to relapse rates.

The Panel noted that Daughton *et al* compared the effects of a patch worn for 24 hours, a patch worn during wakeful hours and placebo. The Panel noted GlaxoSmithKline Consumer Healthcare's submission that the nicotine patches used in the study were NiQuitin CQ patches. NiQuitin CQ patches were licensed to be applied for 24 hours. The Panel considered that the basis of the comparison was not clear as the same patch had been used for either 16 hours or 24 hours. The impression given was that the comparison was of two different products (Nicorette and NiQuitin CQ) and this was not so. The dosing of the NiQuitin CQ was not in accordance with the summary of product characteristics (SPC) recommendations that the treatment programme should occupy three months and the nicotine dose should be reduced over that time.

The Panel noted the additional data cited by GlaxoSmithKline Consumer Healthcare. Pharmacia had not defended the material. On the data before it

**the Panel considered that the bar chart was misleading and not a fair reflection of the evidence. A breach of the Code was ruled. Although the bar charts portrayed the use of NiQuitin CQ for 16 hours, and not for 24-hours as licensed, NiQuitin CQ was not Pharmacia's product. Pharmacia could not promote a competitor product and thus the Panel ruled no breach of the Code in that regard.**

**The Panel considered that its comments were also relevant to the pharmacist/nurse Training Programme and a breach of the Code was ruled.**

**The claims 'No other nicotine patch works harder at beating cigarettes…' and 'No other patch offers smokers a greater chance of success' appeared both in the leavepiece and the detail aid. The claim 'No other patch is proven more effective at beating cigarettes' appeared in the detail aid. GlaxoSmithKline Consumer Healthcare alleged that these claims could not be made without head-to-head comparison with all other patches, which had not been done.**

**The Panel noted that there was no comparative data on all the available nicotine patches. The claims 'No other patch offers smokers a greater chance of success'. 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes' implied that Nicorette Patch was the most effective patch at beating cigarettes. Pharmacia had not provided any material or comment in relation to substantiation of the claims. On the data before it the Panel considered that the claims were not capable of substantiation and each was ruled in breach of the Code.**

GlaxoSmithKline Consumer Healthcare complained about the promotion of Nicorette Patch (transdermal nicotine) by Pharmacia Limited. The Nicorette Patch was to be used for 16 hours in a 24-hour period. The materials at issue as provided by Pharmacia were a detail aid (P8177/08/02 dated December 2001), a leavepiece (P8175-08-02 dated February 2002) and a Smoking Cessation Training Programme for health professionals (503-0335). The detail aid and leavepiece were different to the materials supplied by GlaxoSmithKline Consumer Healthcare. The claims at issue were the same or similar in both leavepieces and both detail aids.

GlaxoSmithKline Consumer Healthcare marketed 24-hour nicotine transdermal patches – NiQuitin CQ.

GlaxoSmithKline Consumer Healthcare stated that in October it had written to Pharmacia about a number of areas that it found misleading in a detail aid (086 dated April 2002) and a leavepiece (503-0392 dated February 2002). Pharmacia agreed to withdraw the two items although it did not agree with all the comments and gave its assurance that any material which contained the claims mentioned in GlaxoSmithKline Consumer Healthcare's letter had been withdrawn.

GlaxoSmithKline Consumer Healthcare was surprised to learn that the withdrawal did not appear to have happened. GlaxoSmithKline Consumer Healthcare had recruited four representatives who had worked on the Pharmacia campaign until early December, a month after GlaxoSmithKline Consumer Healthcare had been assured of the materials' withdrawal. None of them had been informed of the need to withdraw any material and in particular were still detailing from the offending pieces.

### 1 Claim 'Up to 4 times the success of placebo at 1 year'

The claim appeared in the leavepiece. The detail aid included a claim 'Up to 4 times the success of placebo* – abstinence rates at 1 year, $p<0.001$'. The claims were referenced to Tønnesen *et al* (1991). The explanation for the asterisk was given in a footnote as 'Across all clinical trials Nicorette Patch generally doubles the chance of success, however, in one large trial (289 smokers) it was shown to be over 4 times better than placebo at 12 months and up to 5 times better than placebo at 6 months'.

#### COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that this was an unbalanced view of the data; cherry picking a particular study to present did not represent a fair and accurate picture of the likelihood of success compared with placebo. Of the eight published studies on the 16-hour patch, half had a success rate that was only double, or less, compared to placebo. The Cochrane analysis referenced elsewhere in the material recognised the heterogeneity of the data and calculated a two-fold increase in success for a nicotine patch compared with placebo. A breach of Clause 7.2 of the Code was alleged.

### 2 Relapse rates after six months

A bar chart comparing the 16-hour and 24-hour patches in terms of the relapse rates after 6 months for successful short-term abstainers appeared in both the detail aid and the leavepiece. The relapse rate for 16-hour delivery was 10% compared with 45% for 24-hour delivery. The bar chart was referenced to Daughton *et al* (1991). The bar chart appeared beneath the heading referring to proven long-term success with 16-hour nicotine delivery. A footnote beneath the bar chart stated that short-term abstainers were defined as a sub-group of patients recorded as smoke-free for the 4 weeks after initiating treatment.

The Smoking Cessation Training Programme included statements about relapse rates based on Daughton *et al*.

#### COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the bar chart misled the reader into believing the 16-hour patches were superior to 24-hour patches because the relapse rates for 24-hour delivery were significantly higher than 16-hour delivery patches. There were three fundamental reasons why the claims breached the Code. Firstly Daughton *et al* was conducted using NiQuitin CQ patch worn for either 24 or 16 hours – so it was very misleading to represent that any findings from it related to the Nicorette patch. Secondly an unlicensed dosage

regimen was used, and thirdly it was not a fair reflection of the body of evidence.

Daughton *et al* was over 10 years old and was conducted using a 4-week dosing regimen (too short) and with no subsequent stepping down of dosage. This was not compatible with the Nicorette 15mg patch licence and neither was it a reflection of the NiQuitin CQ licence. GlaxoSmithKline Consumer Healthcare alleged that the bar chart contravened the Code as it promoted the product outside the marketing authorization. The prescribing information stated 'the recommended treatment programme should occupy 3 months'. Patients received only 4 weeks of high strength nicotine patch with no subsequent tapered dosing regimen. Immediately adjacent to the bar chart was a large illustration of the 'Gradual step-down programme' which increased the misleading impression that the study had used a licensed dosage regimen.

No indications of initial success rates were given so a true reflection of efficacy could not be made. The explanatory footnote accompanying the bar chart described the short-term abstainers as 'smoke-free for the 4 weeks after initiating treatment' whereas the authors stated that to qualify as smoke-free, participants needed to have abstained for only the final two weeks of the four week trial.

The bar chart implied that there was a significant difference between 16-hour delivery and 24-hour delivery, whereas a statistical comparison had not been made. The study authors repeatedly stated that no significant difference in quit rates between the two active treatments was seen at the time points measured.

GlaxoSmithKline Consumer Healthcare referred to the Nicorette Patch relapse figures from other studies used as reference for the material. Stapleton *et al* (1995) showed a relapse rate of 67% (from 38.3% abstinent at 3 weeks to 12.6% at 6 months). Tønnesen *et al* (1991) showed a similar relapse rate between 6 and 52 weeks, and even a 20% relapse between 6 and 12 weeks. GlaxoSmithKline Consumer Healthcare alleged that the bar chart was not reflective of the body of evidence in breach of Clauses 3.2 and 7.2.

GlaxoSmithKline Consumer Healthcare stated that the pharmacist/nurse Training Programme did not include the bar chart, but conveyed the information relating to relapse rates and a breach of Clause 7.2 of the Code was alleged.

### 3 Claims – 'No other patch offers smokers a greater chance of success' 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes…'

The claims 'No other nicotine patch works harder at beating cigarettes…' and 'No other patch offers smokers a greater chance of success' appeared both in the leavepiece and the detail aid. The claim 'No other patch is proven more effective at beating cigarettes' appeared in the detail aid.

#### COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that these top parity claims could not be made without head-to-head comparison with all other patches, which had not been done. A breach of Clause 7.4 of the Code was alleged.

#### RESPONSE

Pharmacia noted the material in question was a detail aid (P8177/08/02) described by GlaxoSmithKline Consumer Healthcare as 086, a leavepiece (P9175/08/02) described by GlaxoSmithKline Consumer Healthcare as 503.0392 and a pharmacist/nurse Training Programme (503-0335). Pharmacia rejected the allegation that it had not withdrawn the material when it had given its assurance to do so and was extremely concerned that its honesty and integrity had been called into question. Steps had been taken to withdraw the materials in question and the information obtained from GlaxoSmithKline Consumer Healthcare representatives was unreliable.

In October 2002 Pharmacia received a letter from GlaxoSmithKline Consumer Healthcare complaining about claims made in the detail aid and leavepiece and asking Pharmacia to withdraw these items. After reviewing the materials in question, Pharmacia responded stating that the detail aid and leavepiece in question would be withdrawn by the week ending 8 November.. Concurrently, an email was sent to the sales director of the contract sales team using the items in question instructing representatives to stop using the detail aid and leavepiece. On 4 November an email was sent out by the contract sales company to all regional sales managers instructing them to collect all materials by 7 November. This represented a small part of the communication between the management of the contract sales company and its representatives since most communication was conducted via a voice mail service.

Having withdrawn the detail aid and leavepiece Pharmacia received a further letter from GlaxoSmithKline Consumer Healthcare dated 5 November asking Pharmacia to withdraw materials which contained similar claims to the detail aid and leavepiece, with specific reference to the pharmacist/nurse training programme. Once again Pharmacia agreed and took action to withdraw the material in question by sending an email on 15 November to all teams affected by the withdrawal, instructing those concerned to stop using the pharmacist/nurse training manual. A letter was then written to GlaxoSmithKline Consumer Healthcare, dated 18 November confirming that the materials containing the claims in question had been withdrawn.

Having taken steps to withdraw the materials mentioned Pharmacia was surprised that four ex contract representatives, now GlaxoSmithKline Consumer Healthcare representatives, should claim that they were not notified of any withdrawal and that they continued to use the detail aid and leavepiece up until they left the contract sales team in December.

When the representatives tendered their resignations they were told not to detail Nicorette at all, given that they would be going to a competitor. This was common practice.

A document from the contract sales company listed the notice date and leaving date of each representative. Two of the representatives had left by early October and so could not have been promoting Nicorette up until 6 December as stated by GlaxoSmithKline Consumer Healthcare. With regard to the other representatives, Pharmacia had been charged for only 5 days promotional activity during the notice period of one and nothing during the notice period of the other.. Both had been asked to stop promoting Nicorette when their letters of notice had been received.

As acknowledged by GlaxoSmithKline Consumer Healthcare, the smoking cessation field was highly competitive and there had been a number of complaints made under the Code by both companies during 2002. Nonetheless, in this instance, Pharmacia submitted that if GlaxoSmithKline Consumer Healthcare had checked the information it was given against the dates which the representatives in question joined, it would have noted the obvious discrepancy and implausibility discussed above. Critically, the materials in question were withdrawn promptly as agreed when a potential breach of the Code was brought to Pharmacia's attention.

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Pharmacia was advised that the complaint had to be considered regardless of whether the company had withdrawn the items at issue. Pharmacia was asked to respond to the specific allegations.

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In its further response Pharmacia noted that as a consequence of complaints about sleep disturbance claims contained in the detail aid and leavepiece at issue, these materials were withdrawn in July 2002. They were replaced with similar materials with revised sleep disturbance claims. However, the materials now complained about were the original versions and had not been in use for several months. Having said that, the claims about which GlaxoSmithKline Consumer Healthcare now complained, remained in the second versions of the detail aid and leavepiece. Pharmacia subsequently withdrew the second version following its undertaking to GlaxoSmithKline Consumer Healthcare in its letter of 1 November 2002.

GlaxoSmithKline Consumer Healthcare requested further assurances that all materials containing the claims would be withdrawn and included a reference to the nurse/pharmacist Training Programme in its letter to Pharmacia, 5 November 2002. Pharmacia responded giving further confirmation that all materials had been withdrawn. Pharmacia stated that it found itself in a difficult position here and was unclear about how it could better respond to this post hoc complaint about claims which had been withdrawn.

The claims were prepared and signed off in good faith. They were used for some months before GlaxoSmithKline Consumer Healthcare raised this specific complaint. The claims were then scrutinised again. On further review the references used to support the claims were considered less robust than was originally thought and Pharmacia could see that the graphical representation could be debated. Pharmacia was grateful to GlaxoSmithKline Consumer Healthcare for giving it an alternative perspective. Given this, and in order not to waste everyone's time, Pharmacia naturally agreed to promptly withdraw the materials containing the claims and of course the company had no wish to knowingly breach the Code.

Pharmacia's position remained the same in that it had no wish to defend claims that had been withdrawn and if GlaxoSmithKline Consumer Healthcare's purpose of formalising the complaint was to ensure that the claims were never used again, then Pharmacia gave assurances that this was the case.

Pharmacia had acted in good faith throughout, including acting upon the concerns raised by GlaxoSmithKline Consumer Healthcare and had not intended at any time to purposefully breach the Code.

## PANEL RULINGS

The Panel noted that although the materials at issue had been withdrawn it was nonetheless obliged to make rulings on all the matters raised. The Panel was concerned that on further review of the references used to support the material at issue Pharmacia considered that they were less robust than originally thought. Pharmacia had not defended any of the material at issue.

### 1 Claim 'Up to 4 times the success of placebo at 1 year'

### PANEL RULING

The Panel noted that the claims were referenced to Tønnesen *et al* (1991), which had shown that at 52 weeks 17% of those in the nicotine patch group (n=145) and 4% of the placebo group (n=144) were abstinent ($p<0.0001$).

The Cochrane Review (Silagy *et al* 2002) concluded that all of the commercially available forms of nicotine replacement therapy (NRT) increased quit rates by 1.5 to 2 fold regardless of setting. The percentage of smokers abstinent after 12 months was 14% for patch users. When abstinence rates for all trials were pooled using the longest duration of follow-up available 17% of smokers allocated to receive NRT had successfully quit compared with 10% in the control group. The Panel noted that the footnote to the claim which appeared in the detail aid stated that across all clinical trials Nicorette Patch generally doubled the chance of success. There was no footnote to the claim in the leavepiece. The Panel considered that, irrespective of a qualifying footnote, the claims were thus not a fair, balanced evaluation of the data as alleged and each was ruled in breach of Clause 7.2 of the Code.

### 2 Relapse rates after six months

**PANEL RULING**

The Panel noted that Daughton *et al* compared the effects of a patch worn for 24 hours, a patch worn during wakeful hours and placebo. The Panel noted GlaxoSmithKline Consumer Healthcare's submission that the nicotine patches used in the study were NiQuitin CQ patches. NiQuitin CQ patches were licensed to be applied for 24 hours.

The Panel considered that the basis of the comparison was not clear as the same patch had been used for either 16 hours or 24 hours. The impression given was that the comparison was of two different products (Nicorette and NiQuitin CQ) and this was not so. The dosing of the NiQuitin CQ was not in accordance with the SPC recommendations that the treatment programme should occupy three months and the nicotine dose should be reduced over that time.

The Panel noted the additional data cited by GlaxoSmithKline Consumer Healthcare. Pharmacia had not defended the material. On the data before it the Panel considered that the data did not reflect the body of evidence. The Panel considered that the bar chart was misleading and not a fair reflection of the evidence. A breach of Clause 7.2 of the Code was ruled.

Although the bar charts portrayed the use of NiQuitin CQ for 16 hours, and not for 24 hours as the product was licensed, NiQuitin CQ was not Pharmacia's product. Clause 3 of the Code required the promotion of a medicine to be in accordance with the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not, however, promote a competitor product and therefore Clause 3 would not apply. Thus the Panel ruled no breach of Clause 3.2 of the Code. The Panel noted that Clause 7.2 might be relevant in circumstances when information about a competitor product might be inconsistent with the SPC ie misleading. It noted that there was no specific allegation in this regard.

The Panel considered that its comments were also relevant to page 57 of the pharmacist/nurse Training Programme and a breach of Clause 7.2 of the Code was ruled.

**3 Claims – 'No other patch offers smokers a greater chance of success' 'No other patch is proven more effective at beating cigarettes' and 'No other nicotine patch works harder at beating cigarettes…'**

**PANEL RULING**

The Panel noted that there was no comparative data on all the available nicotine patches. The claims implied that Nicorette Patch was the most effective patch at beating cigarettes. Pharmacia had not provided any material or comment in relation to substantiation of the claims. On the data before it the Panel considered that the claims were not capable of substantiation and each was ruled in breach of Clause 7.4 of the Code.

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During its consideration of this case the Panel noted that the front page of the booklet entitled 'Smoking Cessation Training Programme a guide for health professionals' bore in the top left hand corner the Royal College of Nursing name and corporate logo, and at the bottom, 'Sponsored by Nicorette Where there's a will, there's a way'. The Panel was concerned that such a declaration was insufficient to meet the requirements of Clause 9.9 of the Code which required material relating to medicines, whether promotional in nature or not, which was sponsored by a pharmaceutical company to clearly indicate that it had been sponsored by that company. The Panel did not consider that the name of a product was sufficient in that regard and requested that Pharmacia be advised of its views.

**Complaint received** **19 December 2002**

**Case completed** **14 March 2003**

CASE AUTH/1403/12/02

# HOSPITAL PHARMACIST v ROCHE

## Conduct of representatives

**A principal hospital pharmacist complained about the conduct of two representatives from Roche in relation to the promotion of Roaccutane (isotretinoin). Isotretinoin was also available generically from Schering Health Care.**

**The complainant stated that the two representatives arrived at the pharmacy department and asked to speak to someone. The receptionist called the medicine information secretary. When the secretary arrived, the representatives asked her to tell them which brand of isotretinoin the department stocked. At this point the secretary asked the complainant for advice and the complainant introduced himself. The representatives then asked the complainant which brand of isotretinoin was kept and was he aware of the difference in the licences held by Roche and Schering Health Care concerning pregnancy testing. The representatives advised that they had seen consultant dermatologists in the hospital about this issue and that they were not happy to use the contracted Schering Health Care product that required them to carry out a monthly medically supervised pregnancy test under the terms of its summary of product characteristics.**

**The complainant alleged that the representatives' behaviour was in breach of the Code; their visit was not formally arranged, their questions were inappropriate and they had caused confusion and anxiety. The complainant understood that the pharmacist with whom the representative had previously dealt had not had any formal arrangement with the representatives concerning meetings and that the departmental policy might not have been made clear to them. However the departmental policy had been in place for several years and stated that representatives should seek a formal appointment with the relevant pharmacist and not turn up unannounced.**

**The complainant's main concern was that when the medicines information secretary went to the pharmacy reception in response to a request from the representatives to see the previous dermatology pharmacist, they did not introduce themselves or ask to whom they were talking, but immediately asked which brand of isotretinoin was stocked.**

**The representatives might not recall mentioning that the consultant was not happy to use Schering Health Care product (which was on contract), however this was the clear impression that the complainant was left with. The way in which this issue was communicated left the complainant with the understanding that he should not be purchasing the contracted isotretinoin. As a result of this incident the whole of the regional contract had been amended until the issue regarding pregnancy testing had been resolved.**

**In the Panel's view, when learning that the dermatology pharmacist had left, the representatives should have enquired about the arrangements for seeing the replacement pharmacist. They should not have assumed that the arrangements would be the same. Neither should they have assumed that the medicines information secretary was the relevant pharmacist. The Panel considered that the representatives had not been sufficiently careful in their dealings with the pharmacy staff. The manner in which the call had been made caused inconvenience and the wishes of the pharmacy department had not been established and consequently not observed. The Panel ruled a breach of the Code. As the representatives had failed to comply with the Code, the Panel was obliged to ruled a further breach of the Code.**

A principal hospital pharmacist complained about the activities of two representatives from Roche Products Limited in relation to the promotion of Roaccutane (isotretinoin). Isotretinoin was also available from Schering Health Care Limited.

### COMPLAINT

The complainant stated that two representatives from Roche arrived at the pharmacy department and asked to speak to someone. The receptionist called the medicine information secretary assuming that they wished to make an appointment. When the secretary arrived, and without formal introduction or giving a reason for their visit, the representatives asked her to tell them which brand of isotretinoin the department stocked. At this point the secretary asked the complainant for advice as she was under the impression that she should not give this type of information out. The complainant assured her that she was correct and introduced himself.

The complainant stated that the representatives asked him which brand of isotretinoin was kept and was he aware of the difference in the licences concerning pregnancy testing. They told the complainant that they had seen consultant dermatologists in the hospital to tell them of the issue concerning pregnancy testing under the terms of the licences held by Roche and Schering Health Care for isotretinoin. They told the complainant that following their intervention the consultants were not happy to use the contracted Schering Health Care product that required them to carry out a monthly medically supervised pregnancy test under the terms of the summary of product characteristics (SPC).

The complainant assured the representatives that he would look into the issue. He did not tell them which brand was kept but said that as they were undertaking this task he was sure they were aware that the trust had recently tendered for this product under the regional generics contract and that Roche had not been successful.

The complainant alleged that the representatives' behaviour was in breach of the Code. Their visit was not formally arranged, their questions were inappropriate and they had caused confusion and anxiety. Also, the trust had to subsequently delay complying with the regional contract whilst it awaited the outcome of a statement from the NHS Purchasing and Supplies Agency.

When writing to Roche the Authority asked it to comment in relation to Clauses 15.2, 15.4 and 15.9 of the Code.

## RESPONSE

Roche presented the facts as reported by its marketing manager, who accompanied the sales representative on the visit in question.

Roche explained that the marketing manager and the representative had an appointment with one of the specialist registrars in dermatology at the hospital. During the appointment they were joined by one of the consultant dermatologists. The Roche representatives told the dermatologists that the regional contract for isotretinoin had been won by another manufacturer which produced a generic version of Roaccutane (isotretinoin). The SPC of the generic differed substantially from that of Roaccutane, particularly in terms of responsibility for pregnancy testing.

The dermatologists did not know which version of isotretinoin was being provided to their patients and they asked the representatives to establish which product was currently being dispensed from the pharmacy. Clearly it would be important to ensure that the dermatologists were issuing their patients with the appropriate information leaflet and female consent form. The Roaccutane materials would not be appropriate to issue if the generic product was being dispensed.

The pharmacist with whom the representative had previously dealt had, Roche understood, been prepared to see him with no formal appointment. On learning that she was no longer there, the representatives asked to see her replacement or someone with whom it would be possible to discuss isotretinoin. Initially, it was not clear to either of the Roche personnel that the first person they discussed the situation with was not a pharmacist. Once that became clear they again asked to speak with the appropriate person from the department and they then met the complainant. The complainant did not point out that it was now necessary for the representatives to make an appointment to see him.

The purpose for the discussion was explained to the complainant. They attempted to explain the implications of the change over from the Roche product to the generic product, in order to ensure that the dermatologists were fully informed when that change took place, for the reasons given above.

Although the Roche personnel believed that the reasons behind the visit, and the requests from the dermatologists, were fully explained to the complainant, he, nonetheless, had complained. The representatives did not recall mentioning that the consultants were not happy to use the generic product. Indeed, there was no suggestion that this was the case in their discussion with the dermatologists. The dermatologists simply wished to know if and when the generic would be dispensed, as this inferred that different documentation would be required for patients who would receive it.

With reference to Clause 15.2, Roche believed that its personnel had maintained a high standard of ethical conduct by responding to the dermatologists' request to establish which brand of isotretinoin was currently being supplied. However, it was possible that there was some confusion regarding the intention of the visit.

Roche did not believe it was in breach of Clause 15.4 as it appeared that the arrangements at the hospital with respect to making formal arrangements for visits had changed since the representative's last visit. The representatives were unaware of any need to make a formal arrangement to see the pharmacist as, in the past, this had not been required. Indeed, had they been told of the need to make an appointment, they would have been happy to return.

Roche certainly did not want to cause any inconvenience and nor did the representatives believe that any discussions they had would result in the delay of the contract, which they knew had been lost by Roche. Their motivation was simply to comply with the request of the dermatologists.

In summary, Roche did not believe it had breached any clauses of the Code. However, it was concerned and regretted that the complainant felt that this visit had caused 'confusion and anxiety', which might be because he felt the representatives were requesting commercially sensitive information. This was not the intention of the visit.

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The response from Roche was sent to the complainant for comment.

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## FURTHER COMMENTS FROM THE COMPLAINANT

The complainant appreciated Roche's comments and was sure that the representatives did not intend to cause confusion and anxiety by their visit. Nevertheless that was precisely how he felt as a result of the conversation.

The complainant raised several points.

Roche stated that the representatives told the consultant dermatologist and the specialist registrar that the regional contract for isotretinoin had been awarded to another manufacturer. As the contract had already started at the time of their visit the hospital should have already made the relevant changes to ordering patterns. The complainant understood that their meeting with the consultant was to explain the difference between the SPCs and a legitimate concern about supplying the correct information to the patients. However the complainant believed that when asked by the consultant dermatologist to find out which brand of isotretinoin the pharmacy department was keeping the representatives should have referred them to the pharmacy directly.

The complainant understood that the pharmacist with whom the representative had previously dealt had not had any formal arrangement with the representatives

concerning meetings and that the departmental policy might not have been made clear to them. Individual pharmacists sometimes developed good working relationships with representatives and were at liberty to meet on their own terms. However the departmental policy had been in place for several years and stated that representatives should seek a formal appointment with the relevant pharmacist and not turn up unannounced. The complainant suggested that as the representatives knew the purpose of their visit, and considering the importance of the material they wished to discuss, they should have called the pharmacy in advance to arrange an appointment. The complainant appreciated that when he was called he might not have outlined this arrangement but by this point he was already concerned that a member of staff had been asked to supply information concerning purchasing patterns and products and wanted to ascertain exactly what was going on.

The complainant's main concern was that when the medicines information secretary went to the pharmacy reception in response to a request from the representatives to see the previous dermatology pharmacist, they did not introduce themselves or ask to whom they were talking, but immediately asked which brand of isotretinoin was stocked. This was why it was not clear to them that they were not speaking to a pharmacist. In the complainant's opinion it was from this point that the visit became an issue and led to the complaint.

The representatives might not recall mentioning that the consultant was not happy to use the generic product however this was the clear impression that the complainant was left with. The way in which this issue was communicated left the complainant with the understanding that he should not be purchasing the new generic brand.

Roche also stated that the representatives did not want to cause inconvenience or believe that the discussions would result in the delay of the contract. However this issue was not isolated to one hospital. As a result the whole of the regional contract had been amended until the issue of information concerning pregnancy testing contained in the SPC had been resolved. There was a great deal of work involved in setting up and amending contracts and delay and inconvenience was precisely what had occurred.

**PANEL RULING**

The Panel noted that the representatives had been asked by the dermatologists to find out which version of isotretinoin was being dispensed from the pharmacy. The representatives had informed the dermatologists that the contract for isotretinoin had been won by Schering Health Care.

The representatives had gone to the pharmacy expecting to be able to speak to the dermatology pharmacist with whom they had previously dealt. On learning that the pharmacist was no longer there the representatives asked to see her replacement. Roche acknowledged that it was not clear that the first person they discussed the situation with was not a pharmacist (she was the medicines information secretary). The representatives then asked to see the appropriate person.

The Panel queried why the dermatologists had asked the representatives to check which isotretinoin was being dispensed. The Panel noted Roche's submission that the representative had previously been able to see the dermatology pharmacist without an appointment. In the Panel's view when learning that the dermatology pharmacist had left, the representatives should have enquired about the arrangements for seeing the replacement pharmacist. They should not have assumed that the arrangements would be the same. Neither should they have assumed that the medicines information secretary was the relevant pharmacist. The Panel considered that the representatives had not been sufficiently careful in their dealings with the pharmacy staff. The manner in which the call had been made caused inconvenience and the wishes of the pharmacy department had not been established and consequently not observed. The Panel ruled a breach of Clause 15.4 of the Code. As the representatives had failed to comply with the Code, the Panel was obliged to rule a breach of Clause 15.2 of the Code.

**Complaint received** **19 December 2002**

**Case completed** **17 March 2003**

# DIRECTOR v ABBOTT

## Promotion of Uprima

**The Panel had previously considered a complaint (Case AUTH/1368/10/02) that a journal advertisement had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one subject of complaint appeared in the same journal. These were taken up with the companies concerned.**

**The current case concerned a double page spread referring to Abbott's product Uprima (apomorphine). The left hand page was headed 'Erectile dysfunction – advertisement feature' followed by an advertisement in the style of an advertorial on erectile dysfunction and its treatment with Uprima; prescribing information was not included. The right hand page was an advertisement for Uprima which included prescribing information. Both pages bore the same reference number.**

**The Panel had to decide whether the material consisted of two one-page advertisements or one two-page advertisement. The Panel noted that some of the claims on the left hand page were repeated on the right hand page. Each page included its own set of references. The claim 'In one study, 40% of patients with [erectile dysfunction] had undiagnosed [coronary artery disease]' was referenced on the left hand page to reference 8, Pritzker (1999). On the right hand page the claim was repeated, supported by reference 1, also Pritzker (1999). The Panel did not consider that the inclusion of the same reference number on both pages was sufficient to support the submission that the material was one two-page advertisement.**

**The Panel considered that the presentation and style of each page was so different that they were designed to be read separately and not as a double page spread as submitted by Abbott. Each page needed prescribing information and so a breach of the Code was ruled with regard to the page headed 'Erectile dysfunction – Advertisement feature'.**

**Upon appeal by Abbott the Appeal Board noted that the pages in question appeared facing one another; there were similarities in colour and text between the two and when viewed as a whole the prescribing information was clearly visible at the bottom of the right hand page. The Appeal Board considered that the advertisement constituted one double page advertisement for Uprima which included prescribing information. The Appeal Board ruled no breach of the Code. The appeal was successful.**

The Panel had recently considered a complaint (Case AUTH/1368/10/02) that an advertisement in the NHS Journal of Healthcare Professionals (September 2002) had not included prescribing information. A breach of the Code had been ruled. Similar advertisements to the one the subject of complaint appeared in the journal. These were taken up with the companies concerned.

Case AUTH/1410/1/03 concerned a double page spread referring to Abbott Laboratories Limited's product Uprima (apomorphine HCl). The left hand page was headed 'Erectile dysfunction – advertisement feature' followed by an advertisement in the style of an 'advertorial' on erectile dysfunction and its treatment with Uprima; prescribing information was not included. The right hand page was an advertisement for Uprima which included prescribing information. Both pages bore the reference PXUPR2002299.

### COMPLAINT

The design of the double page spread was such that it appeared that it was two, one-page advertisements and not one, two-page advertisement. Both pages would need prescribing information. Attention was drawn to Clause 4.1 of the Code.

### RESPONSE

Abbott submitted that the advertisement appearing on the double page spread was one advertisement. Abbott specifically requested that the publisher laid out the pages as facing pages. The advertisement was reviewed and approved internally by Abbott signatories as a double page spread with a clear statement at the head of the first page in bold capitals stating **'ERECTILE DYSFUNCTION – ADVERTISEMENT FEATURE'**. There then followed the Abbott Urology logo; the Abbott Urology logo appeared again at the end of the advertisement on the facing page.

The word 'Feature' was used to clearly indicate that both pages constituted a single advertising entity. Further, both pages of the advertisement contained the unique internal identifier PXUPR2002299 at the foot of the page and both also carried the same date of preparation indicating they were both part of the same advertisement. The prescribing information for the double page spread was clearly placed at the base of the second page of the advertisement. Both pages of the advertisement were concerned with the common theme – Uprima and erectile dysfunction.

In summary the advertisement was placed across two facing pages, both clearly marked with the Abbott Urology logo. The prescribing information formed an integral part, it was clearly presented and positioned for ease of reference at the base of the second of the two facing pages. Abbott therefore submitted that there was no requirement for the prescribing information to appear on the left hand page of the advertisement and denied a breach of Clause 4.1 of the Code.

### PANEL RULING

The Panel noted that the left hand page of the double page spread was headed 'Erectile dysfunction – Advertisement feature' and the right hand page was advertising for Uprima. The right hand page included prescribing information.

The Panel had to decide whether the material consisted of two one-page advertisements or one two-page advertisement. The left hand page headed 'Erectile dysfunction' was presented in the style of an 'advertorial' whereas the right hand page was clearly a typical journal advertisement.

The Panel noted that some of the claims on the left hand page were repeated on the right hand page. Each page included its own set of references. The claim 'In one study, 40% of patients with ED had undiagnosed CAD' was referenced on the left hand page to reference 8, Pritzker (1999). On the right hand page the claim was repeated, supported by reference 1, also Pritzker (1999). The Panel noted that each page included the same reference number (PXUPR2002299) but did not consider this was sufficient to support the submission that the material was one two-page advertisement.

The Panel considered that the presentation and style of each page was so different that they were designed to be read as two separate pages and not as a double page spread as submitted by Abbott. Each page needed prescribing information and so a breach of Clause 4.1 of the Code was ruled with regard to the page headed 'Erectile dysfunction – Advertisement feature'.

## APPEAL BY ABBOTT

Abbott stated that the double page spread had been reviewed and approved by the company signatories as one double page advertisement. The company had no control over where the advertisement appeared in the journal. It had requested that the pages faced each other. The heading on the left hand page 'Erectile dysfunction – advertisement feature' was used to indicate that the pages to follow were one advertising feature.

Abbott noted that the first page of the advertisement consisted largely of text and the second of a combination of a picture with text at the base. The advertisement feature was designed such that, when viewed, it would represent one advertisement as a double page spread. Consistency within the advertisement across the two pages was ensured as follows: the term 'ADVERTISING FEATURE' was prominently displayed at the head of the left hand page to indicate that the pages that followed constituted one advertisement; the typeface and colour of the font used at the head of the left hand page was identical to that used at the top left of the picture on the right hand page, showing consistency across the double page spread; the typeface used for the copy text on both pages was the same; the Abbott Urology logo was prominently placed at the beginning of the first page of the advertisement and repeated at the end of the advertisement on the facing page in the bottom right hand corner; both pages of the advertisement contained the same date of preparation indicating that they comprised one advertisement; both pages of the advertisement were concerned with the common theme – Uprima and erectile dysfunction. Furthermore both pages specifically addressed the use of Uprima in patients with coronary artery disease who might have been prescribed nitrate therapy; both pages carried the same 'tan' coloured in-fill ie for the table on the left hand page, and the text box on the right hand page.

Abbott submitted that for the ease of the reader the references cited on the left hand page were summarised at the base of the page. Again, for the ease of the reader, references cited on the right hand page were summarised at the base of the page. Abbott was not aware that this practice was contradictory to the Code.

Abbott submitted that in accordance with the Code the prescribing information for the double page advertisement was clearly placed at the base of the second page of the advertisement.

Abbott submitted that in summary the advertisement was placed across two facing pages, both clearly marked with the same Abbott Urology logo, date of preparation and code/reference number. The prescribing information had formed an integral part of the piece and was clearly presented and positioned for ease of reference at the base of the right hand page. There was consistency in typeface, typeface colour, in-fill colour, and the subject matter across the double page clearly demonstrated to the reader that the advertisement was a double page spread.

Abbott further submitted that it was unaware of any features in the advertisement that would have misled the viewer into considering that the left hand page was distinct from the right hand page. Abbott therefore contested that there was any requirement for the placement of the prescribing information on the left hand page and denied a breach of Clause 4.1 of the Code.

## APPEAL BOARD RULING

The Appeal Board noted that it had to decide whether the material was one double page advertisement or two single page advertisements. The Appeal Board noted that the pages in question appeared facing one another; there were similarities in colour and text between the two and when viewed as a whole the prescribing information was clearly visible at the bottom of the right hand page. The Appeal Board considered that the advertisement constituted one double page advertisement for Uprima which included prescribing information. The Appeal Board ruled no breach of Clause 4.1. The appeal was successful.

**Complaint received** **10 January 2003**

**Case completed** **10 April 2003**

CASE AUTH/1413/1/03

# RICHMOND v RECKITT BENCKISER HEALTHCARE

## Promotion of Fybogel

**Richmond complained about the promotion of the laxative Fybogel (3.5g ispaghula husk supplied as effervescent granules for preparation of an oral suspension) by Reckitt Benckiser Healthcare. The complaint concerned a two page detail aid and the conduct of representatives. The detail aid, headed 'Are you following correct dispensing procedures?', was used between September and December 2002 by Reckitt Benckiser Healthcare representatives when detailing pharmacists who stocked and dispensed Richmond's Ispagel.**

**For prescriptions for 'Ispaghula husk effervescent granules 3.5g sachet' only Fybogel could be dispensed. Prescriptions for ispaghula could be filled with Ispagel or Fybogel.**

**Richmond alleged that the claim 'Fybogel contains nearly 12 x less $Na^+$ than Ispagel per sachet', which appeared beneath the subheading 'Fybogel is low in sodium', was inaccurate. Independent testing had shown that Ispagel contained only 2.18 times the sodium of Fybogel. Furthermore, Ispagel contained only 0.015mmol of sodium per dose, which was well within the British National Formulary (BNF) definition of a 'low-sodium' product ie less than 1mmol per dose.**

**The Panel noted that Fybogel contained less sodium per sachet than Ispagel. The theoretical sodium content of Fybogel was 0.31mmol/sachet whilst the measured sodium content for Ispagel was 2.3mmol/sachet. The Panel noted that Fybogel was designated 'low $Na^+$' by the BNF, in that each sachet provided less than 1mmol sodium, whereas Ispagel sachets were not. The claim in question, however, stated that 'Fybogel contains nearly 12 x less $Na^+$ than Ispagel per sachet'. This was not so. The Panel thus considered that the claim was inaccurate and could not be substantiated. Breaches of the Code were ruled.**

**Richmond noted that the claim 'Fybogel was significantly more pleasant tasting than Ispagel' appeared as the first bullet point beneath the subheading 'Customers prefer Fybogel' and was referenced to 'data on file'. The data relied on a trial which included only 73 consumers (not patients) which was of no clinical or statistical significance. By quoting the results in the detail aid whilst failing to reveal the size or make up of the trial Reckitt Benckiser Healthcare had made a deliberate attempt to mislead and influence prescribers and dispensers into believing that Ispagel was in some way defective. It was a subjective opinion produced from a clinically and statistically insignificant test. It was alleged that the claim disparaged Ispagel and was unsubstantiated.**

**The Panel noted that the data on file referred to Reckitt Benckiser Healthcare's own in-house study to measure consumer preference with regard to the appearance, colour, smell, taste and aftertaste of three ispaghula husk products including Fybogel Orange and Ispagel. It was described as a blind taste test. The Panel noted, however, that the participants (healthy volunteers who were employees of Reckitt Benckiser Healthcare) made up each suspension for themselves; Fybogel was supplied as effervescent granules and Ispagel was supplied as powder. The Panel considered that there would thus be obvious physical differences between the two products. Some of the participants might be very familiar with the appearance of Fybogel. The Panel noted the submission that 69% of prescriptions for laxatives were written for the elderly. The Panel questioned whether the population of people who took the taste test mirrored that for whom laxatives were prescribed. Readers of the detail aid would not know that the claim was based upon responses given by healthy volunteers who worked for Reckitt Benckiser Healthcare.**

**The Panel considered that the claim 'Fybogel was significantly more pleasant tasting than Ispagel' was a strong comparative claim. The Panel considered that given the data upon which it was based the claim was misleading and could not be substantiated. Breaches of the Code were ruled. The Panel further considered that by implication the claim disparaged Ispagel and ruled a breach of the Code.**

**Upon appeal by Reckitt Benckiser Healthcare the Appeal Board noted that the claim appeared under the heading '*Customers* prefer Fybogel' (emphasis added) but was substantiated with data from healthy volunteers who were employees of Reckitt Benckiser Healthcare. This was not made clear in the detail aid. The Appeal Board considered that readers would view the claim differently if they knew the basis on which it had been made. The Appeal Board noted that blind taste tests, conducted in-house and using company employees were not an uncommon method of research. The use to which such test results were put was however important; as an aid to product development they were not unacceptable but using them as a basis for promotional claims against a competitor might be unacceptable.**

**The Appeal Board considered that, given the data, the claim 'Fybogel was significantly more pleasant tasting than Ispagel' was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings.**

**The claim 'Fybogel gelled significantly slower than Ispagel' appeared as the second bullet point beneath the subheading 'Customers prefer Fybogel'. Richmond noted that the claim was again referenced to 'data on file'. There was no definition of the word 'significant'. The gelling times of the two products were irrelevant given that the patient instructions for both advised that they should be consumed as soon as they had dissolved in water. The speed of gelling of Ispagel was irrelevant to the efficacy of the product. The detail aid implied that Ispagel was materially defective.**

**The Panel noted that the data supplied by Reckitt Benckiser Healthcare, some of which appeared to be laboratory notes, did not refer to gelling *per se*.**

**Results were given for wettability, flow rate and water absorbency. The Panel considered that only those with any knowledge of physical pharmaceutics would be able to understand how these characteristics related to gelling. The Panel considered that, given the supporting data, the claim was misleading and had not been substantiated. Breaches of the Code were ruled.**

**Upon appeal by Reckitt Benckiser Healthcare the Appeal Board noted that although the gelling time was assessed 15 minutes post-preparation, patients were instructed to drink Fybogel 'straight away' and to drink Ispagel 'promptly'. The Appeal Board considered that the 15 minute delay between making up the suspensions and measurement of gelling invalidated the results, as in the clinical situation the laxatives would have already been drunk. Given the supporting data the Appeal Board considered that the claim was misleading and had not been substantiated. The Panel's rulings of breaches of the Code were upheld.**

**The claim '63% of people were not willing to take Ispagel every day' appeared as the third bullet point beneath the subheading 'Customers prefer Fybogel'. The claim was referenced to Reckitt Benckiser Healthcare's in-house blind taste test referred to above. Richmond made similar criticisms to those made above.**

**The Panel noted that its comments above regarding the claim 'Fybogel was significantly more pleasant tasting than Ispagel' also applied here. The Panel considered that given the data upon which it was based, the claim '63% of people were not willing to take Ispagel every day' was misleading and could not be substantiated. Breaches of the Code were ruled. The Panel further considered that the claim disparaged Ispagel and ruled a breach of the Code. Upon appeal by Reckitt Benckiser Healthcare the Appeal Board upheld the Panel's rulings.**

**The claim 'Customers who are not happy may take their Rx to other pharmacies' appeared as a bullet point beneath the subheading 'Several leading pharmacies are ONLY dispensing Fybogel'. Richmond stated that this claim implied that patients were not happy with Ispagel and was attempting to influence health professionals not to prescribe Ispagel. It disparaged Ispagel and was unsubstantiated.**

**The Panel noted that the claim appeared immediately below a subheading of 'Several leading pharmacies are ONLY dispensing Fybogel' and after the section of the detail aid which discussed why customers preferred Fybogel. The Panel considered that although the claim 'Customers who are not happy may take their Rx to other pharmacies' was self evident, in the context in which it appeared it implied that customers were not happy with Ispagel. The Panel noted its comments above regarding the in-house consumer preference study conducted by Reckitt Benckiser Healthcare. The Panel noted Reckitt Benckiser Healthcare's submission that it had anecdotal evidence of patients declining to accept a product from a pharmacist which was different from that which they had previously had dispensed. Anecdotal evidence was not sufficient to substantiate a claim. The Panel considered that by implication the claim disparaged Ispagel and ruled a breach of the Code. Upon appeal by Reckitt Benckiser Healthcare the Appeal Board upheld the Panel's rulings.**

**The claim 'Give your customer what they prefer' appeared as the third of four concluding bullet points. Richmond alleged that this claim implied that patients preferred Fybogel to Ispagel. It was attempting to influence health professionals not to prescribe Ispagel. It disparaged Ispagel and was unsubstantiated.**

**The Panel considered that its comments above with regard to the in-house consumer preference study applied here also. The Panel considered that in the context in which it appeared the claim disparaged Ispagel as alleged. A breach of the Code was ruled. Upon appeal by Reckitt Benckiser Healthcare the Appeal Board upheld the Panel's rulings.**

**Richmond had received complaints from several of the wholesalers/pharmacists that it had supplied with Ispagel in the past, in connection with the detail aid and the behaviour of Reckitt Benckiser Healthcare representatives. In particular one owner of a very large chain of pharmacies informed Richmond that a call had been received from a representative of Reckitt Benckiser Healthcare threatening to sue should the pharmacies dispense any product other than Fybogel against the prescription 'isphaghula husk'.**

**The Panel noted the nature of the alleged behaviour and considered that if such threats to take legal action had occurred then the representative would have been acting contrary to the requirements of the Code. Nonetheless, as there was insufficient evidence the Panel was not in a position to determine what, if anything, had happened. No breach of the Code was ruled.**

Richmond Pharmaceuticals Ltd complained about the promotion of the laxative Fybogel (3.5g ispaghula husk supplied as effervescent granules for preparation of an oral suspension) by Reckitt Benckiser Healthcare (UK) Limited. The complainant concerned a two page detail aid and the conduct of representatives. The detail aid, headed 'Are you following correct dispensing procedures?', was used between September and December 2002 by Reckitt Benckiser Healthcare representatives when detailing pharmacists who stocked and dispensed Richmond's Ispagel (3.5g ispaghula husk supplied as powder for preparation of an oral suspension).

For prescriptions written for 'Ispaghula husk effervescent granules 3.5g sachet' only Fybogel (regular, orange or lemon) could be dispensed. Generic ispaghula prescriptions could be filled with Ispagel or Fybogel.

### A Detail aid

#### 1 Claim 'Fybogel contains nearly 12 x less $Na^+$ than Ispagel per sachet'

This claim appeared as the first of two bullet points beneath the subheading 'Fybogel is low in sodium'.

## COMPLAINT

Richmond alleged that this claim was inaccurate. Independent laboratory testing of the two products had shown that Ispagel contained only 2.18 times the sodium of Fybogel. Furthermore, Ispagel contained only 0.015mmol of sodium per dose, which was well within the British National Formulary (BNF) definition of a 'low-sodium' product ie less than 1mmol per dose. Richmond considered that the main reason for including this clinically irrelevant and incorrect piece of information was to imply that Ispagel was materially defective (by being 'high' in sodium and therefore risking hypertension in patients) and as an attempt at scaremongering pharmacists and wholesalers. Breaches of Clauses 7.2 and 7.3 were alleged.

## RESPONSE

Reckitt Benckiser Healthcare submitted that the claim was accurate and clinically relevant and complied with Clauses 7.2 and 7.3 of the Code.

A comparative analysis by an independent laboratory service of three different batches of Ispagel, with varying expiry dates, and Fybogel showed that the level of sodium in these batches was nearly twelve times the levels of sodium in Fybogel. These analyses were provided.

The independent laboratory commissioned by Reckitt Benckiser Healthcare conducted these analyses which showed very similar sodium levels in each Ispagel batch, even between batches the variation in sodium levels was only +/–4%. The lowest sodium level obtained for the Ispagel product was 12.1mg/g which gave a sachet content (sachets weighed 4.31g) of approximately 52mg or 2.26mmol per sachet or 4.52mmol/day given that the daily dose was 2 sachets. The analysis of Fybogel showed a sodium level consistent with the formulation of the product [1mg/g]. Reckitt Benckiser explained that the amount of sodium present in Fybogel was on the limits of detection and therefore the figure of 1mg/g would not be the absolute figure [see below for the theoretical amount of sodium]. These analyses were conducted using atomic absorption spectrometry, a methodology which was one of the most up-to-date and accurate measurement techniques for sodium currently available.

The test certificate from the independent laboratory contracted by Richmond reported the sodium levels of Lot 222501 (assumed to be a Fybogel sample as correspondence from Richmond indicated that Ispagel had 2.18 times the level of sodium of Fybogel) as 158mg/sachet, and product R2020 05-2005, which must therefore be Ispagel, at 345.2mg/sachet. A product containing 345.2mg/sachet clearly contained 15mmol/sachet, a level which certainly was not low sodium. Reckitt Benckiser Healthcare assumed that these results had been incorrectly reported and the unit of measurement should have been micrograms. Whatever unit of measurement used in the analysis an impossible sodium level had been reported for Fybogel given its formulation. Reckitt Benckiser Healthcare was at a loss to explain how this result could have been obtained. The company offered to submit samples of Fybogel to independent analysis by a laboratory selected by the Authority and expected that Richmond would do the same.

Reckitt Benckiser Healthcare disagreed with Richmond's allegation that the discussion of sodium levels was clinically irrelevant. Even if the daily dosage of sodium within a product fell within the accepted daily adult sodium intake, certain vulnerable groups common amongst the elderly, for example renal patients and certain hypertensive patients, must maintain a much lower sodium intake. Sodium levels in medicines used by these vulnerable groups were very important. Reckitt Benckiser Healthcare noted that 69% of laxative prescriptions were written for the elderly. The level of sodium in laxatives was therefore obviously very important. The BNF had clearly recognised this issue and as Fybogel met its criterion for a low level of sodium, had allowed it to be classified as a low sodium product. The results of the analyses showed that Ispagel did not meet this criterion and hence the levels of sodium in Ispagel were very relevant.

In response to a request for further information Reckitt Benckiser Healthcare stated that although its report referred to the analysis of the sodium content of the batches of Ispagel and Fybogel tested as being the 'determination of sodium content as sodium bicarbonate' the measurement technique in fact measured the total sodium content of the samples, and that the analysis would have included the levels of sodium that were present both in the form of sodium bicarbonate and sodium saccharin. It referred to the sodium as being from sodium bicarbonate as at the time it conducted the test it believed that sodium bicarbonate was the only source of sodium in the product. Amended certificates of sodium content were provided.

Reckitt Benckiser Healthcare explained that in theory, according to the formulation of Fybogel, the total amount of sodium present in each sachet of each of the Fybogel formulations was 7.1mg/sachet (0.31mmol/sachet). Of this 5.75mg was present as sodium bicarbonate and 1.35mg was present as sodium saccharin.

As the actual weight of each sachet of Fybogel, Fybogel Orange and Fybogel Lemon was slightly different due to small differences in flavour formulation, the levels of sodium in each formulation when measured in mg/g were slightly different and were as follows:

Fybogel (regular) 1.69mg/g – sachet weight being 4.196g
Fybogel Lemon 1.63mg/g – sachet weight being 4.361g
Fybogel Orange 1.62mg/g – sachet weight being 4.396g

The formulation of Fybogel, Fybogel Orange and Fybogel Lemon was identical except for certain flavouring excipients. Accordingly the levels of sodium in each sachet of these products was identical.

## PANEL RULING

The Panel noted that Section 1 of the BNF, which detailed products used for gastrointestinal disorders, defined a low sodium product as one which provided

less than 1mmol per tablet or 10ml dose. The words 'low $Na^+$' were added after product names for those products defined as such. 'Low $Na^+$' appeared in the entry for Fybogel but not for Ispagel (ref BNF No 44 September 2002).

The Panel noted that there was a difference in sodium content between the two products; Fybogel contained less sodium per sachet than Ispagel. The theoretical sodium content of Fybogel was 0.31mmol/sachet whilst the measured sodium content for Ispagel was 2.3mmol/sachet. The Panel noted that Fybogel was designated 'low $Na^+$' by the BNF, in that each sachet provided less than 1mmol sodium, whereas Ispagel sachets were not. The claim in question, however, stated that 'Fybogel contains nearly 12 x less $Na^+$ than Ispagel per sachet'. This was not so. The Panel thus considered that the claim was inaccurate and could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

### 2 Claim 'Fybogel was significantly more pleasant tasting than Ispagel'

This claim appeared as the first of four bullet points beneath the subheading 'Customers prefer Fybogel'.

#### COMPLAINT

Richmond noted that this claim was referenced to 'data on file'. The data relied on was collected from 73 consumers. It was a subjective test and the results irrelevant to the efficacy of Ispagel. A trial which included only 73 consumers (not patients) was of no clinical or statistical significance. By quoting the trial results in the detail aid whilst failing to reveal the size or make up of the trial Reckitt Benckiser Healthcare had made a deliberate attempt to mislead and influence prescribers and dispensers into believing that Ispagel was in some way defective.

It was a subjective opinion produced from a clinically and statistically insignificant test. The claim disparaged Ispagel and was unsubstantiated. Breaches of Clauses 7.2, 7.3 and 8.1 were alleged.

#### RESPONSE

Reckitt Benckiser Healthcare stated that this claim was clinically relevant and derived from statistically significant results of a blinded taste test study. The claim therefore complied with Clauses 7.2, 7.3 and 8.1 of the Code.

The relevance of this statement went to patient compliance; the likelihood of a patient continuing with his/her treatment was very relevant to the effectiveness of that treatment. Lack of patient compliance was a significant clinical issue. The clinical guidance concerning laxative use issued by the National Prescribing Centre (MeReC Bulletin Vol 10, No 9 1999) stated that palatability and convenience were important factors in ensuring patient compliance.

Reckitt Benckiser Healthcare noted that Richmond had challenged the significance of the results reported. Double-blind taste testing on a range of products followed by a market research designed in-depth questionnaire was used to investigate consumer responses to certain aspects of Fybogel and to compare these with consumer responses to certain competitor products. This study sampled seventy-three healthy volunteers drawn from the company's own employees who answered a general request for volunteers for taste testing. Statistical analysis of the results provided support for the claim in question. Richmond was wrong to state that the results of a trial including 73 patients were not of significance. The results showed very clear statistical significance for the claim. The trial was conducted as a blind taste test using techniques which ensured unbiased results. The responses of 68% of the subjects showed that they considered Fybogel to be more pleasant tasting than Ispagel ($p<0.0001$).

#### PANEL RULING

The Panel noted that the claim was referenced to data on file. The data showed that Reckitt Benckiser Healthcare itself had conducted research to measure consumer preference with regard to the appearance, colour, smell, taste and aftertaste of three ispaghula husk products including Fybogel Orange and Ispagel. Participants were also asked to state how willing they would be to take the products on a daily basis. The 73 'consumers' were all healthy volunteers drawn from the company's own employees.

The test undertaken by Reckitt Benckiser Healthcare was described as a blind taste test. The Panel noted, however, that the participants made up each suspension for themselves; Fybogel was supplied as effervescent granules and Ispagel was supplied as powder. The Panel considered that there would thus be obvious physical differences between the two products. Some of the participants might be very familiar with the appearance of Fybogel.

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that care must be taken in using data from volunteer studies so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The participants in the taste test had been healthy volunteers, employees of Reckitt Benckiser Healthcare. The Panel noted the submission that 69% of prescriptions for laxatives were written for the elderly. The Panel questioned whether the population of people who took the taste test mirrored that for whom laxatives were prescribed. No demographic details of the test participants were given. Readers of the detail aid would not know that the claim was based upon responses given by healthy volunteers who worked for Reckitt Benckiser Healthcare.

The Panel considered that the claim 'Fybogel was significantly more pleasant tasting than Ispagel' was a strong comparative claim. The Panel considered that given the data upon which it was based the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel further considered that by implication the claim disparaged Ispagel and ruled a breach of Clause 8.1 of the Code.

## APPEAL BY RECKITT BENCKISER HEALTHCARE

Reckitt Benckiser Healthcare submitted that the fact that it had conducted the trial did not detract from the validity of the trial. It was common practice for companies to conduct their own research in many different disciplines. The Reckitt Benckiser Healthcare site in Hull had a dedicated Sensory Analysis Suite designed specifically for internal tests on product development and improvement. Reckitt Benckiser Healthcare noted that the Panel had considered that the fact that the volunteers were drawn from Reckitt Benckiser Healthcare employees had in some way invalidated the blinding of the study. The implication was that because of the obvious physical differences between the products the volunteers would be able to identify Fybogel and might therefore introduce bias in favour of Fybogel.

Blind taste tests were a standard way of obtaining unbiased responses to similar products and were used widely within the food and other manufacturing industries, not only to benchmark competitor products but when developing new products or improving existing products. Reckitt Benckiser Healthcare submitted that it used blind taste tests extensively when developing new formulations or formulation changes across the whole spectrum of its product portfolio. Blind taste tests did not measure, and were not intended to measure, brand loyalty.

Reckitt Benckiser Healthcare noted that its Hull site comprised manufacturing, research and development, and office facilities covering a broad range of product categories. When its employees were asked to volunteer to take part in studies like this there was a broad spread of representatives across all functions. It was therefore unlikely that a significant proportion of volunteers would have the ability to recognise a specific formulation from its physical characteristics when presented in a blinded manner. Reckitt Benckiser Healthcare submitted that the majority of internal tests conducted examined changes to existing brands. Volunteers, therefore, were unsure whether they were testing current formulations, new formulations or competitor products. In the study at issue only a small minority of the volunteers would have had enough experience or familiarity with Fybogel to differentiate the two products in question. The majority of volunteers did not work directly with the manufacturing or development of Fybogel and so would have had no basis for making any differentiation on physical appearance.

Reckitt Benckiser Healthcare submitted that volunteers were shown products in blank packaging with all reference to any brand names/logos/colours removed. Each product was scored and assessed individually – no direct comparisons were made between the different products tested. This allowed unbiased comparisons to be made across any number of products. Reckitt Benckiser Healthcare had conducted two previous internal studies within the last 2 years where only Fybogel formulations were tested. In the study in question both samples were shown in white sachets and no mention was made of any brand. The volunteers were simply informed that they would be testing fibre drinks. The method of blinding and standardisation of these tests, combined with lack of experience of Fybogel and lack of expectation of the presence of a competitor product, made it highly unlikely that any bias towards Fybogel was present in the test results.

No claim was made regarding clinical efficacy. The claim related specifically to the taste of the product and had produced a statistically significant difference between Ispagel and Fybogel on this measure from a volunteer base that was of sufficient size to be able to produce meaningful results. Reckitt Benckiser Healthcare submitted that in the context in which the detail aid was used, the question of taste of the product was extremely important and whilst the demographics of the volunteers might differ in terms of the average age of patients receiving laxative prescriptions, there was no evidence that taste preference varied either with age or if a consumer was suffering from constipation. The question of preference might be extremely relevant in terms of compliance. Reckitt Benckiser Healthcare submitted therefore that the claim was not misleading. Demographic data was not presented in the detail aid as the company did not believe that it was relevant. Reckitt Benckiser Healthcare submitted that the data was suitable for extrapolation into the clinical situation where it had real relevance for the consumer.

Reckitt Benckiser Healthcare submitted that a comparison of respondents who reported the products to be very pleasant or fairly pleasant (Fybogel: 39/72: 54.2%; Ispagel: 14/72: 19.4%), demonstrated a statistically significant difference ($p<0.0001$). Statistically there was a very strong case to support the claim that 'Fybogel was significantly more pleasant tasting than Ispagel'. Reckitt Benckiser Healthcare contended that the claim was substantiated and did not mislead. The data merely showed that Fybogel was considered significantly more pleasant tasting than Ispagel. It was a fact of life that some products would taste better or worse than others. The fact that the results were more favourable for Fybogel than Ispagel did not imply any defect, in or in any way disparage, Ispagel and as they were statistically valid and did not mislead prescribers or dispensers. They merely demonstrated that Fybogel had a more pleasant taste than Ispagel. Reckitt Benckiser Healthcare did not consider that the claim was in breach of Clauses 7.2, 7.3 or 8.1.

## COMMENTS FROM RICHMOND

Richmond noted Reckitt Benckiser Healthcare's comments on the way in which the trial was conducted, however it still alleged that the use of data obtained from a trial group consisting of only 73 participants who were all healthy volunteers and employees of the company was misleading, particularly when the results were quoted with reference simply to 'data on file'. Further it was a widely held concern of the industry that the 'Reporting of pharmaceutical industry sponsored …… clinical trials often result in biased findings' (Djulbegovic *et al* 2000).

Richmond alleged that despite Reckitt Benckiser Healthcare's assurances about the conduct of the trial, it did not know what the volunteers were told before

taking part, whether any of the volunteers also participated in the previous internal studies conducted over the last 2 years, the demographic make up of the volunteers, how many of them worked with manufacturing or development of Fybogel etc. Richmond could not accept Reckitt Benckiser Healthcare's assumption that the combination of blind testing and standardisation with 'lack of experience of Fybogel and lack of expectation of the presence of a competitor product, made it highly unlikely that any bias towards Fybogel was present in the test results'. Richmond did not know whether the volunteers lacked experience of Fybogel and would have thought it highly likely that they would have expected the presence of a competitor product given the nature of the comparison they were required to undertake.

In Richmond's view a trial which included only 73 volunteers was of no clinical or statistical significance and quoting the results in the detail aid without providing any information on the size or make-up of the trial was deliberately misleading. Care had not been taken to avoid misleading readers as to the relevance and significance of the trial results. In particular Reckitt Benckiser Healthcare had stated that it was not making claims regarding clinical efficacy, but if this phrase was read in context, Richmond suggested that it would be taken to support other claims made in the detail aid, in particular in relation to the sodium content of Ispagel, and therefore would influence the reader's perception of Ispagel's clinical efficacy. Richmond noted that the Panel's rulings on the issue of sodium content were not appealed (point 1 above). In attempting to influence prescribers and dispensers into believing that Ispagel was in some way defective, Reckitt Benckiser Healthcare had clearly disparaged the product both directly and by implication.

## APPEAL BOARD RULING

The Appeal Board noted that the claim 'Fybogel was significantly more pleasant tasting than Ispagel' appeared under the heading '*Customers* prefer Fybogel' (emphasis added). The data, however, to substantiate the claim was from healthy volunteers who were employees of Reckitt Benckiser Healthcare. This was not made clear in the detail aid. The Appeal Board considered that readers would view the claim differently if they knew the basis on which it had been made.

The Appeal Board noted that blind taste tests, conducted in-house and using company employees were not an uncommon method of research. The use to which such test results were put was however important. The Appeal Board considered that using such results as an aid to product development was not unacceptable but using them in a detail aid as a basis for promotional claims against a competitor might be unacceptable.

The Appeal Board also noted the submission of the company representatives that approximately 5% of the study population had a current intimate knowledge of Fybogel and considered that the design of the current study was such that the possibility of bias could not be eliminated.

The Appeal Board considered that the claim 'Fybogel was significantly more pleasant tasting than Ispagel' was a strong comparative claim, and considered that given the data the claim was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful. The Appeal Board further considered that by implication the claim disparaged Ispagel and upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

### 3 Claim 'Fybogel gelled significantly slower than Ispagel'

This claim appeared as the second of four bullet points beneath the subheading 'Customers prefer Fybogel'.

## COMPLAINT

Richmond noted that the claim was again referenced to data on file. There was no definition of the word 'significant'. The gelling times of the two products were irrelevant given that the patient instructions for both products advised that they should be consumed as soon as they had dissolved in water. The speed of gelling of Ispagel was irrelevant to the efficacy of the product. The detail aid was implying that Richmond's product was materially defective. Breaches of Clauses 7.2 and 7.3 were alleged.

## RESPONSE

Reckitt Benckiser Healthcare stated that the claim was clinically relevant and derived from the statistically significant results of laboratory testing of the gelling time of Fybogel and certain of its competitor products. It therefore complied with Clauses 7.2, 7.3 and 8.1 of the Code.

Reckitt Benckiser Healthcare disagreed with Richmond's submission that the gelling times of the products were irrelevant. As with any medicine, patient compliance was very important. A product that had gelled to some degree had an inferior 'mouth feel' compared to a product that was still liquid, leading to a reduced compliance. The Ispagel dosing instructions recognised that the product might gel before dosage was complete in that it was stated 'if mixture thickens, add more liquid and stir. Follow with more liquid to aid the product further'. Additionally, with 69% of laxatives being taken by the elderly, it was very important that products remained palatable and drinkable for a reasonable period of time. Reckitt Benckiser Healthcare also noted that Richmond had stated that both products' patient instructions advised that 'the products should be consumed as soon as they have dissolved in water'; in fact none of these products dissolved in water, they would gel rather than dissolve.

With regard to the laboratory data that it had provided, Reckitt Benckiser Healthcare noted that the ideal measure of gelling would utilise rheology to measure viscosity but because Fybogel contained insoluble material and was not homogenous it was

very difficult to obtain consistent, reproducible results using this technique. In addition, the measurement took 2-3 minutes to complete during which time the characteristics of the gels changed as the gelling process continued. This technique therefore failed to produce meaningful data. Alternative indirect measurements to assess gelling therefore had to be used. The data supplied on wettability, water absorbency and flow rates were examples of such indirect measurements of gelling.

Measuring flow rates through a viscosity cup was a standard industry test method that could give an indirect measure of product's viscosity/thickness at any time point after making up the product in water. Therefore comparisons of product thickness and hence rates of gelling could be made using this methodology and this was shown to be the most reliable method when comparing gelling rates for Fybogel and Ispagel.

## PANEL RULING

The Panel noted that the claim was referenced to data on file. The data supplied by Reckitt Benckiser Healthcare, some of which appeared to be laboratory notes, did not refer to gelling *per se*. Results were given for wettability, flow rate and water absorbency. The Panel noted the company's explanation for the tests undertaken but considered that only those with any knowledge of physical pharmaceutics would be able to understand how these characteristics related to gelling. The Panel considered that, given the supporting data, the claim was misleading and had not been substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

## APPEAL BY RECKITT BENCKISER HEALTHCARE

Reckitt Benckiser Healthcare submitted that gelling speed was relevant to the consumer as the palatability of the product was clearly diminished as gelling took place. The fact that both products came with instructions to take them as soon as they had dissolved was irrelevant as the volume in which Ispagel was dissolved was greater than that for Fybogel and as such would take longer to consume (particularly in an elderly population). Reckitt Benckiser Healthcare had agreed that this had no direct relevance to efficacy and made no such claim. However, palatability was relevant to compliance. This was supported by the National Prescribing Centre in the MeReC Bulletin Vol 10, No 9, 1999 which stated that palatability and convenience were important factors in ensuring patient compliance. Reckitt Benckiser Healthcare took this matter very seriously and a slower gelling Ispaghula formulation was introduced during 2002 and offered a benefit in terms of palatability related to gelling and hence compliance.

Reckitt Benckiser Healthcare submitted that the industry commonly used surrogate measures where it was not possible or feasible to measure a specific variable directly and to report these measures in terms of the impact on the unmeasurable variable. Often these surrogate measures were accepted as standards. As Fybogel and Ispagel contained insoluble material and continued to gel over a long period of time a direct measurement of how much the product had gelled (ie its viscosity) was not possible using more standard rheological techniques. A measure of how much the products had gelled was determined by measuring the time taken for the product to flow through an aperture of fixed diameter (viscosity cup). When the products began to gel the flow time increased. Measuring the flow times of the products at various timepoints after the product had been prepared provided information as to the speed of gelling of the products.

Reckitt Benckiser Healthcare submitted that this was a very simple, standard test and did not require a detailed knowledge of pharmaceutics. The test was based on the definition of viscosity which was defined in standard pharmaceutics text books as resistance to flow or movement – and using flow rate to measure viscosity was an acceptable technique and the results interpretable in terms of gelling.

Reckitt Benckiser Healthcare submitted that the claim was adequately supported by the data, did not require specialist knowledge for its interpretation and as such was not misleading.

## COMMENTS FROM RICHMOND

Richmond alleged that the claim at issue had no relevance as the patient instructions on the Fybogel packaging instructed the user to 'drink straight away' and those on the Ispagel packaging stated 'drink promptly'. Richmond suggested that the average patient would interpret these two instructions in the same way. Reckitt Benckiser Healthcare had previously drawn attention to the more detailed instruction contained within the Ispagel patient information leaflet which stated 'If mixture thickens, add more liquid and stir'. Reckitt Benckiser Healthcare had not included a leaflet within the Fybogel packaging and so had not had the opportunity of giving patients this useful piece of information. However, should patients not follow the instructions for consumption of either product the result would be the same: both would gel. Richmond noted that its leaflet gave patients a way of rectifying this problem. The information was not available on the Fybogel packaging.

Richmond alleged that the claim, in particular with the use of the word 'significantly', implied that the two products behaved very differently.

Richmond again noted that the detail aid had relied on data on file, and having now seen it agreed with the Panel's finding that even if this data were available to an enquirer, it did not refer to gelling *per se* and the results that it did rely on would require specialist knowledge of physical pharmaceutics in order to be interpreted.

Richmond noted Reckitt Benckiser Healthcare's statement that it made no claim as to efficacy of Ispagel, however, taken in context this claim was misleading and was not substantiated.

## APPEAL BOARD RULING

The Appeal Board noted that the claim was referenced

to data on file. Given the difficulties surrounding measurement of gelling the Appeal Board did not consider that the use of surrogate methods in this regard was unacceptable. The Appeal Board noted that although the gelling time was assessed 15 minutes post-preparation patients were instructed to drink Fybogel 'straight away' and to drink Ispagel 'promptly'. The Appeal Board considered that the 15 minute delay between making up the suspensions and measurement of gelling invalidated the results, as in the clinical situation the laxatives would have already been drunk. Given the supporting data the Appeal Board considered that the claim was misleading and had not been substantiated. The Panel's rulings of breaches of Clauses 7.2 and 7.3 of the Code were upheld. The appeal on this point was unsuccessful.

### 4 Claim '63% of people were not willing to take Ispagel every day'

This claim appeared as the third of four bullet points beneath the subheading 'Customers prefer Fybogel'.

#### COMPLAINT

Richmond noted that this claim was referenced to 'data on file' collected from the same 73 consumers as in point 2 above. A trial which included only 73 consumers (not patients) was of no clinical or statistical significance. The detail aid did not contain information on how many people were unwilling to take Fybogel everyday. By quoting the trial results but failing to reveal its size or make up Reckitt Benckiser Healthcare had deliberately attempted to mislead and influence prescribers and dispensers into believing that Ispagel was in some way defective.

There was no comparative statistic for the daily taking of Fybogel. The statistic was produced from a very small number of consumers rather than patients. Richmond alleged that the claim disparaged Ispagel and was unsubstantiated; breaches of Clauses 7.2, 7.3 and 8.1 were alleged.

#### RESPONSE

Reckitt Benckiser Healthcare stated that the claim at issue was relevant and an accurate statement of the results of double-blind taste testing of Fybogel and a range of competitor products. It therefore complied with Clauses 7.2, 7.3 and 8.1 of the Code. Double-blind taste testing of a range of products followed by a market research designed in-depth questionnaire was used to investigate consumer responses to certain aspects of Fybogel and to compare these with consumer responses to certain competitor products. This study sampled seventy-three healthy volunteers drawn from the company's own employees who answered a general request for volunteers for taste testing. A direct arithmetical analysis of the results of this comparative consumer research provided support for this statement. The trial was conducted as a blind taste test using techniques which ensured unbiased results.

Palatability and convenience were important factors in ensuring patient compliance. Lack of patient compliance was a significant clinical issue.

#### PANEL RULING

The claim was based upon the same data on file as that discussed at point 2 above. The Panel noted its comments regarding the in-house consumer preference study carried out by Reckitt Benckiser Healthcare and considered that they applied here also.

The Panel considered that given the data upon which it was based the claim '63% of people were not willing to take Ispagel every day' was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel further considered that the claim disparaged Ispagel and ruled a breach of Clause 8.1 of the Code.

#### APPEAL BY RECKITT BENCKISER HEALTHCARE

Reckitt Benckiser Healthcare submitted that the arguments over the suitability of data from this study were given above in point 2. The data to support the claim demonstrated that 46/72 (63.9%) volunteers were 'not at all willing'/'not very willing' to use Ispagel on a daily basis whereas only 26/73 (35.6%) were similarly unwilling to use Fybogel. The difference between these response rates was again highly statistically significant both using the simple Chi-square test applied to the above proportions ($p=0.0016$), or using the Wilcoxon Rank Sum test with the full set of responses ($p<0.0001$). Thus statistically significantly more volunteers reported that they would be unwilling to use Ispagel on a daily basis, when compared with Fybogel. The claim in the detail aid was therefore accurate and substantiated. The data was also sufficient to show that 'significantly more consumers were unwilling to use Ispagel on a daily basis, compared with Fybogel'. This was not the claim made, but answered the specific point raised by Richmond. The data was available should it be requested.

Reckitt Benckiser Healthcare noted that as in point 2, this claim had related simply to subjective preference and did not make any statement about efficacy or the quality of Ispagel. Clearly if the basis of the study data was acceptable the claim was substantiated and as such neither misleading nor disparaging. It was a simple statement of fact based upon the data. Reckitt Benckiser Healthcare submitted that the claim was not in breach of the Code.

#### COMMENTS FROM RICHMOND

Richmond's view was not altered in any way having had sight of the volunteers' responses to the question 'How willing would you be to use the product on a daily basis?' as the results of a survey of 73 employees should not be considered 'significant'.

Richmond stated that, given the context in which the claim was made, it disagreed with Reckitt Benckiser Healthcare's statement that the claim 'related simply to subjective preference and had not made any statement about efficacy or the quality of Ispagel'. The claim disparaged Ispagel.

#### APPEAL BOARD RULING

The Appeal Board noted its comments at point 2

regarding the in-house consumer preference study carried out by Reckitt Benckiser Healthcare and considered that they applied here also.

The Appeal Board considered that given the data upon which it was based the claim '63% of people were not willing to take Ispagel every day' was misleading and could not be substantiated and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful. The Appeal Board further considered that the claim disparaged Ispagel and upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

### 5 Claim 'Customers who are not happy may take their Rx to other pharmacies'

The claim appeared as the first of two bullet points beneath the subheading 'Several leading pharmacies are ONLY dispensing Fybogel'.

#### COMPLAINT

Richmond stated that this claim implied, when taken in context, that patients were not happy with Ispagel. It was attempting to influence health professionals not to prescribe Ispagel. It disparaged Ispagel and was unsubstantiated. A breach of Clause 8.1 was alleged.

#### RESPONSE

Reckitt Benckiser Healthcare submitted that the claim was a statement of fact and was a fair comment on the reality of dispensing practice. As such it did not disparage Ispagel and was not in breach of Clause 8.1 of the Code. Reckitt Benckiser Healthcare had anecdotal evidence of patients declining to accept a product from a pharmacist which was different from that which they had previously had dispensed. Reckitt Benckiser Healthcare considered that this factor was well known by pharmacists to occur in their dispensing practice.

#### PANEL RULING

The Panel noted that the claim in question appeared immediately below a subheading of 'Several leading pharmacies are ONLY dispensing Fybogel' and after the section of the detail aid which discussed why customers preferred Fybogel. The Panel considered that although the claim 'Customers who are not happy may take their Rx to other pharmacies' was self evident, in the context in which it appeared it implied that customers were not happy with Ispagel. The Panel noted its comments in points 2 and 4 above regarding the in-house consumer preference study conducted by Reckitt Benckiser Healthcare. The Panel noted Reckitt Benckiser Healthcare's submission that it had anecdotal evidence of patients declining to accept a product from a pharmacist which was different from that which they had previously had dispensed. Anecdotal evidence was not sufficient to substantiate a claim. The Panel considered that by implication the claim disparaged Ispagel and ruled a breach of Clause 8.1 of the Code.

#### APPEAL BY RECKITT BENCKISER HEALTHCARE

Reckitt Benckiser Healthcare noted that the arguments over whether customers preferred Ispagel had been discussed at points 2 and 4. The same arguments in favour of using the taste test data applied here.

Reckitt Benckiser Healthcare noted that an Omnibus study, conducted in June 2002, among men and women aged 65 and above who received a regular prescription, showed that 38% would have no concerns if another brand was given instead of their regular medication. 21% would query the change with the pharmacist or GP with a further 17% concerned/worried about the side effects and other reactions. 78% of Fybogel scripts were repeat prescriptions (Source: IMS MDI 12 months to December 2002).

Reckitt Benckiser Healthcare submitted that bearing these figures in mind, the importance of a potential 38% of patients with repeat prescription patients having concerns over substitution of Fybogel for Ispagel in filling open prescriptions was put into context. The detail aid was aimed at pharmacists and the statement served to remind them that choosing to fill an open prescription with a different brand, particularly where there was a strong preference might not be a sound business decision. The use of anecdotal data did not substantiate the claim, but it illustrated the point made by the figures above. If the taste test data was accepted therefore this claim was relevant to the context and therefore not disparaging.

#### COMMENTS FROM RICHMOND

Richmond accepted the Panel's comment that the claim was self-evident and confirmed its view that in the context this claim had been made it had implied that customers were not happy with Ispagel and this could be the cause of pharmacies losing other unconnected business. This claim very clearly disparaged Ispagel.

Richmond noted Reckitt Benckiser Healthcare's comment that 38% of men and women over 65 queried a change in medication or would be worried about the side effects. However, Reckitt Benckiser Healthcare had not quoted any evidence which showed this would lead to the patients going to another pharmacy, indeed such information might not exist. Even Reckitt Benckiser Healthcare admitted that anecdotal data did not substantiate the claim.

Richmond stated that the taste test data was not accepted for the reasons set out in point 2 above.

#### APPEAL BOARD RULING

The Appeal Board noted that the claim in question appeared immediately below a subheading of 'Several leading pharmacies are ONLY dispensing Fybogel' and after the section of the detail aid which discussed why customers preferred Fybogel. The Appeal Board considered that the claim 'Customers who are not happy may take their Rx to other pharmacies' implied that customers were not happy with Ispagel. The Appeal Board noted its comments in points 2 and 4 above regarding the preference study conducted by Reckitt Benckiser Healthcare. The Appeal Board

considered that by implication the claim disparaged Ispagel and upheld the Panel's rulings of a breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

### 6 Claim 'Give your customer what they prefer'

This claim appeared as the third of four concluding bullet points.

#### COMPLAINT

Richmond alleged that this claim implied, when taken in context, that patients preferred Fybogel to Ispagel. It was attempting to influence health professionals not to prescribe Ispagel. It disparaged Ispagel and was unsubstantiated. A breach of Clause 8.1 was alleged.

#### RESPONSE

Reckitt Benckiser Healthcare submitted that as referred to previously, 63% of people in a double-blind taste testing were not willing to take Ispagel every day. The statement 'Give your customer what they prefer' followed from this taste testing and so was accurate and fair. As such this statement did not disparage Ispagel and was not in breach of the Code.

#### PANEL RULING

The Panel noted that Reckitt Benckiser Healthcare had referred to the results from its in-house consumer preference study. The Panel considered that its comments at points 2 and 4 above with regard to that study applied here also. The Panel considered that in the context in which it appeared the claim disparaged Ispagel as alleged. A breach of Clause 8.1 was ruled.

#### APPEAL BY RECKITT BENCKISER HEALTHCARE

Reckitt Benckiser Healthcare noted that the arguments for the use of this study as substantiating data were given under points 2 and 4 above. If these arguments were accepted then the implication that customers preferred Fybogel was substantiated and the claim was neither misleading nor disparaging.

#### COMMENTS FROM RICHMOND

Richmond repeated its view that given the context in which this claim was made it was disparaging to Ispagel. As stated in point 2 above, it did not accept the results of the trial as statistically significant and therefore believed that the reliance on the results in the detail aid was misleading and in breach of Clause 8.1.

#### APPEAL BOARD RULING

The Appeal Board considered that the claim was based upon the results of Reckitt Benckiser Healthcare's in-house consumer preference study and referred to its comments on that study at points 2 and 4 above. The Appeal Board considered that in the context in which it appeared the claim disparaged Ispagel as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

### B Conduct of representatives

#### COMPLAINT

Richmond noted that Clause 15.2 required representatives to maintain a high standard of ethical conduct in the discharge of their duties. Richmond had received complaints from several of the wholesalers/pharmacists that it had supplied with Ispagel in the past, in connection with the detail aid and the behaviour of Reckitt Benckiser Healthcare representatives. In particular one owner of a very large chain of pharmacies informed Richmond that a Reckitt Benckiser Healthcare representative had called, threatening to sue should the pharmacies dispense anything other than Fybogel against the prescription 'isphaghula husk'. This was contrary to the standards required by the Code. A breach of Clause 15.2 was alleged.

#### RESPONSE

Reckitt Benckiser Healthcare noted the allegation regarding the owner of a very large chain of pharmacies and stated that to the best of its knowledge, it was not true. The statement that no other product could be dispensed against a prescription written as 'ispaghula husk' was incorrect and the training received by Reckitt Benckiser Healthcare representatives would leave them in no doubt that this was so. Reckitt Benckiser Healthcare stated that at no time had it briefed its representatives to use such a statement and such a suggestion was not included in its briefing document. Reckitt Benckiser Healthcare was unable to investigate this allegation further without more details but found it difficult to believe that its representatives would be guilty of such behaviour.

#### PANEL RULING

The Panel noted that the information given by Richmond was very imprecise; no representatives or customers had been named and so Reckitt Benckiser Healthcare was unable to investigate the matter fully. The Panel noted the nature of the alleged behaviour and considered that if such threats to take legal action had occurred then the representative would have been acting contrary to the requirements of the Code. Nonetheless, as there was insufficient evidence the Panel was not in a position to determine what, if anything, had happened. No breach of Clause 15.2 was ruled.

**Complaint received** **21 January 2003**

**Case completed** **14 July 2003**

CASE AUTH/1414/1/03

# PHARMACIA v ALCON LABORATORIES

## Travatan leavepiece

Pharmacia complained about a leavepiece for Travatan (travoprost 0.004%) eye drops issued by Alcon Laboratories which compared Travatan with latanoprost (Pharmacia's product Xalatan). The claims at issue were based on Netland *et al* (2001) which compared the efficacy and safety of travoprost (0.0015% and 0.004%), latanoprost (0.005%) and timolol (0.5%) in patients with open-angle glaucoma or ocular hypertension over a period of 12 months.

Pharmacia accepted that the claim 'Equal or superior to latanoprost 0.005% in lowering IOP [intra-ocular pressure] at all treatment visits' was used in Netland *et al* but alleged that it was misleading to use it in a promotional piece. The Netland data demonstrated equivalence of efficacy, not superiority. Netland had mistakenly claimed that the difference in the absolute pressures seen within the two treatment groups represented the difference in IOP-lowering effect. This was incorrect because there had been no adjustment for baseline differences. It represented only the difference in final IOPs. Pharmacia stated that Netland had over-interpreted the data in favour of Travatan; numerous sub-group analyses had been conducted, increasing the probability of obtaining a significant value purely by chance (Type 1 error).

In its review of the Netland data the US Food and Drugs Administration (FDA) concluded 'The IOP lowering ability of [travoprost] 0.004% and Xalatan 0.005% is similar. The change in mean IOP from baseline ranges from –6.6 to –8.1mmHg [travoprost] 0.004% dosed [once daily in the evening] and from –6.2 to –8.1mmHg Xalatan 0.005% dosed [once daily in the evening]'. Pharmacia had plotted the primary efficacy variable data in the FDA's review with the change in mean IOP from baseline per visit and time for the Xalatan and Travatan data. Pharmacia noted that there were no statistics to this graph. Glaucoma was a chronic condition and this data showed equal efficacy. To imply any superiority was alleged to be misleading.

The Panel noted the design of the Netland study and that the authors had concluded that in the treatment of open-angle glaucoma or ocular hypertension travoprost was equal or superior to latanoprost. IOP was measured at baseline, week 2 and at months 1.5, 3, 4.5, 6, 9 and 12. The baseline figures showed that IOP in the latanoprost group was slightly higher at all time points (8am, 10am and 4pm) than in the travoprost 0.004% group. Examinations were made at 8am, 10am and 4pm for some visits and 8am and 10am at months 1.5, 4.5 and 9. One of the stated primary objectives was to show that travoprost was greater than or equal to latanoprost with regard to IOP lowering efficacy.

The Panel considered that the claim at issue was a broad, strong claim and noted that even though it was a quotation it nonetheless had to comply with the Code. The Panel was concerned that the claim did not reflect Netland *et al* which had shown only limited statistically significant advantages for Travatan with respect to mean IOP compared with latanoprost. At the majority of visits there had been no statistically significant difference between the two. There was no statistical analysis in relation to change from baseline. A statistically significant difference in mean IOP at two weeks plus a difference at 4pm for the pooled data with no difference at the other time points measured, was, in the Panel's view, insufficient to justify a claim for superiority for treating a long-term condition such as glaucoma. The claim was misleading and a breach of the Code was ruled.

Alcon appealed the Panel's ruling. In its consideration of the matter the Appeal Board's views echoed those of the Panel. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

Pharmacia noted the claim 'Controls IOP in more patients than latanoprost 0.005% (IOP reductions ≥ 30% or mean IOP ≤ 17mmHg)' was another retrospective sub-group analysis as acknowledged by Alcon. It was very easy to define a responder to fit the data after the event. Whilst this type of analysis might be appropriate for hypothesis generation, it was extremely misleading if used as fact until proven by a trial that had been conducted to prospectively test the hypothesis. Pharmacia alleged that clinicians had been left with the misleading message that travoprost was more efficacious than latanoprost.

The Panel noted that Netland *et al* defined treatment responders as those who showed a 30% or greater IOP reduction from diurnal baseline or final IOP of 17mmHg or less. Travoprost 0.004% had an overall treatment response of 54.7% with the figure for latanoprost being 49.6% ($p \leq 0.043$). The Panel noted that the study did not include a responder analysis; the data had been obtained from a retrospective sub-group analysis. This was not necessarily unacceptable. The Panel noted its comments about the study above. The Panel considered that in the context in which it appeared the claim gave the impression that Travatan was more efficacious than latanoprost. The Panel considered that the claim was misleading and a breach of the Code was ruled.

Alcon appealed the Panel's ruling and provided a letter from Dr Netland confirming that the analysis had been prospectively planned. The Appeal Board noted the data on responders and that this was the only data available at the time of the leavepiece. The Appeal Board considered that the claim was not misleading, it was a fair reflection of the Netland study data and on this narrow point ruled no breach of the Code.

Pharmacia stated that the claim 'Better IOP control at trough than latanoprost 0.005% (4.00pm data, 20 hours post dose)' did not take baseline values into account. The difference in IOPs at 4pm between the 2 groups was 0.8mmHg, but there was a difference of 0.4mmHg between the groups at baseline (4pm). If this had been taken into account, reflecting the

**actual degree of 'control' exerted by the products at this time-point, the difference would have been statistically insignificant and clinically irrelevant. Pharmacia noted that the FDA concluded '[travoprost] 0.004% and Xalatan 0.005% demonstrate similar ability to lower IOP over visit days and time'.**

**The Panel noted its comments above. The pooled data to which Alcon referred had not taken account of changes from baseline. The pooled data as reported by Netland *et al* showed that at 4pm there was a 0.8mmHg difference in measured IOP in favour of travoprost. When adjustments were made for baseline this figure was reduced to a 0.4mmHg advantage. Further the quotation from Netland *et al* referred to by Alcon stated in full that 'In addition pooled results indicate that the intraocular pressure-lowering efficacy of travoprost was enhanced over the day from 8am to 4pm and was significantly greater than latanoprost at 4pm'. The Panel also noted the FDA data referred to by Pharmacia. The Panel considered that the claim was misleading and ruled a breach of the Code.**

**Upon appeal by Alcon the Appeal Board noted that the results from Netland *et al* which had demonstrated statistically significant lower mean IOP for Travatan compared to latanoprost were at the two week time point. The 4pm measurements of differences between the products at months 3, 6 and 12 were not statistically significant. The Appeal Board considered that although the pooled data across the 4pm visits over the 12 month study was shown to be statistically significant, this was due to the effect of the two week data. The Appeal Board noted that glaucoma was a chronic condition and considered that two week data would be of little clinical relevance. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.**

Pharmacia Limited complained about a leavepiece (ref TRA:DC:1102(NCB)) for Travatan (travoprost 0.004%) eye drops issued by Alcon Laboratories (UK) Limited. The leavepiece was aimed at secondary care doctors. Travatan was indicated for decreasing elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma who were intolerant or insufficiently responsive to another IOP lowering medication, as monotherapy or as adjunctive therapy.

Pharmacia marketed Xalatan (latanoprost) eye drops which were indicated for reduction of elevated IOP in patients with open-angle glaucoma and ocular hypertension.

The complaint related to claims based on a paper by Netland *et al* (2001) which compared the efficacy and safety of travoprost (0.0015% and 0.004%), latanoprost (0.005%) and timolol (0.5%) in patients with open-angle glaucoma or ocular hypertension over a period of 12 months. The results were published in the American Journal of Ophthalmology (AJO).

### 1 Claim 'Equal or superior to latanoprost 0.005%* in lowering IOP at all treatment visits'

The explanation for the asterisk was given as a footnote 'For indication please refer to Abbreviated Prescribing Information on reverse'.

### COMPLAINT

Pharmacia accepted that the claim was used in Netland *et al* but alleged it was misleading to use it in a promotional piece. The Netland data demonstrated equivalence of efficacy, not superiority. Netland had mistakenly claimed that the difference in the absolute pressures seen within the two treatment groups represented the difference in IOP-lowering effect. This was incorrect because there had been no adjustment for baseline differences. It represented only the difference in final IOPs.

To include any reference to superiority was not a balanced representation of an up-to-date evaluation of all the evidence from this study. There had been much discussion about the study since it was published and Pharmacia stated that Netland had over-interpreted the data in favour of Travatan. The arguments in favour of this had been succinctly put by Camras in the letters column of the AJO in May 2002. Tables 2, 3 and 4 in the Netland paper showed that numerous sub-group analyses had been conducted, increasing the probability of obtaining a significant value purely by chance (Type 1 error). In fact, part of the argument for the 'or superior' claim was withdrawn following Camras' letter, with Netland conceding that 'a change from baseline analysis shows no statistically significant differences in the black subjects after travoprost treatment compared with latanoprost treatment'.

The US Food and Drugs Administration (FDA) in its comprehensive evaluation of the data from this trial concluded that: 'The IOP lowering ability of [travoprost] 0.004% and Xalatan 0.005% is similar. The change in mean IOP from baseline ranges from –6.6 to –8.1mmHg [travoprost] 0.004% dosed [once daily in the evening] and from –6.2 to –8.1mmHg Xalatan 0.005% dosed [once daily in the evening]'.

Pharmacia stated that the graph plotting the primary efficacy variable data in the FDA's review was difficult to see, but Pharmacia had plotted it with the change in mean IOP from baseline per visit and time for the Xalatan and Travatan data. Pharmacia pointed out that there were no statistics to this graph. As noted above, the p values appearing in Netland *et al* referred only to the difference in final mean IOPs, not change in IOPs. Glaucoma was a chronic condition and this data showed equal efficacy. To imply any superiority was alleged to be misleading in breach of Clause 7.2.

### RESPONSE

Alcon refuted Pharmacia's view that Netland *et al* had been widely contested by the clinical and scientific community. To Alcon's knowledge the only conflicting opinion raised to date had been Camras' letter. Netland himself responded to the letter and he concluded that 'The main conclusions from our study are unchanged'.

Alcon stated that the conclusions of Netland were: 'Travoprost (0.015% and 0.004%) a highly selective,

potent prostaglandin F (FP) receptor agonist, is equal or superior to latanoprost and superior to timolol in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension'; '…travoprost 0.004% is significantly better than either latanoprost or timolol in lowering intraocular pressure in black patients' and 'Travoprost is safe and generally well tolerated in the studied patient population'.

The one-year pivotal study which served as the basis for Netland *et al* was designed as a study of non-inferiority relative to the comparisons to both timolol and latanoprost. This was not an equivalence trial. Non-inferiority design allowed to test for superiority when conditions, which were respected in the published study, were met.

The primary efficacy endpoint set out in this study was mean IOP as specified in the statistical analyses in the clinical protocol. The primary efficacy results demonstrated that mean IOP for Travatan was lower than for latanoprost 0.005% at 13 of 18 visits over the 12-month study period. The difference was statistically significant at two of these visits. There were no statistically significant differences in favour of latanoprost 0.005%. Netland therefore accurately presented the primary conclusions as showing travoprost (Travatan) to be '… equal or superior to latanoprost 0.005% in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension'.

Further, the claim used in the leavepiece was based on Netland *et al*. Alcon was not aware of any peer-reviewed journal articles or formal complaints about this study, other than the cited letter by Camras. In his reply, Netland stated: 'We heartily agree with Dr. Camras that the readers must carefully evaluate the results of this and other drug studies. This is why such a high level of detail was presented in our article. The main conclusions from our study are unchanged'. Furthermore, Alcon was not aware of any articles in any peer-reviewed journals that contradicted Netland *et al*.

Pharmacia's point regarding Netland's apparent concession on this point misrepresented the true response provided. Alcon referred to the rest of the paragraph published in the AJO in which Netland concluded that regarding black patients, 'Nonetheless, a clear trend exists, with travoprost showing a greater change from baseline intraocular pressure at most time points compared to latanoprost'. Pharmacia's comment therefore missed the point as the claim being quoted related to the pre-planned primary efficacy findings of a pivotal clinical study and not a 'sub-group analyses' as detailed by Pharmacia. At no point had Alcon made any claims relating to black patients.

Alcon was unsure of the relevance of the modified graph of the FDA data supplied by Pharmacia, as it had made no reference to this data in the leavepiece, instead it had referenced Netland *et al*. Alcon noted Pharmacia's comments from the FDA, but believed that in a European context the FDA comments became irrelevant. It was also common knowledge that FDA reviewers would only in extreme circumstances make comment on comparable superiority, instead they usually stated equivalence.

Alcon submitted that the claim was a fair and accurate statement of the primary efficacy findings of Netland *et al*.

## PANEL RULING

The Panel noted that Netland *et al* evaluated the safety and IOP lowering efficacy of travoprost (0.004%) (n=200) compared with latanoprost (n=196) and timolol (n=200) in patients with open-angle glaucoma or ocular hypertension. Netland at al concluded that travoprost was equal or superior to latanoprost. IOP was measured at baseline, week 2 and at months 1.5, 3, 4.5, 6, 9 and 12. The baseline figures showed that IOP in the latanoprost group was slightly higher at all time points (8am, 10am and 4pm) than in the travoprost 0.004% group. Examinations were made at 8am, 10am and 4pm for some visits and 8am and 10am at months 1.5, 4.5 and 9. One of the stated primary objectives was to show that travoprost was greater than or equal to latanoprost with regard to IOP lowering efficacy.

The Panel noted that there were statistically significant differences in terms of IOP in favour of travoprost 0.004% compared to latanoprost. These being the pooled data at 4pm and the data at week 2 (10am and 4pm). The data was based on a comparison of the mean actual IOP for each treatment group, not the change from baseline. Netland *et al* stated that there were no significant differences between groups for the mean baseline values for IOP pooled across visit times. The Panel noted that the FDA had concluded that the products had similar IOP lowering ability. This was not irrelevant to the UK as submitted by Alcon.

The Panel considered that the claim at issue was a broad strong claim. The Panel noted that even though the claim was a quotation it nonetheless had to comply with the Code. The Panel was concerned that the claim did not reflect Netland *et al* which had shown only limited statistically significant advantages for Travatan with respect to mean IOP compared with latanoprost. At the majority of visits there had been no statistically significant difference between the two. There was no statistical analysis in relation to change from baseline. A statistically significant difference in mean IOP at two weeks plus a difference at 4pm for the pooled data with no difference at the other time points measured, was in the Panel's view insufficient to justify a claim for superiority for treating a long-term condition such as glaucoma. The claim was misleading and a breach of Clause 7.2 of the Code was ruled.

## APPEAL BY ALCON

Alcon stated that glaucoma, a chronic condition that affected between 150,000-300,000 people in Britain, was a leading cause of registered blindness. The disease was often complicated and difficult to treat. Although there were different types of glaucoma the most common, primary open-angle glaucoma, was primarily characterised by elevated IOP and unstable visual field. Normal healthy eyes had an IOP in the range 9-21mmHg, with a mean IOP of 15mmHg.

Alcon summarised the key papers relating to the importance of lowering IOP.

Leske *et al* (2003) provided conclusive evidence to confirm that reduction in IOP lowered the risk of disease progression. Each higher (or lower) millimetre of mercury of IOP on follow-up was associated with an approximate 10% increased (or decreased) risk of progression.

Van Veldhuisen *et al* (2000) had shown that: lower absolute levels of IOP were more likely to be associated with stabilisation glaucomatous visual field deterioration; no association between extent of IOP drop and field loss; patients with IOP below 18mmHg at all measured times were least likely to show progression; and the protective role of low IOP in visual field deterioration.

Drance *et al* (1998) had shown unequivocally that when IOP was lowered by 30%, the disease showed a slower rate of visual field progression.

Kass *et al* (2002) aimed to reduce IOP by 20% or more or to reach an IOP of 24mmHg or less. Topical ocular hypotensive medication was effective in delaying or preventing the onset of primary open-angle glaucoma individuals with elevated IOP.

The following papers demonstrated the importance of controlling and minimising IOP fluctuations:

Asrani *et al* (2000) showed that large fluctuations in IOP during the day (diurnal) or over consecutive days were associated with a strong and significant risk of disease progression. It was acknowledged that the study findings had implications for the clinical management of patients with glaucoma. It was suggested that certain medicines might be more effective than others at dampening fluctuations.

DuBiner *et al* (2001) showed that both Travatan and Xalatan significantly lowered and maintained IOP throughout the evaluation period; Travatan was more effective at reducing IOP from 16 to 24 hours post dose and Travatan had superior ocular hypotensive efficacy at 24 hours post dose.

In relation to the claim at issue 'Equal or superior to latanoprost 0.005% in lowering IOP at all treatment visits' Alcon noted that the one-year pivotal study which had served as the basis for the Netland article was designed as a study of non-inferiority relative to the comparisons to both timolol and latanoprost. This was not an equivalence trial. The primary efficacy endpoint set out in this study was mean IOP as specified in the statistical analyses in the clinical protocol.

Alcon noted that switching the objective of a trial from non-inferiority to superiority was addressed in ICH guidance. This guidance recognised that the objective of a non-inferiority trial was to demonstrate that the '…new treatment is no less effective than an existing treatment – it may be more effective or it may have a similar effect'. Non-inferiority design allowed to test for superiority when conditions, which were respected in the published study, were met.

Alcon noted that the results of this planned analysis were documented in the US New Drug Application, the EU Centralised Marketing Authorisation Application, and over 70 additional applications for approval of Travatan around the world. To date Alcon held 61 product licences for Travatan, with many more licences pending; no applications for licences for Travatan had been rejected.

With regard to Netland *et al* Alcon noted that the primary efficacy results demonstrated that mean IOP for Travatan was lower than for latanoprost 0.005% at 13 of 18 visits over the 12-month study period. The difference was statistically significant at three of these visits (Travatan European Public Assessment Report (EPAR)). There were no statistically significant differences in favour of latanoprost 0.005%.

Alcon noted that in Netland's supporting letter he restated his belief that Pharmacia was incorrect in its implication that his study showed equivalence between latanoprost and travoprost, and emphasised that the conclusion of the study still stood that 'travoprost 0.004% is equal or superior to latanoprost 0.005%, not equivalent'.

Alcon was still unsure of the relevance of the modified graph of the FDA data supplied by Pharmacia, as it had made no reference to this data on its promotional material, instead it had consistently and accurately referenced the Netland data.

Alcon noted Pharmacia's comments from the FDA, but submitted that in a European context and in relation to this appeal, these FDA comments became irrelevant. Alcon was unaware of any new legislation that allowed mutual recognition of an FDA approval by the EU authorities, and therefore until introduced, a centralised product granted a European-wide approval for a European population after comprehensive review by the Committee for Proprietary Medicinal Products (CPMP) should provide the basis of any appeal discussion. Regulatory affairs professionals familiar with FDA review would support the fact that that only in extreme circumstances would an FDA assessor make comment on superiority. The more general approach taken was to state equivalence.

Alcon referred to comments made in its supporting letter from a glaucoma specialist which although acknowledging that the FDA might have used the extent by which the IOP was lowered as a valid means of comparing two medicines stated that 'in clinical practice this is not the case'. The letter commented on the results from Asrani *et al* that showed that eyes with the least diurnal IOP fluctuations showed the least visual field loss progression in the long-term, and qualified this by stating that in a patient with advanced field loss the clinician might choose the medicine which minimised the diurnal IOP fluctuation. Alcon submitted that support was given in this letter to Netland's method of comparing mean actual IOPs rather than looking at the extent of IOP lowering.

Alcon submitted that it was important to note that if FDA data was considered in a European context, then it should also be noted that as well as being supportable by clinical evidence published in a well respected, peer reviewed journal, the AJO, its claim of being 'Equal or superior to latanoprost 0.005% in lowering IOP at all treatment visits' had also been

pre-reviewed by the FDA and currently continued to be used as a valid claim in the US.

Alcon concluded that based on the pre-planned primary efficacy findings in Netland (which were consistent with the ICH guidance on non-inferiority trial results), and the additional supporting information presented above, the claim 'Equal or superior to latanoprost 0.005% in lowering IOP at all treatment visits' was fair and accurate, based upon a balanced representation of an up-to-date evaluation of all the evidence from this study, and wholly supported by the study author. As Alcon was not claiming anything further than that which was a valid and scientifically justifiable conclusion from a clinical trial, and the claim contained a clear reference to Netland's publication in the AJO, it submitted that this claim did not mislead either directly or by implication.

Alcon submitted that Pharmacia's protest that the Netland data had been 'widely contested' was completely unfounded as to date the only publications contradicting the data presented by Netland *et al* had been from a leading member of the primary research team, Dr Camras, responsible for the development of Pharmacia's latanoprost and a paid consultant to Pharmacia. Alcon referred to Dr Netland's response where he represented himself in this matter.

In addition, Alcon had provided two supporting letters from consultant ophthalmologists. Alcon's Medical Advisor had provided a letter outlining his reasoning and justifications for support of the claims on this promotional piece. Alcon had also included a letter from a glaucoma specialist, who had no financial interest in Alcon nor acted in an advisory role with Alcon and Dr Netland had also provided his comments.

## COMMENTS FROM PHARMACIA

Pharmacia alleged that all three claims that it had challenged served to persuade the reader that Travatan was superior to Xalatan. Travoprost's ability to reduce IOP in patients with open angle glaucoma or ocular hypertension did not differ from Xalatan's. Each claim was misleading in the absence of a full presentation of the study results.

Pharmacia noted that at the time the leavepiece was published Netland *et al*, sponsored by Alcon, was the only head-to-head study comparing Travatan and latanoprost. Pharmacia stated that its support for the Panel's rulings focused on Netland *et al* but noted that a Pharmacia sponsored, randomized-controlled head-to-head study had since been published, Parrish *et al* (2003). This again had shown no significant difference in IOP control as assessed by all the primary and secondary efficacy measures (change in mean IOP from baseline to week 12 at 8am, 12 noon, 4pm and 8pm, or the mean of these 4 time-points). Unfortunately, despite having been made aware of this by letters in March and April 2003, Alcon had still refused to withdraw its leavepiece. Pharmacia could only conclude that this appeal had been initiated to delay the removal of material that Alcon was fully aware did not represent the available evidence and damaged the profile of Xalatan relative to Travatan. Pharmacia considered that this type of action had no place in the industry and was damaging to its trademark. Pharmacia therefore asked the Appeal Board to include in its censure of Alcon an undertaking to circulate a corrective statement to all who might have been influenced by the material.

Pharmacia agreed that there was increasing evidence to support the importance of IOP fluctuations in the rate of disease progression. Pharmacia noted a graph adapted from Fig 2 in the Netland paper, used in a recent Travatan leavepiece (Ref: TRA:DA:1101(NCB)). This showed the mean pressures seen with Xalatan and Travatan at 3 time-points during a 24 hour period. Pharmacia noted that less diurnal fluctuation was apparent with Xalatan. Alcon's justification for presenting trough (4pm) IOP data was that it was a key indicator of 24 hour efficacy. However, this graph showed that trough pressures at 4pm were irrelevant to 24 hour fluctuations when viewed in isolation. Any additional reduction at 4pm served only to increase the difference between the mean pressure seen at 8am and 4pm.

Pharmacia noted that Alcon had questioned why it had presented the 'modified graph of the FDA data'. Pharmacia stated that the graph was not modified, but redrawn because of the poor quality of the graph down-loaded from the FDA website. The FDA had plotted this information to present its analysis of the data, taking baseline differences into account, and supporting its conclusion that: 'The IOP lowering ability of [travoprost] 0.004% and Xalatan 0.005% is similar'. Pharmacia stated that its use of the FDA information was as a legitimate independent review of the available data. To state that an independent review by such a reputable authority was irrelevant was clearly untrue.

Pharmacia noted that Alcon had gone to some length to explain that the data from this trial were robust and had been accepted by regulatory authorities. Pharmacia had never suggested otherwise. The trial was well conducted and the results valid. Pharmacia took issue with some of the conclusions drawn, based on the data, and the use of this by Alcon was misleading clinicians with regard to the two products' relative efficacy. The FDA's views were clear, as documented above.

Pharmacia noted that the claim at issue, whilst taken directly from Netland *et al*, was incorrect and misleading. The claim referred specifically to 'lowering IOP', whereas the Netland analysis and subsequent statement referred to absolute IOP values following treatment. This did not reflect the change in pressure from baseline.

Pharmacia noted that the actual IOP reduction was referred to in Netland *et al*: 'Mean IOP reductions ranged from –6.0 to –7.7mmHg for the travoprost 0.0015% and from –6.6 to –8.1mmHg for the travoprost 0.004% concentration. Mean IOP reductions ranged from –6.2 to 8.1mmHg for latanoprost and from –4.7 to –7.1mmHg for timolol'. Interestingly, there was no statistical analysis of these data.

Pharmacia stated that it was also important to note that this difference in absolute IOP was only

significant at 2 out of 18 visits for travoprost 0.004%, not 3 as stated in Alcon's appeal. This might be a simple misinterpretation of the data table taking an additional value from the travoprost 0.0015% arm or from the pooled analysis. In the end, it was important to understand that the only differences in absolute values were at 2 time-points at week 2. In a chronic conditions, such as glaucoma, this was very misleading, especially as there was no attempt to qualify the claim.

Pharmacia alleged that given that so many p values were calculated in this study, it was perhaps not surprising that 2 less than 0.05 had occurred. This was why a clearly defined single primary end-point was considered so important in hypothesis testing. Data from multiple analyses should be interpreted with caution, as they would be by the regulatory authorities, had they been asked to assess comparative efficacy. Similar caution should be exercised in using them to influence clinicians. The differences reported at 2 weeks did not reflect IOP lowering, and even as absolute values were likely to be spurious, occurring purely by chance, given the number of analyses performed.

Netland *et al* did not take baseline differences into account. Despite this, it remained clear that these products had an equivalent effect. To further clarify this, Pharmacia had plotted the data on a linear x axis creating a graph for each of the time points. The similarity of the data was remarkable, particularly when one considered that this was a chronic condition for which greater emphasis must be placed on long-term outcome. It was worth noting that there were fewer visits at which the 4pm measurement was taken, and that the baseline difference at this time-point was also greater.

Pharmacia also noted that Netland reaffirmed his opinion that travoprost was 'equal or superior to latanoprost 0.005%, not equivalent'. Pharmacia noted the statement from Netland *et al*: 'The mean intraocular pressure was significantly lower for travoprost compared with latanoprost at the week 2 visit and was statistically equivalent at the other visits in the study'. Pharmacia noted that the data from this trial clearly demonstrated long-term equivalence, or non-inferiority in efficacy, but did not demonstrate superiority.

Pharmacia stated that whilst Netland had given his support for this claim, this remained his personal opinion. What was important was whether it was corroborated by the data and whether it was appropriately presented in the context of the piece. There were many instances of inaccurate statistical analyses or clinicians' erroneous opinions being published in peer-reviewed journals, and it was the company signatory's responsibility to make an informed critical assessment. Pharmacia was surprised that Alcon's medical adviser did not seem aware of this. It was covered under the supplementary information to Clause 7.2, sections entitled 'emerging clinical or scientific opinion' and 'statistical information' and Clause 11.2 that 'Care should be taken in quoting from any study or the like to ensure that it does not mislead as to its overall significance'.

The key issue was how a clinician, seeing the entirety of these data, would view the comparative efficacy of these products, versus the impression gained from the claim in question. Clinicians reading promotional material were assessing whether the product could offer their patients additional benefit. The clear implication from the claim was that Travatan could, in terms of efficacy, compared with Xalatan. In reality, the data showed equal efficacy in the treatment of this chronic condition. The leavepiece did not place the data in context – a single study in which the only differences in absolute IOP were seen at an irrelevant time point, week 2. Further, it had actually damaged Xalatan's reputation by suggesting that at some visits, which clinicians would understandably assume had taken place during the chronic management of this chronic condition, Travatan was superior.

### APPEAL BOARD RULING

The Appeal Board considered that the claim at issue was a strong broad claim, which implied superiority. The Appeal Board was concerned that the claim was not a fair reflection of Netland *et al* which had shown only limited statistically significant advantages for Travatan with respect to mean IOP compared with latanoprost. At the majority of visits there had been no statistically significant difference between the two products. A statistically significant difference in mean IOP at two of the three time points measured at two weeks plus a statistically significant difference at 4pm for the pooled data with no statistically significant differences at the other time points measured was, in the Appeal Board's view, insufficient to justify a claim for superiority for treating a long-term condition such as glaucoma. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

## 2 Claim 'Controls IOP in more patients than latanoprost 0.005% (IOP reductions ≥ 30% or mean IOP ≤ 17mmHg)'

### COMPLAINT

Pharmacia stated that this was another retrospective sub-group analysis as acknowledged by Alcon. It was very easy to define a responder to fit the data after the event. Whilst this type of analysis might be appropriate for hypothesis generation, it was extremely misleading if used as fact until proven by a trial that had been conducted to prospectively test the hypothesis. Making claims on this basis had coined the expression 'torturing the data until it eventually confesses'.

Clinicians had been left with the clear message that travoprost was more efficacious than latanoprost. This was alleged to be misleading in breach of Clause 7.2.

### RESPONSE

Alcon stated that it was recognised by the clinical and scientific community that responder analyses were widely used to prove product efficacy. The results of this analysis were included in Netland *et al*. Neither

in the leavepiece, nor in Netland *et al*, had Alcon suggested that this responder analysis was planned prospectively.

Advancing glaucoma opinion at the time suggested that this was acceptable criteria to use and this specific analysis was submitted to both the Committee on Proprietary Medicinal Products (CPMP) and the FDA in the filing for marketing approval for Travatan. It was reviewed and accepted by both regulatory bodies and results of this analysis were included in the European Public Assessment Report (EPAR) for Travatan.

It was considered that the responder analysis was one of the most clinically relevant results of the study. Alcon did not consider the information to be selective. Therefore, the company believed that the claim was fair and accurate.

## PANEL RULING

Netland *et al* defined treatment responders as those who showed a 30% or greater IOP reduction from diurnal baseline or final IOP of 17mmHg or less. Travoprost 0.004% had an overall treatment response of 54.7% with the figure for latanoprost being 49.6% ($p \leq 0.043$). The claim was based on a retrospective sub-group analysis.

The Panel noted that the study had not included a responder analysis. The data had been obtained from a retrospective sub-group analysis. This was not necessarily unacceptable. The Panel noted its comments about the study in point 1 above. The Panel considered that in the context in which it appeared the claim gave the impression that Travatan was more efficacious than latanoprost.

The Panel considered that the claim was misleading and a breach of Clause 7.2 of the Code was ruled.

## APPEAL BY ALCON

Alcon submitted that it was well recognised by the clinical and scientific community that responder analyses were widely used to prove product efficacy, and that more patients responding to treatment might result in better prognosis for patients with this difficult to treat disease. The results of this analysis were included in Netland *et al* which was published in a well-respected, peer-reviewed journal. It was considered that the responder analysis was one of the most clinically relevant results of the study.

Alcon noted that in its response to the complaint, it had stated that neither in the leavepiece, nor in Netland *et al*, had Alcon suggested that this responder analysis was planned prospectively. This was a true and factual statement. Alcon submitted that the Panel's decision had been influenced by Pharmacia's complaint in which Alcon's original statement had been manipulated into 'This was another retrospective sub-group analysis as acknowledged by Alcon …'. Alcon submitted that Pharmacia might have misled the Panel with a misrepresentation of Alcon's comment, which might have resulted in an unjust ruling based on the inconclusive evidence provided.

Alcon referred to Dr Netland's supporting letter, and submitted that this was a prospectively planned analysis using scientifically and clinically legitimate criterion for defining response and was not another 'retrospectively planned sub-group analysis' as misquoted and misrepresented by Pharmacia. Alcon submitted that this argument should not be based upon whether this was a retrospective analysis, it should concentrate on whether Alcon had breached the Code.

Alcon noted that the selection of this criterion for defining response was based on the timolol-lowering results obtained in the three pivotal clinical studies for Travatan. A value of 17mmHg was chosen because this was better than the lowest mean IOP (18.3mmHg) observed while on timolol in these studies and the 30% value was chosen because this was better than the greatest mean IOP reduction (29%) observed while on timolol in these studies.

Alcon noted that these figures were in line with guidelines published by the European Glaucoma Society (EGS) for the treatment of glaucoma which recommended at least a 30% reduction from initial pressure at which damage occurred, and the conclusion from Van Veldhuisen *et al*. The criteria were also considered by the CPMP to constitute a clinically relevant response.

Alcon noted that responder analysis results were documented in the US New Drug Application, the EU Centralised Marketing Authorisation Application, the over 70 additional applications for approval of Travatan around the world. Both the FDA and CPMP had reviewed and accepted the results. The CPMP comments on responders were publicly available in the EPAR for Travatan. Again this claim had been pre-reviewed by the FDA and continued to be used in the US.

Alcon submitted that the studies summarised in its appeal at point 1 above, had provided testament to the importance of lowering and maintaining IOP control, and had emphasised the link between IOP control and progression of disease.

Alcon submitted that further support for its claim could be provided by a review and meta-analysis of four Phase III studies following 2406 patients treated with Travatan 0.004%, timolol 0.5% or latanoprost 0.005%, or as adjunctive therapy to timolol 0.5% which showed that 'significantly larger numbers of patients treated with Travatan 0.004% reached low target IOPs compared to all other treatment groups' (Teus Guezala *et al* 2001).

Alcon concluded that based upon the supporting evidence presented above, the claim at issue was fair, accurate, did not mislead and was important in the treatment of glaucoma.

## COMMENTS FROM PHARMACIA

Pharmacia stated that Alcon's suggestion that Pharmacia might have misled the Panel, was disingenuous. Pharmacia stated that its initial letter to Alcon dated 23 December stated that this appeared to be a retrospective analysis and asked to see the original statistical analysis plan to confirm otherwise.

Alcon's reply on 16 January suggested that it knew that it was a retrospective analysis and made no attempt to provide evidence to the contrary, as requested. Further, Alcon's medical adviser in the letter submitted with its appeal confirmed that it was a retrospective analysis.

Pharmacia noted that the first suggestion that it might after all, have been prospectively planned, came in Dr Netland's letter submitted with the appeal. Given the background, and that some of Dr Netland's own comments were clearly inconsistent with his own paper (referred to in point 1), Pharmacia still wished to see the statistical analysis plan in order to substantiate the robustness of this analysis.

Pharmacia alleged that if this was a retrospective sub-group analysis it was inappropriate to use it as a statement of fact. Such an analysis was acceptable for hypothesis generating but not for hypothesis testing. Further, given the data from Parrish *et al*, this did not represent the balance of evidence or even reflect emerging scientific opinion. Pharmacia considered it was a misleading representation of the products' relative efficacy.

### APPEAL BOARD RULING

The Appeal Board noted the submission of the Alcon representatives that the responder sub-group analysis was prospectively planned and that the letter from Alcon's medical adviser and authorized signatory was incorrect on this point. The Appeal Board was concerned that Alcon had not provided a copy of the study protocol for the Netland study to confirm that the sub-group analysis had been prospectively planned. The Appeal Board noted the letter from Dr Netland which confirmed that the sub-group analysis was prospective.

The Appeal Board noted that the study had defined treatment responders as those who had shown a 30% or greater IOP reduction from diurnal baseline or final IOP of 17mmHg or less. The Appeal Board noted that travoprost 0.004% had an overall treatment response of 54.7% compared to 49.6% ($p \leq 0.043$) for latanoprost. The Appeal Board noted that this was the only data available at the time of the leavepiece. The Appeal Board considered that the claim was not misleading, it was a fair reflection of the Netland study data and on this narrow point ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

## 3 Claim 'Better IOP control at trough than latanoprost 0.005% (4.00pm data, 20 hours post dose)'

### COMPLAINT

Pharmacia stated that Netland *et al* had made this claim without taking baseline values into account. The difference in IOPs at 4pm between the 2 groups was 0.8mmHg, but there was a difference of 0.4mmHg between the groups at baseline (4pm). If this had been taken into account, reflecting the actual degree of 'control' exerted by the products at this time-point, the difference would have been statistically insignificant and clinically irrelevant.

The FDA concluded that: '[travoprost] 0.004% and Xalatan 0.005% demonstrate similar ability to lower IOP over visit days and time'.

Again, owing to the poor quality of the image taken from the FDA website, Pharmacia had plotted this graph showing just the data for Xalatan and Travatan. Pharmacia alleged a breach of Clause 7.2.

### RESPONSE

Alcon submitted that the basis for the claim was derived from the pre-planned primary efficacy analysis results that were described in its response to point 1.

The result, when pooled across the 4pm visits in this 12-month study, demonstrated statistically significantly lower mean IOP for Travatan solution than for latanoprost 0.005%. Netland *et al* stated: '… the intraocular pressure-lowering efficacy of travoprost was enhanced over the day from 8am to 4pm and was significantly greater than latanoprost at 4pm'.

Based on this finding, Alcon submitted the claim was fair and accurate.

Alcon understood that claims made in line with the summary of product characteristics and the marketing authorization, that could be substantiated by a well respected, peer-reviewed journal representing current data/opinion, and that did not contravene any sections of the Code, might be used with care in promotional material. Alcon submitted that the complaint was based on Pharmacia's understandable dislike of Netland *et al* but that this should not preclude the use of the conclusions of the study. Alcon believed that the claims accurately represented the currently available data as to date there had been no publications contradicting Netland *et al* other than from Dr Camras, a leading member of the primary research team responsible for the development of Pharmacia's latanoprost and a consultant to the company.

### PANEL RULING

The Panel noted its comments in point 1 above. The pooled data to which Alcon referred had not taken account of changes from baseline. The pooled data as reported by Netland *et al* showed that at 4pm there was a 0.8mmHg difference in measured IOP in favour of travoprost. When adjustments were made for baseline this figure was reduced to a 0.4mmHg advantage. Further the quotation from Netland *et al* referred to by Alcon stated in full that 'In addition pooled results **indicate** [emphasis added] that the intraocular pressure-lowering efficacy of travoprost was enhanced over the day from 8am to 4pm and was significantly greater than latanoprost at 4pm'. The Panel also noted the FDA data referred to by Pharmacia.

The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

### APPEAL BY ALCON

Alcon submitted that the basis for this claim was derived from the pre-planned primary efficacy analysis results that were described in point 1 above.

The result, when pooled across the 4pm visits in this 12-month study, demonstrated statistically significantly lower mean IOP for Travatan than for latanoprost 0.005%. Netland *et al* stated: '… the intraocular pressure-lowering efficacy of travoprost was enhanced over the day from 8 AM to 4 PM and was significantly greater than latanoprost at 4 PM'.

Alcon stated that the importance of keeping IOP low at all times of day, and minimising diurnal fluctuations could be substantiated by the studies summarised in its appeal at point 1 above. Diurnal fluctuation in IOP had been linked to loss of visual field. Therefore, the clinical benefit of keeping IOPs low towards the end of the day could be seen. At the 20-hour post dose point ('trough') a patient was still 4 hours away from taking their next dose, it was therefore clinically relevant for effective treatments to maintain minimal variation in IOP fluctuation at this time point. Data presented at this timepoint showed travoprost to have better IOP control at 'trough' than latanoprost.

Alcon referred to the supporting letter from a glaucoma specialist who commented on Asrani *et al* which showed that eyes with the least diurnal IOP fluctuations showed the least visual field loss progression in the long-term, and the clinical relevance of this data in treating a patient with advanced field loss (ie the clinician might choose the medicine which minimised the diurnal IOP fluctuation).

This claim had been pre-reviewed by the FDA and continued to be used in the US.

Alcon concluded that the claim was fair, accurate, clinically relevant and did not mislead.

## COMMENTS FROM PHARMACIA

Pharmacia noted that in its introductory remarks in response to Alcon's appeal at point 1 above it had commented on the significance of the 4pm time point to diurnal fluctuation. Alcon had over-interpreted the significance of this one time point, stating in its appeal that: 'Diurnal fluctuation in IOP had been linked to loss of visual field. Therefore, the clinical benefit of keeping intraocular pressures low towards the end of the day could be seen'. The 4pm time-point was no more important than the others, and must be viewed alongside the others, as explained earlier, if being used to inform clinicians of a product's impact on '24-hour fluctuations'. It was the experience of Pharmacia's salesforce, reinforced by Alcon's comments in its letter, that Alcon's intention was to suggest a potential advantage in reducing the risk of visual deterioration.

Pharmacia noted that there were 3 fewer data points for the 4pm measure. This allowed the atypical readings noted at 4pm in week 2 to have an exaggerated impact on the mean value. Of course, the results noted in week 2 had no clinical relevance to the management of glaucoma, and with so many data cuts, occasional spurious results were to be expected (type 1 errors). Of far more relevance was the fact that the difference was just 0.6mmHg at month 12, which amounted to a difference of just 0.2mmHg after the baseline difference of 0.4mmHg had been considered.

Pharmacia alleged that there was no evidence that the actual degree of control exerted by the products differed at this time-point, or any other. The FDA's conclusion that these two medicines 'demonstrate similar ability to lower IOP over visit days and time' was an impartial balanced assessment of these data.

In summary, Pharmacia stated that the leavepiece had been created with the sole aim of claiming superior efficacy for Travatan over Xalatan. It was based on one trial, the data from which did not support this. Each claim was misleading. Further, more recent data from Parrish *et al* confirmed the equivalence of these products in reducing IOP.

## APPEAL BOARD RULING

The Appeal Board noted from Netland *et al* that the results which had demonstrated statistically significant lower mean IOP for Travatan compared to latanoprost were at the two week time point. The 4pm measurements of differences between the products at months 3, 6 and 12 were not statistically significant. The Appeal Board considered that although the pooled data across the 4pm visits over the 12 month study was shown to be statistically significant, this was due to the effect of the two week data. The Appeal Board noted that glaucoma was a chronic condition and considered that two week data would be of little clinical relevance. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

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| **Complaint received** | **28 January 2003** |
| **Case completed** | **17 June 2003** |

CASE AUTH/1416/2/03

# NOVARTIS v FUJISAWA

## Article in Scrip

Novartis complained about an article headed 'Fujisawa leads in UK transplant market' which appeared in Scrip. The article, which featured statements by Fujisawa's chief executive and head of clinical and medical affairs, discussed the relative market shares of Fujisawa's product, Prograf (tacrolimus), and Novartis' product, Neoral (ciclosporin); a graph and bar chart depicted the products' monthly sales and shares of the UK transplant market. The article also discussed the products' relative efficacy, cost-effectiveness and safety.

Prograf was licensed for use only following liver or kidney transplantation. Neoral was for use following bone marrow, kidney, liver, heart, heart/lung, lung and pancreas transplantation. Neoral could also be used for severe psoriasis, severe atopic dermatitis, severe rheumatoid arthritis and in steroid dependent or steroid resistant nephrotic syndrome. Protopic (tacrolimus) could be used in moderate to severe atopic dermatitis unresponsive or intolerant to other therapies.

Novartis was concerned that Fujisawa had supplied information to Scrip with no regard as to its suitability.

Novartis understood that a journalist from Scrip visited the Fujisawa offices to interview the chief executive and head of clinical and medical affairs of Fujisawa at their request, and the resulting article attributed a number of claims to them regarding the financial performance of the company compared with Novartis, and the 'capture rate', cost-effectiveness, efficacy and safety of Prograf compared with Neoral.

The article contained claims about Fujisawa's position as market leader. This was substantiated by the use of Neoral and Prograf sales data which had been manipulated in an attempt to reflect the proportion of these products used in transplantation.

The assertion by Fujisawa that 'two of these graphs appear to have been used in the Scrip article' suggested that the graphs were given to Scrip during the interview. These graphs were supplied to Novartis by Fujisawa in response to its complaint and were clearly prepared by the company. They had little explanation, no clear legend and no mention that only renal and liver transplantation were included.

The Scrip article stated that Fujisawa claimed Prograf was more cost-effective than Neoral. No reference was given to substantiate this. In intercompany correspondence Fujisawa claimed that the reference was 'presumably' a comment made in reference to a presentation at the British Transplantation Society's 4th Annual Congress. Claims of this kind were particularly difficult to substantiate and Craig *et al* (2002), cited by Fujisawa, was insufficient. Moreover, the references only related to kidney transplantation, whereas the claim made no such distinction.

In intercompany correspondence Fujisawa had stated that figures on 'capture rates' for Prograf in liver and renal transplants were based on information received from its representatives. At best, such figures were subjective.

Fujisawa had suggested that the conclusions of O'Grady *et al* (2002) were sufficient to prove the numbers of liver patients being prescribed Prograf. However, the conclusions of any study as to proposed future clinical practice could hardly be used as a reference for numbers of liver transplant recipients actually taking Prograf.

Fujisawa had contended that this represented a paraphrasing of the interview and was not a direct quote. This further showed that Fujisawa had been complacent in its dealings with the media. Clearly, an impression of Prograf's superiority was given to the journalist and, whilst the resulting article might not reflect the exact words of the interview, the content of that interview could not be in question.

In Fujisawa's letter of explanation it had cited a number of papers to reference the 'misquote'. Novartis stated that it could counter this with a number of references to show that Neoral efficacy was comparable with Prograf. Moreover, Novartis was particularly concerned with the statement that long-term safety was 'better' since this was emerging evidence and so had not been proven unequivocally.

Novartis noted that Fujisawa now contended that, despite taking part in the interview, it was not responsible for any of its output, it had no say in the content of the article, nor did it see it before it was printed. For Fujisawa to suggest that it had no responsibility for the outcome was naïve and unacceptable.

Novartis contended that Fujisawa's actions were so serious, and the consequences so far-reaching, as to bring the industry into disrepute in breach of Clause 2.

The Panel noted that detailed comparative clinical safety information about specific medicines had been provided to the journalist. Taking all the circumstances into account, the Panel considered that the matter was subject to the Code.

The Panel noted Fujisawa's account of the circumstances of the interview. The journalist from Scrip had been invited to visit new corporate headquarters and had initiated a conversation which resulted in the article at issue. Those interviewed by the journalist had a clear recollection of what was said. No written account was made during or subsequent to the interview and other than two graphs no written material was provided to the journalist to confirm what was said.

The Panel examined the bar chart and graph provided by Fujisawa to the journalist. The Panel considered that neither the graph nor the bar chart made it sufficiently clear that only data relating to the indications common to both Neoral and Prograf,

**ie renal and liver transplants, were included. The Panel noted Fujisawa's submission that it was made clear to the journalist that the graphs featured renal and liver transplantation data only. The Panel noted that the company had no written record of what was said to the journalist about the products. The Panel considered that the written material provided to the journalist was inadequate. It was not made sufficiently clear that heart transplant data, for which Prograf was not licensed, was not included. The labelling and description of the data were thus inadequate and misleading. The material was not presented in a balanced way. Breaches of the Code were ruled.**

**In relation to statements in the article that Prograf was more cost effective than Neoral, that every liver transplant patient in the UK and 80% of kidney patients were put on Prograf as first choice and that the efficacy of Prograf was better than Neoral, the Panel considered that it was impossible to determine precisely what was said and how the data was presented. The Panel considered that it was obliged to rule no breach of the Code. The Panel was concerned that Fujisawa had failed to provide any written materials to the journalist to confirm what was said. It might be argued that Fujisawa had failed to maintain high standards although there was no allegation in this regard.**

**With regard to the alleged breach of Clause 2, the Panel considered that on balance Fujisawa's activities were not such as to warrant a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.**

Novartis Pharmaceuticals UK Ltd complained about an article headed 'Fujisawa leads in UK transplant market' which appeared in Scrip, 20/25 December 2002. The article, which featured statements by Fujisawa's chief executive and head of clinical and medical affairs, discussed the relative market shares of Fujisawa's product, Prograf (tacrolimus), and Novartis' product, Neoral (ciclosporin); a graph and bar chart depicted the products' monthly sales and shares of the UK transplant market. The article also discussed the products' relative efficacy, cost-effectiveness and safety.

Prograf was licensed for use only following liver or kidney transplantation. Neoral was for use following bone marrow, kidney, liver, heart, heart/lung, lung and pancreas transplantation. Neoral could also be used for severe psoriasis, severe atopic dermatitis, severe rheumatoid arthritis and in steroid dependent or steroid resistant nephrotic syndrome. Protopic (tacrolimus) could be used in moderate to severe atopic dermatitis unresponsive or intolerant to other therapies.

## COMPLAINT

Novartis was concerned that Fujisawa had supplied the information to Scrip with no regard as to its suitability. In Case AUTH/1316/5/02 Fujisawa had been ruled in breach of the Code for its dealings with the media in which it did not declare sponsorship of an article. Fujisawa again refused to take any responsibility for either the content of the Scrip article or the consequences of its publication. Novartis regretted that its only course of action was to bring this matter to the Authority's attention.

Novartis understood that a journalist from Scrip visited the Fujisawa offices to interview the chief executive and head of clinical and medical affairs of Fujisawa at their request, and the resulting article attributed a number of claims to them regarding the financial performance of the company compared with Novartis, and the 'capture rate', cost-effectiveness, efficacy and safety of Prograf compared with Neoral.

Scrip was one of the main industry commentators on company performance and pipelines, which meant that great store was placed in its content both within and outside the industry.

The article contained claims about Fujisawa's position as market leader. This was substantiated by the use of Neoral and Prograf sales data which had been manipulated in an attempt to reflect the proportion of these products used in transplantation. Novartis queried whether Fujisawa had sought permission from the data supplier to use or manipulate the data, let alone draw inferences from it on the proportions of Neoral used in renal and liver transplantation, which even Novartis and third party suppliers found difficult to do.

The assertion by Fujisawa that 'two of these graphs appear to have been used in the Scrip article' suggested that the graphs were given to Scrip during the interview. These graphs were supplied to Novartis by Fujisawa in response to its complaint and were clearly prepared by the company. They had little explanation, no clear legend and no mention that only renal and liver transplantation were included. This was misleading to the reader and in breach of Clause 7.2. Since the article contained data showing a direct comparison between the sales of Prograf and Neoral, it believed that this contravened the data supplier's own principles regarding publication of its data.

Fujisawa had admitted that it had manipulated the data and that it was discussed in the interview with Scrip. Either it was not aware of its contractual obligations to the data supplier or had chosen to ignore those obligations. Whichever was the case, the article sent a strong message to industry, investors and the public alike regarding the financial viability of the company and its future prospects.

It was stated in the Scrip article that Fujisawa claimed Prograf was more cost-effective than Neoral. No reference was given to substantiate this. In intercompany correspondence Fujisawa claimed that the reference was 'presumably' a comment made in reference to a presentation at the British Transplantation Society's 4th Annual Congress. Claims of this kind were particularly difficult to substantiate and along with Craig *et al* (2002), cited by Fujisawa, was insufficient to avoid being in breach of Clause 7.2. Moreover, the references only related to kidney transplantation, whereas the claim made no such distinction.

In intercompany correspondence Fujisawa had stated that figures on 'capture rates' for Prograf in liver and

renal transplants were based on information received from its representatives. Novartis accepted that companies collected information in this way but considered that it was only suitable for internal use. The figures from the representatives had been gleaned from discussions with clinicians which must leave it open to interpretation by those representatives when feeding back to their manager. By its own admission, Fujisawa did not have access to individual patient data. At best, such figures were subjective; to base a claim on such data showed lack of care and little thought for the ramifications.

Fujisawa had suggested that the conclusions of the TMC (tacrolimus versus microemulsified ciclosporin in liver transplantation) study, O'Grady *et al* (2002), were sufficient to prove the numbers of liver patients being prescribed Prograf. However, the conclusions of any study as to proposed future clinical practice could hardly be used as a reference for numbers of liver transplant recipients actually taking Prograf. Moreover, this particular study was of little use in calculating the numbers of renal transplant patients on Prograf.

Fujisawa had contended that this represented a paraphrasing of the interview and was not a direct quote. This further showed that Fujisawa had been complacent in its dealings with the media. Clearly, an impression of Prograf's superiority was given to the journalist and, whilst the resulting article might not reflect the exact words of the interview, the content of that interview could not be in question.

In Fujisawa's letter of explanation it had cited a number of papers to reference the 'misquote'. Novartis stated that it could counter this with a number of references to show that Neoral efficacy was comparable with Prograf. Moreover, Novartis was particularly concerned about the statement that long-term safety was 'better' since this was emerging evidence and so had not been proven unequivocally. As such, these comparative statements were in breach of both Clauses 7.2 and 7.9. Further, the all-encompassing nature of the claims, without stating that Prograf was only licensed in renal and liver transplantation, meant that Clause 7.10 had also been breached. Novartis alleged that Fujisawa had disparaged the reputation of Neoral's safety and efficacy in breach of Clause 8.1.

Novartis noted that Fujisawa now contended that, despite taking part in the interview, it was not responsible for any of its output; it had no say in the content of the article, nor did it see it before it was printed. Novartis considered that, under Clause 20.2, Fujisawa was obliged to take care that whatever was communicated was factual and presented in a balanced way. Novartis understood that Fujisawa had made no attempt to ensure that this happened and had kept no records of the interview. Fujisawa had quoted data from a third party apparently without permission and had made statements which could mislead the public on matters of safety, efficacy and investment potential. For Fujisawa to suggest that it had no responsibility for the outcome was naïve and unacceptable. Novartis alleged a breach of Clause 20.2 of the Code.

Novartis concluded that, in its interview with Scrip, Fujisawa had presented casual conversation as fact, used comparative data without compunction and made sweeping statements regarding efficacy and safety of Prograf. All this had been done in the full knowledge that such information and data would be published and further reported to industry and public alike.

Novartis contended that this displayed disregard for the Code, the data providers IMS Health, the publishers of Scrip, and the readers of the article and alleged that Fujisawa's actions were so serious, and the consequences so far-reaching, as to bring the industry into disrepute in breach of Clause 2.

## RESPONSE

Fujisawa stated that the article in Scrip appeared following discussions initiated by a journalist during the course of a visit to Fujisawa's new UK headquarters. Fujisawa's interpretation of Clause 1 of the Code was such that the complaint did not fall within the scope of the Code. The article was not promotional activity on Fujisawa's part.

In response to a request for further information Fujisawa noted that Novartis had referred to Case AUTH/1316/5/02, wherein Fujisawa acknowledged that it should have insisted on a charity including a declaration that Fujisawa had sponsored an article in a magazine. A breach of Clause 9.9 had been ruled. No other breach of the Code was found and no criticism of Fujisawa's relationship with, or attitude to, the media was made.

In its complaint Novartis made many critical statements; for some of these it was not clear whether any allegation was being made under the Code. For instance Fujisawa's relationship with the data supplier seemed to be a matter entirely between it and Fujisawa. Fujisawa had received no complaint from the data supplier regarding its use of this data. Similarly, whether the article sent a 'strong message to industry, investors and the public alike regarding the financial viability of the company and its future prospects' did not appear to be an appropriate matter for the Panel to consider.

Fujisawa stated that the graphs supplied to Scrip were provided directly from departmental sales charts following a discussion initiated by the journalist. These charts were not fully labelled and had been annotated by Scrip prior to publication. Fujisawa did not provide the graphs in publication-ready mode and no further discussion took place with Scrip regarding their inclusion in the article. Fujisawa stated that the data contained within the charts was accurate. It was made clear to the journalist that the data contained within the graphs was based on a like for like comparison and therefore included kidney and liver transplantation only. All assumptions on the proportion of total Neoral and Prograf sales which were related to the transplant market were extremely conservative in that the proportion of total Neoral sales which related to transplant patients was certainly significantly lower than the 60% figure used in its calculations (even when transplantation other

than kidney and liver was considered). Likewise the proportion of total Prograf sales relating to kidney and liver transplantation was likely to be higher than the 90% figure used. Fujisawa therefore had been deliberately conservative in its assumptions to avoid introducing bias. Although the figures were based on a like for like comparison considering kidney and liver transplantation it believed that the assumptions made were so conservative that the picture would essentially be the same if all transplant indications were included. Therefore the charts which appeared in the Scrip article, although not fully annotated by the Scrip editorial staff, could not be said to be misleading in any way.

Fujisawa noted that Novartis had alleged an attempt to mislead the reader in relation to the cost-effectiveness of Prograf. The claim that 'Prograf is more cost-effective than Neoral' presumably referred to a comment made by Fujisawa in relation to a presentation at the British Transplantation Society's 4th Annual Congress where the study author (Jurewicz *et al*) concluded that in renal transplantation, tacrolimus was more cost-effective than ciclosporin in terms of cost per survivor, cost per patient with a surviving graft and cost per patient with a rejection-free graft. This was supported by Craig *et al*. Fujisawa considered that it had presented this information to the journalist accurately and fairly and was not aware of any published data demonstrating different findings. Although the sentence in the Scrip article referring to cost-effectiveness did not specifically state that the reference was to renal transplantation, it was part of a paragraph which made reference to an ongoing National Institute of Clinical Excellence (NICE) appraisal which referred only to renal transplantation.

In relation to this allegation and others, Fujisawa submitted that the information made available to the Scrip journalist was factual and presented in a balanced way. As Fujisawa had no control over the content of the published article it could take no responsibility for anything other than the information it provided to the journalist.

Fujisawa stated that it was unclear as to whether Novartis had alleged a breach of the Code with regard to its comments about the percentage of patients on Prograf. Fujisawa had provided information in response to questions from the journalist based on what it believed to be very accurate information obtained in the field. In its complaint Novartis misleadingly suggested that Fujisawa 'had suggested that the conclusions of the TMC study were sufficient to prove the number of liver patients being prescribed Prograf'. Fujisawa had never stated this. What it had said was 'The comment that virtually every liver transplant patient in the UK was put on Prograf as first choice relates to a discussion between [the President of Fujisawa UK] and the Scrip journalist referring to 'available' patients (ie excluding patients enrolled in clinical trials)'. Fujisawa believed that the comment made was true and supported by the information received from the field force and by comments from the doctors involved in the TMC study reported in The Lancet where a clear advantage was shown for tacrolimus in terms of the primary endpoint prompting the authors to conclude that 'tacrolimus should be the drug of choice in adult liver transplantation'. The intended meaning in this statement was that based on the information from Fujisawa's sales force, the company understood that 'virtually every liver transplant patient' (who was not recruited into a clinical trial) was commenced on Prograf. The reference to the TMC study in its conversation with the journalist and in its letter to Novartis was meant to suggest that this finding from its sales force would be in keeping with the recommendations from the authors of the TMC study who concluded that 'tacrolimus should be the drug of choice in adult liver transplantation'.

Fujisawa noted that Novartis had made several critical comments in relation to Prograf efficacy. As Fujisawa had no involvement in the Scrip article other than the interview with the journalist Fujisawa addressed its comments to the information given to the journalist. The claim that, in terms of efficacy, Prograf was 'better' than Neoral, paraphrased a discussion that the head of clinical and medical affairs had with the journalist where he referred to a number of significant research papers published in medical journals over the last few years where improved efficacy in terms of reduced incidence of acute rejection in kidney transplantation and the efficacy advantages described in the TMC paper for liver transplantation were described. The phrase that appeared in the article was not a direct quote from the head of clinical and medical affairs. The context of the discussion was important. The question from the journalist was whether there had been anything of significance that had happened in the last year or so that might help to explain the increased sales of Prograf and the continuing decline in Neoral sales. Fujisawa's comments were that the changes in sales reflected a continuing trend but there had been several significant clinical papers published in the last year.

In relation to the safety comparison, the improved renal function in tacrolimus-treated patients compared with ciclosporin-treated patients was supported by several studies. Regarding cardiovascular risk, in discussion with the journalist Fujisawa referred to the reduction in cardiovascular risk factors such as cholesterol and hypertension in tacrolimus-treated patients compared to ciclosporin-treated patients as described in many recent papers. The use of the word 'better' in relation to long-term safety paraphrased a discussion that referred to specific aspects of long-term safety. With regard to the description that the evidence was 'emerging', this presumably made reference to the fact that 5-year data had only relatively recently become available. Fujisawa submitted that the evidence provided to the journalist on this topic was factual and presented in a balanced way (as could be deduced from the phrase 'in safety terms they are comparable').

Fujisawa submitted that the Scrip article was not a promotional activity and that the complaint fell outside the scope of the Code. Nonetheless with regard to Novartis' allegation of a breach of Clause 20.2 of the Code, Fujisawa stated that its understanding of this clause was that it had

responsibility to ensure that the information provided to the journalist was factual and presented in a balanced way. This was something that it had been very careful to do. Similarly Fujisawa did not accept that there was any way that its discussion could be interpreted as raising unfounded hopes of successful treatment or being misleading with respect to the safety of the product'. Furthermore it was clearly not the case that statements were made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

Novartis had made several critical comments regarding Fujisawa's attitude to the interview by the Scrip journalist. It was not clear in what way these comments might relate to alleged breaches of the Code. The suggestion that Fujisawa had made statements which could mislead the public on investment potential were certainly not relevant to any discussion under the Code and was something that it would strongly deny. The questions that led to the article arose spontaneously during a visit by the journalist to view Fujisawa's new office accommodation. For that reason there had been no opportunity to prepare briefing materials. Although Fujisawa had not recorded the interview, under the circumstances it did not consider that this would have been appropriate behaviour. Novartis would be aware that following a spontaneous discussion with an independent journalist it would be extremely unlikely that an opportunity would be afforded to view any subsequent article prior to publication.

In its dealings with the press Fujisawa was very aware of its responsibilities under the Code and treated any requests for information from the press extremely carefully to ensure that statements, whether written or verbal, were non-promotional and represented factual data presented in a balanced way. Although no notes were kept of the conversation with the Scrip journalist both the head of clinical and medical affairs and the President of Fujisawa UK had a clear memory of the conversation that took place and believed that the information given to the journalist was both fair and balanced. As previously emphasised, statements contained in the article itself would not appear to fall within the scope of the Code as Fujisawa had no involvement beyond the initial discussion with the journalist.

Fujisawa submitted that the only area that might fall within the scope of the Code concerned the information that Fujisawa provided to the Scrip journalist. Fujisawa considered that it provided this in a responsible manner and that the consequences of the article were beyond its control. The company denied that its conduct was in any way inappropriate and denied that there was any likelihood of it bringing the industry into disrepute.

## PANEL RULING

The Panel noted that complaints about articles in the media were judged on the information provided by the company and not on the article itself. Clause 20.1 prohibited the advertising of prescription only medicines to the general public and medicines which, although not prescription only, might not be legally advertised to the public. Clause 20.2 permitted information about medicines to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel firstly had to consider whether a complaint about an article in Scrip came within the scope of the Code. Fujisawa had submitted that as the article in question could not be regarded as promotional activity on its part it would not appear to be a matter addressed appropriately under the Code. The Panel noted that Clause 1.1 stated that the Code applied to a number of areas which were non-promotional.

This was the first time that the Panel had been required to consider whether information provided in relation to an article in Scrip came within the scope of the Code. The Panel noted that Scrip subscribers comprised chief executives, medical or corporate directors, senior executives, investment bankers and doctors conducting clinical research (ref www.pjbpubs.com/scrip). Scrip was thus not aimed at prescribers. It might be argued that Scrip was different to the lay media and was not aimed at the general public as such. The Panel noted that under the Code persons who were not health professionals or appropriate administrative staff were treated for the purposes of the Code as members of the public.

The Panel further noted that the supplementary information to Clause 20.2, Financial Information, stated that information about medicines provided to shareholders, the Stock Exchange and such like had to be factual and presented in a balanced way.

The Panel noted that detailed comparative clinical safety information about specific medicines had been provided to the journalist. Taking all the circumstances into account, the Panel considered that the matter was subject to the Code. Further, the information provided went beyond the provision of financial information as described in the supplementary information to Clause 20.2.

The Panel noted that Prograf was licensed only for use following liver or kidney transplantation. Neoral had a wider range of indications and could be used following bone marrow, kidney, liver, heart, combined heart/lung, lung and pancreas transplants. Neoral could also be used in a number of non-transplant indications.

The Panel noted Fujisawa's account of the circumstances of the interview. The journalist from Scrip had been invited to visit new corporate headquarters and had initiated a conversation which resulted in the article at issue. Those interviewed by the journalist had a clear recollection of what was said. No written account was made during or subsequent to the interview and other than two graphs no written material was provided to the journalist to confirm what was said.

The Panel examined the bar chart and graph provided by Fujisawa to the journalist. The bar chart was

headed 'IMS Transplant Cash Market Share Hospital and Retail' and compared the percentage market share of Neoral and Prograf from October 2000 to September 2002; it was reproduced in Scrip beneath the heading 'Share of UK transplant market'. The second graph depicted the products' hospital and retail transplant cash sales for an identical period and was reproduced in Scrip beneath the heading 'Prograf/Neoral sales for transplant use (October '00 – Sept '02)'. A footnote to the graph and the bar chart in Scrip read 'hospital and retail sales. Source: Fujisawa (IMS data)'. The Panel considered that neither the graph nor the bar chart made it sufficiently clear that only data relating to the indications common to both Neoral and Prograf, ie renal and liver transplants were included. The Panel noted Fujisawa's submission that it was made clear to the journalist that the graphs featured renal and liver transplantation data only. The Panel noted that the company had no written record of what was said to the journalist about the products. The Panel considered that the written material provided to the journalist was inadequate. It was not made sufficiently clear that heart transplant data, for which Prograf was not licensed, was not included. The labelling and description of the data were thus inadequate and misleading. The material was not presented in a balanced way. Breaches of Clauses 7.2 and 20.2 were ruled.

The Panel noted Novartis' comments on this point about the failure of Fujisawa to seek permission from the data supplier but considered that this was irrelevant when determining whether material provided to the journalist complied with Clauses 7.2 and 20.2 of the Code.

In relation to the statement in the article that Prograf was more cost-effective than Neoral the Panel noted Fujisawa's submission that the claim was supported by Jurewicz *et al* (2001) and Craig *et al* (2002) in relation to kidney transplantation; in the Panel's view the article did not make this sufficiently clear. Fujisawa submitted that it presented the data in a fair and accurate manner to the journalist. It was impossible to determine precisely what was said and how the data was presented and the Panel was thus obliged to rule no breach of Clauses 7.2 and 20.2 of the Code.

In relation to the statement in the article, attributable to Fujisawa's UK President, that virtually every UK liver transplant patient in the UK was put on Prograf as first choice and about 80% of kidney transplant patients, the Panel noted Fujisawa's submission that the data was based on information received from Fujisawa's sales force and related to available patients. The Panel queried whether such data was sufficient to substantiate such claims. Fujisawa had no access to individual patient data. The Panel noted that Fujisawa had discussed the TMC study with the journalist. Fujisawa submitted that it had put the data in context. The Panel noted Fujisawa's comment that it was unclear whether a breach of the Code was alleged in relation to this. The Panel considered that the allegation was caught by the generality of the alleged breach of Clause 20.2. It was impossible to determine precisely what was said and how the data was presented and the Panel was thus obliged to rule no breach of Clause 20.2 on this point.

The final paragraph of the Scrip article stated that in terms of efficacy Prograf was better than Neoral but in safety terms they were comparable and that there was emerging evidence that Prograf's long-term safety was better in terms of nephrotoxicity and cardiovascular risk. The statements were attributed to the head of Fujisawa's clinical and medical department. Fujisawa stated that the article paraphrased discussions with the head of clinical and medical affairs. The Panel was extremely concerned that comments about the products' comparative safety had been made in such circumstances. It was impossible for the Panel to determine precisely what was said and how the information was presented and the Panel was thus obliged to ruled no breach of Clauses 7.2, 7.9, 7.10, 8.1 and 20.2.

The Panel noted the nature of the discussion with the journalist. In particular the company had discussed comparative long-term safety in relation to nephrotoxicity and cardiovascular risk. The Panel was concerned that the company had failed at the time or subsequently to provide any written material to the journalist to confirm what was said. Such documentation might have avoided problems. Companies would be well advised to back up oral interviews with written material. It might be argued that the company had failed to maintain high standards as required by Clause 9.1 of the Code. There was no allegation in this regard.

With regard to the alleged breach of Clause 2, the Panel considered that on balance Fujisawa's activities were not such as to warrant a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

**Complaint received** **7 February 2003**

**Case completed** **8 May 2003**

CASE AUTH/1418/2/03

# PFIZER v LILLY

## Conduct of representative

**Pfizer complained about what a Lilly representative had written on her business card which she had left with a specialist diabetes nurse. The representative had written about a lunch meeting, mentioned Cialis and its indication, erectile dysfunction (ED), listed promotional messages and referred to the price. Pfizer further stated that this unacceptable activity must be viewed in the context of a recent ruling of a breach of Clause 2 against Lilly and the activity of its representatives [Case AUTH/1346/7/02] and so it asked that the Panel consider that this was a further breach of Clause 2.**

**The Panel noted that on the front of her business card the representative had written 'Lunch! See reverse'. On the back of the card was written 'Lunch meeting – Cialis-ED 24 hrs period of responsiveness no interaction with food or drink £19.34 for 10 & 20mg dose => saving at higher strength'. The Panel considered that the representative had, in effect, written her own promotional copy for Cialis; the product had been named and claims made for it. The material had not been certified and nor had prescribing information been included. The Panel considered that the representative had failed to maintain a high standard of ethical conduct in the discharge of her duties and to comply with all relevant provisions of the Code. A breach of the Code was ruled. High standards had not been maintained. A further breach of the Code was ruled. The Panel did not consider that the conduct of the representative warranted a ruling of a breach of Clause 2.**

**The Panel noted that Case AUTH/1346/7/02 concerned the promotion of Cialis prior to the granting of a marketing authorization permitting its sale or supply. At the time that the Lilly representative in question left her business card Cialis had been granted a marketing authorization and there could thus be no failure on Lilly's part to comply with the undertaking given in the previous case. No breach of the Code was ruled in that regard.**

Pfizer Limited complained about the activities of a representative of Eli Lilly and Company Limited.

### COMPLAINT

Pfizer stated that a specialist diabetes nurse was given the business card of the Lilly representative just before Christmas. A photocopy of the original card was provided. The representative had written about a lunch meeting and had named Cialis, and its indication, erectile dysfunction (ED), and had proceeded to list promotional messages in addition to a reference to the price. The nurse specialist, who wished to remain anonymous, had passed the card to Pfizer's local representative.

Pfizer stated that in view of the seriousness of this action, coming as it did immediately after the ruling of a breach of Clause 2 against Lilly and the activity of its representatives [Case AUTH/1346/7/02], it was complaining directly to the Authority. Pfizer alleged that this type of activity was unacceptable in breach of Clauses 9.1 and 15.2 of the Code. Pfizer further stated that this unacceptable activity must be viewed in the context of Lilly's recent breach of Clause 2 and so it asked that the Panel consider that this was a further breach of Clause 2.

Pfizer added that the Panel might wish to consider a breach of Clause 22. Pfizer stated that it could not make a formal complaint under Clause 22 as it had not yet been informed of the exact nature of the undertaking given by Lilly following the appeal in Case AUTH/1346/7/02.

Pfizer later confirmed that its representative had visited the hospital unit on 6 January when the staff had told her about the Lilly representative visiting them just before Christmas. The Pfizer representative had previously visited the unit on 22 November when there had been no sign of the Lilly representative's business card.

### RESPONSE

Lilly was disappointed that Pfizer had not attempted to ascertain the facts or to resolve this matter by inter-company discussions, but had referred the matter directly to the Authority instead. Given that Pfizer was unable or unwilling to provide the Authority with any concrete details about the alleged incident owing to the alleged reluctance of a health professional to be involved directly (or even be named) it seemed unlikely that it had been able to ascertain exactly what took place or even taken any steps to discover why or how the information came to be written on the representative's business card. For these reasons alone Lilly considered that the complaint should be disallowed.

Lilly stated that the representative in question visited the specialist diabetes nurse at the Diabetes Clinic on Monday, 25 November 2002. The specialist diabetes nurse arranged the departmental lunch meetings for the diabetes team at the hospital and had received a number of complaints from the medical staff regarding the quality and 'appropriateness' of some of the pharmaceutical presentations. The medical staff considered that pharmaceutical company representatives were using the lunchtime education meeting to boost numbers of medical practitioners seen rather than adding any quality to the diabetes service by way of education. As head of the nursing team the specialist diabetes nurse decided to put the ball back in the medical staff's court, so that she was no longer to blame for just booking lunch meetings, and implemented a system of getting representatives to write on the back of their business card a brief synopsis of what the lunch meeting would be about so that she could brief her medical colleagues at the next departmental meeting thus allowing them to approve or disapprove the choice of meeting.

The specialist diabetes nurse was very busy when the representative called to see her in November 2002. The representative therefore merely did a brief Cialis detail and asked for a lunch meeting. The specialist diabetes nurse explained the new process and asked the representative to write 'Lunch Meeting' on the front of her card and put the product characteristics on the back. She asked the representative to include the price details because the department was very interested in controlling prescribing costs. Because the specialist diabetes nurse had to go about her duties she asked the representative to leave the card propped against the notice board in a prominent position so that she could progress the matter as soon as possible.

When the representative left her card there were two others from different companies' representatives propped against the notice board also with 'Lunch meeting' on the front.

The specialist diabetes nurse's office was not locked and could be accessed very easily. It was possible that the business card was removed without her knowledge.

Lilly noted that Pfizer's account of the incident was somewhat sketchy: it had been alleged that a specialist diabetes nurse (who was alleged to wish to remain anonymous) was given the business card of a Lilly representative just before Christmas. The business card was alleged to have had a message about Cialis handwritten on it by the representative. Given the dates provided by Pfizer in a letter of clarification the alleged incident could have taken place at any time between 22 November 2002 and 6 January 2003, a period of over 6 weeks. Lilly noted that at the start of the alleged time window (and on the date when the meeting actually took place) a licence had already been granted for Cialis (EU licence granted 12 November 2002). Thus, the representative's actions were not an example of pre-marketing or a breach of any undertaking about representative activity as alleged by Pfizer. Suggestions of breaches of Clause 22 and Clause 2 were therefore unfounded, as indeed was the implied allegation of a breach of Clause 3.

Lilly confirmed that the handwriting on the business card was that of the representative named on the card. Other than the observation that the representative had written the message on her card, no allegation was made by Pfizer in relation to the text. Despite this, Pfizer considered that this type of activity was unacceptable and was in breach of Clauses 9.1 and 15.2 of the Code. Pfizer, however had not troubled itself to discover the circumstances under which the message was written on the card and had not stated in what way such activity breached the clauses mentioned. Lilly suggested that no evidence had been provided to prove that there had been any failure on its part to maintain high standards. On the contrary Lilly stated that it had maintained high standards by providing the information requested by a busy health professional in the form required. Indeed the Lilly representative appeared to have been particularly sensitive to the special nature of the specialist diabetes nurse's profession and had maintained a high standard of ethical conduct in the discharge of her duties. Suggestions of breaches of Clauses 9.1 and 15.2 of the Code were therefore entirely unfounded.

In response to a request for further information Lilly stated that its approach to training representatives focussed on ensuring that they were conversant with two source documents which defined acceptable standards of behaviour. These were the Code and Lilly's own corporate code of practice. Relevant pages were provided. Representatives' training included instructions on the arrangements of meetings and copies of relevant training material were provided.

With regard to business cards Lilly stated that their use had important cultural implications in some parts of the world. For example in Japan (and therefore in Japanese companies), great care must be taken over the giving and receiving of business cards. Lilly's corporate culture was broadly North American and therefore Lilly did not have any standard operating procedures in relation to the use of business cards, nor was it aware of any other pharmaceutical company in the UK having these. Similarly, the Code did not contain any specific references to the use of business cards nor to the requirement for there to be written procedures in this respect. However in the case now under consideration the key Code issue was not a procedural one about the use of business cards but rather a practical one about the appropriateness of a representative's conduct in responding to a specific request for information from a health professional by writing that information on a piece of Lilly stationery (a business card). Clearly, if the information supplied was written down only in response to a specific request from a health professional, the situation was no different to the writing of a medical information letter by a medical information officer. In such circumstances the text on the company stationery was not promotional material and need not carry prescribing information or be certified. However when such an activity was carried out by sales staff it might be construed as being promotional and Lilly therefore had taken the opportunity of a Code refresher session at the recent UK sales conference to brief sales representatives on this point. Copies of the relevant slides were provided.

## PANEL RULING

The Panel noted that on the front of her business card the representative had written 'Lunch! See reverse'. On the back of the card was written 'Lunch meeting – Cialis-ED 24 hrs period of responsiveness no interaction with food or drink £19.34 for 10 & 20mg dose => saving at higher strength'. The Panel noted that the representative had written the outline of a proposed lunchtime meeting at the request of the nursing sister responsible for arranging such meetings. The first priority for representatives must be to ensure that their activities complied with the Code regardless of their customers' wishes.

The Panel noted Lilly's submission regarding responses made in response to specific requests from a health professional. Clause 1.2 of the Code stated that the term promotion did not include, *inter alia*,

replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature. The Panel noted that the representative had visited the nursing sister to promote Cialis. This exemption to Clause 1.2 of the Code applied to unsolicited requests, not to the request in question which was made as a result of a visit from a representative wanting to organise a meeting. The Panel considered that it would be rare for medical representatives to be able to claim exemption under this clause of the Code as representatives were employed to promote medicines and their conduct would always be viewed in this context.

The Panel considered that the representative had, in effect, written her own promotional copy for Cialis; the product had been named and claims made for it. The material had not been certified as required by Clause 14 and prescribing information for the product had not been included as required by Clause 4.1. The Panel appreciated that the representative had acted in accordance with the wishes of the nursing sister but considered that in the circumstances she should have attached her business card, on which she could have written 'Lunch meeting' but nothing about the product, to a piece of Cialis promotional material such as a leavepiece. The Panel considered that by writing her own promotional copy the representative had failed to maintain a high standard of ethical conduct in the discharge of her duties and to comply with all relevant provisions of the Code as required under Clause 15.2. A breach of that clause was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

Clause 2 was reserved for use as a sign of particular censure. The Panel did not consider that the conduct of the representative warranted such a ruling.

The Panel noted that Case AUTH/1346/7/02 concerned the promotion of Cialis prior to the granting of a marketing authorization permitting its sale or supply. At the time that the Lilly representative left her business card, 25 November, Cialis had been granted a marketing authorization and there could thus be no failure on Lilly's part to comply with the undertaking given in the previous case. No breach of Clause 22 was ruled.

**Complaint received** **18 February 2003**

**Case completed** **1 April 2003**

CASE AUTH/1419/2/03

# VOLUNTARY ADMISSION BY FUJISAWA

## Prograf advertisement to the public

**Fujisawa voluntarily advised the Authority that due to an oversight an advertisement for Prograf (tacrolimus), rather than a corporate advertisement, had appeared in the World Transplant Games Federation Journal, distributed to both health professionals and members of the public.**

**The Director of the Authority decided that as the matter related to the promotion of a prescription only medicine to the general public, it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code.**

**The Panel noted that the advertisement for Prograf had appeared in a journal published in the UK and circulated to UK health professionals and UK patients amongst others. The publication of the advertisement was due to an error by Fujisawa's European Central Marketing Group which had sent the wrong advertisement by email to the journal and had also failed to follow company procedure regarding copy approval. The advertisement was for a prescription only medicine and had appeared in a journal for a mixed audience. The Panel therefore ruled a breach of the Code as acknowledged by Fujisawa.**

### COMPLAINT

Fujisawa Limited voluntarily advised the Authority that due to an oversight an advertisement for Prograf (tacrolimus), rather than a corporate advertisement, had appeared in the November 2002 edition of the World Transplant Games Federation Journal, distributed to both health professionals and members of the public.

The Director of the Authority decided that as the matter related to the promotion of a prescription only medicine to the general public it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Authority requested that Fujisawa respond in relation to the provisions of Clause 20.1 of the Code.

### RESPONSE

Fujisawa explained that on 17 February 2003 it obtained a copy of the November 2002 edition of the World Transplant Games Federation Journal, the official journal of the World Transplant Games Federation, which was published twice a year. 10,000 copies of the journal were sent to members of the federation, which included doctors, other health professionals and transplant patients. Fujisawa was dismayed to find an inappropriate advertisement for Prograf on the inside front cover.

The Prograf International Product Manager was urgently contacted. Although the journal had been published in the UK, the Prograf advertisement had been placed by Fujisawa's European Central Marketing Group based in Munich. Steps were immediately taken to contact the World Transplant Games Federation but unfortunately all copies of the journal had already been printed and distributed.

Fujisawa had been a regular sponsor of World Transplant Games Federation events. In November 2002 the European Central Marketing Group had been asked to supply a half page advertisement for the journal. Unfortunately, due to an error, instead of submitting a corporate message (similar in style to the other advertisement sharing the same page) a copy of an early draft of a Prograf advertisement was provided. This advertisement was still at a rough stage and was being prepared for placement in a professional journal some time in the future. The wrong file was attached to an email and sent electronically to the journal. As a result the advertisement was not submitted for copy approval either within the UK or Munich.

Following this episode Fujisawa had reminded its European Central Marketing Group of its obligation to ensure that it submitted all advertisements destined for journals produced in the UK to the copy approval process at Fujisawa in the UK. A firm commitment to this principle had been agreed at the highest level between Fujisawa and its European headquarters. All members of the European Central Marketing Group had been reminded of their responsibilities in this respect. Although this principle had been established prior to this recent episode it appeared that on this occasion this agreed arrangement had not been followed. Although the intention had been to send a corporate advertisement this should have still have been done via Fujisawa in the UK.

Fujisawa had voluntarily informed the Authority of this admitted breach of Clause 20.1 as it took its obligations under the Code very seriously indeed. There was a very strictly adhered to copy approval system which not only scrutinised promotional material but also required all material regarded as having 'non-promotional' status to be verified before the go-ahead was given for production. Furthermore Fujisawa had always taken great care to avoid any possibility of promotional materials being viewed by patients.

Fujisawa therefore accepted that a breach of Clause 20.1 of the Code had occurred and apologised for this uncharacteristic error. The company had taken every possible step to avoid any repetition.

### PANEL RULING

The Panel noted that the advertisement for Prograf had appeared in a journal published in the UK and circulated to UK health professionals and UK patients, among others.

The Panel noted that the publication of the advertisement was due to an error by Fujisawa's European Central Marketing Group which had sent the wrong advertisement by email to the journal and had also failed to follow company procedure regarding copy approval. The advertisement was for a prescription only medicine and had appeared in a journal for a mixed audience. The Panel therefore ruled a breach of Clause 20.1 of the Code as acknowledged by Fujisawa.

During its consideration of this matter the Panel noted that the agreed company procedure was to send all materials for journals produced in the UK to Fujisawa Limited for copy approval. The Panel considered, however, that in accordance with the supplementary information to Clause 1.1 of the Code, Journals with an International Distribution, materials for journals intended for a UK audience should also be sent to the UK for approval. The Panel requested that Fujisawa be advised of its concerns in this regard.

**Proceedings commenced 21 February 2003**

**Case completed 25 March 2003**

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**CASE AUTH/1420/2/03**

# MERCK SHARP & DOHME v PFIZER

## Istin journal advertisement

**Merck Sharp & Dohme complained about a journal advertisement for Istin (amlodipine) issued by Pfizer. The advertisement featured a picture of an academic mortar-board above which appeared the claim 'ALL HATs off to Istin'. Beneath the mortar-board was the claim 'With the results of the ALLHAT study, lowering blood pressure with ISTIN in high risk hypertensive patients is now proven to be equivalent to a diuretic in stroke outcome'. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study compared major outcomes in high risk hypertensive patients randomised to an ACE inhibitor (lisinopril), calcium channel blocker (amlodipine) or a diuretic (chlorthalidone). The objective was to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowered the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events versus treatment with a diuretic.**

**Istin was indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris and Prinzmetals (variant) angina when diagnosed by a cardiologist. The summary of product characteristics (SPC) stated that in hypertensive patients, Istin had been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent or an ACE inhibitor. The SPC also stated that Istin was well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.**

**Merck Sharp & Dohme alleged that the claim 'ALL HATs off …', was all-embracing, implying overwhelming success. It implied that Istin succeeded in proving superiority in the primary endpoint. There was no evidence of significant benefit of Istin, when compared with the control arm. The editorial accompanying the publication of the study stated 'the major finding of ALLHAT was a striking and unequivocal null result'. Such use of the heading 'ALL HATs off …' was therefore a gross exaggeration of the success of Istin in the study.**

**The Panel noted that the primary outcome measure of the ALLHAT study was combined fatal CHD or non fatal MI analysed by intent-to-treat. Secondary outcomes were all cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization) and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease).**

**The Panel noted that the expression 'hats off to' was described as 'a call to acknowledge the outstanding qualities of a person or a thing' (Shorter Oxford Dictionary).**

**In the Panel's view the results of the ALLHAT study could not be described as outstanding with regard to Istin given there was no difference between it and a diuretic with regard to the primary outcome. Similarly the results for stroke (a secondary outcome measure) showed no significant difference between the two (p=0.28). The only difference in secondary outcomes was in relation to heart failure which was a component of the combined CVD secondary outcome. The Panel considered that the claim 'ALL HATs off to Istin' was thus exaggerated. A breach of the Code was ruled.**

**In relation to the claim '… proven to be equivalent to a diuretic in stroke outcome' Merck Sharp & Dohme stated that the ALLHAT study was not designed to show equivalence and this could not therefore be claimed. A prepublished statement indicated an 83% power to detect a difference of 16.3% in favour of amlodipine over chlorthalidone, based on cardiac events (fatal CHD/ non fatal MI) not stroke. There was no pre-specified equivalence statement regarding stroke in either the protocol design paper or the study report. The claim at issue could not be supported. The study failed to show superiority of amlodipine over chlorthalidone which was what it set out to demonstrate. No more could be claimed.**

**The Panel noted that the primary hypothesis of the ALLHAT study was that the combined incidence of fatal CHD and non-fatal MI (the primary endpoint) would be lower in patients treated with amlodipine or lisinopril first line than in those treated with chlorthalidone. It was further stated that although**

**secondary endpoints would be examined these would be regarded as 'soft data' that would at best confirm or supplement the primary endpoint.**

**The Panel noted that the ALLHAT study had shown no difference between amlodipine and chlorthalidone with regard to stroke outcome. In the Panel's view this was not the same as proving that the products were equivalent in that regard. The Panel considered that the claim that Istin was now 'proven to be equivalent to a diuretic in stroke outcome' was misleading and not supported by the ALLHAT data. A breach of the Code was ruled.**

**Merck Sharp & Dohme stated that stroke was not the primary endpoint nor was it a component of it. Stroke was one of seven secondary endpoints of which three relative risk ratios were below one and three were above one. The focus on one cardiovascular secondary endpoint at the expense of other equally important clinical cardiovascular endpoints, and having ignored the primary endpoint completely, was not a fair representation of all the available evidence.**

**The Panel considered that the prominence given to stroke (a secondary outcome) was such that the advertisement would mislead readers into thinking that this was a primary objective and this was not so. In the Panel's view the omission of the adverse heart failure data whilst referring only to the positive stroke data was not misleading but the failure to make it clear that stroke was a secondary endpoint was not a fair representation of all the available evidence. A breach of the Code was ruled in that regard.**

**Merck Sharp & Dohme alleged that the tenor of the advertisement was not supported by the authors' interpretations of the data. The authors' data and conclusions could not be used to support an equivalence claim.**

**The Panel noted its rulings above. It considered that the impression given by the advertisement was not capable of substantiation by the ALLHAT study results. The Panel therefore ruled a breach of the Code.**

Merck Sharp & Dohme Limited complained about a journal advertisement (ref IST 275b) for Istin (amlodipine) issued by Pfizer Limited. The advertisement featured a picture of an academic mortar-board above which appeared the claim 'ALL HATs off to Istin'. Beneath the mortar-board was the claim 'With the results of the ALLHAT study, lowering blood pressure with ISTIN in high risk hypertensive patients is now proven to be equivalent to a diuretic in stroke outcome'. An approach to Pfizer by Merck Sharp & Dohme had failed to resolve its concerns.

ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was published in the Journal of the American Medical Association, December 2002. The study compared major outcomes in high risk hypertensive patients randomised to an ACE inhibitor (lisinopril), calcium channel blocker (amlodipine) or a diuretic (chlorthalidone). The objective was to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowered the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events versus treatment with a diuretic.

Istin was indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris and Prinzmetals (variant) angina when diagnosed by a cardiologist. The summary of product characteristics (SPC) stated that in hypertensive patients, Istin had been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent or an ACE inhibitor. The SPC also stated that Istin was well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

### 1 Claim 'ALL HATs off to Istin'

#### COMPLAINT

Merck Sharp & Dohme alleged that the use of 'ALL HATs off …', whilst clearly a pun on the study title, was all-embracing implying overwhelming success. From it, the reader might reasonably infer that Istin succeeded in proving that the hypothesis set out in the study was true, ie proven superiority in the primary endpoint. There was no evidence of significant benefit of Istin, when compared with the control arm. The editorial accompanying the publication stated 'the major finding of ALLHAT was a striking and unequivocal null result'. Such use of the heading 'ALL HATs off …' was therefore a gross exaggeration of the success of Istin in the study. A breach of Clause 7.10 of the Code was alleged.

#### RESPONSE

Pfizer stated that it had not claimed superiority or overwhelming success as Merck Sharp & Dohme alleged. The claim denoted a successful result in the largest ever hypertension trial (ALLHAT) and one that was run independently by the National Heart Lung and Blood Institute.

The claim clearly related to the stroke data and no connection was made to the primary endpoint of the study, combined fatal CHD and non-fatal myocardial infarction (MI), which would be outside the current licensed indications for Istin. In the paper which set out the design of the ALLHAT study, it was apparent that the study was testing for superiority of newer agents for the primary endpoint only but not the secondary endpoints such as stroke. Pfizer believed the stroke data demonstrated a successful result for Istin for the following reasons:

- The active comparator in ALLHAT was chlorthalidone (a thiazide diuretic), which had proven efficacy at reducing stroke by a dramatic 36% compared to placebo as seen in the SHEP (Systolic Hypertension in the Elderly Programme) trial.
- In ALLHAT, there were no significant differences in the event rates of stroke between Istin and chlorthalidone.
- By extrapolation this result was a success for Istin where it was shown to be comparable to an agent with proven efficacy at reducing stroke.

Istin had therefore been shown to be equivalent to a comparator that had proven efficacy at reducing stroke, and as such this was a successful result for Istin.

Pfizer noted that a recent editorial in the BMJ commenting on ALLHAT and the importance of the outcomes for Istin stated 'The new information also dismisses previous concerns about the safety and efficacy of calcium channel blockers for the treatment of hypertension. This sends out an important and powerful message to those who generate and publish unsound conclusions from small studies, post hoc analyses and observational data'. For these reasons Pfizer submitted the information presented was fair, accurate and balanced and did not breach Clause 7.10 of the Code.

## PANEL RULING

The Panel noted that the primary outcome measure of the ALLHAT study was combined fatal CHD or non fatal MI analysed by intent-to-treat. Secondary outcomes were all cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization) and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease). The objective of the study was to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowered the incidence of CHD or other CVD events versus treatment with a diuretic.

Participants aged 55 years or older with mild to moderate hypertension and at least one other CHD risk factor were randomly assigned to receive chlorthalidone, 12.5 – 25mg/day (n=15,255); amlodipine, 2.5 – 10mg/day (n=9,048); or lisinopril, 10 – 40mg/day (n=9,054) for planned follow up of approximately 4 to 8 years. The additional CHD risk factors included previous (>6 months) myocardial infarction or stroke, left ventricular hypertrophy, history of type 2 diabetes, current smoking, high-density lipoprotein cholesterol of less than 0.91mmol/L, or documentation of other atherosclerotic CVD. Individuals with a history of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction of less than 35% were excluded.

Mean follow-up was 4.9 years. The primary outcome occurred in 2,956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risk was 0.98 (95% Cl, 0.90-1.07) for amlodipine (6-year rate, 11.3%). Likewise, all-cause mortality did not differ between the two groups. Compared with chlorthalidone five-year systolic blood pressures were significantly higher with amlodipine (0.8mmHg, p< 0.03) and 5-year diastolic blood pressure was significantly lower (0.8mmHg, p<0.001). Secondary outcomes were similar except for a higher 6-year rate of heart failure with amlodipine (10.2% vs 7.7%; relative risk, 1.38; 95% Cl, 1.25-1.52) compared with chlorthalidone. The study concluded that thiazide-type diuretics were superior in preventing one or more major forms of CVD and were less expensive. They should be preferred for first-step antihypertensive therapy.

The Panel noted that the expression 'hats off to' was described as 'a call to acknowledge the outstanding qualities of a person or a thing' (Shorter Oxford Dictionary).

The Panel noted the results of the ALLHAT study. In the Panel's view they could not be described as outstanding with regard to Istin given there was no difference between it and a diuretic with regard to the primary outcome. Similarly the results for stroke (a secondary outcome measure) showed no significant difference between the two (p=0.28). The only difference in secondary outcomes was in relation to heart failure which was a component of the combined CVD secondary outcome. Compared to the chlorthalidone group the Istin group had a 38% higher risk of heart failure (p<0.001) with a 6-year absolute risk difference of 2.5% and a 35% higher risk of hospitalized/fatal heart failure (p<0.001).

The Panel considered that the claim 'ALL HATs off to Istin' was thus exaggerated. A breach of Clause 7.10 of the Code was ruled.

### 2 Claim '…proven to be equivalent to a diuretic in stroke outcome'

## COMPLAINT

Merck Sharp & Dohme stated that the ALLHAT study was not supposed to show equivalence and this could not therefore be claimed. A prepublished statement indicated an 83% power to detect a difference of 16.3% in favour of amlodipine over chlorthalidone, based on **cardiac** events (fatal CHD/non fatal MI) not stroke. There was no pre-specified equivalence statement regarding stroke in either the protocol design paper or the study report. Typically, a much greater power to exclude a much smaller difference would be required to come close to claiming non-inferiority of one medicine compared with the other. The use of the phrase 'proven to be equivalent', particularly in relation to only one of many secondary endpoints, could not be supported. The study failed to show superiority of amlodipine over chlorthalidone which was what it set out to demonstrate. No more could be claimed. The claims of proof of evidence were therefore alleged to be unsupported and misleading in breach of Clause 7.2 of the Code.

## RESPONSE

Pfizer stated that it was very clear that this claim was referenced to stroke outcome. Stroke was a secondary endpoint and as such no test for superiority was made. ALLHAT was the largest ever hypertension trial with over 42,000 patients and as such was powerful enough to look for small differences in outcome. As there were comparable event rates of stroke between Istin and diuretic this proved equivalence. Pfizer pointed out that there was a trend of superiority for Istin over diuretic in stroke, but as this difference was not statistically significant Pfizer had not claimed any superiority.

As there was no statistically significant difference between Istin and diuretic in stroke event rates, it was acceptable in the scientific and clinical context to refer to equivalence.

Pfizer believed the claim was accurate and not misleading and therefore did not breach Clause 7.2 of the Code.

### PANEL RULING

The Panel noted that the paper describing the rationale and design of the ALLHAT study stated that the primary hypothesis of the study was that the combined incidence of fatal CHD and non-fatal MI (the primary endpoint) would be lower in patients treated with amlodipine or lisinopril first line than in those treated with chlorthalidone. It was further stated that although secondary endpoints would be examined these would be regarded as 'soft data' that would at best confirm or supplement the primary endpoint.

The Panel noted that the ALLHAT study had shown no difference between amlodipine and chlorthalidone with regard to stroke outcome. In the Panel's view this was not the same as proving that the products were equivalent in that regard. The Panel considered that the claim that Istin was now 'proven to be equivalent to a diuretic in stroke outcome' was misleading and not supported by the ALLHAT data. A breach of Clause 7.2 of the Code was ruled.

## 3 Focus on 'stroke outcome'

### COMPLAINT

Merck Sharp & Dohme stated that stroke was not the primary endpoint nor was it a component of it. Stroke was one of seven secondary endpoints detailed in table 5 of the results paper, of which three relative risk ratios were below one and three were above one. For instance, the combined cardiovascular disease endpoint demonstrated a risk increase of 4% with amlodipine, with confidence intervals that very nearly reached significance. In fact, the only chlorthalidone-amlodipine comparisons reaching nominal significance were the 35-38% increases in heart failure events. The focus on one cardiovascular secondary endpoint at the expense of other equally clinically important cardiovascular endpoints, and having ignored the primary endpoint completely, was not a fair representation of all the available evidence, contrary to Clause 7.2 of the Code.

### RESPONSE

Pfizer stated that the primary endpoint of ALLHAT was combined fatal CHD and non-fatal MI. The secondary endpoints were all-cause mortality, combined CHD, stroke, combined CVD, end-stage renal disease, cancer and hospitalized gastrointestinal bleedings. Heart failure was neither a primary or a secondary endpoint in its own right, but a component of a secondary endpoint and was therefore not the main objective of the trial.

Stroke was a secondary endpoint and correlated strongly with blood pressure. Hypertension was therefore a well recognised surrogate for stroke and was therefore mentioned in the advertisement in the context of blood pressure reduction with Istin.

Hypertension was a less well accepted surrogate for the primary endpoint and other secondary endpoints and therefore these endpoints had not been promoted as they fell outside the current licensed indications for Istin.

Pfizer submitted that the result of the primary endpoint where Istin and diuretic were comparable was a very important result for clinicians, particularly because diuretics had proven efficacy at reducing cardiovascular morbidity and mortality. Pfizer would welcome an opportunity to promote this endpoint but considered that it would be outside the current licensed indications for Istin.

Heart failure was not an endpoint in its own right and was part of a composite of combined CVD. There was no statistically significant difference between Istin and diuretic for combined CVD, and, although again an excellent result for Istin, it fell outside the current licensed conditions for Istin. Furthermore, there were concerns amongst clinicians regarding the validity of the heart failure data. An editorial in the BMJ commented that the heart failure results of ALLHAT 'must be viewed with caution'.

Secondary endpoints in trials were just as important as primary endpoints and Pfizer considered that it could promote endpoints other than the primary ones provided that they were within the licensed indications for Istin. Istin was licensed to treat hypertension and patients in the ALLHAT study randomised to treatment with Istin enjoyed a successful lowering of their blood pressure and a concomitant lowering in their risk of stroke. It was justifiable and highly relevant to make a claim about effect on stroke – in the UK the third commonest cause of mortality after heart disease and cancer and the single biggest cause of disability in the whole population.

The fact that stroke was a secondary endpoint in ALLHAT was irrelevant. Indeed, Merck Sharp & Dohme itself made claims on stroke outcome for its product in the context of the LIFE study. Such a claim when appropriately expressed was not in itself unacceptable (Case AUTH/1341/7/02).

For these reasons Pfizer submitted that it had provided a fair balance of the clinical outcomes that it was currently permitted to promote for Istin and as such denied a breach of Clause 7.2 of the Code.

### PANEL RULING

The Panel noted that stroke was a secondary endpoint and that heart failure was one component of another secondary endpoint, ie combined CVD which included CHD or stroke or coronary revascularization procedures or angina (hospitalized or medically treated) or congestive heart failure (CHF) (hospitalized or medically treated) or peripheral arterial disease (hospitalized or outpatient revascularization procedure). The secondary hypothesis was given in the rationale paper as 'The following endpoints (or their incidence) will be reduced in patients randomised to receive amlodipine, lisinopril or doxazosin relative to those receiving chlorthalidone'. The secondary endpoints

would be regarded as 'soft data' that would at best confirm or supplement the primary endpoint.

The Panel noted Pfizer's submission that the primary endpoint was not within the licensed indications for Istin.

The Panel considered that the prominence given to stroke (a secondary outcome) was such that the advertisement would mislead readers into thinking that this was a primary objective and this was not so. Although one of the only differences demonstrated was in relation to heart failure this was one component of another secondary endpoint, CVD; heart failure was not a secondary endpoint in its own right. In the Panel's view the omission of the adverse heart failure data whilst referring only to the positive stroke data was not misleading but the failure to make it clear that stroke was a secondary endpoint was not a fair representation of all the available evidence. A breach of Clause 7.2 of the Code was ruled in that regard.

### 4 Misrepresentation of the publication

#### COMPLAINT

Merck Sharp & Dohme stated that the data from the study were clear. The interpretation of the data from the authors was also clear – amlodipine was not superior to chlorthalidone at preventing cardiac events and was worse at preventing heart failure. There was no mention in the paper of 'equivalence'. Therefore the authors recommended diuretic therapy as first line treatment, reserving calcium channel blockers for the few patients intolerant to diuretics, '…and with due regard to their higher risk of one or more manifestations of cardiovascular disease'. The tenor of the advertisement was not supported by the authors' interpretations of the data. The authors' data and conclusions could not be used to support an equivalence claim, contrary to Clause 7.4 of the Code.

#### RESPONSE

Pfizer stated that the publication highlighted that Istin was comparable to diuretic in cardiovascular outcomes including stroke. The authors' comments included 'it is not surprising that no significant differences in CHD and stroke rates were found between chlorthalidone and amlodipine…' and '…evidence would indicate no difference between [calcium channel blocker] based treatment and diuretic based treatment for [stroke and CHD event rates]'. Pfizer had not claimed superiority and therefore it submitted the advertisement was consistent with both the authors' conclusions of the ALLHAT study and also the clinical data.

Additionally, the publication highlighted the need for combination therapy to achieve good blood pressure control and that diuretic therapy should be part of such a regimen. This was consistent with Pfizer's own strategy where it believed there was a role for Istin as part of a diuretic based combination regimen in the achievement of aggressive blood pressure targets that would ultimately benefit the patient.

The authors' comments, data from the trial, as well as the view of the editorial published in the BMJ substantiated Pfizer's promotional message. For these reasons Pfizer submitted that it had not breached Clause 7.4 of the Code.

#### PANEL RULING

The Panel noted its rulings in points 1, 2 and 3 above. It considered that the impression given by the advertisement was not capable of substantiation by the ALLHAT study results. The Panel therefore ruled a breach of Clause 7.4 of the Code.

**Complaint received** **25 February 2003**

**Case completed** **6 May 2003**

**CASE AUTH/1421/2/03**

# SCHERING-PLOUGH v UCB PHARMA

## Xyzal journal advertisement

**Schering-Plough complained about a journal advertisement for Xyzal (levocetirizine), issued by UCB Pharma, which referred to a comparison of Xyzal with Schering-Plough's product NeoClarityn (Day *et al* 2002). Schering-Plough alleged that the claim 'Both treatments had placebo-level side effects' misled the reader into believing that the side effect profile of Xyzal was similar to placebo. This was not the case. The Xyzal summary of product characteristics (SPC) stated 'Incidence of slightly sedating adverse drug reactions such as somnolence, fatigue and asthenia was altogether more common (8.1%) under levocetirizine 5mg than after placebo (3.1%)'. Further, 'In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5mg group had at least one adverse drug reaction compared to 11.3% in the placebo group'. To claim that Xyzal had 'placebo-level side effects' was therefore inaccurate, misleading, not capable of substantiation and did not reflect all the available evidence.**

**The Panel noted the Xyzal SPC. The prescribing information which accompanied the advertisement stated that the side effects reported more frequently with Xyzal (% in excess of placebo) were somnolence (3.8%), dry mouth (1%) and fatigue (1.3%). The Panel noted that the claim in question was based on the conclusions of Day *et al* who found that the incidence of adverse effects for levocetirizine and desloratadine was similar to placebo.**

**The Panel considered that it was misleading to claim that Xyzal had placebo-level side effects when the SPC and the prescribing information referred to some side effects which occurred more frequently with Xyzal than with placebo. The claim did not reflect all the available evidence and could not be substantiated. The Panel therefore ruled breaches of the Code. Claims for a product must be consistent with the SPC.**

Schering-Plough Ltd complained about a journal advertisement (ref UCB-XYZ-02-57) for Xyzal (levocetirizine) issued by UCB Pharma Limited. Headline text, referred to a study by Day *et al* (2002), stated 'In a head-to-head trial, Xyzal had more teeth than NeoClarityn'. NeoClarityn (desloratadine) was marketed by Schering-Plough.

### COMPLAINT

Schering-Plough alleged that the claim 'Both treatments [levocetirizine and desloratadine] had placebo-level side effects' was in breach of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code.

The claim misled the reader into believing they could expect the side effect profile of Xyzal to be similar to placebo. This was not the case. The summary of product characteristics (SPC) for Xyzal stated in Section 4.8 'Incidence of slightly sedating adverse drug reactions such as somnolence, fatigue and asthenia was altogether more common (8.1%) under levocetirizine 5mg than after placebo (3.1%)'. Further, 'In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5mg group had at least one adverse drug reaction compared to 11.3% in the placebo group'.

To claim that Xyzal had 'placebo-level side effects' was therefore inaccurate, misleading, not capable of substantiation and did not reflect all the available evidence.

### RESPONSE

UCB Pharma stated that the advertisement presented data from a recent head-to-head trial (Day *et al* 2002) in which the incidence of adverse events for levocetirizine and desloratadine was similar to placebo. The frequency of somnolence or fatigue was 3.5% with levocetirizine, 5.7% with desloratadine and 3.3% with placebo. It had never been the company's intention to mislead or present inaccurate data and the claim that Xyzal and NeoClarityn had placebo-level side effects referred specifically to this head-to-head trial.

After careful consideration, UCB had decided to remove the statement 'placebo-level side effects' and the materials were therefore now obsolete.

### PANEL RULING

The Panel noted that the Xyzal SPC stated that the incidence of slightly sedating adverse drug reactions such as somnolence, fatigue and asthenia was altogether more common (8.1%) after levocetirizine 5mg than after placebo (3.1%). The prescribing information which accompanied the advertisement stated that the side effects reported more frequently with Xyzal (% in excess of placebo) were somnolence (3.8%), dry mouth (1%) and fatigue (1.3%). The Panel noted that the claim in question was based only on the conclusions of Day *et al* who found that, in a two day study, the incidence of adverse effects for levocetirizine and desloratadine were similar to placebo.

The Panel considered that it was misleading to claim in the advertisement that Xyzal had placebo-level side effects when the SPC and the prescribing information referred to some side effects which occurred more frequently with Xyzal than with placebo. The claim did not reflect all the available evidence and could not be substantiated. The Panel therefore ruled breaches of Clauses 7.2, 7.3, 7.4 and 7.9 of the Code. Claims for a product must be consistent with the SPC.

**Complaint received** **26 February 2003**

**Case completed** **27 March 2003**

# BOEHRINGER INGELHEIM and PFIZER v GLAXOSMITHKLINE

## Promotion of Seretide

**Boehringer Ingelheim and Pfizer complained that GlaxoSmithKline was promoting Seretide (salmeterol/fluticasone) for use in chronic obstructive pulmonary disease (COPD) whereas the product was only indicated for use in asthma.**

**Boehringer Ingelheim and Pfizer provided the results of market research which listed the recollections of GPs and hospital doctors immediately after being detailed by GlaxoSmithKline representatives. On several occasions clearly expressed messages had been recalled about the use of Seretide in COPD. This was a clear reference to GlaxoSmithKline's application for a marketing authorization for the use of Seretide in COPD. The market research was carried out between July 2002 and January 2003.**

**GlaxoSmithKline had told its sales force in February 2003 not to detail a specific clinical paper pertaining to Seretide in COPD but the company had not provided Boehringer Ingelheim and Pfizer with evidence that it had adequately briefed its sales teams before then. Boehringer Ingelheim and Pfizer submitted that this explained the continuing evidence from doctors who were detailed between July 2002 and January 2003 that Seretide was being advocated for the treatment of COPD.**

**GlaxoSmithKline had denied that any of its representatives' briefing materials discussed or recommended Seretide in COPD. Boehringer Ingelheim and Pfizer alleged that these materials must be at fault in that they either encouraged discussion of Seretide and COPD or at least failed to discourage such unlicensed promotion; a breach of Clause 2 of the Code was alleged.**

**The Panel noted that the complaint was based on the results of market research carried out between July 2002 and January 2003. The market research established that some health professionals recalled discussions with GlaxoSmithKline representatives about Seretide and a forthcoming new licence. There was very little detail. It was possible that the discussion of Seretide in COPD had been raised by the health professional. The Panel considered that very little evidence had been supplied by the complainants.**

**GlaxoSmithKline provided copies of representatives' briefing material. The customer Q&A briefing document (dated 22 March 2002) was clearly marked 'For internal use only – not to be left with customers. Reactive purpose only'. It instructed representatives that they could answer questions about Seretide in COPD if a customer asked. Representatives were instructed that 'Under no circumstances should the subject of the [sic] Seretide in COPD be raised proactively'. The questions and answers provided covered issues relating to the licence application and also some clinical issues. The Panel considered that it might have been more appropriate to instruct the representatives to refer clinical questions to the company's medical information department for response. The Panel considered that the briefing material was on the limits of acceptability in that regard.**

**The Panel considered that the situation was unusual as salmeterol as a single entity (GlaxoSmithKline's product Serevent) was licensed for use in COPD but in combination with fluticasone as Seretide was not. Health professionals were likely to be interested in the status of Seretide with regard to its use in COPD.**

**The Panel considered that there was no evidence that GlaxoSmithKline representatives had promoted Seretide for COPD. The Panel therefore ruled no breach of the Code.**

Boehringer Ingelheim Limited and Pfizer Limited complained about the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK Limited.

Seretide was indicated for the regular treatment of asthma where use of a combination product was appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long acting beta-2-agonist.

GlaxoSmithKline's product Serevent (salmeterol) was indicated to treat reversible airways obstruction in patients requiring long-term regular bronchodilator therapy including those with asthma and with chronic obstructive pulmonary disease (COPD). Seretide was not licensed to treat COPD.

### COMPLAINT

Boehringer Ingelheim and Pfizer provided the results of market research which listed the recollections of GPs and hospital doctors immediately after being detailed by GlaxoSmithKline representatives. On several occasions clearly expressed messages had been recalled about the use of Seretide in COPD. For example one GP specifically recalled discussing with a GlaxoSmithKline representative 'the main points [of Seretide] and also forthcoming new licence'. This was a clear reference to the application that GlaxoSmithKline had made to the European Medicines Evaluation Agency (EMEA) for a marketing authorization for the use of Seretide in COPD. Seretide was only indicated for the treatment of asthma. The market research was carried out between July 2002 and January 2003.

Boehringer Ingelheim and Pfizer expressed concern in a letter to GlaxoSmithKline in December and GlaxoSmithKline stated that it went '… to great lengths to ensure that there is no promotion of Seretide outside its product licence'. Further dialogue between the companies took place in February. GlaxoSmithKline sent details of a briefing issued to its sales force in February 2003 providing guidance not to

detail a specific clinical paper pertaining to Seretide in COPD. GlaxoSmithKline had not provided Boehringer Ingelheim and Pfizer with evidence that it had adequately briefed its sales teams prior to February 2003. Boehringer Ingelheim and Pfizer submitted that this explained the continuing evidence from doctors who were detailed between July 2002 and January 2003 that Seretide was being advocated for the treatment of COPD. Boehringer Ingelheim and Pfizer alleged that GlaxoSmithKline was promoting outside the Seretide marketing authorization in breach of Clause 3 of the Code.

Boehringer Ingelheim and Pfizer stated that the provision of any clinical data or publications to health professionals concerning an unlicensed product or indication should be the responsibility of the medical department and then only in response to a documented and unsolicited request from a customer. This information should be non-promotional. The proactive provision of such documents or information by representatives under any circumstances constituted promotion of a medicine outside its marketing authorization. If this were the process by which GlaxoSmithKline was informing doctors of the clinical evidence for Seretide in COPD, this would itself constitute a breach of Clause 3 of the Code.

GlaxoSmithKline had denied that any of its representatives' briefing materials discussed or recommended Seretide in COPD. Boehringer Ingelheim and Pfizer disputed this. These materials must be at fault in that they either encouraged representatives to discuss Seretide and COPD or at least failed to discourage such activity. As GlaxoSmithKline's materials appeared to be inadequate in preventing unlicensed promotion, a breach of Clause 15.9 of the Code was alleged.

In the light of such activity occurring and in the face of this denial by GlaxoSmithKline, Boehringer Ingelheim and Pfizer also alleged a breach of Clause 2 of the Code.

## RESPONSE

GlaxoSmithKline submitted that the market research did not supply sufficient detail for any investigation of individual cases to be undertaken.

Boehringer Ingelheim and Pfizer stated that the market research listed the recollections of GPs and hospital doctors immediately after being detailed by GlaxoSmithKline representatives. GlaxoSmithKline was familiar with such market research and in its experience it was not necessarily undertaken immediately after representatives' meetings with health professionals. It might not therefore represent immediate recall. More importantly, it did not detail the content or context of any discussion. There was no way of knowing whether the representative spontaneously raised any particular issue, or whether the matter in question was raised by the health professional as a query to which the representative responded. Accordingly there was no way of knowing whether, if such an occasion arose, the use of Seretide in COPD was raised by the health professional or the representative. If the subject had been raised by the health professional, the representative would be permitted under the Code to respond to the specific enquiry. If evidence could be produced that a representative initiated a discussion on Seretide in COPD, such an action would be contrary to the instructions in the briefing material. GlaxoSmithKline stated that it would be pleased to investigate any such instance.

There were no detail aids or leavepieces regarding the use of Seretide in COPD. There was no mention in the Seretide summary of product characteristics (SPC) of the use of Seretide in COPD.

GlaxoSmithKline explained that as Seretide did not have a licence in COPD, it would only be mentioned in briefing materials in very exceptional circumstances. A customer question and answer (Q&A) briefing document, signed off in March 2002, was produced when an early indication was received that the licence application for Seretide in COPD would have to enter the European Regulatory arbitration process, and that this could result in a significant delay before Seretide could be launched for use in COPD. As it was likely that news of this delay would leak through to the media and customers it was necessary to produce a briefing document for use if, and only if, questions were raised by customers. That the information within the document was only to be used reactively, was clear from the bolded injunction at the start of the document 'Under no circumstances should the subject of Seretide in COPD be raised proactively'. A copy of the document was provided.

GlaxoSmithKline submitted that the customer Q&A briefing document was not in breach of the Code. There had been no further briefing materials regarding the use of Seretide in COPD.

A Q&A document was also produced to give the necessary information to representatives (ref SFC/EML/02/1662). A copy was provided.

The documents (customer Q&A briefing document and the representatives' Q&A document) were sent to the representatives via an email 'Seretide in COPD licence communications' dated 28 March 2002 which contained a covering explanation of the reason for the documents. A copy of this email was provided. It clearly stated that the customer document was 'a Q&A for reactive use only if customers ask direct questions on the licence'. GlaxoSmithKline asked that the details of the contents of this email were not disclosed to Boehringer Ingelheim and Pfizer.

A copy of Calverley *et al* (2002) was provided together with a copy of the briefing document (SFC/BRD/03/5383) that was in preparation regarding this study. This briefing document had not yet received final approval, and had not been circulated to representatives.

GlaxoSmithKline did not consider that its activities or materials were, or had been, in breach of Clauses 3, 15.9 and 2 of the Code.

## PANEL RULING

The Panel noted that the complaint was based on the results of market research carried out between July

2002 and January 2003. The market research established that some health professionals recalled discussions with GlaxoSmithKline representatives about Seretide and a forthcoming new licence. There was very little detail. It was possible that the discussion of Seretide in COPD had been raised by the health professional. The Panel considered that very little evidence had been supplied by the complainants.

GlaxoSmithKline provided copies of representatives' briefing material. The customer Q&A briefing document (dated 22 March 2002) was clearly marked 'For internal use only – not to be left with customers. Reactive purpose only'. It instructed representatives that they could answer questions about Seretide in COPD if a customer asked. Representatives were instructed that 'Under no circumstances should the subject of the [sic] Seretide in COPD be raised proactively'. The questions and answers provided covered issues relating to the licence application and also some clinical issues. The Panel considered that it might have been more appropriate to instruct the representatives to refer clinical questions to the company's medical information department for response. In particular questions about data and evidence to support the application for the marketing authorization. The Panel considered that the briefing material was on the limits of acceptability in that regard.

Clause 1.2 excluded from the definition of promotion replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them but only if they related solely to the subject of the enquiry, were accurate, did not mislead and were not promotional in nature. The situation was unusual as salmeterol as a single entity (Serevent) was licensed for the use in COPD but in combination with fluticasone as Seretide was not. Health professionals were likely to be interested in the status of Seretide with regard to its use in COPD.

The Panel considered that there was no evidence that GlaxoSmithKline representatives had promoted Seretide for COPD. The Panel therefore ruled no breach of Clauses 3, 15.9 and 2.

**Complaint received** **26 February 2003**

**Case completed** **6 May 2003**

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**CASE AUTH/1423/3/03** *NO BREACH OF THE CODE*

# MEDIA/DIRECTOR v PFIZER

## Istin journal advertisement

**A letter in The Pharmaceutical Journal, headed 'Drug advertising continues to mislead', was critical of an advertisement for Istin (amlodipine) issued by Pfizer. In accordance with established practice, the matter was taken up as a complaint under the Code.**

**The letter stated that in the landmark ALLHAT (the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) study, a thiazide diuretic was shown to be superior to amlodipine in preventing heart failure, overall and for hospitalized or fatal cases, and superior to lisinopril on several endpoints. It was alleged that the claim 'ALLHATs off to Istin. With the results of the ALLHAT study lowering blood pressure with ISTIN in high risk hypertensive patients is now proven to be equivalent to a diuretic in stroke outcome. It's Istin isn't it.' was not an untruth, but it was highly selective reporting. Pfizer had neglected to add 'but if you use amlodipine (Istin) first line instead of a thiazide one out of 61 patients so treated would be admitted or die as a result of heart failure'.**

**When the author was advised that his letter would be treated as a complaint under the Code, he submitted additional comments. He referred to a comment made in the BMJ that spin doctors were countering the clear message of ALLHAT that cheaper was better, even if that just meant playing it down. Heart failure was common in the elderly population and caused much morbidity, mortality and many cases of hospital admission. The individual, community and economic burden of heart failure would continue to rise as the elderly population increased. Reducing the morbidity and mortality from heart failure was a priority for primary care trusts. Hypertension was a significant risk factor for developing heart failure. The individual components of the combined outcomes in ALLHAT were prespecified and examined as endpoints. Heart failure was a common occurrence in the ALLHAT population and a serious, albeit secondary outcome.**

**As the authors of ALLHAT stated 'chlorthalidone was superior to amlodipine in preventing heart failure, overall and for hospitalized or fatal cases'. The author of the letter stated that for every 48 patients treated for five years with amlodipine instead of chlorthalidone, one would suffer from heart failure that they would not otherwise have done. In addition, one out of 61 so treated would be admitted or die as a result of this heart failure. This was a serious clinical outcome. The editorial accompanying the publication of ALLHAT noted that 'chlorthalidone was superior to amlodipine in preventing heart failure' and that 'the increased risk of heart failure associated with amlodipine most certainly represents a drug-specific effect rather than a difference in achieved BP'. The ALLHAT authors concluded 'the results of ALLHAT indicate that thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension. They are unsurpassed in lowering BP,**

**reducing clinical events, and tolerability, and they are less costly'.**

**The Panel noted that ALLHAT compared major outcomes in high risk hypertensive patients randomized to an ACE inhibitor (lisinopril), calcium channel blocker (amlodipine) or a diuretic (chlorthalidone). The objective was to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowered the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events versus treatment with a diuretic.**

**Istin was indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist. The summary of product characteristics (SPC) stated that in hypertensive patients, Istin had been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent or an ACE inhibitor. The SPC also stated that Istin was well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.**

**The Panel noted that the primary outcome measure of ALLHAT was combined fatal CHD or non fatal MI analysed by intent to treat. Secondary outcomes were all cause mortality, stroke, combined CHD (primary outcome, coronary revascularisation, or angina with hospitalisation) and combined CVD (combined CHD, stroke, treated angina without hospitalisation, heart failure and peripheral arterial disease). There was no difference between Istin and a diuretic with regard to the primary outcome. Similarly the results for stroke (a secondary outcome measure) showed no significant difference between the two (p=0.28). The only difference in secondary outcomes was in relation to heart failure which was a component in the combined CVD secondary outcome. Compared with the chlorthalidone group the Istin group had a 38% higher risk of hospitalized/fatal heart failure (p<0.001).**

**The Panel noted that stroke was a secondary endpoint and that heart failure was one component of another secondary endpoint, ie combined CVD which included CHD or stroke or coronary revascularisation procedures or angina (hospitalized or medically treated) or congestive heart failure (CHF) (hospitalized or medically treated) or peripheral arterial disease (hospitalized or outpatient revascularisation procedure). The secondary hypothesis was given in the rationale paper as 'the following endpoints (or their incidence) will be reduced in patients randomized to amlodipine, lisinopril or doxazosin relative to those receiving chlorthalidone'. The secondary endpoints would be regarded as 'soft data' that would at best confirm or supplement the primary endpoint.**

**In the Panel's view given the circumstances, and the weight attached to the secondary endpoint data by the study authors, the omission of the heart failure data was not in itself misleading. No breach of the Code was ruled.**

A letter in The Pharmaceutical Journal of 1 March was critical of a journal advertisement (ref 1ST 275b) for Istin (amlodipine) issued by Pfizer Limited. The letter was headed 'Drug advertising continues to mislead'. In accordance with established practice, the matter was taken up as a complaint under the Code.

## COMPLAINT

The author of the letter stated that in the recent landmark study ALLHAT (The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), a thiazide diuretic, chlorthalidone, was shown to be superior to amlodipine in preventing heart failure, overall and for hospitalized or fatal cases, and superior to lisinopril on several endpoints.

The author alleged that the claim 'ALLHATs off to Istin. With the results of the ALLHAT study, lowering blood pressure with ISTIN in high risk hypertensive patients is now proven to be equivalent to a diuretic in stroke outcome. It's Istin isn't it.' was not an untruth, but it was highly selective reporting. Pfizer had neglected to add 'but if you use amlodipine (Istin) first line instead of a thiazide, one out of 61 patients so treated would be admitted to hospital or die as a result of heart failure'.

When the author was advised that his letter would be treated as a complaint under the Code, he submitted additional comments.

The author referred to a comment in the BMJ that 'The spin doctors are swinging into action to counter the clear message of ALLHAT that cheaper is better, even if that means just playing it down'.

Heart failure was common in the elderly population and was the cause of much morbidity and mortality and many cases of hospital admission. The individual, community, and economic burden of heart failure would continue to rise as the proportion of elderly persons in the population increased. Reducing the morbidity and mortality from heart failure was a priority for primary care trusts. Hypertension was a significant risk factor for developing heart failure.

The individual components of the combined outcomes in ALLHAT were prespecified and examined as endpoints. Heart failure was a common occurrence in the ALLHAT population and a serious, albeit secondary outcome. It was deemed to be of sufficient importance for the doxazosin arm of ALLHAT to be prematurely terminated, largely due to an excess of heart failure.

As the authors of ALLHAT stated 'chlorthalidone was superior to amlodipine in preventing heart failure, overall and for hospitalised or fatal cases'. The author referred to the data:

| Heart failure | chlorth-alidone | amlodi-pine | ARI | p-value | 5-year NNH |
|---|---|---|---|---|---|
| Hospital-ized | 5.7% | 7.8% | 2.1% | <0.001 | 48 |
| Fatal | 4.75% | 6.39% | 1.64% | <0.001 | 61 |

The author stated that for every 48 patients treated for 5 years with amlodipine instead of chlorthalidone, one would suffer from heart failure that they would

not have otherwise done. In addition, one out of 61 so treated would be admitted or die as a result of this heart failure. This was a serious clinical outcome.

The editorial accompanying the publication of ALLHAT noted that 'chlorthalidone was superior to amlodipine in preventing heart failure' and that 'the increased risk of heart failure associated with amlodipine most certainly represents a drug-specific effect rather than a difference in achieved BP'.

The ALLHAT authors concluded 'the results of ALLHAT indicate that thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension. They are unsurpassed in lowering BP, reducing clinical events, and tolerability, and they are less costly'.

Prescribers, and those that advised them, could only make rational and cost-effective decisions when they were aware of all the facts. Who would promote thiazides if advisers did not?

The author stated that his message was 'all hats off to chlorthalidone' and 'it's a thiazide isn't it'.

When writing to Pfizer, the Authority asked it to respond in relation to Clause 7.2 of the Code.

## RESPONSE

Pfizer referred to its rebuttal published in The Pharmaceutical Journal wherein it strongly refuted these allegations and believed it had acted within the Code in its advertisement of this important result from the ALLHAT study.

The purpose of an advertisement was to convey important medical messages that were within the licensed indications of the product to health professionals. Hypertension was a well-recognised surrogate for stroke, and as such was within the licensed indications of Istin in the context of blood pressure lowering. In contrast hypertension was a less well-accepted surrogate for the primary outcome (combined fatal coronary heart disease (CHD) and non-fatal myocardial infarction (MI)) and other secondary outcomes of the ALLHAT trial. It might therefore be considered inappropriate to promote outcomes other than stroke in conjunction with lowering blood pressure with Istin, as they would fall outside the current licensed indications of Istin. Pfizer noted that the results of the primary and secondary outcomes were comparable between Istin and chlorthalidone and as such were very positive and important results for Istin. Pfizer welcomed the opportunity to disseminate these outcome results.

Pfizer noted that the complainant had selectively commented on the heart failure data and omitted commenting on both the primary and secondary outcomes of the trial. In ALLHAT heart failure was not an outcome in its own right, and certainly was not a secondary outcome as the complainant claimed. It was a component of the secondary outcome 'combined cardiovascular disease'. There was no statistically significant difference between Istin and chlorthalidone for 'combined cardiovascular disease' and as such this was a good result for Istin. However, Pfizer considered it fell outside the current licensed indications for Istin and as such it did not promote it.

Pfizer noted that clinicians were concerned about the validity of the heart failure data. It was stated in a recent editorial on ALLHAT in the BMJ that, 'This finding [heart failure] must be viewed with caution. It should be emphasised that this was not a primary or major secondary endpoint of the study and it was not well validated'.

Pfizer also noted that chlorthalidone was a diuretic licensed to treat heart failure and as such it was not surprising that the diuretic favoured better than Istin in this outcome. The complainant pointed out a 'drug-specific effect' but the context in which it was used in the actual editorial reflected the drug-specific effect of diuretic as a treatment for heart failure. Clinical trials had shown that Istin was well tolerated in patients with moderate to severe heart failure confirming its safety in patients with heart failure. Interestingly, lisinopril (the ACE inhibitor in ALLHAT), which had a licence for the treatment of heart failure, was also noted to have more cases of heart failure than the diuretic. This finding further raised doubts around the validity of the heart failure data and in the editorial it was commented, 'It is not surprising that patients randomised to diuretic got less oedema than those randomised to ACE inhibitor or calcium channel blocker'.

The secondary endpoint 'all-cause mortality' (ie death from any cause) was no different between Istin and the diuretic, and thus the assertion by the complainant that placing patients on Istin therapy instead of thiazide diuretic cost lives was totally unfounded. This was supported by the ALLHAT editorial in the BMJ where the author stated, 'The new information also dismisses previous concerns about the safety and efficacy of calcium channel blockers for the treatment of hypertension. This sends out an important and powerful message to those who generate and publish unsound conclusions from small studies, post hoc analyses and observational data'.

Pfizer noted that the complainant's comments that the doxazosin arm of ALLHAT was prematurely terminated, largely due to an excess of heart failure, was not entirely true. The ALLHAT investigators stated, 'The decision to discontinue the doxazosin arm of the antihypertensive trial component was based on several factors. Foremost was a significantly higher incidence of combined CVD events and in particular, CHF events, for the doxazosin group compared with the chlorthalidone group. In addition, with essentially equal rates in the 2 treatment groups for the primary CHD outcome and total mortality, a beneficial effect of doxazosin at the scheduled trial termination was highly unlikely based on conditional power calculations'.

It was again worth remembering the issues around the validity of the heart failure data, which drove the differences in the secondary outcome of 'combined CVD' with doxazosin. As there was no placebo arm in ALLHAT, the investigators further commented, 'It is difficult to judge whether in ALLHAT the CHF rate with doxazosin is the same as, less than, or more than would be expected without antihypertensive drug treatment'. The same interpretation would apply for both Istin and lisinopril, and therefore causality for heart failure could not be attributed to either agent.

All the patients in ALLHAT had hypertension which Istin was licensed to treat. Patients randomised to treatment with Istin had their blood pressure lowered and also showed a concomitant lowering in their risk of stroke. It was justifiable and highly relevant to make a claim about effects on stroke which, in the UK, was the third commonest cause of mortality after heart disease and cancer and the single biggest cause of disability.

It was for these reasons that Pfizer considered that its advertisement represented a fair balance of the clinical outcomes of the ALLHAT study that it could discuss in the context of Istin promotion. Pfizer submitted that it had not breached Clause 7.2 of the Code.

## PANEL RULING

The Panel noted that a previous case, Case AUTH/1420/2/03, concerned the advertisement at issue in the case now before it. Case AUTH/1420/2/03 had not completed. One of the allegations had related to the focus on stroke outcome and the failure to refer to the heart failure data. The case now before the Panel (Case AUTH/1423/3/03) was different to the previous case.

ALLHAT was published in the Journal of the American Medical Association, December 2002. The study compared major outcomes in high risk hypertensive patients randomised to an ACE inhibitor (lisinopril), calcium channel blocker (amlodipine) or a diuretic (chlorthalidone). The objective was to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowered the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events versus treatment with a diuretic.

Istin was indicated for the treatment of hypertension, the prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist. The summary of product characteristics (SPC) stated that in hypertensive patients, Istin had been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent or an ACE inhibitor. The SPC also stated that Istin was well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

The Panel noted that the primary outcome measure of the ALLHAT study was combined fatal CHD or non fatal MI analysed by intent-to-treat. Secondary outcomes were all cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization) and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease).

There was no difference between Istin and a diuretic with regard to the primary outcome. Similarly the results for stroke (a secondary outcome measure) showed no significant difference between the two ($p=0.28$). The only difference in secondary outcomes was in relation to heart failure which was a component of the combined CVD secondary outcome. Compared with the chlorthalidone group the Istin group had a 38% higher risk of heart failure ($p<0.001$) with a 6-year absolute risk difference of 2.5% and a 35% higher risk of hospitalized/fatal heart failure ($p<0.001$).

The Panel noted that stroke was a secondary endpoint and that heart failure was one component of another secondary endpoint, ie combined CVD which included CHD or stroke or coronary revascularization procedures or angina (hospitalized or medically treated) or congestive heart failure (CHF) (hospitalized or medically treated) or peripheral arterial disease (hospitalized or outpatient revascularization procedure). The secondary hypothesis was given in the rationale paper as 'The following endpoints (or their incidence) will be reduced in patients randomised to receive amlodipine, lisinopril or doxazosin relative to those receiving chlorthalidone'. The secondary endpoints would be regarded as 'soft data' that would at best confirm or supplement the primary endpoint.

In the Panel's view given the circumstances, and the weight attached to the secondary endpoint data by the study authors, the omission of the heart failure data was not in itself misleading. No breach of Clause 7.2 of the Code was ruled.

**Proceedings commenced** **3 March 2003**

**Case completed** **4 May 2003**

# HOSPITAL DOCTOR v YAMANOUCHI PHARMA and GLAXOSMITHKLINE

## Avodart journal advertisement

**A hospital doctor complained about a journal advertisement for Avodart (dutasteride) issued by Yamanouchi Pharma and GlaxoSmithKline. The advertisement was headed 'Turn BPH [benign prostatic hyperplasia] around' followed by the claim 'The only dual inhibitor of DHT [dihydrotestosterone] production' which appeared as a strapline beneath the brand logo. The complainant alleged that the advertisement was misleading. He accepted that it was true that Avodart was 'The only dual inhibitor of DHT production', and noted that no efficacy benefits were claimed for this property. The complainant considered, however, that a reader would assume that the dual inhibition of DHT would lead to some kind of additional clinical benefit compared with a medicine like finasteride (Proscar), a selective 5-alpha-reductase inhibitor. As far as the complainant was aware no such additional benefit had been demonstrated. The complainant was concerned that the claim might entice physicians to prescribe Avodart in preference to finasteride, believing Avodart to be more efficacious.**

**The Panel had some sympathy with the view that the heading to the advertisement 'Turn BPH around' in conjunction with the claim 'The only dual inhibitor of DHT production' might be read as comparing existing treatments with Avodart. The heading referred to BPH not to BPH treatment. Avodart was the only dual inhibitor of DHT production. The advertisement did not mention any product other than Avodart. On balance the Panel decided that in general the advertisement would not be read as implying that the dual inhibition of DHT would lead to some kind of additional efficacy benefit over finasteride as alleged. The Panel ruled no breach of the Code.**

**Upon appeal by the complainant, the Appeal Board considered that both statements, 'Turn BPH around' and 'The only dual inhibitor of DHT production', were factually correct. The context in which claims appeared was important and in that regard the Appeal Board noted that the advertisement had not mentioned any product other than Avodart. On balance the Appeal Board did not consider that the advertisement implied that the dual inhibition of DHT had led to an additional efficacy benefit over finasteride in the management of BPH as alleged. The Appeal Board upheld the Panel's ruling of no breach of the Code.**

A hospital doctor complained about a journal advertisement for Avodart (dutasteride) (ref ADT/DPS/03/5160) issued by Yamanouchi Pharma Limited and GlaxoSmithKline UK Limited. The advertisement at issue appeared in Hospital Doctor (6 March 2003).

Avodart was indicated for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). It was also indicated for the reduction in the risk of acute urinary retention and surgery in patients with moderate to severe symptoms of BPH.

The advertisement was headed 'Turn BPH around' followed by the claim 'The only dual inhibitor of DHT [dihydrotestosterone] production' which appeared as a strapline beneath the brand logo.

### COMPLAINT

The complainant alleged that the advertisement was misleading and referred to the claim that Avodart was 'The only dual inhibitor of DHT production', which he accepted was a true statement. Although no efficacy benefits were claimed for this property, the complainant believed a reader would assume that the dual inhibition of DHT would lead to some kind of additional clinical benefit to a BPH sufferer over a medicine like finasteride (Proscar), a selective 5-alpha-reductase inhibitor. As far as the complainant was aware no such additional benefit had been demonstrated.

The complainant was concerned therefore that the claim might entice physicians to prescribe Avodart in preference to finasteride, which had a large safety database having been on the market for several years, believing Avodart to be more efficacious.

The Authority asked Yamanouchi and GlaxoSmithKline to respond in relation to the requirements of Clause 7.2 of the Code.

### RESPONSE

GlaxoSmithKline responded on behalf of both companies and denied that the claim 'the only dual inhibitor of DHT production' was misleading. The advertisement provided a true, non-comparative, statement of fact. No other product was referred to and therefore the claim regarding the pharmacological properties of Avodart was non-comparative. It reflected a statement in the Avodart summary of product characteristics (SPC) regarding mode of action that 'Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5-alpha-reductase isoenzymes which are responsible for the convertion of testosterone to 5-alpha-DHT'.

DHT was the primary androgenic stimulator of prostate growth and was produced from the conversion of testosterone by the enzyme 5-alpha-reductase. The enzyme existed in two isoforms, type 1 and type 2, both of which were present within benign and malignant prostate tissue. At therapeutic dosing levels, Avodart suppressed the production of DHT to very low levels, through its dual inhibition of both the type 1 and 2 isoforms of 5-alpha-reductase. The claim 'the only dual inhibitor of DHT production' was therefore factual and accurate, and described the pharmacological properties of Avodart. There was no claim made regarding the benefit or efficacy of dual inhibition.

With respect to the complainant's reference to finasteride having a much larger safety database, the advertisement made no claim regarding safety or comparative safety.

## PANEL RULING

The Panel had some sympathy with the complainant in that the heading to the advertisement 'Turn BPH around' in conjunction with the claim 'The only dual inhibitor of DHT production' might be read as comparing existing treatments with Avodart. The heading referred to BPH not to BPH treatment. Avodart was the only dual inhibitor of DHT production. The advertisement did not mention any product other than Avodart. On balance the Panel decided that in general the advertisement would not be read as implying that the dual inhibition of DHT would lead to some kind of additional efficacy benefit over finasteride as alleged. The Panel ruled no breach of Clause 7.2 of the Code.

## APPEAL BY THE COMPLAINANT

The complainant noted that 'The only dual inhibitor of DHT production' was a true statement and that no direct claim was made regarding the benefit or efficacy of this characteristic. However it was a statement that differentiated Avodart from the other member of its class, by placing it in an advertisement under the heading 'Turn BPH around'; it also implied that it had a unique relevance to the management of BPH. Avodart's dual inhibition of DHT had failed to demonstrate any clinical advantages in BPH over single inhibition provided by finasteride. The complainant alleged that the claim breached Clause 7.2 of the Code as it misled through implication.

The complainant noted that the fact that this statement had been included at all by the companies suggested that they considered it might influence prescribing by the assumption of the reader that dual inhibition was a clinically important property in the management BPH.

## COMMENTS FROM YAMANOUCHI AND GLAXOSMITHKLINE

GlaxoSmithKline responded on behalf of both companies and noted that the complainant agreed that the statement 'The only dual inhibitor of DHT production' was true and accurate. The statement provided a factual and clinically accurate description of the pharmacological properties of Avodart. There was no claim or implication made regarding the benefits or efficacy of dual inhibition. The complainant had noted ''The only dual inhibitor of DHT production' was a true statement and no direct claim was made regarding the benefit or efficacy of this characteristic'. No other product was referred to and thus, the statement regarding the pharmacological properties of Avodart was non-comparative and not misleading.

GlaxoSmithKline noted that the complainant had linked the headline 'Turn BPH around' to the strapline about dual inhibition which appeared elsewhere in the advertisement. BPH was a progressive disease characterised by increasing prostate volume, increasing severity of symptoms, deterioration in urinary flow rate and an increasing risk of acute urinary retention and BPH-related surgery. 'Turn BPH around' was a statement to illustrate that the disease process could be 'turned around' by shrinking the prostate, reducing symptoms, improving urinary flow rate and reducing the risk of acute urinary retention and BPH-related surgery. GlaxoSmithKline submitted that achieving these reductions where otherwise the disease and risk would continue to progress, accurately reflected a 'turning around' of the condition. It not merely stabilised or halted, but positively returned the patient to an earlier disease stage.

GlaxoSmithKline noted that Avodart was evaluated in 4325 men with symptomatic BPH in three identical, pivotal, 2-year, double-blind, placebo-controlled clinical trials and the results were pooled for analysis (Roehrborn *et al* 2002). Data from these trials demonstrated that Avodart 0.5mg significantly reduced prostate volume by 25.7% ($p<0.001$), significantly improved symptoms (as measured by the American Urological Association Symptom Index – AUA-SI) by 4.5 points ($p<0.001$), significantly improved urinary flow rate by 2ml/s ($p<0.001$), and significantly reduced the risk of acute urinary retention (57% risk reduction; $p<0.001$) and BPH-related surgery (48% risk reduction; $p<0.001$). There was no claim or implication made in the advertisement that 'turning BPH around' was unique to Avodart. Proscar, the only other product in the class, had shown similar effects as described in its SPC, which stated:

> 'Proscar is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:
>
> – cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH.
>
> – reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy'.

GlaxoSmithKline submitted that the advertisement was designed to illustrate two points; what Avodart did and how it worked. The mode action of Avodart was linked to its efficacy because the mode of action was essentially a description of how it produced its effect. There was no direct or indirect comparison with finasteride, or indeed with any other product in this therapeutic area.

GlaxoSmithKline noted that the complainant commented that the inclusion of the statement suggested that the companies must consider that they could influence prescribing by the addition of this statement, otherwise why would they include it. The addition of the statement 'The only dual inhibitor of DHT production' was not to show any comparative clinical or other comparative benefit with dual inhibition, but to illustrate that Avodart had a new and different mode of action, and thus provided an additional treatment choice for prescribers.

### FURTHER COMMENTS FROM THE COMPLAINANT

The complainant alleged that the statement 'The only dual inhibitor of DHT production' differentiated Avodart from the other member of its class, Proscar. There might be *in vitro* or animal data to suggest that dual inhibition had a relevance to prostatic growth but the complainant had not seen any data from phase 3 studies to suggest it had clinical relevance. The fact that GlaxoSmithKline/Yamanouchi were not making any clinical comparisons with Proscar suggested that any phase 3 studies performed with Proscar as an active comparator were at best equivocal. Therefore Avodart's action in BPH, like Proscar's, was mediated through its type 2 inhibition not dual inhibition and thus it did not have 'a new and different mode of action', the reason the companies had given for inclusion of the statement in the advertisement. The complainant alleged that the statement 'The only dual inhibitor of DHT production' suggested that dual inhibition had a unique relevance to the management of BPH and therefore it breached Clause 7.2 of the Code, as it misled through implication.

### APPEAL BOARD RULING

The Appeal Board considered that the strap line 'The only dual inhibitor of DHT production', in conjunction with the heading 'Turn BPH around', might be read as implying an advantage for Avodart compared to existing treatments for BPH. However, the Appeal Board considered that both statements were factually correct. The context in which claims appeared was important and in that regard the Appeal Board noted that the advertisement had not mentioned any product other than Avodart. On balance the Appeal Board did not consider that the advertisement implied that the dual inhibition of DHT had led to additional efficacy benefit over finasteride in the management of BPH as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal was unsuccessful.

**Complaint received** **4 March 2003**

**Case completed** **19 June 2003**

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**CASE AUTH/1427/3/03**

# SOCIAL AUDIT v GLAXOSMITHKLINE

## Promotion of Seroxat

**Social Audit complained about the promotion of Seroxat (paroxetine) by GlaxoSmithKline referring in particular to a 'Reactive Key Messages and Issues Document'. GlaxoSmithKline stated that this document was used, in house, between 19 December 2001 and May 2002 to brief relevant employees to respond to media enquiries about Seroxat, a selective serotonin reuptake inhibitor (SSRI).**

**Social Audit's concern was that GlaxoSmithKline knew, or ought to have known, (a) that significant numbers of patients found it both difficult and distressing to stop taking Seroxat when they decided to do so – even when they gradually reduced the dosage over long periods of time; (b) that significant numbers of patients were not advised by their doctors that this might be so; (c) that the dangers of mistaking withdrawal symptoms for relapse were real; and above all (d) that deep misunderstandings surrounded the meaning of 'dependence'. Social Audit stated that it had supplied ample evidence of these problems and the reasons for them, both from learned journals and from patient testimonies.**

**The World Health Organisation (WHO) continued to express concern about the situation. The WHO Uppsala Monitoring Centre's database of adverse drug reactions identified paroxetine above all other medicines as causing withdrawal symptoms indicative of 'dependence' – and WHO was concerned about the confusion that surrounded the word 'dependence'.**

**At its meeting on 27 September 2002, the WHO Expert Committee on Drug Dependence again drew attention to this problem, and would shortly publish a report on it.**

**The WHO statement generally accorded with public understanding. People generally considered and described themselves 'addicted' to or 'dependent' on a medicine when they tried hard to stop taking it and found they could not. Many patients said they had experienced this with paroxetine and other SSRIs.**

**GlaxoSmithKline had emphasised that Seroxat was 'non habit-forming,' not 'addictive' and not a medicine of 'dependence' in the Reactive Key Messages and Issues Document. This was an important document that should have been prepared with particular care – a direct link between the company and the consumers of its products, and the public at large.**

**Social Audit was concerned about the statement 'Seroxat is not addictive. There are well-defined international criteria for drug dependency and addiction and Seroxat is clearly shown as being neither addictive nor causing dependence'. The categorical statement, 'Seroxat is not addictive', in the absence of any qualification, was highly misleading. The assertion, 'Seroxat is clearly shown as being neither addictive nor causing dependence', was also highly misleading and inconsistent with the summary of product characteristics (SPC). No such thing had been 'clearly shown': the lack of available evidence clearly precluded any such statement (EMEA, 2000). This was tantamount to claiming a medicine was safe, without qualification.**

**This categorical denial of risk was inappropriate: it should at least be as circumspect as the message relayed to health professionals in the SPC. The European Medicines Evaluation Agency (EMEA)/Committee for Proprietary Medicinal Products (CPMP) (2000) found 'The available clinical evidence does not suggest that the SSRIs cause dependence. However the lack of evidence does not prove the absence of a problem…'; 'For the majority of compounds, evidence from well-designed preclinical studies with respect to dependency and withdrawal was incomplete …'; 'The available preclinical and clinical evidence does not suggest that SSRIs cause dependence'.**

**Social Audit noted the phrase 'Discontinuation symptoms are completely different to addiction or dependence …' and alleged that the term 'discontinuation symptoms' was inappropriate and highly misleading – in suggesting that the symptoms experienced on stopping medication were different from 'withdrawal symptoms,' which they were not. Persistent use of the term 'discontinuation' was not consistent with the SPC. The EMEA (2000) evaluation on which GlaxoSmithKline otherwise relied stated 'The term 'withdrawal reactions' should be used, not 'discontinuation reactions', as has been proposed by some marketing authorisation holders'.**

**Similarly, the Committee on Safety of Medicines (CSM)/Medicines Control Agency (MCA) (26 March 1998) concluded 'that it would be inappropriate to change medical terminology in this way'. In effect, GlaxoSmithKline was claiming that the symptoms experienced when trying to stop taking the medicine were not withdrawal symptoms at all. This was not true. The whole point of the regulatory decisions by the EMEA and the CSM was that withdrawal symptoms and discontinuation symptoms should not be differentiated – which GlaxoSmithKline had persisted in doing.**

**The statement 'The European Regulatory Body the CPMP (Committee for Proprietary Medicinal Products) have recently completed (April 2000) a thorough review of safety data collected following the discontinuation of all SSRIs and other newer *serotonergic* antidepressant medications. The MCA (Medicine Control Agency) and CPMP have concluded that SSRIs do not cause dependency/ addiction' was misleading, in the absence of any qualification. For lack of evidence, both the CSM and the EMEA were a great deal more tentative in their conclusions. GlaxoSmithKline had wrongly concluded that lack of clear evidence of dependence was equivalent to clear evidence of lack of dependence.**

**With regard to the statement 'There has been no reliable scientific evidence from either preclinical studies, long term clinical trials or clinical experience, to suggest that 'Seroxat' is addictive, shows dependence or is a drug of abuse', Social Audit stated that GlaxoSmithKline again relied on lack of evidence to make exaggerated, inaccurate and misleading assertions. In fact, dependence syndrome had been reported for all SSRIs through the Uppsala Monitoring Centre (UMC), and paroxetine (with fluoxetine and sertraline) was among the top 30 medicines for which drug dependence had ever been reported to the UMC (to June 2002).**

**There was also evidence of abuse from the US Drug Abuse Warning Network which had published data received from a sample of hospitals operating 24-hour emergency departments, in 21 US metropolitan areas, of episodes involving deliberate use of prescribed/diverted medicines. Accidental overdose or adverse reactions were excluded, unless these occurred in combination with an illicit medicine. Benzodiazepines accounted for 8% of mentions; antidepressants for 6% of mentions. In 2000, the most frequently mentioned SSRIs were: citalopram (3,458 mentions), which more than doubled from 1999 to 2000; sertraline (6,670 mentions), which was unchanged from the previous 2 years; fluoxetine (7,939 mentions), which decreased 19 percent from 1998 to 2000; and paroxetine (8,020 mentions), which rose 105 percent from 1994 to 2000.**

**In relation to the statement 'As recommended by the British National Formulary (BNF) and the European Medicines Evaluation Agency (EMEA), the likelihood of discontinuation symptoms is minimised by gradually tapering the daily dose', Social Audit noted that neither the BNF nor the EMEA statement used the word 'minimise'. It was inappropriate because it added to the impression that withdrawal reactions might readily be controlled although, 'as yet there is no controlled data to recommend its effectiveness, the length of time over which it should occur or the minimum dose that one should taper to' (Haddad, 2001). The BNF proposed a six month taper in patients ending long-term treatment: that made it quite clear that it could be very hard to stop, even if many people managed well.**

**Social Audit stated that the messages in GlaxoSmithKline's Reactive Key Messages and Issues Document demonstrated pedantic and unyielding reliance on technical definitions and interpretations that almost defied public understanding. These messages failed to recognise and address the widespread and evident controversy and confusion over definitions and meanings, as explained above. The company fell far short of Code requirements to provide clear, reliable and balanced information.**

**Social Audit noted that in its previous complaint, Case AUTH/1318/5/02, it offered to drop its appeal if GlaxoSmithKline accepted the need to properly address the problems Social Audit had described. These had become progressively more serious and widespread over the years. The company had failed to rise to the occasion, and the promotional materials about which Social Audit complained gave evidence of an established pattern of unacceptable behaviour. On these grounds, Social Audit alleged a breach of Clause 2 of the Code in that GlaxoSmithKline had been and was involved in promotional activities that brought discredit upon, or reduced confidence in, the pharmaceutical industry.**

**The Panel noted that both parties referred to a previous case, Case AUTH/1318/5/02, wherein Social Audit complained about statements made about Seroxat in relation to addiction, dependency and discontinuation symptoms which appeared in media articles attributed to the UK Director of Corporate Media, GlaxoSmithKline. The Panel had decided that on the evidence before it, it was not possible to determine precisely what had been said; in such circumstances it had no option other than to make rulings of no breach of the Code. These rulings were appealed by Social Audit. The Appeal Board rulings were noted by the Panel; breaches of the Code had been ruled.**

**The Panel noted that in Case AUTH/1318/5/02 it had not ruled on the content of the briefing document as such as there was no complaint about it. The complaint concerned what had been said and the briefing document was provided by GlaxoSmithKline in its response to the complaint. The Appeal Board could only consider rulings made by the Panel. It could not rule on other matters as this would be outside the Constitution and Procedure.**

**In Case AUTH/1318/5/02 GlaxoSmithKline had provided the requisite undertaking and assurance to avoid a similar breach of the Code in the future. A form of undertaking and assurance related not only to the material the subject of the complaint but also to any other similar material. GlaxoSmithKline had undertaken to ensure that all relevant documentation was withdrawn and that future documentation and verbal information provided, including internal briefing documents, complied with this undertaking. The undertaking had been received on 5 November 2002. The briefing document at issue in the present case, Case AUTH/1427/3/03, had thus been withdrawn pursuant to the undertaking in Case AUTH/1318/5/02.**

**Turning to the present case, Case AUTH/1427/3/03, the Panel noted that there was no evidence that the material at issue had been used after GlaxoSmithKline had given the undertaking in Case AUTH/1318/5/02.**

**The Panel considered that there were differences between the previous case and Case AUTH/1427/3/03 which concerned statements in The Reactive Key Messages and Issues Document. The Panel did not accept GlaxoSmithKline's suggestion that the matter had been fully considered in Case AUTH/1318/5/02. Whilst the Appeal Board referred to the document now at issue in Case AUTH/1318/5/02 it made no ruling upon it as the complaint had concerned what the spokesperson was reported to have said. The previous case was nonetheless relevant.**

**The Panel considered that GlaxoSmithKline needed to be extremely careful about references to addiction, withdrawal symptoms and discontinuation symptoms. People's understanding of these terms differed depending on their background. The position was complex. The complaint related to the content of the Reactive Key Messages and Issues Document which as a briefing document was used to assist staff with media enquiries and thus needed to be in accordance with the Code. Given that the information might be provided directly or indirectly to the general public it was beholden upon the company to ensure that the terms used within the document were explained in such a way as to be meaningful and unambiguous to the intended audience.**

**In relation to the statements 'Seroxat is not addictive' and '… Seroxat is clearly shown as being neither addictive nor causing dependence', the Panel noted that the patient information leaflet (PIL) in force at the relevant time stated 'Remember that you cannot become addicted to Seroxat'. The content of the PIL was not a matter that came within the scope of the Code. The use of statements from the PIL and/or SPC in other material was potentially covered by the Code. The Code required that it must not be stated that a product had no side-effects, toxic hazards or risks of addiction. The Panel also noted Section 4.8 of the SPC. The Panel considered given Section 4.8 of the SPC, the ultimate audience and people's differing understanding of the meaning of addiction and dependence the claims 'Seroxat is not addictive', 'Seroxat is clearly shown as being neither addictive nor causing dependence' were misleading. Breaches of the Code were ruled.**

**In relation to the phrase 'Discontinuation symptoms are completely different to addiction or dependence …', the Panel noted its general comments above about addiction, discontinuation and withdrawal symptoms. The Panel noted the CPMP Proposal for Principles of SPC Wording on Withdrawal Reactions for SSRIs to be harmonised throughout the European Union (April 2000) stated that 'The term 'withdrawal reactions' should be used, not 'discontinuation reactions'. It should be made clear that withdrawal reactions by themselves are insufficient to imply dependence'. The Panel also noted Section 4.8 of the SPC, Undesirable Effects. The Panel considered that insufficient information had been provided about discontinuation; it had not been placed sufficiently within the regulatory and clinical framework. Breaches of the Code were ruled. The Code required that the promotion of a medicine must not be inconsistent with the SPC. The Panel did not consider that the document at issue constituted promotion of Seroxat and no breach was accordingly ruled.**

**The Panel noted that the bullet point 'The European Regulatory Body the CPMP (Committee for Proprietary Medicinal Products) have recently completed (April 2000) a thorough review of safety data collected through the discontinuation of all SSRIs and other newer serotonergic antidepressant medications. The MCA (Medicines Control Agency) and CPMP have concluded that SSRIs do not cause dependency/addiction' appeared within the section headed 'Addiction/Dependence'. One of the CPMP Position Paper recommendations was that 'The available evidence does not suggest that SSRIs cause dependence. However the lack of evidence for dependence does not prove the absence of a problem and any evidence which will emerge or will be produced should continue to be evaluated'. The Panel considered that the bullet point in the**

**document at issue was unequivocal and thus not a fair reflection of the CPMP recommendation. Breaches of the Code were ruled.**

**In relation to the statement in the document at issue that 'There has been no reliable evidence from either preclinical studies, long term clinical trials or clinical experience, to suggest that Seroxat is addictive, shows dependence or is a drug of abuse', the Panel considered that its comments and rulings above were relevant and also noted Section 4.8 of the SPC. The Panel considered that the statement was unequivocal and not a fair reflection of the SPC. The Panel ruled breaches of the Code.**

**The Panel considered that the statement in the document at issue 'As recommended by the British National Formulary (BNF) and the European Medicines Evaluation Agency (EMEA), the likelihood of discontinuation symptoms is minimized by gradually tapering of the daily dose' was too dogmatic and did not reflect the available evidence. The Panel noted that Section 4.3 of the BNF September 2001, Antidepressant drugs, gave general advice on dose titration upon withdrawal and further noted that 'SSRIs have been associated with a specific withdrawal syndrome'. The paroxetine entry referred to CSM advice that withdrawal syndrome was reported to the CSM more commonly with paroxetine than with other SSRIs. The Panel noted its rulings above. The Panel ruled breaches of the Code.**

**The Panel noted its rulings above and considered, taking all the circumstances into account, on balance, that a ruling of a breach of Clause 2, which was reserved as a sign of particular censure, was not warranted.**

Social Audit Ltd complained about the promotion of Seroxat (paroxetine) by GlaxoSmithKline UK Limited referring in particular to a 'Reactive Key Messages and Issues Document' dated 19 December 2001. GlaxoSmithKline stated that the Reactive Key Messages and Issues Document was an internal document in use between 19 December 2001 and May 2002 and was used to brief relevant employees to respond to media enquiries about Seroxat.

Seroxat was an antidepressant which belonged to the group of medicines known as selective serotonin reuptake inhibitors (SSRIs).

## COMPLAINT

Social Audit stated that it was disappointed that its concerns had not been addressed as an integral part of its earlier complaint (Case AUTH/1318/5/02). It was up to the Authority to see that the Code was upheld.

Social Audit's concern was that GlaxoSmithKline knew, or ought to have known, (a) that significant numbers of patients found it both difficult and distressing to stop taking Seroxat when they decided to do so – even when they gradually reduced the dosage over long periods of time; (b) that significant numbers of patients were not advised by their doctors that this might be so; (c) that the dangers of mistaking withdrawal symptoms for relapse were real; and above all (d) that deep misunderstandings surrounded the meaning of 'dependence'. Social Audit stated that it had supplied ample evidence of these problems and the reasons for them, both in citations from learned journals and in testimony from patients.

The World Health Organisation (WHO) continued to express concern about the situation. The WHO Uppsala Monitoring Centre's database of ADRs identified paroxetine above all other medicines as causing withdrawal symptoms indicative of 'dependence' – and WHO was concerned about the confusion that surrounded the word 'dependence'.

> 'There is obviously some confusion about the concept of dependence ... The simplest definition of drug dependence given by WHO is 'a need for repeated doses of the drug to feel good or to avoid feeling bad' (WHO, Lexicon of alcohol and drug terms, 1994). When the patient needs to take repeated doses of the drug to avoid bad feelings caused by withdrawal reactions, the person is dependent on the drug. Those who have difficulty coming off the drug even with the help of tapered discontinuation should be regarded as dependent, unless a relapse into depression is the reason for their inability to stop the antidepressant medication. … In general, all unpleasant withdrawal reactions have a certain potential to induce dependence and this risk may vary from person to person. Dependence will not occur if the withdrawal symptoms are so mild that all patients can easily tolerate them. With increasing severity, the likelihood of withdrawal reactions leading to dependence also increases …' (WHO Drug Information, 1998).

At a meeting in September 2002, (which Social Audit attended by invitation), the WHO Expert Committee on Drug Dependence again drew attention to this problem, and would shortly publish a report on it.

The above WHO statement generally accorded with public understanding. People generally considered and described themselves 'addicted' to or 'dependent' on a medicine when they tried hard to stop taking it and found they could not. Many patients said they had experienced this with paroxetine and other SSRIs.

GlaxoSmithKline had emphasised that Seroxat was 'non habit-forming,' not 'addictive' and not a medicine of 'dependence'. It did so in the Reactive Key Messages and Issues Document. This was an important document that should have been prepared with particular care – a direct link between the company and the consumers of its products, and the public at large.

Social Audit was concerned about the statement 'Seroxat is not addictive. There are well-defined international criteria for drug dependency and addiction and Seroxat is clearly shown as being neither addictive nor causing dependence'. The categorical statement, 'Seroxat is not addictive', in the absence of any qualification, was highly misleading. The assertion, 'Seroxat is clearly shown as being neither addictive nor causing dependence', was also highly misleading and inconsistent with the summary of product characteristics (SPC). No such thing had been 'clearly shown': the lack of available evidence

clearly precluded any such statement (EMEA, 2000). This was tantamount to claiming a medicine was safe, without qualification. This categorical denial of risk was inappropriate: it should at least be as circumspect as the message relayed to health professionals in the SPC. The European Medicines Evaluation Agency (EMEA)/Committee for Proprietary Medicinal Products (CPMP) (2000) found 'The available clinical evidence does not suggest that the SSRIs cause dependence. However the lack of evidence does not prove the absence of a problem…'; 'For the majority of compounds, evidence from well-designed preclinical studies with respect to dependency and withdrawal was incomplete …'; 'The available preclinical and clinical evidence does not suggest that SSRIs cause dependence'.

Social Audit noted the phrase 'Discontinuation symptoms are completely different to addiction or dependence …' and alleged that the term 'discontinuation symptoms' was inappropriate and highly misleading – in suggesting that the symptoms experienced on stopping medication were different from 'withdrawal symptoms,' which they were not. Persistent use of the term 'discontinuation' was not consistent with the SPC (Section 3.2). The EMEA (2000) evaluation on which GlaxoSmithKline otherwise relied stated 'The term 'withdrawal reactions' should be used, not 'discontinuation reactions', as has been proposed by some marketing authorisation holders'.

Similarly, the Committee on Safety of Medicines (CSM)/Medicines Control Agency (MCA) (26 March 1998) concluded 'that it would be inappropriate to change medical terminology in this way'. In effect, GlaxoSmithKline was claiming that the symptoms experienced when trying to stop taking the medicine were not withdrawal symptoms at all. This was clearly not true. The whole point of the regulatory decisions by the EMEA and the CSM was that withdrawal symptoms and discontinuation symptoms should not be differentiated – which GlaxoSmithKline had persisted in doing.

The statement 'The European Regulatory Body the CPMP (Committee for Proprietary Medicinal Products) have recently completed (April 2000) a thorough review of safety data collected following the discontinuation of all SSRIs and other newer *serotonergic* antidepressant medications. The MCA (Medicine Control Agency) and CPMP have concluded that SSRIs do not cause dependency/ addiction' was misleading, in the absence of any qualification. For lack of evidence, both the CSM and the EMEA were a great deal more tentative in their conclusions. GlaxoSmithKline had wrongly concluded that lack of clear evidence of dependence was equivalent to clear evidence of lack of dependence.

With regard to the statement 'There has been no reliable scientific evidence from either preclinical studies, long term clinical trials or clinical experience, to suggest that 'Seroxat' is addictive, shows dependence or is a drug of abuse', Social Audit stated that GlaxoSmithKline again relied on lack of evidence to make exaggerated and misleading assertions. Nor were they accurate. In fact, dependence syndrome had been reported for all SSRIs through the Uppsala Monitoring Centre (UMC), and paroxetine (with fluoxetine and sertraline) was among the top 30 medicines for which drug dependence had ever been reported to the UMC (to June 2002). Details were provided.

There was also some evidence of abuse from the US Drug Abuse Warning Network (DAWN) which had recently published tabulations of reports received from a sample of hospitals operating 24-hour emergency departments, in 21 US metropolitan areas, of episodes involving deliberate use of prescribed/ diverted medicines. Details were provided.

In relation to the statement 'As recommended by the British National Formulary (BNF) and the European Medicines Evaluation Agency (EMEA), the likelihood of discontinuation symptoms is minimised by gradually tapering the daily dose', Social Audit noted that neither the BNF nor the EMEA statement used the word 'minimise'. It was inappropriate because it added to the impression that withdrawal reactions might readily be controlled although, 'as yet there is no controlled data to recommend its effectiveness, the length of time over which it should occur or the minimum dose that one should taper to' (Haddad, 2001). The BNF proposed a six month taper in patients ending long-term treatment: that made it quite clear that it could be very hard to stop, even if many people managed well.

The messages in GlaxoSmithKline's Reactive Key Messages and Issues Document demonstrated pedantic and unyielding reliance on technical definitions and interpretations that almost defied public understanding and failed to recognise and address the widespread and evident controversy and confusion over definitions and meanings. The company fell far short of Code requirements to provide clear, reliable and balanced information, as specified below. Specifically, Social Audit contended that the document fell short of the following Code requirements:

'…. All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks ….' (Article 7: World Health Organisation, Ethical criteria for medicinal drug promotion, 1998).

'Information must be provided with objectivity, truthfulness and in good taste, accurate, fair and objective and presented in such a way as to conform … to high ethical standards' (I.2) … based on an up-to-date evaluation of evidence that is scientifically valid and should not give an incorrect or misleading impression (I.3) …'… in 'Communications to the Public' … all information 'should be accurate, fair and not misleading', and companies 'should adhere to the highest standards of accuracy' (I.7). (IFPMA Code)

'Information about medicinal products must be accurate, balanced, fair, objective and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal

product concerned. It should be based on an up-to-date evaluation of scientific evidence and reflect that evidence clearly. It must not mislead by distortion, undue emphasis, omission or in any other way.' (EFPIA Code, Article 3)

With regard to the ABPI Code, Social Audit cited the following:

'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication.' (Clause 7.2)

'Information about medicines made available to the public ... must be … presented in a balanced way … and must not … be misleading with respect to the safety of the product.' (Clause 20.2)

As stated above, use of the term 'discontinuation symptoms' instead of 'withdrawal symptoms' was inconsistent with the SPC. GlaxoSmithKline would not be allowed to use the term 'discontinuation symptoms' in statements directed to prescribers. It was a flagrant breach of both the spirit and letter of the Code to do so in communication (via the press and media) with consumers. (Clause 3.2)

Social Audit noted that in its previous complaint, it offered to drop its appeal if GlaxoSmithKline accepted the need to properly address the problems Social Audit had described. These had become progressively more serious and widespread over the years. The company had failed to rise to the occasion, and the promotional materials about which Social Audit complained gave evidence of an established pattern of unacceptable behaviour. On these grounds, Social Audit alleged a breach of Clause 2 of the Code in that GlaxoSmithKline had been and was involved in promotional activities that brought discredit upon, or reduced confidence in, the pharmaceutical industry.

References and further data on which Social Audit relied were provided in relation to Case AUTH/1427/3/03.

## RESPONSE

GlaxoSmithKline submitted that the document at issue was developed for reactive use in response to media enquiries about Seroxat; it was not used to promote Seroxat. This position was supported by the ruling of the Appeal Board in Case AUTH/1318/5/02 wherein it was stated that 'The statements were issued to the media and as such did not constitute the promotion of Seroxat'. Further, in this case Social Audit had not produced any further evidence of information made available to the public to which Clauses 1.1 and 20.2 of the Code would apply. Therefore GlaxoSmithKline suggested that the matter had already been fully considered by the Panel in Case AUTH/1318/5/02 and GlaxoSmithKline had given appropriate undertakings which it would continue to abide by.

GlaxoSmithKline nonetheless submitted that the information contained in the document was consistent with the Seroxat SPC, patient information leaflet (PIL) and published data as of December 2001. Furthermore, GlaxoSmithKline considered that the document was factual and balanced. Any issues that Social Audit had concerning the wording of the Seroxat SPC and PIL or the safety of Seroxat should be taken up with the MCA. As noted in the Appeal Board ruling in Case AUTH/1318/5/02, it was not the role of the Authority to assess these.

As part of the proceedings for Case AUTH/1318/5/02, GlaxoSmithKline had provided evidence to support all the statements subject to the current complaint. As the document at issue was discontinued almost a year ago, GlaxoSmithKline relied on these previous submissions and documents in dealing with this complaint.

GlaxoSmithKline disagreed with the assertion that the statement 'Seroxat is not addictive' was misleading. In fact the MCA had approved a statement (intended for a lay audience) in the Seroxat PIL that clearly stated 'Seroxat is not addictive'. A copy of the Seroxat PIL current throughout the period in which this item was in use was provided. Furthermore Section 4.8 of the Seroxat SPC and the EMEA/CPMP April 2002 position paper supported the point that Seroxat and other SSRIs did not cause addiction or dependence.

GlaxoSmithKline disagreed that the term 'discontinuation symptoms' was inappropriate and misleading. While the SPC referred to withdrawal symptoms, the terms 'discontinuation reactions/symptoms' and 'withdrawal reactions/symptoms' were used interchangeably by health professionals for describing symptoms on stopping treatment. Therefore, GlaxoSmithKline considered that it was justified in using this term, particularly when quoting from the paper by Haddad *et al* entitled 'Antidepressant discontinuation reactions are preventable and simple to treat'.

GlaxoSmithKline rejected the complaint that the statement 'The European Regulatory body the CPMP have recently completed (April 2000) a thorough review …' was misleading. In GlaxoSmithKline's opinion this statement was a valid conclusion of the EMEA/CPMP position paper.

The statement that 'there has been no reliable scientific evidence either from preclinical studies, long term clinical trials or clinical experience, to suggest Seroxat is addictive, shows dependence or is a drug of abuse' was a statement of fact; it was neither inaccurate nor misleading.

Finally, noting that the document was intended to provide an overview of relevant information in response to enquiries from the media, GlaxoSmithKline considered that the statement 'As recommended by the British National Formulary (BNF) and the European Medicines Evaluation Agency (EMEA), the likelihood of discontinuation symptoms is minimised by gradually tapering the daily dose' was an accurate summary of the BNF and EMEA statements.

In summary, GlaxoSmithKline did not accept that this briefing document, now discontinued, was in breach of Clauses 3.2, 7.2 or 20.2 of the Code. GlaxoSmithKline continued to uphold its previous undertaking with

respect to the ruling in Case AUTH/1318/5/02. Furthermore, GlaxoSmithKline strenuously denied that a breach of Clause 2 had occurred.

## PANEL RULING

The Panel noted that both parties referred to a previous case; Case AUTH/1318/5/02 wherein Social Audit complained about statements made about Seroxat in relation to addiction, dependency and discontinuation symptoms which appeared in media articles attributed to the UK Director of Corporate Media, GlaxoSmithKline. The Panel had decided that on the evidence before it, it was not possible to determine precisely what had been said; in such circumstances it had no option other than to make rulings of no breach of the Code. These rulings were appealed by Social Audit; the Appeal Board ruling recorded, *inter alia*, the following:

> 'The Appeal Board noted that Section 4.8 of the Seroxat SPC stated 'In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of 'Seroxat'. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering be carried out'. The Appeal Board also noted the 'Reactive and Key Messages and Issues Document' (September 2001) stated 'Abrupt stopping of any antidepressant can result in a small number of patients experiencing discontinuation symptoms'; this was updated in December 2001 to read 'Stopping any antidepressant can result in some patients experiencing discontinuation symptoms'.
>
> The Appeal Board noted GlaxoSmithKline's submission that the Director of Corporate Media UK was one of only three employees working in a very busy environment. He was an experienced senior member of staff fully aware of the Seroxat briefing documents. There could be no absolute certainty as to precisely what was said. At the appeal hearing GlaxoSmithKline's representatives stated that if the Director of Corporate Media UK had been reported accurately then there was a breach of the Code. In its original response GlaxoSmithKline had accepted that if the Director of Corporate Media UK had made the statement 'There have been one or two reports of discontinuation symptoms with abrupt cessation' then a breach of the Code would have occurred.
>
> The Appeal Board noted the parties' submissions regarding the various definitions of 'dependence', 'withdrawal symptoms/reactions', 'discontinuation symptoms/reactions' and 'addiction'. People's understanding of these terms differed depending on their background. The Appeal Board noted that at the appeal the GlaxoSmithKline representatives stated that the Seroxat patient information leaflet (PIL) stated that Seroxat was not addictive.
>
> It was not the Appeal Board's role to assess the safety of a medicine or to approve the contents of its SPC or PIL; these were roles for the regulatory authorities. In the case now before it the Appeal Board had to decide firstly whether the Director of Corporate Media UK had been quoted accurately and, if so, whether what was said met the requirements of the Code.
>
> The Appeal Board was concerned that the quotations were not consistent with the briefing documents. The Appeal Board considered that given the importance and sensitivity of the matter, the company must be very clear about the issues to avoid confusion. This was particularly important when providing information directly or indirectly to the public about side effects. In the Appeal Board's view the briefing documents did not sufficiently address the need for caution. The Appeal Board considered that although there was no written/recorded evidence of the interviews available it was very unlikely that one person would be misquoted twice on the same issue, especially considering the sensitivity of the matter. The Appeal Board considered that on the balance of probability the Director of Corporate Media UK had been quoted accurately. It was misleading to state that 'There's no reliable scientific evidence to show that they [Seroxat or other SSRIs] cause withdrawal symptoms …' or that 'There have been one or two reports of discontinuation symptoms with abrupt cessation' when the SPC clearly stated that 'withdrawal symptoms have been reported on stopping treatment'. The information supplied by the GlaxoSmithKline spokesperson to the press was misleading with respect to withdrawal symptoms. The Appeal Board ruled breaches of Clauses 7.2, 7.9 and 20.2 of the Code. The appeal of these aspects was successful. The Appeal Board noted that Clause 3.2 required that the promotion of a medicine must not be inconsistent with the particulars listed in the SPC. The statements were issued to the media and as such did not constitute the promotion of Seroxat; Seroxat was a prescription only medicine and should not be promoted to the public. On this narrow point the Appeal Board upheld the Panel's ruling of no breach of Clause 3.2. The appeal of this aspect was unsuccessful.
>
> The Appeal Board noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such circumstances. The Appeal Board considered that, given the nature of the evidence, on balance the circumstances did not warrant a ruling of such a serious breach of the Code. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 2. The appeal of this aspect was unsuccessful.'

The Panel noted that in Case AUTH/1318/5/02 it had not ruled on the content of the GlaxoSmithKline briefing document as such as there was no complaint

about it. The complaint concerned what had been said and the GlaxoSmithKline briefing document was provided by GlaxoSmithKline in its response to the complaint. The Appeal Board could only consider rulings made by the Panel. It could not rule on other matters as this would be outside the Constitution and Procedure.

In Case AUTH/1318/5/02 GlaxoSmithKline had provided the requisite undertaking and assurance to avoid a similar breach of the Code in the future. A form of undertaking and assurance related not only to the material the subject of the complaint but also to any other similar material. GlaxoSmithKline had undertaken to ensure that all relevant documentation was withdrawn and that future documentation and verbal information provided, including internal briefing documents, complied with this undertaking. The undertaking had been received on 5 November 2002. The briefing document at issue in the present case, Case AUTH/1427/3/03, had thus been withdrawn pursuant to the undertaking in Case AUTH/1318/5/02.

Turning to the present case, Case AUTH/1427/3/03, the Panel noted that there was no evidence that the material at issue had been used after GlaxoSmithKline had given the undertaking in Case AUTH/1318/5/02.

The Panel considered that there were differences between the previous case and Case AUTH/1427/3/03 which concerned statements in The Reactive Key Messages and Issues Document. The Panel did not accept GlaxoSmithKline's suggestion that the matter had been fully considered in Case AUTH/1318/5/02. Whilst the Appeal Board referred to the document now at issue in Case AUTH/1318/5/02 it had made no ruling upon it as the complaint had concerned what the spokesperson was reported to have said. The previous case was nonetheless relevant.

The Panel considered that GlaxoSmithKline needed to be extremely careful about references to addiction, withdrawal symptoms and discontinuation symptoms. People's understanding of these terms differed depending on their background. The position was complex. The complaint related to the content of the Reactive Key Messages and Issues Document which as a briefing document was used to assist staff with media enquiries and thus needed to be in accordance with the Code. Given that the information might be provided directly or indirectly to the general public it was beholden upon the company to ensure that the terms used within the document were explained in such a way as to be meaningful and unambiguous to the intended audience.

In relation to the statements in the briefing document at issue 'Seroxat is not addictive' and '… Seroxat is clearly shown as being neither addictive nor causing dependence' the Panel noted that the PIL in force at the relevant time stated 'Remember that you cannot become addicted to Seroxat'. The content of the PIL was not a matter that came within the scope of the Code. The use of statements from the PIL and/or SPC in other material was potentially covered by the Code. Clause 7.9 of the Code required that it must not be stated that a product had no side-effects, toxic hazards or risks of addiction. The Panel also noted Section 4.8 of the SPC, reproduced above. The Panel considered that given Section 4.8 of the SPC, the ultimate audience and people's differing understanding of the meaning of addiction and dependence, the claims 'Seroxat is not addictive' and 'Seroxat is clearly shown as being neither addictive nor causing dependence' were misleading. Breaches of Clauses 20.2 and 7.2 were ruled.

In relation to the phrase 'Discontinuation symptoms are completely different to addiction or dependence …', the Panel noted its general comments above about addiction, discontinuation and withdrawal symptoms. The Panel noted the CPMP Proposal for Principles of SPC Wording on Withdrawal Reactions for SSRIs to be harmonised throughout the European Union (April 2000) stated that 'The term 'withdrawal reactions' should be used, not 'discontinuation reactions'. It should be made clear that withdrawal reactions by themselves are insufficient to imply dependence'. The Panel also noted Section 4.8 of the SPC, Undesirable Effects, as reproduced above. The Panel considered that insufficient information had been provided about discontinuation; it had not been placed sufficiently within the regulatory and clinical framework. Breaches of Clause 20.2 and 7.2 were ruled. Clause 3.2 of the Code required that the promotion of a medicine must not be inconsistent with the SPC. The Panel did not consider that the document at issue constituted promotion of Seroxat and no breach of Clause 3.2 was accordingly ruled.

The Panel noted that the bullet point 'The European Regulatory Body the CPMP (Committee for Proprietary Medicinal Products) have recently completed (April 2000) a thorough review of safety data collected through the discontinuation of all SSRIs and other newer serotonergic antidepressant medications. The MCA (Medicines Control Agency) and CPMP have concluded that SSRIs do not cause dependency/addiction' appeared within the section headed 'Addiction/Dependence'. One of the CPMP Position Paper recommendations was that 'The available evidence does not suggest that SSRIs cause dependence. However the lack of evidence for dependence does not prove the absence of a problem and any evidence which will emerge or will be produced should continue to be evaluated'. The Panel considered that the bullet point in the document at issue was unequivocal and thus not a fair reflection of the CPMP recommendation. Breaches of Clause 20.2 and 7.2 were thus ruled.

In relation to the statement that 'There has been no reliable evidence from either preclinical studies, long term clinical trials or clinical experience, to suggest that Seroxat is addictive, shows dependence or is a drug of abuse', the Panel considered that its comments and rulings above were relevant and also noted Section 4.8 of the SPC. The Panel considered that the statement was unequivocal and not a fair reflection of the SPC. The Panel ruled breaches of Clauses 20.2 and 7.2.

The Panel considered that the statement 'As recommended by the British National Formulary (BNF) and the European Medicines Evaluation Agency (EMEA), the likelihood of discontinuation symptoms is minimized by gradually tapering of the

daily dose' was too dogmatic and did not reflect the available evidence. The Panel noted that Section 4.3 of the BNF September 2001, Antidepressant drugs, gave general advice on dose titration upon withdrawal and further noted that 'SSRIs have been associated with a specific withdrawal syndrome'. The paroxetine entry referred to CSM advice that withdrawal syndrome was reported to the CSM more commonly with paroxetine than with other SSRIs. The Panel noted its rulings above. The Panel ruled breaches of Clauses 20.2 and 7.2.

The Panel noted its rulings above and considered taking all the circumstances into account, on balance, that a ruling of a breach of Clause 2, which was reserved as a sign of particular censure, was not warranted.

**Complaint received** **11 March 2003**

**Case completed** **23 May 2003**

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**CASE AUTH/1428/3/03**

# WYETH v LUNDBECK

## Cipralex leavepiece

**Wyeth complained about a leavepiece for Cipralex (escitalopram) issued by Lundbeck. Lundbeck also supplied Cipramil (citalopram) and Wyeth supplied Efexor (venlafaxine).**

**Cipramil was a selective serotonin reuptake inhibitor (SSRI). Cipramil was a racemic mixture, consisting of an 'R' and an 'S' isomer. Cipralex was the 'S' isomer of Cipramil and was thus also a SSRI.**

**Wyeth stated that one would predict from being an isomer that Cipralex's efficacy would be similar to Cipramil. There had been some data presented using observed analyses to suggest that Cipralex was more efficacious than Cipramil, though generally speaking the more robust intention-to-treat (ITT) analyses showed no statistical differences between the two as would be anticipated. Neither Cipramil nor Cipralex had any action on the reuptake of noradrenaline. Efexor was a selective serotonin and noradrenaline reuptake inhibitor (SNRI). This 'dual action' was thought to be the mechanism by which Efexor had superior efficacy over the SSRIs as demonstrated in single studies and numerous meta-analyses.**

**The leavepiece at issue stated that 'Now when you want more efficacy there's no need to switch classes'. The claim ran down pages one and two and was printed in blue. The word 'no' was extended in light lilac to read noradrenaline. Wyeth considered that the subliminal use of the word noradrenaline suggested that Cipralex had some action on noradrenaline, which was untrue. This was misleading, and had been used to explain and underpin the added efficacy claimed by Lundbeck, which was also misleading.**

**Wyeth alleged that the phrase 'Now when you want more efficacy' was a hanging comparison and also ambiguous. The suggestion was that when a patient had failed to improve on an SSRI they could be switched to Cipralex. There was no data to support this.**

**The Panel noted that the first three pages of the leavepiece unfolded to read 'Now when you want more efficacy', 'There's no need to switch classes' and 'Simply start prescribing Cipralex' respectively. On the second page the word 'no', in blue, was followed by 'radrenaline' in a light lilac such that it read noradrenaline. The third page highlighted the letters SSRI in the claim 'Simply Start Prescribing Cipralex' and page four was headed 'SSRICan'.**

**The Panel did not consider that the subliminal use of the word noradrenaline suggested that Cipralex had some action on noradrenaline as alleged. The overall promotional message was to persuade clinicians to switch to Cipralex rather than to a different class of medicines. There was no express or implied suggestion that Cipralex had an effect upon noradrenaline *per se*. Page two was not misleading in this regard and no breach was ruled.**

**The Panel did not accept that the phrase 'Now when you want more efficacy' was a hanging comparison within the context of the first three pages, which opened out in isolation from the rest of the leavepiece; it was implicit that the efficacy of Cipralex was being compared with the efficacy of other antidepressants in the same class. The claim 'Now when you want more efficacy …' was not misleading on this point and no breach was ruled.**

**The Panel noted that there was some data comparing the efficacy of Cipralex and Cipramil in severely depressed patients (Gorman *et al* 2002). The Panel noted that the authors concluded that the data '… suggest [Cipralex] may have a faster onset and greater overall magnitude of effect than [Cipramil] …'. The Panel noted that it had no data before it comparing Cipralex and other SSRIs. Lundbeck had submitted that Cipramil was a benchmark for the SSRI class and that it had been shown to have comparable efficacy with fluoxetine and sertraline overall but with advantages over both in terms of speed of onset.**

**Lundbeck had stated that the leavepiece was intended to demonstrate that where additional antidepressant efficacy was required for patients treated with Cipramil, clinicians might wish to consider Cipralex as an alternative. The design of the leavepiece, however, was such that the first three-page spread could be opened out in isolation from the rest of the piece. Page one included the Cipralex product logo and pages one to three together read 'Now when you want more efficacy there's [no] need to switch classes simply start prescribing Cipralex'. There was no mention of**

**Cipramil on the first three pages. The Panel considered that the opening three-page spread was misleading; in the absence of any reference to Cipramil it implied that when a patient had failed to respond adequately on any SSRI then they could be switched to Cipralex. There was no data to show that this was the case and breaches of the Code were ruled.**

Wyeth Pharmaceuticals complained about a leavepiece (ref 0103/ESC/525/064(980)M) for Cipralex (escitalopram) issued by Lundbeck Ltd. The leavepiece had also been used as mailing to psychiatrists. Contact between the parties had not resolved the issue. In addition to Cipralex, Lundbeck also supplied Cipramil (citalopram). Wyeth supplied Efexor (venlafaxine). Cipralex, Cipramil and Efexor were all antidepressants.

## COMPLAINT

Wyeth explained that Cipramil was a selective serotonin reuptake inhibitor (SSRI). Cipramil was a racemic mixture, consisting of an 'R' and an 'S' isomer. Cipralex was the 'S' isomer of Cipramil and was thus also an SSRI. One would predict from being an isomer that its efficacy would be similar to Cipramil. There had been some data presented using observed analyses to suggest that Cipralex was more efficacious than Cipramil, though generally speaking the more robust intention-to-treat (ITT) analyses showed no statistical differences between the two as would be anticipated. Neither Cipramil nor Cipralex had any action on the reuptake of noradrenaline.

Efexor was a serotonin and noradrenaline reuptake inhibitor (SNRI), which blocked the reuptake of serotonin and noradrenaline in the brain. This 'dual action' was thought to be the mechanism by which Efexor had superior efficacy over the SSRIs as demonstrated in single studies and numerous meta-analyses.

The leavepiece at issue clearly stated that 'Now when you want more efficacy there's no need to switch classes'. The claim ran down pages one and two and was printed in blue. The word 'no' was extended in light lilac to read **no**radrenaline.

Wyeth's considered that the subliminal use of the word noradrenaline suggested that Cipralex had some action on noradrenaline, which was untrue. This was clearly misleading (in breach of Clause 7.3), and had been used to somehow explain and underpin the added efficacy claimed by Lundbeck, which was also misleading.

Wyeth further complained about the phrase 'Now when you want more efficacy' which it alleged was a hanging comparison and also ambiguous in breach of Clause 7.2. The suggestion was that when a patient had failed to improve on an SSRI (such as fluoxetine), then they could be switched to Cipralex. There was no data to support this. Thus this leavepiece as written was both ambiguous (in breach of Clause 7.2) and misleading (in breach of Clause 7.3). Even if the statement had read 'more efficacy than Cipramil', this would be still unlikely to be justifiable as observed case analyses had been used rather than the more robust ITT analyses which were the norm these days, the latter in general showing no difference between the two medicines.

## RESPONSE

Lundbeck explained that Cipralex was the active S-enantiomer of the racemic mixture Cipramil. Cipralex and Cipramil were both SSRI antidepressants; prior to the introduction of Cipralex, Cipramil was the most selective of the SSRIs (Hyttel 1994). The ability to inhibit the reuptake of serotonin accounted for the antidepressant activity and it was suggested that this selectivity (for serotonin activity alone) might account for the tolerability profile as compared to less selective antidepressants (Stahl 1998). Lundbeck had always emphasised the selectivity of Cipramil. Of note, Cipralex was even more selective than Cipramil (Owens *et al* 2001), and Lundbeck would never claim otherwise, especially as unwanted effects might be caused by additional neurotransmitter activity (eg noradrenergic, dopaminergic, histaminergic).

The leavepiece was intended to demonstrate that where additional antidepressant efficacy was required for patients treated with Cipramil, clinicians might wish to consider Cipralex as an alternative. Three reasons were given to support this:

- Cipralex was significantly more effective than Cipramil in severe depression. This would be of interest as the leavepiece was intended for use with specialist psychiatrists
- Cipralex offered earlier symptom relief than Cipramil
- More moderately depressed patients responded to treatment with Cipralex than Cipramil

Wyeth cast doubt on the strength of the data showing superiority for Cipralex over Cipramil (Gorman *et al* 2002). This reference was a meta-analysis of all three studies which had been conducted comparing Cipralex, Cipramil and placebo. Meta-analysis was an accepted methodology, widely used to further evaluate treatment differences and was recommended as the top category (1A) of evidence considered by the National Institute for Clinical Excellence in its appraisal process. This particular work had been rigorously inclusive and had been published in a well-respected and peer-reviewed journal. Statistically significant differences were shown in favour of Cipralex compared to Cipramil in both the observed cases (OC) and last observation carried forward (LOCF) analyses for patients overall and for the subset of severely depressed patients. Both analyses were carried out on an ITT patient population defined as all patients who received at least one dose of double-blind study medication and had at least one post-baseline assessment. Wyeth was therefore incorrect when it stated, on both occasions, that a more robust ITT analysis showed no statistical differences between the two medicines.

Where additional efficacy was required in the treatment of depression, clinicians would often switch to an antidepressant from a different class (Maudsley Guidelines). The message from the leavepiece was simply that for such patients treated with Cipramil, the prescriber might wish to consider Cipralex before resorting to switching class. The reference to the word noradrenaline on the second page ... 'there's noradrenaline need to switch classes' was simply a reference to the fact that patients treated with Cipramil

in the past and who required additional efficacy might have been switched to a class of antidepressant which included inhibition of the reuptake of the noradrenaline neurotransmitter as part of its pharmacology eg reboxetine, Efexor and all tricyclic antidepressants. This allusion was not meant to imply that Cipralex affected the reuptake of noradrenaline.

To support the proposition that Cipralex might be an appropriate treatment option in Cipramil patients who required additional efficacy, compared to a switch in antidepressant class, data were presented comparing Cipralex to an antidepressant belonging to a different class – in this case Efexor, an SNRI. These data showed that Cipralex was at least as efficacious as Efexor, with some advantages in terms of time to sustained remission and tolerability profile (Montgomery *et al* 2002).

For the various reasons outlined above (selectivity and relation to tolerability), Lundbeck would not claim that Cipralex had noradrenergic activity. It therefore refuted the allegation that the leavepiece was misleading and denied any breach of Clause 7.3.

Lundbeck noted the definition of hanging comparison as set out in the supplementary information to Clause 7.2. The statement 'Now when you want more efficacy' in an item about Cipramil and Cipralex in depression and including reference to an antidepressant from a different class, followed by the words 'there's no need to switch classes' clearly implied that where efficacy additional to that available with Cipramil was required then Cipralex should be considered as an alternative to switching antidepressant class.

The focus of the leavepiece was to emphasise the benefits of Cipralex over Cipramil (as discussed above, and reflected in the pooled analysis by Gorman *et al*), and to suggest Cipralex as an alternative to a noradrenergic compound if considering a therapeutic change from Cipramil. Lundbeck was unsure of the ambiguity referred to by Wyeth. Lundbeck had not discussed other SSRIs as Wyeth alluded to in its complaint. In this regard, however, Cipramil could be considered as an excellent benchmark for the SSRI class. It had been shown to have comparable efficacy with fluoxetine and sertraline overall but with advantages over both in terms of an earlier onset of recovery and earlier symptom relief (Patris *et al* 1996, Stahl 2000). Consequently, the benefits experienced by Cipralex-treated patients compared to those on Cipramil might also be available to those patients receiving other SSRIs and prescribers might wish to consider Cipralex in such patients who would otherwise be switched to an antidepressant from a different class.

Lundbeck denied that the leavepiece contained a hanging comparison or was ambiguous or misleading. Lundbeck denied breaches of Clauses 7.2 or 7.3 of the Code.

## PANEL RULING

The Panel noted that the first three pages of the leavepiece unfolded to read 'Now when you want more efficacy', 'There's no need to switch classes' and 'Simply start prescribing Cipralex' respectively. On the second page the word 'no', in blue was followed by 'radrenaline' in a light lilac such that it read noradrenaline.

The third page highlighted the letters SSRI in the claim 'Simply Start Prescribing Cipralex' and page four was headed 'SSRICan'.

The Panel did not consider that the subliminal use of the word noradrenaline suggested that Cipralex had some action on noradrenaline as alleged. The overall promotional message of the three-page spread was to persuade clinicians to switch to Cipralex rather than to a different class of medicines. There was no express or implied suggestion that Cipralex had an effect upon noradrenaline *per se*. Page two was not misleading in this regard and no breach of Clause 7.3 was ruled.

The Panel noted that a hanging comparison was defined in the supplementary information to Clause 7.2 as being where a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared. The Panel did not accept that the phrase 'Now when you want more efficacy' was a hanging comparison within the meaning of the supplementary information to Clause 7.2; within the context of the first three pages, which opened out in isolation from the rest of the leavepiece, the Panel considered that it was implicit that the efficacy of Cipralex was being compared with the efficacy of other antidepressants in the same class (SSRIs). The claim 'Now when you want more efficacy …' was not misleading on this point as alleged and no breach of Clause 7.2 was ruled.

The Panel noted that there was some data comparing the efficacy of Cipralex and Cipramil in severely depressed patients, Gorman *et al*. The Panel noted that the authors concluded that the data 'suggest [Cipralex] may have a faster onset and greater overall magnitude of effect than [Cipramil] …'. The Panel noted that it had no data before it comparing Cipralex and other SSRIs. Lundbeck had submitted that Cipramil was a benchmark for the SSRI class and that it had been shown to have comparable efficacy with fluoxetine and sertraline overall but with advantages over both in terms of speed of onset.

The Panel noted Lundbeck's submission that the leavepiece was intended to demonstrate that where additional antidepressant efficacy was required for patients treated with Cipramil, clinicians might wish to consider Cipralex as an alternative. The design of the leavepiece, however, was such that the first three-page spread could be opened out in isolation from the rest of the piece. Page one included the Cipralex product logo and pages one to three together read 'Now when you want more efficacy there's [no] need to switch classes simply start prescribing Cipralex. There was no mention of Cipramil on the first three pages. The Panel considered that the opening three-page spread was misleading; in the absence of any reference to Cipramil it implied that when a patient had failed to respond adequately on any SSRI then they could be switched to Cipralex. There was no data to show that this was the case and breaches of Clauses 7.2 and 7.3 were ruled.

**Complaint received** **11 March 2003**

**Case completed** **16 May 2003**

CASE AUTH/1429/3/03

# GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

## Conduct of representatives

**A general practitioner complained that two representatives from Boehringer Ingelheim came into a lunchtime meeting at the surgery after which they canvassed both of the practice nurses asking them to do work in a blood pressure clinic and offering to pay them in cash. The nurses were taken aback by this conversation which occurred after the complainant had left the premises.**

**The complainant alleged that the representatives had displayed a poor standard of ethical conduct and had brought the industry into disrepute; their behaviour was unethical. Representatives from Boehringer Ingelheim would now not be allowed into his surgery again.**

**The Panel noted that although the parties' accounts of events differed, Boehringer Ingelheim had not denied that its representatives had become involved in a conversation regarding the payment of nurses and the possibility of one of the nurses undertaking work for other practices within the primary care trust. Whether this conversation was initiated by the representatives or by the nurses themselves was unclear. Nonetheless the representatives had started discussing a topic on which they had no in-depth knowledge. The representatives were at the surgery on behalf of Boehringer Ingelheim. The impression given by representatives was important.**

**Companies were responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions they had been given. The Panel considered that although the representatives had become involved in a conversation that the company would not expect them to, the company was nonetheless responsible for their conduct. The Panel considered that the representatives had not maintained a high standard of ethical conduct and breaches of the Code were ruled. The Panel did not consider that the circumstances warranted ruling a breach of Clause 2.**

A general practitioner complained about the conduct of two representatives from Boehringer Ingelheim Limited.

### COMPLAINT

The complainant stated that the two representatives came into a lunchtime meeting at the surgery after which they canvassed both of the practice nurses asking them to do work in a blood pressure clinic and offering to pay them in cash. The nurses were taken aback by this conversation which occurred after the complainant had left the premises.

The complainant considered that the representatives had displayed a poor standard of ethical conduct and had brought the industry into disrepute; their behaviour was unethical. Representatives from Boehringer Ingelheim would now not be allowed into his surgery again.

When writing to Boehringer Ingelheim to advise it of the complaint, the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 15.2 of the Code.

### RESPONSE

Boehringer Ingelheim stated that it appeared that a different interpretation of events from that made by the complainant was entirely possible. The two representatives did not initiate any conversations about involving the practice nurses in hypertension clinics but were responding to questions asked by one of them. However they became involved in a conversation relating to the payment of a part time practice nurse working for the complainant were she to undertake work for other practices within the primary care trust (PCT). As part of that conversation they discussed specific hourly rates and methods of payment for such work.

Boehringer Ingelheim considered that whilst this was done in good faith and in response to questions from the practice nurses, this was not something it would expect its representatives to become involved in. The company suggested that their behaviour was naïve since they were discussing this without in-depth knowledge of the subject and without the direction of the company to do so, but no more than that. As a result of this case, Boehringer Ingelheim undertook to write to all representatives clearly stating this and restating the company's commitment to maintaining the highest ethical standards in line with Clause 15.2 of the Code.

Boehringer Ingelheim explained that although it had on occasions sponsored blood pressure clinics in response to individual requests, it did not have any specific initiatives in relation to blood pressure clinics.

Boehringer Ingelheim submitted that if any offence had been caused to the complainant then it was not intentional on the part of the company or indeed the two representatives. The company considered that this event was no more than the misunderstanding of the actions of two naïve representatives acting alone and in response to a customer. This would be dealt with internally and would prompt actions by the company to ensure that the highest ethical standards were maintained in its sales force. Since it was not a company strategy, or indeed a consistent occurrence, Boehringer Ingelheim did not believe that the company had brought the industry into disrepute. Boehringer Ingelheim's sales force strove for the highest quality at all times and was committed to providing its customers with the best possible standards of service by providing top quality interactions at all times. It was regrettable that was not achieved with the complainant on this occasion. Boehringer Ingelheim hoped that he would reconsider his decision not to see representatives from the company again.

**PANEL RULING**

The Panel noted that although the parties' accounts of events differed, Boehringer Ingelheim had not denied that its representatives had become involved in a conversation regarding the payment of nurses and the possibility of one of the nurses undertaking work for other practices within the PCT. Whether this conversation was initiated by the representatives or by the nurses themselves was unclear. Nonetheless the representatives had started discussing a topic on which they had no in-depth knowledge. The representatives were at the surgery on behalf of Boehringer Ingelheim. The impression given by representatives was important.

The Panel noted that Clause 15.10 of the Code stated that companies were responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions they had been given.

The Panel considered that although the representatives had become involved in a conversation that the company would not expect them to, the company was nonetheless responsible for their conduct. The Panel considered that the representatives had not maintained a high standard of ethical conduct and breaches of Clauses 15.2 and 9.1 were ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

**Complaint received** **13 March 2003**

**Case completed** **30 April 2003**

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**CASE AUTH/1430/3/03**

# LILLY v NOVO NORDISK

## 'Dear Healthcare Professional' letter about diabetes and insulin

**Lilly complained about a 'Dear Healthcare Professional' letter sent by Novo Nordisk to all senior doctors in diabetes care and all diabetes nurse specialists. The letter concerned Novo Nordisk's services in relation to diabetes and included a table comparing the costs of Novo Nordisk's insulin analogues and comparable products from Lilly. Lilly alleged that the letter misinformed the reader regarding the impact of its recent price increases, and thus gained Novo Nordisk an unfair competitive advantage.**

**The statement 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, …' was unbalanced as it only alluded to one end of the spectrum of possibilities. To be fair and balanced, it needed to mention that not all similar analogue products would give this degree of price differential and that in some conditions Lilly insulins would be cheaper.**

**Further, the cost comparison table did not include the whole of Lilly's analogue range; this was also unbalanced given that the context of the letter was one of overall 'commitment to diabetes care'.**

**The Panel noted that the statement 'Below, a comparison is made between our prices of insulin analogues and those of comparable products from our main competitor' preceded the table which compared various presentations of Lilly's and Novo Nordisk's rapid-acting analogue insulins and premixed analogue insulins. The Panel did not accept that the table should have included Lilly's products for which Novo Nordisk had no comparable product. The Panel considered that although the description of the table was such that the basis of the comparison was sufficiently clear it, would have been helpful if that description had appeared immediately above the table, at the top of page two, rather than at the bottom of page one. However, the Panel did not consider that the letter was misleading in this regard and no breach of the Code was ruled.**

**The claim 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, …' appeared beneath the cost comparison table. The Panel noted Novo Nordisk's submission that the claim at issue did not state that Novo Nordisk insulins would be less expensive in all cases. The Panel considered that the use of the word 'can' rarely negated the impression of 'would'. The claim gave the impression that Novo Nordisk products would always be less expensive and that was not so. A breach of the Code was ruled.**

**Lilly alleged that the letter clearly targeted Lilly, with unjustified knocking of both products and activity. The statement that 'established manufacturers have undergone significant changes in their levels of activity and support' clearly implied a decrease in activity. By making this statement in the context of a message on 'Novo Nordisk's commitment to diabetes care' and then only comparing prices with Lilly products, the clear implication was that Lilly was no longer committed to diabetes care. That this was the intended implication was exemplified by the concluding statement 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, with a clear promise of a lasting commitment to you and your patients'. Price changes were an accepted practice within the pharmaceutical industry and did not in themselves mean any change in commitment.**

**The Panel noted that the letter began by mentioning Novo Nordisk's work in the field of diabetes and**

**discussed changes in the therapy area and the companies and professionals involved in the past few years. It was stated that new manufacturers had entered the diabetes arena and that some established manufacturers had undergone 'significant changes in their levels of activity and support'. The letter continued 'What has not changed however is our commitment to you and your patients and this will not change for many years to come …'. Discussion of Novo Nordisk's role in diabetes research, products and services and examples of the company's commitment followed.**

**The letter stated that the current pricing of Novo Nordisk products allowed the company to provide 'lasting commitment to the highest possible level of service and support'. The final sentence referring to the recent price increases by Eli Lilly concluded that a £35 cost saving per patient per year with Novo Nordisk insulin was with 'a clear promise of a lasting commitment to you and your patients'.**

**The Panel noted Novo Nordisk's submission that the reference to some established manufacturers undergoing significant changes in their levels of activity and support referred to a number of companies. The Panel considered that the statement implied that such established companies were providing less support in relation to those activities undertaken by Novo Nordisk. Lilly was the only company mentioned in the letter; attention was drawn to recent increases in the price of its insulin analogues. The letter clearly linked the current pricing of Novo Nordisk's products to the company's commitment to high levels of service and support. The Panel considered that the letter overall gave the impression that Lilly, an established insulin manufacturer, was less committed to helping people with diabetes and professionals involved in their care than Novo Nordisk. Such an impression was disparaging. A breach of the Code was ruled.**

Eli Lilly and Company Limited complained about a 'Dear Healthcare Professional' letter dated 19 December 2002 (ref INS/220/1202) sent by Novo Nordisk Limited to all senior doctors in diabetes care and all diabetes nurse specialists. The letter concerned Novo Nordisk's services in relation to diabetes and included a table comparing the costs of Novo Nordisk's insulin analogues and comparable products from Lilly. Correspondence between the companies had failed to resolve the issues.

## COMPLAINT

Lilly alleged a breach of Clause 7.2 of the Code which required that 'comparisons must be accurate, balanced, fair, objective and unambiguous'. The mailing misinformed the reader regarding the impact of recent Lilly price increases, and by doing so gained Novo Nordisk an unfair competitive advantage.

Lilly alleged that the statement 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, …' was clearly unbalanced, in breach of Clause 7.2, as it only alluded to one end of the spectrum of possibilities. To be fair and balanced, it needed to mention that not all similar analogue products would give this degree of price differential and in some conditions, Lilly insulins would be cheaper.

Further, the cost comparison table in the letter did not include the whole analogue range produced by Lilly, which was also unbalanced given that the context of the letter was one of overall 'commitment to diabetes care'. Lilly supplied pre-mixed analogue insulin, in the form of Humalog Mix50, which had no comparable Novo Nordisk insulin.

## RESPONSE

Novo Nordisk stated that the primary objective of the letter was to clear up growing confusion amongst its customers. Following Lilly's announcement to stop pen sampling (stop giving them away to clinics for free) and to make them available on prescription only, Novo Nordisk had had many enquiries with regard to its own sampling policy. This was not helped by several customers' comments that they had been told by Lilly that it would only be a matter of months before other companies did the same. Clearly Novo Nordisk could not confirm this to be true but its customers had no reason to lie, there was more than one unrelated occurrence of this statement and indeed Novo Nordisk's customers were challenging it to confirm or refute this statement. Novo Nordisk decided that it had to respond with a clarification mailing.

Novo Nordisk did not believe that any recipient of the mailing at issue would be misled into believing that all possible insulin regimens would be cheaper if the prescriber used Novo Nordisk insulins, rather than Lilly insulins, since the mailing stated 'Below, a comparison is made between our prices of insulin analogues and those of comparable products from our main competitor'. The letter did not claim that all of Novo Nordisk's insulins were cheaper than any of Lilly's insulins including non-analogues. The mailing stated that '…treatment with similar products can be more then £35 cheaper per patient per year when using Novo Nordisk insulin…'. This was absolutely correct. It did not state that it necessarily would be cheaper in all cases. Indeed Novo Nordisk took care to highlight the fact that Humalog Pen was confirmed as being cheaper than NovoRapid FlexPen and it submitted that the change of highlighting would make the reader aware of this fact.

Novo Nordisk appreciated that diabetics were treated on a variety of insulin regimens with both analogues and non-analogues. This mailing compared the prices of Novo Nordisk insulin analogues with comparable products. Clause 7.2 of the Code stated that 'Valid comparisons can only be made where like is compared with like' and this was exactly what was done. Novo Nordisk did not agree that this was in breach of Clause 7.2 which stated that 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous'. To the contrary Novo Nordisk believed that if it had compared its analogues with all of Lilly's insulins, including human insulins, then this would have been in breach of the Code since it would not be a fair comparison. Since the mailing stated that the comparison was '…

between our prices of insulin analogues and those of comparable products …' Novo Nordisk submitted that it was obvious that this price information was of no relevance for patients on human insulins. Similarly Novo Nordisk could not compare the price of an analogue it did not currently have but it had compared the prices of all its analogues to the nearest equivalent, exactly as the mailing stated.

To state that because Novo Nordisk did not currently have an equivalent of Humalog Mix 50 was somehow indicative of a lack of commitment was ridiculous. Novo Nordisk had the largest diabetes research and development programme of any pharmaceutical company, continued to support diabetes clinics with a field based sales force and continued to provide free insulin delivery devices amongst many other activities. There was currently no company more committed to diabetes care than Novo Nordisk, both in the UK and globally.

### PANEL RULING

The Panel noted that the statement 'Below, a comparison is made between our prices of insulin analogues and those of comparable products from our main competitor' preceded the table which compared various presentations of Lilly's and Novo Nordisk's rapid-acting analogue insulins and premixed analogue insulins. The Panel did not accept that the table should have included Lilly's Humalog 1.5ml cartridge or Humalog Mix 50 pre-filled pen for which Novo Nordisk had no comparable product. The Panel considered that although the description of the table was such that the basis of the comparison was sufficiently clear, it would have been helpful if that description had appeared immediately above the table, at the top of page two, rather than at the bottom of page one. However, the Panel did not consider that the letter was misleading in this regard as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the supplementary information to Clause 7.2 stated, *inter alia*, that 'price comparisons must be accurate, fair and must not mislead'. The claim 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, …' appeared beneath the cost comparison table. The Panel noted Novo Nordisk's submission that the claim at issue did not state that Novo Nordisk insulins would be cheaper in all cases. The Panel however considered that the use of the word 'can' rarely negated the impression that a product 'would' do something. The Panel considered that the claim gave the impression that Novo Nordisk products would always be cheaper and that was not so; a breach of Clause 7.2 was ruled.

## 2 Knocking copy

### COMPLAINT

Lilly alleged a breach of Clause 8.1 of the Code which stated that 'The medicines, products and activities of other pharmaceutical companies must not be disparaged'; the letter clearly targeted Lilly, with unjustified knocking of both products and activity. This letter stated that 'established manufacturers have undergone significant changes in their levels of activity and support' which clearly implied a decrease in activity. By making this statement in the context of a message on 'Novo Nordisk's commitment to diabetes care' and then only comparing prices with Lilly products, the implication was that Lilly was no longer committed to diabetes care.

That this was the intended implication was exemplified by the concluding statement 'The recent price increases by Eli Lilly means that treatment with similar products can be more than £35 cheaper per patient per year when using Novo Nordisk insulin, with a clear promise of a lasting commitment to you and your patients'. Price changes were an accepted practice within the pharmaceutical industry and did not in themselves mean any change in commitment.

### RESPONSE

Novo Nordisk stated that Lilly was the only other company which marketed short acting and premixed insulin analogues in the UK so clearly it was not surprising that only Lilly was mentioned in the price comparison. The recent price increase by Lilly that was mentioned was a fact and not a disparaging comment. The reference to a change in the level of support referred to a number of companies with both increased and decreased support in diabetes care (at least four others sprang to mind apart from Lilly) and Novo Nordisk had taken great care not to single out any individual company. However it was a fact that Lilly withdrew its diabetes sales force in or around the summer of 2002 but Novo Nordisk chose to concentrate on the positive aspects of what it was doing for diabetes clinics which could be seen in the attachment to its letter in which it emphasised some of the support activities it provided to the diabetes community.

In Novo Nordisk's reference to the diabetes market and manufacturers there was no mention of any specific company and no inference was intended since this was a general statement about the market over the last 2-3 years and the changes in activity that had taken place in many companies.

Novo Nordisk denied a breach of Clause 8.1.

### PANEL RULING

The supplementary information to Clause 8.1 stated that unjustified knocking copy in which products or activities of a competitor were unfairly denigrated was prohibited.

The Panel noted that the letter began by mentioning Novo Nordisk's work in the field of diabetes and discussed changes in the therapy area and the companies and professionals involved in the past few years. It was stated that new manufacturers had entered the diabetes arena and that some established manufacturers had undergone 'significant changes in their levels of activity and support'. The letter continued 'What has not changed however is our commitment to you and your patients and this will not change for many years to come …'. Discussion of Novo Nordisk's role in diabetes research, products

and services and examples of the company's commitment followed.

The Panel noted that the letter stated that the current pricing of Novo Nordisk products allowed the company to provide 'lasting commitment to the highest possible level of service and support'. The final sentence referring to the recent price increases by Eli Lilly concluded that a £35 cost saving per patient per year with Novo Nordisk insulin was with 'a clear promise of a lasting commitment to you and your patients'.

The Panel noted Novo Nordisk's submission that the reference to some established manufacturers undergoing significant changes in their levels of activity and support referred to a number of companies. The Panel considered that the statement implied that such established companies were providing less support in relation to those activities undertaken by Novo Nordisk. Lilly was the only company mentioned in the letter; attention was drawn to recent increases in the price of its insulin analogues. The letter clearly linked the current pricing of Novo Nordisk's products to the company's commitment to high levels of service and support. The Panel considered that the letter overall gave the impression that Lilly, an established insulin manufacturer, was less committed to helping people with diabetes and professionals involved in their care than Novo Nordisk. Such an impression was disparaging. A breach of Clause 8.1 of the Code was ruled.

**Complaint received** **17 March 2003**

**Case completed** **29 May 2003**

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**CASES AUTH/1431/3/03 and AUTH/1432/3/02**

# CLINICAL HOSPITAL PHARMACIST v PHARMACIA and BOEHRINGER INGELHEIM

## Christmas cards

**A clinical hospital pharmacist complained that two Christmas cards which he had received from Pharmacia and from Boehringer Ingelheim had not included prescribing information; he questioned the appropriateness of such cards in the first place.**

**The greeting inside the unsigned card from Pharmacia read '… and a Happy New Year from the Xalatan Team'. Below the greeting was the product logo incorporating the generic name (latanoprost) and a downward and a horizontal arrow. The back of the card carried the Pharmacia ophthalmology logo and the reference number.**

**Inside the card from Boehringer Ingelheim, under 'From the team', were fourteen signatures (first names only) and at the bottom Viramune nevirapine appeared beneath a product logo. The company's name, address and telephone number appeared on the back of the card.**

**The Panel considered that the sending of these Christmas cards was a promotional activity and the cards themselves promotional items. Each card bore a product name and neither was a purely corporate card. It was a principle under the Code that, in general, the mention of a product name in a promotional item sent to health professionals meant that prescribing information must be provided unless the item was an abbreviated advertisement or a promotional aid.**

**The exemption for abbreviated advertisements was not applicable. Promotional aids were permitted as long as they were, *inter alia*, relevant to the practice of the recipient's profession or employment. In the Panel's view the Christmas cards had no functional use and so were not relevant to the practice of anyone's profession or employment. The cards could thus not be considered to be promotional aids. No prescribing information had been provided with either card.**

**A breach of the Code was ruled in each case.**

**The Panel did not consider that sending a Christmas card was itself a breach of the Code as long as the card complied with the Code or was a corporate card which would be exempt from the Code.**

A clinical hospital pharmacist complained about Christmas cards which he had received from Pharmacia Limited and from Boehringer Ingelheim Limited.

The greeting inside the card from Pharmacia read '… and a Happy New Year from the Xalatan Team'. Below the greeting was the product logo incorporating the generic name (latanoprost) and a downward and a horizontal arrow. The back of the card carried the Pharmacia Ophthalmology logo and the reference number P8864/12/02. The card, which was unsigned, had been sent to ophthalmologists and hospital pharmacists.

Inside the card from Boehringer Ingelheim, under 'From the team', were fourteen signatures (first names only) and at the bottom appeared Viramune nevirapine beneath a product logo. The company's name, address and telephone number appeared on the back of the card.

### COMPLAINT

The complainant stated that the cards were sent without prescribing information which he alleged was in breach of the Code. There might be a case for arguing that the card bore only the brand name but the complainant hoped that the Authority would

consider whether it was appropriate for such a card to be sent in the first place.

When writing to Pharmacia and Boehringer Ingelheim the Authority invited the companies to respond in relation to Clauses 4.1 and 9.1 of the Code.

### Case AUTH/1431/3/03 – Xalatan Christmas card

### RESPONSE

Pharmacia submitted that the card did not promote the use of Xalatan, but merely used it as an identifier for the senders, as most company personnel were strongly associated with the name of their key product. No claims were made and no indication for use was listed. It had no intrinsic value and could not, therefore, be described as an inducement. If the sentiments expressed in the card were meaningless to the recipient, then it could be discarded in an instant. The only message related to the season's greetings.

It would be nonsense to allow product logos without prescribing information to appear on post-its or calendars, items that had intrinsic value and were likely to be retained, having sustained influence, and yet prohibit mention of a product name on a piece of paper imparting only Christmas 'best wishes'.

Pharmacia noted that Clause 9.1 of the Code required the materials and activities of pharmaceutical companies to recognise the special nature of medicines and the professional standing of the audience. Health professionals were no less likely to send and receive Christmas cards than any other sector of society. The card was tasteful and appropriate in design.

### PANEL RULING

The Panel noted that Clause 1.2 of the Code defined the term 'promotion' as meaning any activity undertaken by a pharmaceutical company or with its authorisation which promoted the prescription, supply, sale or administration of its medicines. Clause 1.2 listed exemptions to the term promotion but the Panel did not consider that any of the activities so listed were relevant in this case. The Panel considered that the sending of the Christmas card was thus a promotional activity and the card itself a promotional item. The card bore the name of the product, Xalatan. It was not a purely corporate card. The Panel noted that it was a long standing principle under the Code that, in general, the mention of a product name in a promotional item sent to health professionals meant that prescribing information must be provided as required by Clause 4.1. There were, however, two exemptions to this requirement listed in Clause 4.1, these being abbreviated advertisements and promotional aids.

The Panel considered that the exemption to the requirement to provide prescribing information in abbreviated advertisements was not applicable to this case.

The Panel noted that promotional aids were allowable under the Code as long as they were inexpensive and relevant to the practice of the recipient's profession or employment. In the Panel's view the Christmas card had no functional use and so was not relevant to the practice of anyone's profession or employment. Conversely, post-its and calendars, as referred to by Pharmacia, were useful and had been held to be relevant to a health professional's work. The Christmas card could thus not be considered a promotional aid. No prescribing information had been provided. A breach of Clause 4.1 was ruled.

The Panel did not consider that sending a Christmas card was itself a breach of the Code as long as the card complied with the Code or was a corporate card which would be exempt from the Code. The Panel thus ruled no breach of Clause 9.1 of the Code.

### Case AUTH/1432/3/03 – Viramune Christmas card

### RESPONSE

Boehringer Ingelheim stated that the sending of Christmas cards in the name of companies or their products had been a common practice within the pharmaceutical industry for many years.

The Viramune card was sent as a gesture of seasonal greetings and in Boehringer Ingelheim's experience such cards had been received as such and without any suggestion that they were intended as promotion of the product. About 1,000 of these cards were sent to selected doctors with special responsibility for communicable/infectious diseases, hospital pharmacists, drug information pharmacists, NHS directorate managers, clinical directors and directorate managers, nurse managers and service managers, all of whom would have had involvement in the HIV anti-retroviral Viramune.

Boehringer Ingelheim noted that Clause 4.1 of the Code concerned the requirements for prescribing information on promotional material. On a strict interpretation of the definition of promotion as given in Clause 1.2 of the Code, this Christmas card could not reasonably be said to promote the prescription, supply, sale or administration of Viramune. Since the card only contained the name of the product, there was no information on which a decision with regard to any of these actions could be made.

However, some might consider that any use of a brand name promoted the product. There were at least two situations where the use of brand names was permitted without the requirement for prescribing information. One of these was in public relations activities and the other was on promotional aids (Clause 18.3). A Christmas card could be regarded as fulfilling either or both of these criteria, but particularly the latter.

Boehringer Ingelheim therefore considered that prescribing information was not required on a Christmas card, such as this one relating to Viramune, where only the name of the product was given and that it therefore did not breach Clause 4.1.

Boehringer Ingelheim noted that Clause 9.1 of the Code concerned format, suitability and causing offence. The complainant queried whether such Christmas cards should be sent in the first place. It should be noted that the Viramune card did not

contain any Christian symbolism so it should not offend anyone who was not of that religion. The phrase contained in the card was 'Wishing you the best for Christmas'. This clearly related to a seasonal greeting over the Christmas period. It was a very common practice to send such sentiments to people at Christmas time regardless of any religion they might uphold.

Without the complainant being more specific as to why he thought such a card might not be appropriate, it was difficult to know how else to consider the application of Clause 9.1 to the Viramune Christmas card.

Boehringer Ingelheim therefore considered that the Viramune Christmas card did not breach Clause 9.1 of the Code.

**PANEL RULING**

The Panel noted its comments in Case AUTH/1331/3/03 above and considered that they applied here. A breach of Clause 4.1 was ruled and no breach of Clause 9.1 was ruled.

With regard to Boehringer Ingelheim's submission that the Christmas card could be considered a promotional aid the Panel noted that in addition to the product name the Christmas card also bore the name, address and telephone number of the company. The prescribing information for a medicine as required by Clause 4.1 did not have to be provided on a promotional aid but only if the promotional aid contained no more than the following: the name of the medicine; an indication that the name was a trade mark and the name of the company responsible for marketing the product. The inclusion of the Boehringer Ingelheim's address and telephone number on the Christmas card would thus have triggered the need for prescribing information even if the item could have been regarded as a promotional aid.

**Complaint received** **17 March 2003**

**Case completed** **28 April 2003**

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**CASE AUTH/1433/3/03**

# ASTRAZENECA v MERCK SHARP & DOHME

## Promotion of Zocor

**AstraZeneca complained about the promotion of Zocor (simvastatin) by Merck Sharp & Dohme. The materials at issue were two journal advertisements and a 'Dear Healthcare Professional' letter. Zocor was for use in patients with, *inter alia*, coronary heart disease (CHD) together with a plasma cholesterol of ≥ 5.5mmol/l.**

**The claim 'HIGH-level performance in the Heart Protection Study. Independent interim analysis of the Heart Protection Study showed that over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l' appeared in one of the advertisements. It featured a picture of a group of people on a fairground ride and included the strapline 'the drop of their lives'. AstraZeneca noted that, of the initial 32,145 patients entered into the run-in phase of the study, during which they all took simvastatin 40mg/day, only 40% were subsequently randomised due to issues of continuing therapy and lack of response to simvastatin. Although Merck Sharp & Dohme had addressed why this had been so, the reasons given were not satisfactory since these patients could have withdrawn due to adverse events. AstraZeneca alleged that the claim that 90% of CHD patients treated with Zocor 40mg achieved LDL-C levels of <3mmol/l was inaccurate and misleading because it reflected a highly selected group of patients.**

**AstraZeneca further noted that patients in the study had initial LDL-C levels of 3.4 ± 0.8mmol/l. It was misleading to suggest that 90% of CHD patients had achieved a LDL-C target of <3mmol/l, when some patients were below this level before even starting the randomisation part of the study. The advertisement promoted the use of Zocor 40mg to reduce cholesterol in CHD patients but the starting dose according to the summary of product characteristics (SPC) was 20mg daily.**

**The Panel noted that the Heart Protection Study included 20,536 adults with coronary heart disease, other occlusive arterial disease or diabetes. The patients were described as high risk. This had not been stated in the advertisement. The Panel noted the reasons for the difference between the numbers of patients that entered the study and those subsequently randomised. The Panel considered that the claim that '…over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l' was misleading and inaccurate as it was not made clear that the study was in high risk patients and ruled a breach of the Code. The base level of LDL-C was 3.4mmol/l ±0.8mmol. The Panel considered that the claim that '…over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l' was misleading as the result had not been placed within the context of baseline values and ruled a breach of the Code. The Panel did not consider that the advertisement promoted 40mg as the starting dose for treatment of Zocor. No breach of the Code was ruled in that regard.**

**Two advertisements included the claim 'exciting potential for cost savings' beneath which it was stated that the Zocor patent would expire on 5 May. A table showed the potential financial impact on a GP practice with 100 patients currently taking Zocor 20-80mg, atorvastin (Lipitor) 20-80mg or pravastatin**

**(Lipostat) 20-40mg, all of which cost £29.69 for 28 tablets. The exact price of generic simvastatin was not yet known but on the assumption that it would be £20 per 28 tablets the table showed that the savings could be £12,632 annually, compared to prescribing branded statins, which would mean that 48 additional patients could be treated with simvastatin 20-80mg. If generic simvastatin cost only £10 per 28 tablets potential annual savings would be £25,667, allowing 197 additional patients to be treated with simvastatin 20-80mg/day.**

**AstraZeneca alleged that since there were still approximately three months to go before patent expiry of Zocor, it was misleading to state that GPs could make potential cost savings when the price of generic simvastatin had not yet been determined. It was not stated explicitly in the advertisement that these were estimated cost savings, based on a potential price decrease of generic simvastatin. Evidence of such savings would only be available after Zocor had come off patent.**

**AstraZeneca noted that the advertisements encouraged health professionals to switch patients on any statin to simvastatin in order to save a practice thousands of pounds a year. This was clearly not based on efficacy or any particular dose and did not involve the costs associated with titration or associated blood tests. The advertisement disparaged doctors; it implied that their clinical judgement was based purely on cost savings and not efficacy.**

**The Panel considered that the introduction of generic simvastatin would have the potential to reduce prescribing costs. Generic medicines were invariably less expensive than branded products. In the circumstances the Panel did not consider that the claim 'exciting potential for cost savings' was unreasonable and no breach of the Code was ruled. With regard to the estimated cost savings the Panel noted that the purpose of the advertisements was to give an idea of the potential financial impact on a practice. This was based on conjecture about what might happen if the cost of simvastatin was to be £20 or £10 for 28 tablets. The Panel considered that it was misleading to base claims on conjecture. There was no way of substantiating the information until the cost of generic simvastatin was known. The Panel ruled breaches of the Code.**

**The Panel considered that the advertisements encouraged doctors to switch patients on any statin to simvastatin. No mention was made of any of the associated costs of doing this. The Panel noted its ruling above regarding the estimated savings. It considered that it was also misleading to fail to take into account the costs of switching patients to simvastatin. The Panel ruled breaches of the Code. The material did not imply that clinical judgement was based purely on cost savings. The Panel thus did not accept that the advertisement disparaged doctors and no breach was ruled.**

**The 'Dear Healthcare Professional' letter was headed 'MAY 2003 – Potential for significant cost savings with statin treatment'. A paragraph entitled 'Why act now?' stated that the first generic simvastatin was likely to be available in May 2003 at which time prescribers should immediately benefit from the expected price decrease. The brand price of any other statin was expected to remain at £29.69 for 28 tablets. The letter stated that prescribing Zocor for new CHD patients, or switching existing CHD patients to Zocor, 'could be even better value for your practice in the long term'. A paragraph entitled 'is patent expiry the only consideration?' stated that in the Heart Protection Study Zocor demonstrated 'excellent tolerability'. AstraZeneca considered that actively encouraging health professionals to switch existing CHD patients to Zocor, based primarily on costs, was misleading, unsubstantiable and disparaged the health professional and their prescribing judgement.**

**AstraZeneca noted that in a paragraph entitled 'Is patent expiry the only consideration?' the interim results of the Heart Protection Study using 40mg Zocor were stated. The claim for Zocor was similar to that considered above. AstraZeneca considered that this promoted the use of Zocor 40mg in the treatment of CHD when a dose of 20mg was indicated in the SPC.**

**AstraZeneca noted references to the 'excellent tolerability' of Zocor 40mg in other materials and considered this not to be the case as signified in the Heart Protection Study. AstraZeneca alleged that such a claim was misleading and unsubstantiable.**

**The Panel noted that a doctor's potential to realise the full cost savings on the introduction of generic simvastatin depended upon Zocor being prescribed generically. Prescriptions written for Zocor, even after the introduction of generic simvastatin, would be met with the branded product. A doctor prescribing simvastatin would not make savings whilst only the branded product was available but would potentially make savings when the product became available generically. Prescriptions written for 'Zocor' would not result in cost savings on the introduction of generic simvastatin. The Panel did not consider that it was misleading to encourage switching to simvastatin on cost *per se* as alleged. The Panel thus ruled no breach of the Code. The Panel did not consider that the letter disparaged prescribing judgements. The Panel noted that it had ruled a breach above in relation to estimated cost savings.**

**With regard to the claim that Zocor 40mg 'demonstrated clinical benefits and excellent tolerability…' the Panel did not accept that the letter promoted 40mg as the starting dose for treatment with Zocor. The Panel thus ruled no breach of the Code. The Zocor SPC stated that Zocor was generally well tolerated. The Panel considered that the claim for excellent tolerability was misleading and not capable of substantiation. It went beyond the statement in the SPC. The Panel ruled breaches of the Code.**

AstraZeneca UK Limited complained about the promotion of Zocor (simvastatin) by Merck Sharp & Dohme Limited. The materials at issue were two advertisements (refs 04-03 ZCR.02.GB.70102.J and 12-03 ZCR.02.GB.70252.J) and a 'Dear Healthcare Professional' letter (ref 10-03 ZCR.02.GB.70232.M.10.5m.HO.1102).

Zocor was licensed for use in patients with coronary heart disease with a plasma cholesterol of 5.5mmol/l or greater; as an adjunct to diet for hyperlipidaemia and for homozygous familial hypercholesterolaemia.

**1 Claim 'HIGH-level performance in the Heart Protection Study. Independent interim analysis of the Heart Protection Study showed that over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l'**

This claim appeared in advertisement ref 04-03 ZCR.02.GB.70102.J. The advertisement featured a picture of a group of people on a fairground ride. Beneath the product logo in the bottom right-hand corner was the strapline 'the drop of their lives'.

## COMPLAINT

AstraZeneca noted that, of the initial 32,145 patients entered into the run-in phase of the Heart Protection Study, during which they all took simvastatin 40mg/day for 4-6 weeks, only 40% were subsequently randomised due to issues of continuing therapy and lack of response to simvastatin. Although Merck Sharp & Dohme had tried to address why so many patients did not enter the randomisation phase of the study, the reasons were not satisfactory since these patients could have withdrawn due to adverse events. AstraZeneca considered that the claim that 90% of CHD patients treated with Zocor 40mg achieved LDL-C levels of <3mmol/l was inaccurate and misleading because it reflected a highly selected group of patients. A breach of Clause 7.2 of the Code was alleged.

AstraZeneca further considered it misleading to suggest that 90% of CHD patients treated with Zocor 40mg achieved an LDL-C target of <3mmol/l since the patients in the study had an initial LDL-C level of 3.4 ± 0.8mmol/l. Since some patients had a starting LDL-C level of <3mmol/l, it was misleading to suggest that 90% of CHD patients had achieved an LDL-C target of <3mmol/l, when they were below this level before even starting the randomisation part of the study. A breach of Clause 7.2 of the Code was alleged.

AstraZeneca considered that the advertisement promoted the use of Zocor 40mg to reduce cholesterol in CHD patients but noted that the licensed starting dose according to the summary of product characteristics (SPC) was 20mg daily. A breach of Clause 3.2 of the Code was alleged in this regard.

## RESPONSE

Merck Sharp & Dohme stated that AstraZeneca was wrong about the number of patients who entered the Heart Protection Study and were then subsequently randomised. The reference to which AstraZeneca's statement was linked stated that 11,609 patients who entered the run-in period were not randomised; one of the reasons for this was that 65% chose not to continue. In addition 17% did not seem likely to be compliant long-term. It was important for any trial, but especially for those anticipated to run over many years, to exclude patients who failed to demonstrate compliance during the run-in period. If such patients were to continue in the trial the results would be inaccurate. A further 13% of those who did not enter the randomisation phase were considered by their own doctor to have a clear indication for or contraindication to statin therapy after review of the screening lipid blood results. It would clearly be unethical for doctors to place patients, considered by them to require active treatment, in a trial with the potential to be randomised to receive placebo therapy. Similarly, the inclusion in the study of patients in whom a statin was considered to be contraindicated, would have raised ethical and safety issues. In addition 10% had abnormal screening blood results; 9% reported problems associated with the run-in treatment; 1% had experienced myocardial infarction, stroke, hospitalisation for angina or had cancer diagnosed during the run-in period and 1% had other reasons for not continuing.

This did not mean that the patients who were chosen were a highly selected group as AstraZeneca had stated. The patients who were not included were removed for medical and ethical reasons, leaving only those patients who were willing to continue and met with the inclusion criteria to carry on with the study. Merck Sharp & Dohme submitted that this was typical of a large randomised control trial, particularly over such a long period of time. The interim analysis of those who were randomised showed that 90% achieved an LDL-C of 3mmol/l. Merck Sharp & Dohme therefore submitted that the claim was correct and not in breach of Clause 7.2 of the Code.

Merck Sharp & Dohme submitted that the percentage of patients who achieved the LDL-C target of <3mmol/l was correctly stated at 90%. The company denied a breach of Clause 7.2 in that regard.

Merck Sharp & Dohme noted that the advertisement overall highlighted the results from an interim analysis of the Heart Protection Study in which the 40mg dose of simvastatin was used. It did not promote the use of 40mg as a starting dose for CHD patients *per se* as alleged by AstraZeneca. Health professionals were clearly advised to consult the SPC before prescribing, in which it was stated that the starting dose for patients with CHD was 20mg daily. Merck Sharp & Dohme thus denied a breach of Clause 3.2 of the Code.

## PANEL RULING

The Panel noted that the Heart Protection Study included 20,536 adults with coronary heart disease, other occlusive arterial disease or diabetes. The participants were described as high risk. This had not been stated in the advertisement at issue.

The Panel noted the reasons for the difference between the numbers of patients that entered the Heart Protection Study and those subsequently randomised. The Panel considered that the claim that '... over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l' was misleading and inaccurate as it was not made clear that the study was in high risk patients. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that the base level of LDL-C was 3.4mmol/l with a standard deviation of 0.8mmol. The Panel considered that the claim that '... over 90% of CHD patients treated with ZOCOR 40mg achieved an LDL-C target of <3mmol/l' was misleading as the result had not been placed within the context of baseline values. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel did not consider that the advertisement promoted 40mg as the starting dose for treatment with Zocor. The Panel thus ruled no breach of Clause 3.2 of the Code.

### 2 'Patent expiry' advertisement

Two similar advertisements featured the claim 'Exciting potential for cost savings' and drew the reader's attention to the fact that the Zocor patent would expire on 5 May. The advertisements included a table showing the potential financial impact on a GP practice with 100 patients currently taking Zocor 20-80mg, atorvastatin (Lipitor) 20-80mg or pravastatin (Lipostat) 20-40mg all of which cost £29.69 for 28 tablets. The exact price of generic simvastatin was not yet known but on the assumption that it would be £20 per 28 tablets the table showed that the savings incurred could be £12,632 annually, compared to prescribing branded statins, which would mean that 48 additional patients could be treated with simvastatin 20-80mg. If generic simvastatin cost only £10 per 28 tablets potential annual savings would be £25,667, allowing 197 additional patients to be treated with simvastatin 20-80mg/day.

#### COMPLAINT

AstraZeneca stated that since there was still approximately 3 months to go before patent expiry of Zocor, it was misleading to state that GPs could make potential cost savings when the NHS Drug Tariff price of generic simvastatin had not yet been determined. The company alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

It was not stated explicitly in the advertisement that these were estimated cost savings, based on a potential price decrease of generic simvastatin. Informing GPs that such a price decrease was forthcoming with no substantial evidence until after Zocor had come off patent was alleged to be misleading, in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

AstraZeneca noted that the advertisement stated that there were potential cost savings associated with prescribing generic simvastatin; by implication this encouraged health professionals to switch patients on any statin to simvastatin in order to save a practice thousands of pounds a year on an annual basis. This was clearly not based on efficacy or on any particular dose of statin and did not involve the costs associated with titration or associated blood tests. AstraZeneca alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code. AstraZeneca also alleged that the advertisement disparaged the prescribing intention of doctors in breach of Clause 8.2; it implied that their clinical judgement was based purely on cost savings and not efficacy.

AstraZeneca noted that in a previous case, Case AUTH/921/9/99, the Panel considered it was misleading to base a cost comparison on estimated savings.

#### RESPONSE

Merck Sharp & Dohme noted that currently nobody knew what the exact price of generic simvastatin would be. The company considered that it had made this point very clear in the advertisement by stating 'while the exact price of generic simvastatin is not yet known'. Having clarified this fact, the price comparison was used by way of example only to give physicians an 'idea' of potential cost savings. Merck Sharp & Dohme did not therefore agree that this was misleading and considered that the material was not in breach of Clauses 7.2, 7.3 or 7.4 of the Code.

Merck Sharp & Dohme disagreed with AstraZeneca's allegation that it had not given any indication in the advertisement that the cost savings were estimated. The company considered that this was quite clear from the outset when it was stated that the exact price of generic simvastatin was not known. The examples given were illustrative only to give physicians an idea of potential cost savings should the generic price of simvastatin be £20 or £10 for a 28 tablet pack compared to the current cost of £29.69. It was not misleading as the advertisement did not claim or guarantee that the price of generic simvastatin would be reduced and, if so, on what basis. Merck Sharp & Dohme denied breaches of Clauses 7.2, 7.3 or 7.4 of the Code.

The aim of the advertisement was to alert physicians to the potential cost savings of prescribing simvastatin should the price of generic simvastatin turn out to be less than £29.69 for 28 tablets. No specific claims on efficacy were made. Whilst simvastatin had significant efficacy data from the 4S and, more recently, the Heart Protection Study, this advertisement did not compare efficacy parameters but estimated potential cost savings in light of the patent expiry of simvastatin.

Merck Sharp & Dohme noted that current tablet packs did not take into consideration the cost of titration or blood testing etc so the company did not consider that it was appropriate to make the comparison suggested by AstraZeneca.

When prescribing any medicine a physician had to take into consideration many factors, of which efficacy and tolerability were undoubtedly important. Merck Sharp & Dohme did not consider that informing physicians of the possibility of being able to prescribe generic simvastatin was misleading or that it disparaged the opinions of physicians. Merck Sharp & Dohme denied breaches of Clauses 7.2, 7.3 and 8.2 of the Code.

#### PANEL RULING

The Panel considered that the introduction of generic simvastatin would have the potential to reduce prescribing costs. Generic medicines were invariably less expensive than branded products. In the circumstances the Panel did not consider that the

claim 'exciting potential for cost savings' was unreasonable and no breach of Clauses 7.2, 7.3 and 7.4 of the Code was ruled.

With regard to the estimated cost savings the Panel noted that the purpose of the advertisement was to give an idea of the potential financial impact on a GP practice. This was based on conjecture about what might happen if the cost of simvastatin was to £20 or £10 for 28 tablets. The Panel considered that it was misleading to base claims on conjecture. There was no way of substantiating the information until the cost per month of generic simvastatin was known. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

The Panel considered that the advertisements encouraged doctors to switch patients on any statin to simvastatin. No mention was made of any of the associated costs of doing this. The Panel noted its ruling above regarding the estimated savings. It considered that it was also misleading to fail to take into account the costs of switching patients to simvastatin. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.4 of the Code. The material did not imply that clinical judgement was based purely on cost savings. The Panel thus did not accept that the advertisement disparaged the prescribing intentions of doctors and ruled no breach of Clause 8.2 of the Code.

### 3 'Dear Healthcare Professional' letter

This letter was headed 'MAY 2003 – Potential for significant cost savings with statin treatment'. A paragraph entitled 'Why act now?' stated that the first generic simvastatin was likely to be available in May 2003 at which time prescribers of simvastatin should immediately benefit from the expected price decrease. The brand price of any other statin was expected to remain at £29.69 for 28 tablets. The letter stated that prescribing Zocor for new CHD patients, or switching existing CHD patients to Zocor, 'could be even better value for your practice in the long term'. A paragraph entitled 'Is patent expiry the only consideration?' stated that in the Heart Protection Study Zocor demonstrated 'excellent tolerability'.

#### COMPLAINT

AstraZeneca considered that actively encouraging health professionals to switch existing CHD patients to Zocor, based primarily on costs, was misleading, unsubstantiable and disparaged the health professional and their prescribing judgement, in breach of Clauses 7.2, 7.3 and 8.2 of the Code.

AstraZeneca noted that in a paragraph entitled 'Is patent expiry the only consideration' the interim results of the Heart Protection Study using 40mg Zocor were stated. The claim for Zocor was similar to that considered at point 1 above. AstraZeneca considered that this promoted the use of Zocor 40mg in the treatment of CHD when a dose of 20mg was indicated in the SPC. A breach of Clause 3.2 was alleged.

AstraZeneca noted references to 'excellent tolerability' of Zocor 40mg in other materials such as in advertisements promoting clinical trials using simvastatin (including the Heart Protection Study and the 4S study) and considered this not to be the case as signified in the Heart Protection Study. AstraZeneca considered such a claim was misleading and unsubstantiable in breach of Clauses 7.2 and 7.4 of the Code.

#### RESPONSE

Merck Sharp & Dohme stated that the letter was intended to inform physicians of the likelihood of generic simvastatin being available from May 2003 and the potential savings to a general practice should its price be lower than currently available statins treatments. In the letter it was clearly explained that should patients be switched to simvastatin now it 'could' be better value to the practice in the long term on the assumption that 'other statins continue to be charged a brand price of up to £29.69'. The company did not consider that this was in breach of Clauses 7.2, 7.3 and 8.2 of the Code.

With regard to the reference to the Heart Protection Study and the significant LDL-C lowering that was seen in CHD patients from an interim analysis of this study, Merck Sharp & Dohme noted that at no time was it stated that 40mg of simvastatin was the starting dose for CHD patients. The 40mg dose was mentioned as this was the dose used in the study. To clarify this further, the letter had prescribing information on the reverse side where it clearly stated that the starting dose for CHD patients was 20mg daily, therefore not breaching Clause 3.2 of the Code.

Merck Sharp & Dohme considered that reference to excellent tolerability was justified. In the Heart Protection Study, involving over 20,000 patients, the tolerability profile in the Zocor 40mg treated group of patients was similar to the placebo arm. Similar outcomes were also seen in the 4S study where simvastatin 20mg was compared to placebo. The company considered that the use of this claim was justified by the tolerability profile that simvastatin had shown in such landmark clinical studies ie the Heart Protection Study and 4S. Merck Sharp & Dohme denied a breach of Clause 3.2 of the Code.

#### PANEL RULING

The Panel noted that a doctor's potential to realise the full cost savings on the introduction of generic simvastatin depended upon Zocor being prescribed generically. Prescriptions written for Zocor, even after the introduction of generic simvastatin, would be met with the branded product. A doctor prescribing simvastatin would not make savings whilst only the branded product was available but would potentially make savings when the product became available generically. Prescriptions written for 'Zocor' would not result in cost savings on the introduction of generic simvastatin. The Panel did not consider that it was misleading to encourage switching to simvastatin based on cost *per se* as alleged. The Panel thus ruled no breach of Clauses 7.2 and 7.3 of the Code. The Panel did not consider that the letter disparaged prescribing judgements and no breach of

Clause 8.2 of the Code was ruled. The Panel noted that in point 2 above it had ruled a breach of the Code in relation to estimated cost savings.

With regard to the claim that Zocor 40mg '... demonstrated clinical benefits and excellent tolerability ...' the Panel did not accept that the letter promoted 40mg as the starting dose for treatment with Zocor. The Panel thus ruled no breach of Clause 3.2 of the Code.

The Panel noted that the Zocor SPC stated that Zocor was generally well tolerated. The Panel considered that the claim for excellent tolerability was misleading and not capable of substantiation. It went beyond the statement in the SPC. The Panel ruled breaches of Clauses 7.2 and 7.4 of the Code in this regard.

**Complaint received** **18 March 2003**

**Case completed** **19 May 2003**

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**CASE AUTH/1434/3/03** *NO BREACH OF THE CODE*

# BOEHRINGER INGELHEIM and PFIZER v GLAXOSMITHKLINE

## Promotion of Seretide

**Boehringer Ingelheim and Pfizer complained jointly about the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline.**

**Boehringer and Pfizer stated that a CD ROM set documented the highlights of a meeting entitled 'European COPD Workshop' held in Amsterdam in 2002. The meeting was attended by UK doctors. It was not part of an independent international conference and one of the two CDs featured a lecture entitled 'Seretide, Clinical effect in COPD'.**

**Seretide had no marketing authorization for the treatment of COPD anywhere in Europe or in the US. Boehringer Ingelheim and Pfizer alleged that this was evidence of the promotion of Seretide outside its marketing authorization and a breach of the Code was alleged.**

**The Panel noted that the CD ROM set documented the highlights of a meeting entitled 'European COPD Workshop'. The meeting took place in Amsterdam and was attended by UK doctors and others. The meeting was organised by GlaxoSmithKline Global, rather than the UK company, and discussed various aspects of COPD. One lecture was about Seretide's effect in COPD. Highlights from the meeting had been made into a CD set consisting of two CD ROMs. GlaxoSmithKline submitted that the CD set had not been distributed to UK health professionals.**

**The Director decided that as the CD set had not been distributed by GlaxoSmithKline to UK health professionals it did not come within the scope of the Code. There was no *prima facie* case to answer.**

**The Panel did not consider that Boehringer Ingelheim and Pfizer had made a specific complaint about the meeting. GlaxoSmithKline had limited its response to the CD set. The Panel thus did not consider whether the meeting itself amounted to promotion prior to the grant of the marketing authorization.**

**A journal advertisement was headed 'Why it's time to change the way you think about COPD' and referred to recent developments in the understanding of COPD and the multi-component nature of the disease which could help explain why bronchodilator therapy alone could leave some management issues unresolved. It concluded 'This understanding of the disease may offer valuable insight in terms of management approaches and improving patient outcomes. COPD – A multi-component disease'.**

**Boehringer Ingelheim and Pfizer stated that the advertisement introduced the concept of COPD as a multi-component disease highlighting the role of inflammation. It went on to state 'This understanding of the disease may offer valuable insight in terms of management approaches …'. It was alleged that this 'teaser' advertisement clearly highlighted GlaxoSmithKline's forthcoming therapy for COPD addressing inflammation, namely its combination of fluticasone and salmeterol, Seretide.**

**The Panel noted that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply.**

**The advertisement referred to COPD and described its underlying process as being driven by inflammation, tissue damage and mucociliary dysfunction. The only reference to treatment was to bronchodilator therapy which, according to the advertisement, could leave some management issues unresolved. It was stated that the understanding of the disease '… may offer valuable insight in terms of management approaches and improving patient outcomes'.**

**No reference, actual or implied, was made to any specific medicine. The Panel considered that the advertisement was a corporate advertisement about a disease, COPD. The information given in the advertisement was too general to be about any specific medicine. The Panel considered that the amount of general information about the disease and its treatment meant that the advertisement was not a 'teaser' as alleged. No breach of the Code was ruled.**

Boehringer Ingelheim Limited and Pfizer Limited jointly complained about the promotion of Seretide

(salmeterol/fluticasone) by GlaxoSmithKline UK Limited.

Seretide was indicated for the regular treatment of asthma where use of a combination product was appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long acting beta-2-agonist. GlaxoSmithKline's product Serevent (salmeterol) was indicated to treat reversible airways obstruction in patients requiring long-term regular bronchodilator therapy including those with asthma and with chronic obstructive pulmonary disease (COPD). Seretide was not licensed to treat COPD.

### 1 CD Set 'European COPD Workshop Highlights'

#### COMPLAINT

Boehringer Ingelheim and Pfizer stated that a CD ROM set documented the highlights of a meeting entitled 'European COPD Workshop' held in Amsterdam on 13 March 2002. The meeting was attended by UK doctors. It was not part of an independent international conference and one of the two CDs featured a lecture entitled 'Seretide, Clinical effect in COPD'.

Seretide had no marketing authorization for the treatment of COPD anywhere in Europe or in the United States. Boehringer Ingelheim and Pfizer alleged that this was evidence of promotion of Seretide outside its marketing authorization, and a breach of Clause 3 of the Code was alleged.

#### RESPONSE

GlaxoSmithKline denied that the CD set was in breach of the Code.

The meeting entitled 'European COPD Workshop' was organised by GlaxoSmithKline Global not by GlaxoSmithKline UK. The meeting was attended by a total of 56 respiratory specialists with a special interest in COPD. The delegates came from 13 European countries and 8 (14%) were from the UK. The agenda and delegate list was provided. Whilst UK prescribing information for Seretide in asthma was available at the meeting, the only materials distributed at the meeting were six clinical papers. Copies were provided.

GlaxoSmithKline stated that the CD was recorded at the European COPD Workshop and contained edited highlights of the meeting. The CD was an audio-visual presentation on two CD ROM disks. The lecture at issue was the second presentation on CD 2 entitled 'Seretide – Clinical Effects in COPD' by Professor P Calverley. The lecture was addressed to all the delegates and a transcript was provided.

The CD set was produced by the global arm of GlaxoSmithKline and not GlaxoSmithKline UK. The CD set was never distributed in the UK and was not available through the UK company. The CD set was offered only to non-UK attendees who were at the meeting. It was delivered to those requesting it following the meeting. The CD set was not distributed to any UK physicians either at the meeting or subsequently in the UK.

Since Boehringer Ingelheim did not mention how it came across the CD set it was difficult to address any specifics in this instance. GlaxoSmithKline thought that Boehringer Ingelheim must have obtained the CD from a physician from another country or from a physician in the UK who had obtained the CD from such a colleague.

In summary GlaxoSmithKline did not accept that the CD set was in breach of the Code. The UK doctors attended a truly international meeting of high scientific standing at which 86% of the attendees came from other European countries. The discussion of Seretide in COPD was only one of 6 presentations relating to COPD and was a presentation of the Tristan study which was generally regarded as a landmark study in COPD management and was later published in The Lancet. The CD set was distributed only to conference attendees from other European countries and was never distributed to UK consultants or attendees by either the UK or global company.

#### PANEL RULING

The Panel noted that the complaint concerned a CD ROM set which documented the highlights of a meeting entitled 'European COPD Workshop'. The meeting took place in Amsterdam and was attended by UK doctors and others. The meeting was organised by GlaxoSmithKline Global, rather than the UK company, and discussed various aspects of COPD. One lecture was about Seretide's effect in COPD. Highlights from the meeting had been made into a CD set consisting of two CD ROMs. GlaxoSmithKline submitted that the CD set had not been distributed to UK health professionals.

The Director decided that as the CD set had not been distributed by GlaxoSmithKline to UK health professionals it did not come within the scope of the Code. The Director decided that there was no *prima facie* case to answer.

The Panel did not consider that Boehringer Ingelheim and Pfizer had made a specific complaint about the meeting. GlaxoSmithKline had limited its response to the CD set. The Panel thus did not consider whether the meeting itself amounted to promotion prior to the grant of the marketing authorization.

### 2 Advertisement in GP 10 March 2003

The advertisement at issue (ref SFC/AVL/03/5649-FP) was headed 'Why it's time to change the way you think about COPD'. The copy referred to recent developments in the understanding of COPD and the multi-component nature of the disease which could help explain why bronchodilator therapy alone could leave some management issues unresolved. It concluded 'This understanding of the disease may offer valuable insight in terms of management approaches and improving patient outcomes. COPD – A multi-component disease'.

## COMPLAINT

Boehringer Ingelheim and Pfizer stated that the advertisement introduced the concept of COPD as a multi-component disease highlighting the role of inflammation. It went on to state 'This understanding of the disease may offer valuable insight in terms of management approaches …'.

Boehringer Ingelheim alleged that this 'teaser' advertisement clearly highlighted GlaxoSmithKline's forthcoming therapy for COPD addressing inflammation, namely its combination of fluticasone and salmeterol, Seretide. Breaches of Clauses 3 and 9.1 of the Code were alleged.

## RESPONSE

GlaxoSmithKline denied a breach of the Code. It stated that the purpose of the advertorial was to challenge traditional thinking about the patho-physiology of COPD and encourage the reader to think in broader terms, that COPD treatment was about more than bronchodilation.

The patho-physiology of COPD was complex. It could not be attributed to any single process and hence it could be described as a multi-component/ multi-factorial disease. This concept of a multi-component disease was currently used in the promotion of Serevent, since there was evidence that Serevent had actions other than bronchodilation that might be beneficial in patients with COPD. These actions included impact on mucocilliary dysfunction and subsequent tissue damage. Serevent was licensed for use in COPD patients. GlaxoSmithKline provided material focussing on the multi-component nature of COPD, explaining the non-bronchodilator effects of Serevent.

It had not made any reference to forthcoming licences, products due to be launched or future therapies.

Bronchodilators were not the only treatments used in the treatment of COPD, the following were some of the management approaches (pharmacological and non-pharmacological) which were recognised in the treatment of COPD and COPD exacerbations, theophyllines, oxygen therapy, pulmonary rehabilitation, oral steroids, antibiotics, physiotherapy, mucolytics, smoking cessation and vaccination.

Whilst the exact mechanism of action of all of these therapies in COPD might not be fully understood, they were known to be effective. An understanding of the multi-component nature of the pathophysiology of COPD might help clinicians understand these therapies, and might improve patient care.

GlaxoSmithKline therefore believed that this item raised disease awareness and helped provoke interest in the complex nature of COPD and its therapies.

Since GlaxoSmithKline already promoted Serevent in COPD within licence and had an interest in this disease area, it submitted that it was reasonable, responsible and within the Code to place the item.

## PANEL RULING

The Panel noted that Clause 3.1 of the Code stated that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply.

The Panel noted that the advertisement referred to COPD and described its underlying process as being driven by inflammation, tissue damage and mucociliary dysfunction. The only reference to treatment was to bronchodilator therapy which, according to the advertisement, could leave some management issues unresolved. The advertisement stated that the understanding of the disease '… may offer valuable insight in terms of management approaches and improving patient outcomes'.

No reference, actual or implied, was made to any specific medicine. The Panel considered that the advertisement was a corporate advertisement about a disease, COPD. The information given in the advertisement was too general to be about any specific medicine. No breach of Clause 3.1 was ruled. The Panel considered that the amount of general information about the disease and its treatment meant that the advertisement was not a 'teaser' as alleged. No breach of Clause 9.1 was ruled.

**Complaint received** **18 March 2003**

**Case completed** **3 June 2003**

# PHARMACIST v FRESENIUS KABI

## Remuneration of representatives

**A pharmacist complained that in an advertisement for hospital sales specialists placed by Fresenius Kabi in The Sunday Telegraph, the company had offered, *inter alia*, an open-ended bonus. The complainant questioned whether this met the requirement of the Code that representatives must be paid a fixed basic salary and any additional payment 'must not constitute an undue proportion of their remuneration'.**

**The Panel noted that the complainant's concern was whether an open-ended bonus scheme was in compliance with the Code; it was not a complaint about the advertisement *per se*. The Panel noted Fresenius Kabi's submission that all representatives' contracts contained a bonus structure, but did not contain, and had never contained, an uncapped or an open-ended bonus structure. In that regard the Panel ruled no breach of the Code.**

A pharmacist complained about an advertisement for hospital sales specialists placed by Fresenius Kabi Limited in the Appointments Section of The Sunday Telegraph.

### COMPLAINT

The complainant noted that Fresenius Kabi was offering a high competitive basic salary along with an open-ended bonus.

The complainant questioned whether an open-ended bonus was in line with the requirements of Clause 15.7 of the Code which stated that representatives must be paid a fixed basic salary and any additional payment 'must not constitute an undue proportion of their remuneration'.

### RESPONSE

Fresenius Kabi stated that it had reviewed the advertisement and the bonus structure for its sales representatives. All representative contracts included a bonus structure that rewarded on-target performance. Details were provided. The bonus was either a fixed percentage of salary or a specified cash value. Fresenius Kabi considered that the amount it awarded its representatives was within the scope of the Code and in line with the industry norm.

Fresenius Kabi stated that representatives' contracts did not contain, and had never contained, an uncapped or an open-ended bonus structure. It submitted that no other 'non-contract' bonus scheme had ever existed, and incentive programmes which were run from time to time only rewarded successful sales staff very modestly (details were provided).

To avoid any misinterpretation, Fresenius Kabi stated that it would ensure that any future advertisement did not include the term 'open-ended bonus'.

### PANEL RULING

The Panel noted that the complainant's concern was whether an open-ended bonus scheme was in compliance with the Code; it was not a complaint about the advertisement *per se*. Clause 15.7 required that any addition to the salary proportional to sales of a medicine must not constitute an undue proportion of a sales representative's remuneration. The Panel noted Fresenius Kabi's submission that the contracts did not contain, and had never contained, an uncapped or an open-ended bonus structure. In that regard the Panel ruled no breach of Clause 15.7 of the Code. The merits of the bonus scheme provided by Fresenius Kabi were not the subject of the complaint and thus were not considered.

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| **Complaint received** | **20 March 2003** |
| **Case completed** | **14 May 2003** |

# MEDIA/DIRECTOR and ANONYMOUS v GLAXOSMITHKLINE and BAYER

## Levitra journal advertisement

**A letter in The Pharmaceutical Journal was critical of an advertisement for Levitra (vardenafil) issued jointly by GlaxoSmithKline and Bayer. Subsequently an anonymous complainant provided a highlighted copy of the published letter. In accordance with established practice as regards both media criticism and anonymous complaints, they were treated as complaints under the Code.**

**Levitra was indicated for the treatment of erectile dysfunction. The advertisement featured a photograph of a woman wearing 3D spectacles above which were the words 'There are erections …' and beneath which were the words 'and there are 3D erections'. Text beneath stated: '3D erections; Hard enough for penetration; Maintained long enough for completion; Reliable time after time'.**

**The author thought that The Pharmaceutical Journal always tried to maintain high standards until he saw the advertisement at issue and in that regard stated 'Are these sorts of sleazy advertisements not out of place in a professional journal?'**

**The Panel considered that although some people would find the advertisement offensive it was unlikely to be so to the majority of those who would see it. The Panel noted the companies' submission that the 3 dimensions referred to related to important outcomes for patients. The Panel ruled no breach of the Code.**

A letter in The Pharmaceutical Journal, 22 March, was critical of an advertisement (ref 3LEV179) for Levitra (vardenafil) which had appeared in the journal on 15 March. Subsequently an anonymous complainant sent in a highlighted copy of the published letter but made no additional comment. In accordance with established practice as regards both media criticism and anonymous complaints, they were treated as complaints under the Code and taken up with Bayer plc, Pharmaceutical Division, and GlaxoSmithKline UK Limited, both of which were named on the advertisement.

Levitra was indicated for the treatment of erectile dysfunction. The advertisement featured a photograph of a woman wearing 3D spectacles. Above the photograph were the words 'There are erections …' and below the photograph 'and there are 3D erections'. Text beneath stated:

'3D erections

- Hard enough for penetration
- Maintained long enough for completion
- Reliable time after time'

### COMPLAINT

The author of the published letter stated that he had thought that The Pharmaceutical Journal always tried to maintain high standards until he saw the 15 March edition. Referring, *inter alia*, to the Levitra advertisement, he stated 'Are these sorts of sleazy advertisements not out of place in a professional journal?'

An editorial comment published beneath the letter stated that the Levitra campaign had been launched simultaneously in a number of medical and pharmacy titles. The advertisement, although clearly not to everyone's taste, was neither illegal nor making misleading claims and there were no grounds to reject it.

When writing to Bayer and GlaxoSmithKline the Authority asked them to respond in relation to Clause 9.1 of the Code.

### RESPONSE

A joint response was received from Bayer and GlaxoSmithKline.

The companies stated that their intention with the Levitra advertising was to be both specific and matter of fact about the clinically recognised aspects of erectile dysfunction. It was not an attempt to shock or to be 'sleazy'. The companies considered that the best way to ensure that this potentially taboo disease area was recognised and managed was to refer directly to symptoms and treatment, and thus to avoid euphemism or misguided humour. It was this approach which had led historically to the removal of stigma from diseases like depression and encouraged the specific and open dialogue that had led to improved treatment and management.

In view of the potential sensitivity in this area, and the fact that with this approach they were 'breaking new ground', the companies had taken great care to test the proposed advertising with GPs and urologists, asking specifically about its suitability and taste. Whilst there were a range of responses, the vast majority of respondents welcomed the companies' stance and saw this as helping to highlight that erectile dysfunction was a genuine medical condition. It was seen as both an arresting but appropriate advertisement for the product.

The '3 Dimensions' of erectile dysfunction referred to in the advertisement were those of hardness, maintenance and reliability. These were regarded as important outcomes by patients for the successful treatment of their condition.

The companies explained that an estimated 2.3 million men in the UK were affected by erectile dysfunction and that only 10 percent were treated. There was a significant body of evidence to suggest treatment rates

were low because of a cultural reluctance of sufferers to come forward, or for doctors to raise the subject proactively.

In addition, erectile dysfunction was acknowledged to be a marker of previously undiagnosed serious conditions such as diabetes, hyperlipidaemia and hypertension.

The companies hoped that they had managed to allay the complainants' concerns and contextualise the advertisement in question.

**PANEL RULING**

The Panel noted that Clause 9.1 of the Code stated, *inter alia*, that all material and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence.

The Panel considered that although some people would find the advertisement offensive it was unlikely to be so to the majority of those who would see it. The Panel noted the companies' submission that the 3 dimensions referred to related to important outcomes for patients. The Panel ruled no breach of Clause 9.1 of the Code.

**Cases AUTH/1438/3/03 and AUTH/1439/3/03**

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| **Proceedings commenced** | **24 March 2003** |
| **Case completed** | **6 May 2003** |

**Cases AUTH/1448/4/03 and AUTH/1449/4/03**

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| **Complaint received** | **2 April 2003** |
| **Case completed** | **23 April 2003** |

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**CASE AUTH/1440/3/03**

# ASTRAZENECA v PFIZER

## Promotion of Lipitor

**AstraZeneca complained about a Lipitor (atorvastatin) leavepiece issued by Pfizer. The two-page leavepiece, headed 'Lipitor – starting dose', depicted a baseline LDL-C scale from 3mmol/l to 5.8mmol/l superimposed on which was a Lipitor starting dose. From 3mmol/l – 5mmol/l a pale blue band showed that the starting dose was 10mg; 5mmol/l – 5.3mmol/l, 20mg (pale lemon) and 5.3mmol/l – 5.8mmol/l 40mg (pale lilac). An asterisk adjacent to each dose referred to a footnote 'Titrate upwards if required'. A strapline read 'Choose a starting dose of Lipitor to achieve a target right from the start'.**

**AstraZeneca noted that the LIpitor summary of product characteristics (SPC) stated 'The usual starting dose is 10mg once a day. Doses should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response'. The SPC also stated that patients with heterozygous familial hypercholesterolaemia (FH) '… should be started with Lipitor 10mg daily'. This indicated that Lipitor should be started at a dose of 10mg and titrated according to response to reach the desired goal. AstraZeneca alleged that the overall impression from the leavepiece was that Lipitor had a range of start doses which were equally acceptable.**

**AstraZeneca disagreed with Pfizer's argument in intercompany correspondence that the baseline LDL-C scale with the corresponding Lipitor starting doses below implied that most patients would start on 10mg. Firstly, GPs in particular frequently did not distinguish between LDL-C and total cholesterol. If the LDL-C scale was interpreted as total cholesterol the vast majority of patients would be started on doses of 20mg or 40mg Lipitor. Secondly, there was no justification in the literature or any guidelines for the starting doses Pfizer recommended at the various baseline LDL-C levels; the recommendations were not referenced to any external source. Thirdly, the marketing authorization implied the importance of individualising treatment according to response. Individuals with very high baseline cholesterol could respond very effectively to 10mg of a statin just as those with lower levels could have a minimal response. The leavepiece implied that patients with an LDL-C level >5mmol/l necessarily required 20mg as a start dose. This was not the case and as discussed above there was no independent justification for this view. Fourthly, the start dose in FH patients was 10mg. Many such patients would have LDL-C levels of >5mmol/l at which level this leavepiece advocated use of 20mg Lipitor in direct contravention of the marketing authozation for these patients.**

**Finally, the overall impression from the leavepiece, despite the LDL-C scale, was that 20mg and 40mg Lipitor were equally acceptable starting doses as 10mg. This was not an accurate reflection of the emphasis given in the marketing authorization to the 10mg starting dose.**

**AstraZeneca alleged that the leavepiece promoted Lipitor outside the terms of its marketing authorization and was misleading and that the recommendation for start dose against baseline LDL-C was not substantiable.**

**The Panel noted that the Lipitor SPCs stated that the usual starting dose was 10mg daily. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response. Adjustment of dose should be made at intervals of four weeks or more. The majority of patients with primary hypercholesterolaemia and combined (mixed) hyperlipidaemia were controlled on 10mg daily. Patients with heterozygous familial hypercholesterolaemia 'should be started with**

**Lipitor 10mg daily'. A table in the Lipitor 10, 20, and 40mg SPC headed 'Dose-Response in Patients with Primary Hypercholesterolaemia' provided the adjusted mean percentage change from baseline for, *inter alia*, LDL-C, for Lipitor 10, 20, 40 and 80mg. This table was the basis of the LDL-C dose scale at issue.**

**The Panel noted Pfizer's submission that as the majority of CHD patients had LDL-C levels of ≤ 5mmol/l then 10mg was the start dose for 80% of the patient population. The Panel considered that it would have been helpful if the leavepiece had reproduced the SPC statement that '10mg was the usual starting dose'. The Panel noted that in relation to patients with heterozygous FH the SPC stipulated a starting dose of 10mg daily. This was not made sufficiently clear in the leavepiece. The Panel considered that the leavepiece gave the impression that the starting doses depicted were suitable for all patient groups for whom Lipitor was indicated and that was not so; the leavepiece was misleading and inconsistent with the SPC in this regard. Breaches of the Code were ruled.**

**The Panel did not consider that the recommendation of starting dose against baseline LDL-C was incapable of substantiation and no breach of the Code was ruled.**

**AstraZeneca had received several reports from clinicians that the promotion of Lipitor by Pfizer representatives had similar features to the above leavepiece. In addition several clinicians had commented that Pfizer had 'a new licence' for Lipitor which allowed it to be used at higher start doses. There had been no feedback that there was any qualification on this advice. Pfizer had commented that it had not briefed its representatives that the licence was 'new'. Whilst AstraZeneca accepted this, the consistency of feedback suggested that physicians were picking up the impression that the company did have a 'new' licence. AstraZeneca had no direct evidence showing how Pfizer representatives had been briefed on this issue but the weight of comment coming back to AstraZeneca about the Lipitor start dose led it to believe that Pfizer was not clearly communicating the direction given in the marketing authorization about the 10mg start dose.**

**AstraZeneca regarded this as a serious matter. Statin-related side-effects such as rhabdomyolysis, which although rare could be serious and even fatal, occurred more commonly if higher start doses were used. Regulatory authorities thus made particular recommendations within the SPCs of the various statins to dictate how physicians started patients on treatment. AstraZeneca did not believe this was open to reinterpretation at an arbitrary time-point without clear direction in terms of marketing authorization change from regulatory authorities.**

**The Panel noted that Pfizer had briefed its sales representatives about a 'flexible start dose'. Pfizer provided a copy of a training slide and a question and answer document. The slide headed 'What is Flexible Start Dose (FSD)?' referred to the ability 'to start patients on 10mg, 20mg, or 40mg' and 'Gets >80% of patients to target 'right from the start''. The Panel did not have the other slides in the presentation before it. Given Pfizer's submission that 'in practice 10mg was the appropriate start dose for approximately 80% of the population' and that the SPC stated that 'the usual starting dose was 10mg daily' the Panel queried whether the training slide provided made it sufficiently clear that 10mg was the usual starting dose.**

**The Panel noted the Flexible Start Dose Q & A stated that 'the usual starting dose was 10mg daily'. All three doses of Lipitor were, however, presented as possible starting doses. The Panel noted that the answer to the question 'Can I initiate a patient on Lipitor 80mg' was 'Our current recommendation is that 10, 20 or 40mg is adequate therapy for the vast majority of patients'. It was stated that Lipitor did not have a new licence. The Panel considered that it was not made sufficiently clear that 10mg daily was the appropriate starting dose for the majority of patients. The Panel was concerned about the documents for the representatives in relation to the starting dose of Lipitor. The Panel noted that it had no evidence before it as to precisely what had been said by representatives when detailing clinicians on this point. The Panel was thus obliged to rule no breach of the Code.**

AstraZeneca UK Limited complained about the promotion of Lipitor (atorvastatin) by Pfizer Limited. At issue were a leavepiece and the activities of Pfizer representatives.

### 1 Lipitor leavepiece

The two-page leavepiece (ref LIP497), headed 'Lipitor – starting dose' depicted a baseline LDL-C scale from 3mmol/l to 5.8mmol/l superimposed on which was a Lipitor starting dose. From 3mmol/l – 5mmol/l a pale blue band showed that the starting dose was 10mg; 5mmol/l – 5.3mmol/l, 20mg (pale lemon) and 5.3mmol/l – 5.8mmol/l 40mg (pale lilac). An asterisk adjacent to each dose led the reader to a footnote which read 'Titrate upwards if required'. A strapline read 'Choose a starting dose of Lipitor to achieve a target right from the start'.

### COMPLAINT

AstraZeneca noted that the summary of product characteristics (SPC) for Lipitor stated 'The usual starting dose is 10mg once a day. Doses should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response'. The SPC also stated that for patients with heterozygous familial hypercholesterolaemia (FH) 'Patients should be started with Lipitor 10mg daily'.

AstraZeneca stated that in practical terms this indicated that Lipitor should be started at a dose of 10mg and titrated according to response to reach the desired goal. The need to titrate to higher doses would be determined in part by the baseline LDL-C concentration but since all statins demonstrated a wide variation of response this was not the only consideration. Furthermore it was clear from the licence that even FH patients who had very high baseline cholesterol levels should be started on 10mg

Lipitor and titrated upwards. AstraZeneca stated that the overall impression from the leavepiece was that Lipitor had a range of start doses which were equally acceptable.

In intercompany correspondence Pfizer had indicated that the baseline LDL-C scale with the corresponding Lipitor starting doses below implied that most patients would start on 10mg. AstraZeneca had five principal contentions with this argument.

Firstly, GPs in particular frequently did not distinguish between LDL-C and total cholesterol. If the LDL-C scale was interpreted as total cholesterol the vast majority of patients would be started on doses of 20mg or 40mg Lipitor.

Secondly, there was no justification in the literature or any guidelines for the starting doses Pfizer recommended at the various baseline LDL-C levels; Pfizer had not referenced these recommendations to any external source.

Thirdly, the marketing authorization implied the importance of individualising treatment according to response. Individuals with very high baseline cholesterol could respond very effectively to 10mg of a statin just as those with lower levels could have a minimal response. The leavepiece implied that patients with an LDL-C level above 5mmol/l necessarily required 20mg as a start dose. This was not the case and as discussed above there was no independent justification for this view.

Fourthly, the marketing authorization stated clearly that the start dose in FH patients was 10mg. Many patients with FH would have LDL-C levels in excess of 5mmol/l at which level this leavepiece advocated use of 20mg Lipitor. This advice was therefore in direct contravention of the marketing authorization for these patients.

Finally, the overall impression from the leavepiece, despite the LDL-C scale, was that 20mg and 40mg Lipitor were equally acceptable starting doses as 10mg. This was not an accurate reflection of the emphasis given in the marketing authorization to the 10mg starting dose.

AstraZeneca alleged that the leavepiece promoted Lipitor outside the terms of its licence in breach of Clause 3.2 and was misleading in breach of Clause 7.2. Furthermore AstraZeneca alleged that the recommendation for start dose against baseline LDL-C was incapable of substantiation in breach of Clause 7.4.

## RESPONSE

Pfizer referred to the Lipitor SPC which stated 'the usual starting dose is 10mg once a day. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response'. Pfizer submitted that the inclusion of the word 'usual' meant that this was not always the case. Hence doses other than 10mg might be used at initiation of treatment. The SPC stated that 'doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response'. Clearly the former two, baseline LDL-C therapy and the goal of therapy, were known before treatment started and therefore dictated the initial dose. Equally clearly, it would not be sensible to use the baseline LDL-C as a baseline for subsequent titration when a later measure of LDL-C would be more useful. The response to therapy could clearly only dictate the titration of subsequent doses. The SPC then recommended that 'adjustment of dosage should be made at intervals of four weeks or more'.

AstraZeneca had not requested the data which supported the choice of the appropriate starting dose. The Lipitor SPC provided the mean percentage change from baseline (dose response to Lipitor in patients with primary hypercholesterolaemia) in LDL-C (along with the other lipid fractions) in Table 1 of Section 5.1. This table was the basis of the 'slide-rule' shown in the leavepiece. The level of reduction, and hence the right starting dose, was identified and applied to bring the baseline levels down to target level, as defined by the Joint British Recommendations. This formula had been in the public domain for some years and it seemed odd that it should be challenged now for the first time.

Pfizer stated that FH patients were a special case. In practice they were not treated by GPs, but by specialists as recommended in national guidelines. The LDL-C reducing effect of statins varied from one FH patient to another. This inter-individual variation was poorly understood and was the subject of intense research. The focus in recent years had been to identify genetic loci and environmental factors responsible for this variability. Until these factors were better understood, it was not possible to predict how an individual patient with heterozygous FH would respond to individual statin doses. Furthermore, management of FH was optimal when combination therapy was employed. Current guidelines recommended that a combination of statins, fibrates and/or resins be employed to achieve adequate lipid fraction reductions. In severe cases, LDL apheresis also had a role in preventing the progression of coronary artery disease in heterozygotes with severe dyslipidaemia.

In this context a start dose of 10mg for this select group of patients, with unpredictable dose-response, was reasonable and distinct from the general primary hypercholesterolaemic population. However, in practice, specialist management of these patients often meant that higher start doses were used.

In April 2002, Pfizer discussed the issue of 'targeted starting dose' with the Medicines Control Agency (MCA) [now the Medicines and Healthcare products Regulatory Agency (MHRA)] whose advice was that the present labelling allowed it to propose such usage and so no change to the labelling was recommended. No specific discussions on FH were held.

In summary, Pfizer believed that the recommendation of a variable start dose, on the basis of baseline LDL-C level and the goal of therapy, was justified by the Lipitor SPC (as confirmed with the MCA).

This leavepiece was designed to assist GPs when starting a patient on Lipitor. The individual targets for LDL-C reduction in each country varied according to local guidelines, eg The CREST guidelines in Northern Ireland (LDL-C <3mmol/l) or the National Service Framework (NSF) for coronary heart disease

(CHD) in England and Wales (LDL-C <3mmol/l or reduced by 30%, whichever was greater). The slide-rule guideline in the leavepiece was applicable to all of the targets laid-down in the individual regions where it would be used.

The leavepiece indicated which dose of Lipitor should be initiated depending on baseline LDL-C levels, target LDL-C and efficacy demonstrated by Lipitor as detailed in the SPC. Each of the three doses of Lipitor shown (10, 20 & 40mg) was represented in a different colour. All three doses were presented as possible starting doses, depending on the patient's baseline LDL-C. This was in accordance with current Lipitor labelling and guidance received from the MCA. Lipitor did indeed have a range of equally acceptable start doses.

Pfizer stated that Neil *et al* (1999) showed that approximately 80% of CHD patients in the UK, currently considered for lipid-lowering therapy, had a baseline LDL-C level of 5mmol/l or less. Pfizer's guidance for choosing a starting dose of Lipitor implied that, for 80% of patients, 10mg was the appropriate choice. Therefore, the 'usual starting dose is 10mg'. Patients with baseline LDL-C greater than 5mmol/l could be started on 20mg or 40mg as appropriate. The slide-rule also pointed out that upward titration was possible, if required.

Pfizer disagreed with AstraZeneca's specific comments as follows:

- GPs were well versed in statin therapy and cholesterol targets. Physicians involved in cholesterol management understood the difference between total cholesterol and LDL-C. Since 1998, guidelines surrounding target cholesterol levels had been widely discussed. More recent publications had focussed on the need for LDL-C reduction. The leavepiece clearly stated that baseline LDL-C level should be considered if using the slide-rule as a prescribing tool.
- Pfizer justified its recommendations for the Lipitor starting dose above.
- The licence stated how the starting dose could be individualised according to baseline LDL-C levels, treatment targets and patient response. The implications of the marketing authorization had been explained to Pfizer by the MCA as discussed above.
- AstraZeneca had stated that the licensed start dose in FH patients was 10mg. This was not what was stated in the SPC. The Lipitor SPC divided the recommendation for dosing in FH into homozygous FH for which no additional instruction was given and heterozygous FH where it was stated 'patients should be started with Lipitor 10mg daily'. Heterozygous FH was a complicated condition best managed by specialists. The leavepiece in question was not used with such physicians but only in primary care.

In the interests of clarity and providing differentiation between patient types for prescribers, Pfizer was happy to add a note to the leavepiece reminding prescribers that patients with heterozygous hypercholesterolaemia were not included.

- No additional weight was given in this leavepiece to 20mg and 40mg. Visually, 10mg was the dose most frequently recommended. In practice, 10mg was the appropriate start dose for approximately 80% of the population. Pfizer submitted that the leavepiece emphasised 10mg – especially when viewed in its original colour it was darker and the 10mg strip was much wider than the other two together. This was in keeping with the fact that 80% of patients would achieve their LDL-C goal on 10mg of Lipitor.

**PANEL RULING**

The Panel noted that Section 4.2 of the Lipitor SPCs stated that the usual starting dose was 10mg daily. Doses should be individualised according to baseline LDL-C levels, the goal of therapy and patient response. Adjustment of dose should be made at intervals of four weeks or more. The majority of patients with primary hypercholesterolaemia and combined (mixed) hyperlipidaemia were controlled on 10mg daily. Patients with heterozygous familial hypercholesterolaemia 'should be started with Lipitor 10mg daily'.

The Panel noted that the table in Section 5.1 of the Lipitor 10, 20, 40mg SPC headed 'Dose-Response in Patients with Primary Hypercholesterolaemia' provided the adjusted mean percentage change from baseline for, *inter alia*, LDL-C, for Lipitor 10, 20, 40 and 80mg. This table was the basis of the LDL-C dose scale at issue.

The Panel noted Pfizer's submission that given that the LDL-C levels of the majority of CHD patients was ≤ 5mmol/l then 10mg was the start dose for 80% of the patient population. The Panel considered that it would have been helpful if the leavepiece had reproduced the SPC statement that '10mg was the usual starting dose'. The Panel noted that in relation to patients with heterozygous FH the SPC stipulated a starting dose of 10mg daily. This was not made sufficiently clear in the leavepiece. The Panel considered that the leavepiece gave the impression that the starting doses depicted were suitable for all patient groups for whom Lipitor was indicated and that was not so; the leavepiece was misleading and inconsistent with the SPC in this regard. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel did not consider that the recommendation of start dose against baseline LDL-C was incapable of substantiation as alleged; no breach of Clause 7.4 was ruled.

**2 Pfizer sales force activity**

**COMPLAINT**

AstraZeneca had received several reports from clinicians in various parts of the country that the promotion of Lipitor by Pfizer representatives had similar features to the above leavepiece. In addition several clinicians had commented that Pfizer had 'a new licence' for Lipitor which allowed it to be used at higher start doses. There had been no feedback that there was any qualification on this advice. Pfizer had commented that it had not briefed its representatives that the licence was 'new'. Whilst AstraZeneca accepted this, the consistency of feedback it was

getting suggested that physicians were picking up the impression from Pfizer's sales force that the company had a 'new' licence. AstraZeneca had no direct evidence showing how Pfizer representatives had been briefed on this issue but the weight of comment coming back to AstraZeneca about the Lipitor start dose led it to believe that Pfizer was not clearly communicating the direction given in the licence as regards a 10mg start dose.

AstraZeneca alleged breaches of Clauses 3.2 and 7.2 of the Code.

AstraZeneca regarded this as a serious matter. Statin-related side-effects such as rhabdomyolysis, which although rare, could be serious and even fatal, occurred more commonly if higher start doses were used. Regulatory authorities, cognisant of this, made particular recommendations within the SPCs of the various statins to dictate how physicians started patients on treatment. AstraZeneca did not believe this was open to reinterpretation at an arbitrary time-point without clear direction in terms of licence change from regulatory authorities.

**RESPONSE**

Pfizer stated that it had briefed its sales force about what it described as a 'flexible start dose'. Pfizer expected, therefore, that clinicians would have fed this back to other companies. The representatives had been briefed at this year's sales conference when materials for 2003 were introduced. Pfizer provided a copy of the slide which showed how it was discussed together with a follow-up Question & Answer document. No reference had been made to a 'new licence'. The fact that no licence change was required had been communicated and Pfizer could not understand how this could have been interpreted in any other way.

Pfizer did not wish to imply that it had a new licence and it could only assume that somewhere an incorrect impression had been inferred by a customer or inadvertently implied by a representative. Pfizer submitted that it had given clear instructions to its representatives, consistent with both the spirit and the letter of its SPC and of its discussions on this issue with the MCA. Additionally, there had been no lack of clarity in briefing the 'flexible start dose'. Nowhere, including in its briefing material, had it been suggested that this was a new marketing authorization. Pfizer had now taken steps to ensure that no such misunderstanding continued.

Pfizer stated that the information supplied in this promotional campaign was accurate, balanced and not misleading and so was not in breach of Clause 7.2. As it was within Lipitor's licence, Pfizer stated that it was not in breach of Clause 3.2. Pfizer therefore denied breaches of either of these clauses.

AstraZeneca had raised new issues around side effects and patient safety and the relationship between these and the starting dose while not raising them in the body of its complaint and, moreover, failing to give background references to support its implications. Nevertheless Pfizer responded.

Rhabdomyolysis was an extremely rare side effect of treatment with Lipitor, which among the statins appeared to have favourable long-term safety records in this regard. A soon to be published study, which was currently held as data on file with Pfizer, compared the efficacy and safety of atorvastatin at starting doses of 10, 20, 40 and 80mg in approximately 900 patients with dyslipidaemia. The overall incidence of adverse events was similar for all dosage groups and a dose response effect was not observed in any of the treatment emergent adverse events leading to discontinuation from the study. In summary, this study showed that patients at risk of coronary heart disease benefited from starting therapy at higher doses of atorvastatin without any additional safety risks.

Pfizer had clarified the nature of its marketing authorization with the regulatory authorities and the advice from the MCA had confirmed its interpretation of the acceptable starting dose.

Pfizer was strongly aware of the patient's safety imperative in adequately treating hypercholesterolaemia and it was equally cogniscent of the risks of adverse reactions to medicines. Pfizer put the issue of patient safety above all else in everything it did.

**PANEL RULING**

The Panel noted that Pfizer had briefed its sales representatives about a 'flexible start dose'. Pfizer provided a copy of a training slide and a question and answer document.

The Panel noted that the training slide headed 'What is Flexible Start Dose (FSD)?' referred to the ability 'to start patients on 10mg, 20mg, or 40mg' and 'Gets >80% of patients to target 'right from the start''. The Panel did not have the other slides in the presentation before it. Given Pfizer's submission at point 1 that 'in practice 10mg was the appropriate start dose for approximately 80% of the population' and that the SPC stated that 'the usual starting dose was 10mg daily' the Panel queried whether the training slide provided made it sufficiently clear that 10mg was the usual starting dose.

The Panel noted the Flexible Start Dose Q & A stated that 'the usual starting dose was 10mg daily'. All three doses of Lipitor were, however, presented as possible starting doses. The Panel noted that in response to the question 'Can I initiate a patient on Lipitor 80mg' the answer read 'Our current recommendation is that 10, 20 or 40mg is adequate therapy for the vast majority of patients'. It was stated that Lipitor did not have a new licence. The Panel considered that it was not made sufficiently clear that 10mg daily was the appropriate starting dose for the majority of patients.

The Panel was concerned about the documents for the representatives in relation to the starting dose of Lipitor. The Panel noted that it had no evidence before it as to precisely what had been said by representatives when detailing clinicians on this point. The Panel was thus obliged to rule no breach of Clauses 3.2 and 7.2 of the Code.

**Complaint received** **25 March 2003**

**Case completed** **27 May 2003**

CASE AUTH/1441/3/03

# PHARMACIA v ALLERGAN

## Lumigan exhibition panels

Pharmacia complained about Lumigan (bimatoprost) exhibition panels produced by Allergan which bore the claim 'More effective than latanoprost'. Pharmacia marketed Xalatan (latanoprost). Lumigan and Xalatan were both licensed for the treatment of glaucoma and ocular hypertension.

Pharmacia stated that four randomised controlled trials had compared bimatoprost and latanoprost, three of which had shown equivalence; DuBiner *et al* (2001), Gandolfi *et al* (2001) and Parrish *et al* (2003 in press). The fourth study, Noecker *et al* (2003), showed an intraocular pressure (IOP) lowering effect not in keeping with these or previous latanoprost studies. Pharmacia alleged that the claim 'More effective than latanoprost' was not a fair and objective representative of the available evidence in breach of the Code.

The Panel noted that Allergan had used a set of three exhibition panels to summarise the results of Noecker *et al*. The first exhibition panel featured a graph showing the mean IOP reduction (mmHg) from baseline at noon. Results were shown for week one and months 1, 3 and 6. All timepoints showed a statistically significant advantage ($p<0.001$) for Lumigan compared with latanoprost. The second exhibition panel featured a bar chart which depicted the percentage of responders/non-responders at month 6, noon time point, which again showed a statistically significant advantage for Lumigan ($p<0.001$). Both the graph on the first panel and the bar chart on the second were headed 'NEW 6 month study vs latanoprost shows:' and above this heading on each was the claim 'Lumigan monotherapy more effective than latanoprost'. The third exhibition panel featured the claim 'Lumigan monotherapy ✓ More effective than latanoprost' followed by four bullet points all referenced to Noecker *et al*.

The results featured on the exhibition panels had come from the only one of four studies which had shown a clear advantage for Lumigan compared with latanoprost. Noecker *et al* lasted for 6 months; two of the other studies lasted 3 months (Gandolfi *et al* and Parrish *et al*) and the fourth study (DuBiner *et al*) lasted one month. The Panel noted, however, that the results from Noecker *et al* depicted on the first exhibition panel appeared to indicate that maximum IOP lowering was achieved at one week with mean IOP reduction remaining almost constant thereafter. The study thus showed that efficacy for Lumigan and latanoprost observed in the short-term was maintained in the long-term. In the Panel's view this meant that, in terms of assessing the comparative efficacy of Lumigan and latanoprost, the study was no more relevant than shorter-term studies.

Parrish *et al*, in which patient numbers were comparable to those in Noecker *et al*, had shown no statistically significant differences in efficacy between Lumigan and latanoprost. Gandolfi *et al* was a slightly smaller study and although the mean IOP was lower with Lumigan than with latanoprost at all time points during the three month follow-up, the between group difference was not always statistically significant. Patients in the Lumigan group were significantly more likely than patients in the latanoprost group to achieve low target pressures ($\leq$ 15mmHg; $p=0.009$). The authors, however, were cautious in their discussion of the results and stated 'The present study *suggests* (emphasis added) that [Lumigan] is superior to latanoprost …' and '[Lumigan], however, *appeared* (emphasis added) to provide superior diurnal control …'. DuBiner *et al* was a small (n=64) short-term study and although the results showed a trend towards greater efficacy with Lumigan the authors stated that 'The small sample size made it difficult to discern statistically significant differences in IOP lowering between the [Lumigan] and latanoprost treatment groups at any individual time points'.

In Noecker *et al* the mean change from baseline IOP for latanoprost at 6 months ranged from approximately 6.1mmHg (8am) to approximately 5mmHg (4pm) (the actual figures were not stated in the paper). Previous studies with latanoprost had demonstrated drops in mean diurnal IOP of 27-33% and actual drops of between 6.7-8.5mmHg (Watson *et al* 1996; Hedman and Alm 2000; O'Donoghue *et al* 2000; Camras *et al* 1996; Alm *et al* 1995). Suzuki *et al* (2000) showed that in Japanese patients latanoprost consistently reduced IOP between 5.4mmHg and 6.3mmHg throughout a 52 week treatment period. The Panel noted that the studies varied in the way IOP reduction was reported and the times of day IOP was measured and so results could not be directly compared. Nonetheless, the IOP lowering effect of latanoprost observed by Noecker *et al* appeared to be at the low end of what might be expected. Parrish *et al* had commented on the uncharacteristic results obtained for latanoprost by Noecker *et al* although the authors also noted that the response to Lumigan in that study was consistent with previous findings. Parrish *et al* were unable to explain why latanoprost-treated patients had a poorer than expected response in Noecker *et al*.

The Panel considered that overall there was data to show a trend in favour of Lumigan compared with latanoprost. Although Noecker *et al* had shown clear differences in efficacy between the two in favour of Lumigan three other studies had not. There was a suggestion that the results obtained for latanoprost in Noecker *et al* were not as good as might have been expected from other studies. The Panel did not consider that the results of Noecker *et al* outweighed the results of the other studies; in the Panel's view the balance of evidence was still that there was no statistically significant difference, in terms of efficacy, between Lumigan and latanoprost. The Panel considered that the claim 'Lumigan monotherapy more effective than latanoprost' thus did not represent the balance of the evidence. The Panel noted that on two of the exhibition panels the claim at issue was followed by the statement 'NEW 6 month study vs latanoprost shows' but did not consider highlighting that the results were from one study negated the impression that they represented an up-to-date evaluation of all the evidence. A breach of the Code was ruled.

Pharmacia Limited complained about Lumigan (bimatoprost) exhibition panels produced by Allergan Limited which bore the claim 'More effective than latanoprost'. Pharmacia marketed Xalatan (latanoprost). Intercompany dialogue had failed to resolve the issues.

Lumigan was licensed as monotherapy for the treatment of glaucoma and ocular hypertension in patients who had not responded adequately to first line therapy or who were intolerant of, or had a contraindication to, such therapy. Lumigan could also be used as adjunctive therapy to beta-blockers. Xalatan was licensed for the reduction of intraocular pressure in patients with open angle glaucoma and ocular hypertension.

## COMPLAINT

Pharmacia stated that four randomised controlled trials had compared bimatoprost and latanoprost, three of which had shown equivalence; DuBiner *et al* (2001), Gandolfi *et al* (2001) and Parrish *et al* (2003 in press). The fourth study, Noecker *et al* (2003), showed an intraocular pressure (IOP) lowering effect not in keeping with these or previous latanoprost studies. Pharmacia alleged that the claim 'More effective than latanoprost' did not represent the balance of evidence in breach of Clause 7.2 of the Code.

Pharmacia noted that it had sponsored the study by Parrish *et al*; the other three were conducted by Allergan.

DuBiner *et al* compared the efficacy and safety of bimatoprost and latanoprost in patients with elevated intraocular pressure over a period of 30 days. There were three patient groups: latanoprost (n=22); bimatoprost (n=21) and vehicle alone (n=21). The primary endpoint was the change in IOP from baseline. Analysis of both day 14 and day 29 showed equivalence for reduction of IOP.

A further analysis reported in the original paper claimed that the diurnal reduction in IOP was greater for bimatoprost, as assessed by calculating the area under the curve (AUC) for IOP. Re-analysis of the data had shown that the difference between groups in terms of their AUC was present at baseline. It remained constant throughout the study, rather than representing a treatment effect (Eisenberg *et al* 2002).

Gandolfi *et al* conducted a three-month comparison of bimatoprost (n=119) and latanoprost (n=113) in patients with glaucoma and ocular hypertension. The primary efficacy outcome measure was mean IOP at 8am. Mean baseline IOP at 8am was 25.7mmHg for both groups. No significant difference in mean IOP response was found between groups at 8am for any visit.

Pharmacia stated that from intercompany correspondence it was clear that Allergan had chosen as evidence a different timepoint from that pre-specified in the protocol – 12 noon. Eisenberg *et al* explained that differences seen at this timepoint reflected the numerically lower mean IOP at baseline in the bimatoprost group versus the latanoprost group at 12 noon. Taking the mean IOP at this timepoint, rather than the reduction in IOP, was meaningless as an efficacy assessment. It was evident that Eisenberg *et al* had had access to more information than was presented in the original publication and this had allowed the authors to fully evaluate any potential difference in efficacy. The review clearly stated that this study did not support greater efficacy for bimatoprost.

Parrish *et al* compared latanoprost (n=136), bimatoprost (n=137), and travoprost (n=138) in patients with elevated intraocular pressure in a 12 week, randomized, masked-evaluator, multicenter study. The primary efficacy outcome was mean change between baseline and week 12 in IOP at 8am. Comparison of latanoprost and bimatoprost showed no significant differences between the two. The secondary efficacy outcomes were mean change between baseline and week 12 in IOP at 12 noon, 4pm and 8pm and in diurnal IOP. Diurnal IOP was defined as the mean of IOP measurements at 8am, 12 noon, 4pm and 8pm. Pharmacia submitted that again no significant differences between treatments were evident.

Pharmacia noted that in intercompany correspondence Allergan had stated that this study was of reduced power because it had three arms. Pharmacia strongly disagreed. The study was appropriately powered, and the numbers enrolled in each arm were greater than in Gandolfi *et al* and comparable to Noecker *et al*. Allergan had also accused the authors of 'failing to provide data for the diurnal timepoints (12pm, 4pm, and 8pm) on the week 6 visit. These were neither primary nor secondary outcomes, and given that this was a chronic condition, were irrelevant in a study of 12 weeks' duration.

Allergan had also claimed that for the timepoints presented in the paper, bimatoprost had a numerically lower mean IOP. Pharmacia considered that this again was an incorrect interpretation of values within a publication. Whilst the absolute mean value might appear lower, it was statistically equivalent and should not be used as a basis for a superiority claim.

Noecker *et al* was a six-month, randomized, comparative clinical trial of bimatoprost (n=133) and latanoprost (n=136) in patients with ocular hypertension or glaucoma. The primary outcome measure was mean change from baseline IOP. The bimatoprost group showed a greater reduction in IOP at all time points when compared to latanoprost. The reduction in IOP in this study was not in keeping with that seen in other similar previous randomized controlled trials involving latanoprost. The reduction in IOP was 5.5mmHg or a 23.4% decrease; previous latanoprost studies of comparable size and chronic (12 weeks or more) duration had consistently shown an IOP reduction of between 7.15 – 8.6mmHg or 27.8 – 34.7%.

Pharmacia stated that Allergan's claim that 'In no instance was a lower mean IOP or greater mean IOP reduction found with latanoprost treatment, although this would be expected to occur at approximately 50% of the measurements if the drugs were, in fact, equivalent in efficacy' was an incorrect assumption. Simply looking at absolute values and ignoring the statistical analysis implied a lack of understanding.

Pharmacia stated that with three out of the four studies to date showing equivalence, the claim 'More effective than latanoprost' could not be considered a balanced reflection of the evidence. Pharmacia

alleged that the claim was not a fair and objective representation of the available information in breach of Clause 7.2 of the Code.

## RESPONSE

Allergan stated that the claim 'More effective than latanoprost' was based on Noecker *et al* which compared latanoprost and bimatoprost; the results showed significantly greater mean IOP reductions and significantly lower mean IOP with bimatoprost compared with latanoprost at each of the 12 follow-up timepoints in the study. Allergan noted that the statement 'NEW 6 month study vs latanoprost' was clearly stated on two of the three exhibition panels directly under the claim. On the third exhibition panel the claim was clearly referenced to Noecker *et al*.

Allergan stated that the fact that Noecker *et al*, published in January 2003, was the first, and only, six month study comparing latanoprost and bimatoprost, with diurnal measurements at 4 follow-up visits across the six month period, supported its presentation as a new study in its own right. Additionally the balance of evidence from the published data indicated that bimatoprost provided greater IOP lowering than latanoprost. Therefore, based on both of these arguments, Allergan considered that the claim 'More effective than latanoprost' was a balanced reflection of the current evidence and was not in breach of Clause 7.2 of the Code.

Allergan noted that DuBiner *et al* conducted a 30 day trial in 64 patients assigned to one of three groups (bimatoprost, latanoprost or vehicle). The primary endpoint was reduction in IOP from baseline on day 14 and day 29. Bimatoprost lowered IOP numerically more than latanoprost at every time point measured, although the between group differences did not reach statistical significance. However, over the 12-hour course of IOP measurements on day 29, bimatoprost provided better diurnal IOP control than latanoprost (p=0.0378). When overall mean reductions were analyzed, the difference between bimatoprost and latanoprost approached statistical significance (p=0.0572).

Allergan stated that the AUC analysis reported by DuBiner *et al* was of mean IOP reductions, not IOP, and it showed greater IOP lowering with bimatoprost. Eisenberg *et al* was correct that small differences occurring by chance between the treatment groups at baseline might have influenced the differences in IOP lowering between groups. However, the presentation of the Eisenberg *et al* post-hoc analysis was misleading; Eisenberg *et al* did not evaluate the AUC of mean IOP at baseline and study exit and did not show that differences between the treatment groups at baseline were maintained throughout the study with no effect of study medication.

Bimatoprost demonstrated numerically greater IOP reductions from baseline than did latanoprost at every measurement. Allergan stated that if, as Eisenberg *et al* had stated, the difference between treatments remained constant throughout the study, the differences between the treatments in IOP reduction would have been zero. This was not the case. Allergan noted that the study was not powered to show statistically significant differences between any two treatments. The lack of statistically significant differences did not equal 'equivalence'. Allergan further noted that whilst this was a small 30 day trial the results indicated a clear trend towards greater IOP lowering efficacy with bimatoprost compared with latanoprost.

Gandolfi *et al* conducted a 3 month trial in 232 patients assigned to bimatoprost or latanoprost. The primary endpoint was IOP at 8am, measured at all study visits. Additionally, twelve hour diurnal IOP (8am, 12 noon, 4pm and 8pm) was measured at baseline and month 3. The paper presented results from all timepoints (ie 8am at all visits and the diurnal at baseline and month 3). Mean IOP was lower with bimatoprost than with latanoprost at all time points during the 3 month follow up, although the between-group difference was not always statistically significant.

Eisenberg *et al's* contention that the differences observed at the 12 noon timepoint reflected the numerically lower mean IOP at baseline in the bimatoprost group versus the latanoprost group at this timepoint was incorrect. The baseline IOP values at 12 noon were 24.4mmHg and 24.7mmHg in the bimatoprost and latanoprost groups, respectively. This difference at baseline did not approach statistical significance (p=0.593) and could not explain the 1mmHg difference seen at 12 noon at month 3.

There was no evidence that Eisenberg *et al* had had access to more information than was presented in the original publication and so any extrapolations that contradicted the data in the original publication were conjecture.

Allergan submitted that both DuBiner *et al* and Gandolfi *et al* indicated a clear trend towards greater IOP lowering efficacy with bimatoprost compared with latanoprost.

Parrish *et al* conducted a 3 month trial comparing latanoprost (n=136), bimatoprost (n=137), and travoprost (n=138). The primary efficacy outcome measure was change between baseline and week 12 in IOP measured at 8am. This trial showed no significant among-group differences in mean IOP reductions at month 3 in the intent-to-treat patient population. The authors concluded from these results that the medicines were 'equivalent' in efficacy.

Allergan noted that the sample size in Parrish *et al* was based on detecting a difference between two treatment groups of 1.5mmHg in mean IOP reduction. There was no consideration of the fact that three treatments were being compared. The methodology used for the primary analysis (analysis of variance comparing all three treatments) was different than that used as a basis of sample size determination (two-sample t-tests). Thus, the power of the study was not as claimed in the publication.

Six week data were arguably no more irrelevant than 12 week data in a chronic condition like glaucoma. The data were collected; they should be analyzed and presented to help clarify the relative efficacy of the medicines. With IOP reductions at only 4 measurements used as the only efficacy endpoints in the trial, there appeared to have been bias in the study design to fail to find differences among groups.

Allergan stated that its interpretation of values within Parrish *et al* was correct. Every representation of IOP data showed bimatoprost results to be numerically superior to both latanoprost and travoprost results. The use of the term 'equivalent' throughout this publication, however, was incorrect and misleading. There was a difference between 'lack of statistical significance' and 'statistically equivalent'. This study was planned as a superiority trial and, as such, criteria for 'equivalence' were never specified. The among-group p-values presented for the week 12 visit 12 noon, 4pm and 8pm timepoints were all ≤ 0.1, indicating that they approached statistical significance. Pairwise comparisons at one or more of these timepoints would likely reveal statistically significant between-treatment differences. It was erroneous to state that the three treatments were equivalent because the among-group p-values were > 0.05.

Noecker *et al* conducted a six month trial comparing bimatoprost (n=133) with latanoprost (n=136). The primary efficacy measure was mean change from baseline IOP (8am, 12pm and 4pm). Secondary outcomes measures included mean IOP, the percentage of patients reaching specific target IOPs and the percentage of patients achieving at least a 15% or 20% decrease in IOP from baseline.

Bimatoprost lowered IOP significantly more than did latanoprost at all timepoints throughout the 6 months of the study. At every measurement, mean changes from baseline IOP were significantly greater with bimatoprost than they were with latanoprost ($p< 0.025$). By the end of the study, mean changes from baseline were 1.2 – 2.2mmHg greater than with latanoprost ($p<0.004$).

At the end of the study, the percentage of patients achieving ≥20% IOP decrease was 69 – 82% with bimatoprost and 50 – 62% with latanoprost ($p\leq 0.003$). In addition, the distribution of patients achieving target pressures in each range (≤ 13 to ≤ 15mmHg, >15 to ≤ 18mmHg, and >18mmHg) showed that bimatoprost produced lower target pressures compared with latanoprost at all times measured ($p<0.026$).

Allergan noted Pharmacia's submission that the reduction in IOP in this study was not in keeping with that seen in other previous randomized controlled latanoprost trials. However, in two 6-month pivotal trials of latanoprost vs timolol the mean IOP reductions provided by latanoprost at month 6 were approximately 6.7mmHg and 8.6mmHg (Alm *et al* 1995 and Camras *et al* 1996). In another large trial, latanoprost provided a mean IOP reduction of 6mmHg at month 6 and 5.4mmHg at month 12 (Suzuki *et al* 2000). The reasons for the inconsistent effectiveness of latanoprost across trials were unexplained. Allergan stated that its trial found a mean IOP reduction with latanoprost of 7.1mmHg at month 3 and 6mmHg at month 6, clearly within the range of IOP reductions found with latanoprost in previous studies. Allergan stated that it was impossible for it to compare the non-responder rates found in its study with those found in Parrish *et al*, because Parrish *et al* did not report these data. Allergan stated that unfortunately, most studies of latanoprost had not reported response rates, yet some studies, in addition to Allergan's, had suggested that a significant number of patients (at least 20%) might fail to achieve at least 20% IOP lowering on latanoprost monotherapy.

The design of Noecker *et al* was refined based on DuBiner *et al* and Gandolfi *et al*. Glaucoma was a chronic disease and it was important to evaluate both long-term IOP reduction as well as reduction in diurnal IOP. In Noecker *et al*, diurnal IOP was measured at week 1, and months 1, 3, and 6 to ensure a clear understanding of the efficacy of these two medicines throughout the day over the six month period. Additionally, the profile of patients entering the study with respect to washout medications was consistent with what was reported on the marketed prescription rate of glaucoma medications (eg, approximately 25% of patients enrolled were previously on latanoprost, which was washed out).

Allergan stated that this study was the only one of the four discussed conducted over 6 months, hence it showed longer-term efficacy. In addition, IOP was measured at multiple times of the day at each follow-up visit; results for the intent-to-treat and per-protocol patient populations were consistent (increasing the reliability of the results); both mean IOP and mean IOP reductions from baseline were reported; and all data were analyzed and presented.

Overall, the four studies comparing bimatoprost with latanoprost provided good evidence to support significant differences in efficacy between latanoprost and bimatoprost. Notably, of the 30 reported measurements comparing the two (all of the follow-up measurements in DuBiner *et al*, Gandolfi *et al* and Noecker *et al*, and the 6 reported follow-up measurements in Parrish *et al*) bimatoprost provided greater mean IOP reductions than latanoprost at 29 measurements and lower mean IOP than latanoprost at 28 measurements. In no instance was a lower mean IOP or greater mean IOP reduction found with latanoprost treatment, although this would be expected to occur at approximately 50% of the measurements if the two were equivalent in efficacy.

Allergan stated that a failure to find statistically significant results might reflect study design rather than efficacy, and a lack of statistical significance did not imply a lack of clinical importance. The alpha level chosen for statistical significance in any trial was arbitrary, but the consistent results across all trials, even the Pharmacia-sponsored trial, showing lower mean IOP and greater IOP reductions with bimatoprost than with latanoprost, indicated that the results were not due to chance, but to superiority of bimatoprost.

In conclusion, Allergan considered that the information presented in its exhibition panels was balanced and correctly reflected the data in Noecker *et al*, the only 6-month head-to-head comparison of bimatoprost and latanoprost, with diurnal measurements at 4 follow up visits across the six month period. This new 6-month study was clearly of more clinical relevance to ophthalmologists than the previous shorter-term head-to-head studies. Both mean IOP and mean IOP reductions from baseline were reported. Therefore, this study should be presented in its own right.

Secondly, considering all four studies and the trends within each, Allergan believed that the balance of

evidence indicated that bimatoprost provided greater IOP lowering than latanoprost.

Therefore, for the above two reasons, Allergan did not consider that the claim 'More effective than latanoprost' as presented in the context of the exhibition panels, was in breach of Clause 7.2 of the Code.

Allergan stated that the meeting at which the exhibition panels were used was organised by the Midlands Ophthalmological Society. A copy of the programme was provided. The subject for the meeting was Vitreo-Retinal Surgery and the audience was ophthalmic surgeons of all grades from across the Midlands. Allergan stated that it was one of many companies invited to have a stand at the meeting and that it had no other involvement.

## PANEL RULING

The Panel noted that Allergan had used a set of three exhibition panels to summarise the results of Noecker *et al*. From the left the first exhibition panel featured a graph showing the mean IOP reduction (mmHg) from baseline at noon. Results were shown for week one and months 1, 3 and 6. In all timepoints the results showed a statistically significant advantage ($p<0.001$) for Lumigan compared with latanoprost. The second, and central, exhibition panel featured a bar chart which depicted the percentage of responders/non-responders at month 6, noon time point, which again showed a statistically significant advantage for Lumigan ($p<0.001$). Both the graph on the first panel and the bar chart on the second were headed 'NEW 6 month study vs latanoprost shows:' and above this heading on each was the claim 'Lumigan monotherapy **more effective** than latanoprost'. The third exhibition panel featured the claim 'Lumigan monotherapy ✓ More effective than latanoprost' followed by four bullet points all referenced to Noecker *et al*.

The Panel noted that the results featured on the exhibition panels had come from the only one of four studies which had shown a clear advantage for Lumigan compared with latanoprost. Noecker *et al* lasted for 6 months; two of the other studies lasted 3 months (Gandolfi *et al* and Parrish *et al*) and the fourth study (DuBiner *et al*) lasted one month. The Panel noted, however, that the results from Noecker *et al* depicted on the first exhibition panel appeared to indicate that maximum IOP lowering was achieved at one week with mean IOP reduction remaining almost constant thereafter. The study thus showed that efficacy for Lumigan and latanoprost observed in the short-term was maintained in the long-term. In the Panel's view this meant that, in terms of assessing the comparative efficacy of Lumigan and latanoprost, the study was no more relevant than shorter-term studies.

The Panel noted that Parrish *et al*, in which patient numbers were comparable to those in Noecker *et al*, had shown no statistically significant differences in efficacy between Lumigan and latanoprost. Gandolfi *et al* was a slightly smaller study and although the mean IOP was lower with Lumigan than with latanoprost at all time points during the three month follow-up, the between group difference was not always statistically significant. Patients in the Lumigan group were significantly more likely than patients in the latanoprost group to achieve low target pressures (≤ 15mmHg; $p=0.009$). The authors, however, were cautious in their discussion of the results and stated 'The present study *suggests* (emphasis added) that [Lumigan] is superior to latanoprost …' and '[Lumigan], however, *appeared* (emphasis added) to provide superior diurnal control …'. DuBiner *et al* was a small (n=64) short-term study and although the results showed a trend towards greater efficacy with Lumigan the authors stated that 'The small sample size made it difficult to discern statistically significant differences in IOP lowering between the [Lumigan] and latanoprost treatment groups at any individual time points'.

The Panel noted that in Noecker *et al* the mean change from baseline IOP for latanoprost at 6 months ranged from approximately 6.1mmHg (8am) to approximately 5mmHg (4pm) (the actual figures were not stated in the paper). Previous studies with latanoprost had demonstrated drops in mean diurnal IOP of 27-33% and actual drops of between 6.7-8.5mmHg (Watson *et al* 1996; Hedman and Alm 2000; O'Donoghue *et al* 2000; Camras *et al* 1996; Alm *et al* 1995). Suzuki *et al* (2000) showed that in Japanese patients latanoprost consistently reduced IOP between 5.4mmHg and 6.3mmHg throughout a 52 week treatment period. The Panel noted that the studies varied in the way IOP reduction was reported and the times of day IOP was measured and so results could not be directly compared. Nonetheless, the IOP lowering effect of latanoprost observed by Noecker *et al* appeared to be at the low end of what might be expected. Parrish *et al* had commented on the uncharacteristic results obtained for latanoprost by Noecker *et al* although the authors also noted that the response to Lumigan in that study was consistent with previous findings. Parrish *et al* were unable to explain why latanoprost-treated patients had a poorer than expected response in Noecker *et al*.

The Panel considered that overall there was data to show a trend in favour of Lumigan compared with latanoprost. Although Noecker *et al* had shown clear differences in efficacy between the two in favour of Lumigan three other studies had not. There was a suggestion that the results obtained for latanoprost in Noecker *et al* were not as good as might have been expected from other studies. The Panel did not consider that the results of Noecker *et al* outweighed the results of the other studies; in the Panel's view the balance of evidence was still that there was no statistically significant difference, in terms of efficacy, between Lumigan and latanoprost. The Panel considered that the claim 'Lumigan monotherapy **more effective** than latanoprost' thus did not represent the balance of the evidence. The Panel noted that on two of the exhibition panels the claim at issue was followed by the statement 'NEW 6 month study vs latanoprost shows' but did not consider highlighting that the results were from one study negated the impression that they represented an up-to-date evaluation of all the evidence. A breach of Clause 7.2 was ruled.

**Complaint received** **27 March 2003**

**Case completed** **4 June 2003**

**CASE AUTH/1442/3/03**

# LILLY v PFIZER

## Viagra journal advertisement

**Lilly complained about a journal advertisement for Viagra (sildenafil) issued by Pfizer.**

**Lilly stated that the advertisement, and other Viagra material, carried the strap line 'speaks for itself' directly underneath the product logo. Lilly alleged that the strapline was an all-embracing exaggerated claim and not capable of substantiation.**

**The Panel noted that in a previous case about a Viagra advertisement, Case AUTH/1312/5/02, it had ruled that the claim 'speaks for itself' would be viewed within the context of the advertisement as a whole. The advertisement at issue in that case featured the clasped hands of a couple and the prominent phrase 'SPECIAL again'. The Panel had considered that the claim 'speaks for itself' would be seen as a general claim for the efficacy of the product within the context of a consequential beneficial effect upon the couple's relationship. The Panel had not considered the claim misleading, unsubstantiated or exaggerated as alleged; no breach of the Code had been ruled.**

**Turning to the present case, Case AUTH/1442/3/03, the Panel noted that the advertisement now at issue was different to that considered previously in that it did not include the phrase 'special again'. Further, two more oral treatments had been launched, Cialis (Lilly) and Levitra (Bayer and GlaxoSmithKline). The Panel noted that there might be difficulties for couples following successful treatment of ED. Taking all the circumstances into account the Panel did not consider that the claim 'speaks for itself' was misleading, exaggerated or incapable of substantiation as alleged; it did not imply that Viagra was unique or that it had the most favourable anti-impotence properties as alleged by Lilly. The Panel ruled no breach of the Code.**

**Lilly noted that the prescribing information in the advertisement at issue, and in all other Viagra material that it had seen, stated, *inter alia*, 'One single dose per day is recommended' whereas the Viagra summary of product characteristics (SPC) stated 'The maximum recommended dosing frequency is once per day'. These two phrases meant very different things. The first actively advocated daily dosing. The second stated that daily dosing was the maximum permitted frequency. Lilly alleged that the prescribing information misled as to the meaning of the SPC.**

**The Panel considered that the prescribing information advocated regular daily dosing whereas the SPC recommended a maximum permitted dosage frequency of once per day when needed. The Panel considered that the prescribing information did not make the maximum daily dosing frequency sufficiently clear. The prescribing information was misleading and inconsistent with the particulars listed in the SPC. Breaches of the Code were ruled which were upheld on appeal by Pfizer.**

Eli Lilly and Company Limited complained about an advertisement for Viagra (sildenafil) (VIA 412) issued by Pfizer Limited which appeared in Practical Diabetes International January/February 2003.

Viagra was an oral phosphodiesterase type 5 (PDE5) inhibitor for the treatment of erectile dysfunction (ED). Lilly marketed Cialis (tadalafil), also an oral PDE5 inhibitor for the treatment of ED.

Lilly stated that intercompany dialogue had failed to resolve the issues. Pfizer had refused to withdraw the advertisement or claims at issue citing as its main reason the ruling of no breach of the Code in Case AUTH/1312/5/02 which predated the availability of other oral active PDE5 inhibitors.

### 1 Claim 'speaks for itself'

#### COMPLAINT

Lilly stated that the advertisement, and other Viagra material, carried the strap line 'speaks for itself' directly underneath the prominent Viagra product logo.

Lilly alleged that the claim 'speaks for itself' (which referred to Viagra) was an all-embracing exaggerated claim and not capable of substantiation. Setting aside the obvious nonsense of inanimate objects such as pharmaceuticals speaking for themselves, Lilly noted that the Panel had previously ruled that 'speaks for itself' was a figure of speech and that, in the context of 'special again' and a picture of a couple 'clasping hands', 'speaks for itself' was a reasonable claim indicating the general efficacy of Viagra (Case AUTH/1312/5/02).

In Lilly's view, the circumstances regarding the claim 'speaks for itself' had changed and it was no longer the case that Viagra 'speaks for itself'. Lilly noted that success rates at obtaining improved erections varied between 62% and 82% for Viagra (summary of product characteristics (SPC)) but improved erections did not always lead to successful intercourse. The probability of successful intercourse ranged from as low as 50% at the first attempt to about 80% after 10 attempts depending upon the severity of the ED and persistence of the parties involved (McCullough *et al* 2002). Furthermore continuation rates with Viagra treatment had been shown to be quite variable (El-Galley *et al* 2001, Giuliano *et al* 2000, Madduri 2001, Souverein *et al* 2002). Lilly also noted that the ability to obtain an erection once more led to problems of partner acceptance in a significant proportion of cases (McCullough *et al*). Furthermore data on success at re-establishing intercourse showed that, even with the use of Viagra, success was by no means universal. The graph illustrating the point in Pfizer's leavepiece (VIA 507) highlighted the fact that even after 10 attempts between 20% and 40% of couples had still not achieved successful intercourse. Thus use of Viagra was not always associated with self evident or 'speaks for itself' effects portrayed in the advertisement.

In addition, Lilly contended that 'speaks for itself' was a figure of speech suggesting that something was

self evident to the extent that no explanation was required. In the context of an advertisement, the use of this claim suggested that Viagra had some unique or highly favourable property, which was self evident to the point where no qualification was required. Whereas this might have been true at the time when the Panel considered Case AUTH/1312/5/02, the recent introduction of other oral anti-impotence medicines, including Lilly's product Cialis, meant that Viagra was now neither unique nor necessarily the anti-impotence agent with the most favourable properties: thus the claim was alleged to be misleading, exaggerated and incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10.

## RESPONSE

Pfizer disagreed with Lilly's assumption that the circumstances regarding the claim 'speaks for itself' had changed. Pfizer believed that although the ruling in Case AUTH/1312/5/02 predated the availability of these other PDE5 inhibitors, this did not make it invalid.

Pfizer noted that Lilly had quoted success rates at obtaining erections of 62-82% from the Viagra SPC. Lilly had stated that the probability of successful intercourse, as reported by McCullough *et al*, ranged from as low as 50% at the first attempt to about 80% after 10 attempts depending on the severity of ED and the persistence of the parties involved. Pfizer stated Lilly had not quoted the actual figures in the reference. The correct figures were a 54% cumulative probability after the first dose, and a plateau cumulative probability of 86% was achieved on repeated attempts.

The availability of other oral PDE5 inhibitors did not invalidate the above data. Viagra had been available for almost 5 years in the UK, and during this time there had been extensive experience in patient usage with it. The advertisement did not make a claim of immediate success with Viagra but was supported by the data above (86% cumulative probability of success on repeated attempts). Lilly's comments about 'the acquiescence of a partner' was relevant in that normally erectile dysfunction was a two person issue. Lilly had referred to another promotional item, VIA507, as evidence that Pfizer recognised this issue.

Lilly had quoted 'the ability to obtain an erection once more leads to problems of partner acceptance in a significant proportion of patients [McCullough 2002]'. This statement had been adapted from some text in this reference. The final paragraph of the introductory section of the reference had a line 'On the other hand, failure to continue using the drug on a long-term basis could be caused by numerous issues including ... (4) relationship problems (their partner may not be interested in resuming sexual activity), ...'. This was not examined in the study. Pfizer failed to understand how Lilly could make this statement based on these data when the statement was speculative and in the introductory section, not in the results or comments section.

Pfizer stated that 'speaks for itself' was not a comparative claim against any other medicine. Viagra was unique in the respect that it was the first oral ED treatment to be made available. The Oxford English Dictionary defined the phrase 'speaks for itself' as 'to be significant or self-evident'. In Pfizer's view, it was beyond argument that Viagra was and had been significant since the grant of its marketing authorization on 15 September 1998.

Viagra was the joint winner of the prestigious Prix Galien for scientific excellence and innovation in 2000. Professor Sir Michael Rawlins, Chair of the National Institute for Clinical Excellence presented the award to Pfizer and said: 'This drug has become a household name'. He continued, 'It is innovative, well tolerated, and provides treatment where existing therapies have been shown to be suboptimal'.

Pfizer was awarded the Queen's Award for Enterprise for innovation in the discovery and development of Viagra. The citation for the award stated that the Queen's Award for Enterprise was granted to Pfizer 'for discovering and developing sildenafil (Viagra), the first licensed oral treatment for erectile dysfunction. Prior to the drug's introduction, most treatment for erectile dysfunction involved injection, intra-urethral administration or vacuum extraction devices. The compound was a novel, potent and selective phosphodiesterase (PDE) 5 inhibitor. Sildenafil (Viagra) had been shown to provide benefit in over 70% of individuals suffering from erectile dysfunction'.

Pfizer stated that treatments such as intracavernosal injection therapy and vacuum constriction devices were available for the treatment of ED before Viagra but these treatments were perceived by many patients to have material shortcomings either in terms of efficacy or patient acceptability. Viagra therefore represented a significant step forward in the treatment of ED as it worked regardless of the underlying cause of the ED.

Pfizer stated that presentation rates for ED had increased markedly since the marketing of Viagra. The Panel had previously accepted that Viagra had had an impact on the taboo of talking about ED. In Case AUTH/1175/4/01, the Panel stated 'The fact that [ED] was more openly discussed was in part due to Viagra'. Pfizer submitted that it was widely accepted within the medical community, and also among the general population, that ED was no longer the source of great shame that it once was and that this enormous step forward was due to the availability of Viagra to a significant extent.

The Panel ruling in Case AUTH/1312/5/02 stated 'Viagra had been a significant development in the treatment of ED'. The Panel did not accept that the majority of readers might infer that 'speaks for itself' related to every aspect of the medicine's profile or that it suggested a broad and all-encompassing superiority. Pfizer submitted that the Panel's ruling still applied here.

Pfizer therefore denied breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

## PANEL RULING

The Panel noted its previous ruling in Case AUTH/1312/5/02 that the claim 'speaks for itself'

would be viewed within the context of the advertisement as a whole. The advertisement at issue in that case featured the clasped hands of a couple and the prominent phrase 'SPECIAL again'. The Panel had considered that the claim 'speaks for itself' would be seen as a general claim for the efficacy of the product within the context of a consequential beneficial effect upon the couple's relationship. Viagra had been a significant development in the treatment of ED. The Panel did not accept, as alleged by the complainant, that the majority of readers might infer that it related to every aspect of the medicine's profile or that it suggested a broad and all-encompassing superiority. The Panel had not considered the claim misleading, unsubstantiated or exaggerated as alleged; no breach of Clauses 7.2, 7.4 and 7.10 had been ruled.

Turning to the present case, Case AUTH/1442/3/03, the Panel noted that the advertisement now at issue was different to that considered in Case AUTH/1312/5/02. The advertisement now at issue did not include the phrase 'special again'. Furthermore, two more oral treatments had been launched, Cialis (Lilly) and Levitra (Bayer and GlaxoSmithKline). The Panel noted that there might be difficulties for couples following successful treatment of ED. Taking all the circumstances into account the Panel did not consider that the claim 'speaks for itself' was misleading, exaggerated or incapable of substantiation as alleged. The Panel considered that its previous ruling that the claim would be seen as a general claim for efficacy within the context of a consequential beneficial effect upon the couple's relationship was relevant. Viagra had been a significant development in the treatment of ED. The claim now at issue did not imply that Viagra was unique nor that it had the most favourable anti-impotence properties as alleged by Lilly. The Panel ruled no breach of Clauses 7.2, 7.4 and 7.10 of the Code.

### 2 Statement in prescribing information 'One single dose per day is recommended'

#### COMPLAINT

Lilly noted that the prescribing information in the advertisement at issue, and in all other Viagra material that it had recently collected, stated, *inter alia*, 'One single dose per day is recommended' whereas the Viagra summary of product characteristics (SPC) stated 'The maximum recommended dosing frequency is once per day'. These two phrases meant very different things. The first actively advocated daily dosing. The second stated that daily dosing was the maximum permitted frequency. Lilly alleged that the prescribing information misled as to the meaning of the SPC in breach of Clause 7.2, was not a succinct summary of the SPC in breach of Clause 4.2 and was not compatible with the SPC in breach of Clause 3.

#### RESPONSE

Pfizer stated that the SPC for Viagra did not discourage daily dosing, although Pfizer was not advocating daily dosing here. This was in contrast to the SPC for Cialis where in addition to the phrase 'The maximum recommended dosing frequency is once per day', there followed the statement 'Daily use of the medication is strongly discouraged because the long term safety after prolonged daily dosing is not established.' A similar statement was not included in the Viagra SPC. Pfizer therefore denied a breach of Clauses 3, 4.2 and 7.2 of the Code.

#### PANEL RULING

The Panel noted that the Viagra SPC stated that the recommended dose was 50mg taken as needed approximately one hour before sexual activity and 'The maximum recommended dosing frequency is once per day'. The prescribing information stated that 'One single dose per day is recommended'.

The Panel considered that the prescribing information advocated regular daily dosing whereas the SPC recommended a maximum permitted dosage frequency of once per day when needed.

The Panel considered that the prescribing information in the advertisement was not a succinct statement of the dosage information in the SPC as set out in Clause 4.2. The prescribing information did not make the maximum daily dosing frequency sufficiently clear.

Clause 4.1 required that prescribing information be provided. Clause 4.2 set out the content of the prescribing information. It was not possible to breach Clause 4.2 of the Code. The Panel thus ruled a breach of Clause 4.1 of the Code. The prescribing information was misleading and was inconsistent with the particulars listed in the SPC. The Panel thus ruled breaches of Clauses 3.2 and 7.2 of the Code.

#### APPEAL BY PFIZER

Pfizer maintained that the statement 'One single dose per day is recommended' in the Viagra prescribing information was a fair representation of the Viagra SPC. Viagra was indicated for the treatment of erectile dysfunction and it was only taken when it was necessary to achieve a penile erection. It was stated in Section 4.2 (Posology and method of administration) of the Viagra SPC – and it was implicit in its usage – that it was taken 'as needed' and was only effective in the period after its administration and then only with sexual stimulation. Pfizer submitted that there was nothing in the Viagra SPC to discourage daily usage of the product although the four tablets typically dispensed against a prescription would militate against everyday use. It would, therefore, be acceptable for a patient to use all his tablets on consecutive days should he wish to do so. Both the SPC and the prescribing information fairly represented this acceptable pattern of usage. Pfizer submitted that the prescribing information for Viagra was not therefore in breach of Clause 3.2 of the Code as it was not inconsistent with the particulars listed in its SPC. Similarly the Viagra prescribing information was not in breach of Clause 4.1 of the Code as it was consistent with the SPC for the medicine.

Pfizer stated that the Viagra prescribing information had included the wording in question for almost five

years. This wording had successfully undergone scrutiny on many occasions since the product's launch and it had been reviewed by the regulatory authority. If the wording was misleading it was inconceivable that it would not have been remarked upon or complained about by now, such was the scrutiny of Viagra since its launch. Pfizer submitted that in view of this and the fact that there was no inconsistency between the prescribing information and the SPC the prescribing information was not in breach of Clause 7.2 of the Code as it was not misleading.

## COMMENTS FROM LILLY

Lilly was surprised at Pfizer's decision as the Panel's ruling had left no room for doubt that the wording 'One single dose per day is recommended' in the prescribing information had a completely different meaning in plain English to the wording 'the maximum recommended dosing frequency is once per day' in the SPC. The former advocated a once daily dosing regimen whereas the latter actively contraindicated a dosing frequency of less than a day but did not recommend any particular dosing regimen.

Lilly noted that in its appeal Pfizer maintained that the statement 'One single dose per day is recommended' in the Viagra prescribing information was a fair representation of the Viagra SPC. Section 4.2 of the Viagra SPC contained a statement about the maximum daily frequency but did not recommend a once daily regimen. According to the SPC, treatment was to be on an as needed basis.

Lilly noted that Pfizer had stated that Viagra was indicated for the treatment of erectile dysfunction. Viagra was only taken when it was necessary to achieve a penile erection. It was stated in Section 4.2 (Posology and method of administration) of the Viagra SPC – and it was implicit in its usage – that it was taken 'as needed' and was only effective in the period after its administration and then only with sexual stimulation. Lilly's view was that Pfizer had confirmed the correctness of Lilly's interpretation of the SPC as outlined above.

Lilly noted Pfizer's view that there was nothing in the Viagra SPC to discourage the daily usage of Viagra although the four tablets typically dispensed against a prescription would militate against everyday use. It would, therefore, be acceptable for a patient to use all his tablets on consecutive days should he wish to do so. Both the SPC and the prescribing information fairly represented this acceptable pattern of usage. Lilly stated that Pfizer was attempting to justify misrepresenting a statement about maximum dosing frequency on the basis that it was possible to use Viagra once at that maximum frequency without breaking the rules set out in the SPC. Although this might be true, it negated the fact that the two statements at the heart of the complaint had very different meanings: the statement in the prescribing information was not a fair representation of the one in the SPC. Equally the fact that once a day dosing was possible did not make it 'recommended'. Indeed Lilly was not aware of any clinical trials in patients on Viagra which had involved long-term once daily dosing on a regular basis (none were listed in the European Public Assessment Report (EPAR)). In this respect the SPC was an accurate reflection of the clinical data which formed the basis for registration. The prescribing information did not reflect this.

With regard to Pfizer's view that the prescribing information for Viagra was not in breach of Clause 3.2 of the Code as it was not inconsistent with the particulars listed in its SPC, Lilly stated that this argument was based on a misunderstanding on Pfizer's part of the reason that the Panel ruled a breach of Clause 3.2. The statement 'One single dose per day is recommended' was not a fair summary of Section 4.2 of the SPC for Viagra. For this reason a breach of Clause 3.2 was ruled; for the same reason it must also be in breach of Clause 4.1.

Lilly stated that the fact that the misleading wording had gone unchallenged for nearly five years was not a reason to believe that it must be right. Pfizer had not shown how the wording reflected that of Section 4.2 of the SPC in a fair or reasonable manner. Lilly submitted that for the same reason as the statement 'One single dose per day is recommended' was in breach of Clause 3.2 it must also be in breach of Clause 7.2.

Lilly stated that as Pfizer had failed to show how the statement at issue 'One single dose per day is recommended' had the same meaning in plain English as the wording 'the maximum recommended dosing frequency is once per day' (SPC) the appeal should fail on all three counts.

## APPEAL BOARD RULING

The Appeal Board noted that the statement in the Viagra SPC that 'The maximum recommended dosing frequency is once per day' was translated in the prescribing information as 'One single dose per day is recommended'.

The Appeal Board considered that the failure to adequately reflect that once daily dosage was the maximum frequency at which Viagra should be taken was such that the prescribing information was not a succinct statement of the dosage information in the SPC as set out in Clause 4.2. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 4.1 of the Code. The appeal on this point was unsuccessful. The prescribing information was also misleading on this point and inconsistent with the SPC. The Appeal Board upheld the Panel's ruling of breaches of Clauses 3.2 and 7.2 of the Code. The appeal on this point was unsuccessful.

**Complaint received** **31 March 2003**

**Case completed** **18 July 2003**

CASE AUTH/1446/4/03

# FOREST LABORATORIES v PROFILE PHARMA

## Promotion of Promixin

**Forest Laboratories complained about the promotion of Promixin (colistimethate sodium) by Profile Pharma. Promixin was presented as a dry powder to be dissolved in water for injections or normal saline and used in a nebuliser for the treatment of *Pseudomonas aeruginosa* lung infections. Three items were at issue; an advertisement, a mailing and a detail aid.**

**Forest alleged that all three items made misleading claims and comparisons. The headline claim 'An Inhaled CF [cystic fibrosis] Antibiotic Treatment = Promixin + AAD [delivery system] + 4.08 minutes' indicated that the dose of Promixin was delivered in 4.08 minutes. This was based on data on file which related to *in vitro* work with 300µl solution, whereas, according to the Promixin summary of product characteristics (SPC), the full dose should be 2-4ml. There was no evidence that the 4.08 minutes related to the licensed dose nor that 300µl was clinically effective *in vivo*. Forest alleged that the claim was misleading.**

**The Panel noted that the claim was referenced to data on file and also to a footnote which read '2MIU of Promixin dissolved in 2ml of Water for Injections (WFI) took an average of 4 minutes and 5 seconds to complete delivery of dose using the standard CEN breathing pattern for assessment of nebulising systems EN13544-1'.**

**The Promixin SPC stated that dosage was determined by several factors, including the severity and type of infection, sensitivity of causative bacteria, age and weight of the patient. Recommended doses were provided for guidance only and should be adjusted according to clinical response. For children over 2 years and adults the recommended dose was 1-2MIU twice daily. Promixin was a powder presented in a 1MIU vial for dissolution in 2-4ml of water for injections or saline for use in a nebuliser. The SPC stated that Promixin could be used with any conventional nebuliser suitable for delivery of antibiotic solutions. Promixin was supplied with a Prodose Disc for use with the Prodose AAD System and the SPC referred the reader to the detailed instructions provided with the device.**

**The data on file referred to use of a fill volume of 2ml (1MIU/ml) and a disc programmed to deliver a dose of 300µl at 7.8µl/sec. Prodose delivered a pre-programmed 300µl of Promixin (1MIU/ml) in an average time of 4 minutes 5 seconds. The Prodose AAD System had gained its CE mark for use as a jet nebuliser for the delivery of medicines by inhalation; the relevant British Standard formed part of the substantiation for the claim.**

**The Panel noted Profile's submission that to refer to a dose for a medicine to be administered by a nebuliser system was not appropriate. The Prodose AAD System had gained a CE mark and to prevent overdosing it was programmed to deliver 300µl of solution irrespective of the fill volume. The Panel noted that 2-4ml quoted in the SPC was the fill volume. Promixin was approved for use in any nebuliser and the fill volume would vary depending on the nebuliser used. The manufacturer's recommended fill volume for the Prodose AAD System was 2ml. The Panel did not consider that the claim in question was misleading with regard to dosing information. No breach of the Code was ruled in this regard.**

**The Panel considered that the claim 'An Inhaled CF Antibiotic Treatment = Promixin + AAD + 4.08 minutes' gave the impression that 4.08 minutes was the delivery time obtained in patients and that was not so; there was no data in patients using the Prodose AAD System. This impression was compounded by the prominent claim 'Time matters' which appeared in the same visual field as the claim at issue on each promotional item. The Panel noted that there was some patient data which related to the Halolite system (the predecessor of the Prodose AAD System) but considered that this alone was insufficient given the overall impression. The Panel ruled a breach of the Code on this point.**

**The claim 'Nebulisation with Prodose AAD takes approximately 4 minutes' appeared within a section of the detail aid headed 'Does compliance matter?' and was followed by '2MIU Promixin in 2ml'. Forest noted that the data again referred to *in vitro* data which indicated that 300µl of such a solution was nebulised in 4 minutes and 5 seconds. The dose information was misleading. Similarly, there was no *in vivo* data to support these claims.**

**The Panel considered that its rulings and comments above in relation to both dose information and *in vitro* data were relevant here. There were differences between the present claim and that considered above. The claim appeared on a page headed 'Does compliance matter?' which presented clinical data in relation to completion of started AAD doses. The Panel considered that the reference to patient compliance and clinical data strengthened the impression that the claim 'Nebulisation with Prodose AAD takes approximately 4 minutes' referred to patient data and considered the claim misleading in this regard. A breach of the Code was ruled.**

**The Panel noted its comments and ruling above regarding the dose information and considered that its ruling was relevant here. The Panel thus ruled no breach of the Code.**

**Forest noted page 6 of the detail aid was headed 'Does AAD matter?' and beneath the heading details were given of adaptive aerosol delivery. These claims might be misleading as they ignored the *in vivo* findings of Spencer *et al* which indicated that for the delivery of colistimethate sodium by nebulisation, AAD was inferior to conventional nebulisation. No relevant clinical data had been presented to support the claims.**

**The Panel noted that beneath the heading 'Does AAD matter? Adaptive Aerosol Delivery (AAD)' was a series of six bullet points; 'is breath-actuated;**

**adapts to individual breathing patterns; only delivers aerosol during inhalation phase; minimizes atmospheric contamination compared to conventional nebulisers; provides feedback to patients during treatment; signals the end of the treatment'. A graph headed 'Prodose AAD adapts to individual breathing patterns' stated that 'AAD Systems automatically pulse aerosol into the first half of each inhalation'. The Panel considered that overall the page did not directly or indirectly compare the clinical effects of Prodose AAD System to conventional nebulisers and thus on this narrow point was not misleading as alleged. No breach of the Code was ruled.**

**Forest noted that page 7 was headed 'Does simplicity matter?' and gave details as to how to use Promixin. Forest alleged that the data were inconsistent with the Promixin SPC. The detail aid suggested a volume of dissolution of 2ml, but the SPC indicated 2-4ml. There was no data or information to support choosing this volume over any other.**

**The Panel considered that its comments and ruling above about dosage and fill volume applied here and ruled no breach of the Code.**

**Forest referred to the claim 'Prodose is preferred by 80% of patients' which appeared on a page of the detail aid headed 'Does support matter?'. Forest recognised that whilst the claim referred to a study covered in more detail elsewhere in the detail aid, the Code indicated that when a comparison was made, the comparator should be referred to. In this case the comparison was unqualified.**

**The Panel noted that the claim at issue was the eighth out of ten bullet points on the final page. The sixth bullet point read 'Compliance with conventional nebulisers may be an issue'. There was no other reference to any other form of nebuliser or delivery system. The Panel considered that the claim 'Prodose is preferred by 80% of patients' was misleading; the comparator had not been made sufficiently clear. A breach of the Code was ruled.**

Forest Laboratories UK Ltd complained about the promotion of Promixin (colistimethate sodium) by Profile Pharma Ltd. Promixin was indicated for the treatment by nebulisation of lung infections where sensitivity testing suggested they were caused by susceptible *Pseudomonas aeruginosa* (ref summary of product characteristics (SPC)). Promixin was presented as a dry powder to be dissolved in water for injections or normal saline and used in a nebuliser for the treatment of *Pseudomonas aeruginosa* lung infections. Three items were at issue; an advertisement in the BMJ 8 March 2003 (ref PrPh/008), a mailing (ref PrPh/006) and a detail aid (ref PrPh/009).

### Background information on nebulisers from Profile Pharma

Companies developing medicines for delivery by nebulisers always experienced the challenge that the dose delivered to a patient's lungs was out of their control as it was dependent upon the nebuliser used to deliver the medicine. Unlike metered dose inhalers where the medicine and device were sold as a unit, medicines for nebulisation were sold for use in a suitable nebuliser designed for such use. The efficiency of nebulisers could vary by up to a factor of 10 (Boe *et al* 2001). Boe *et al* stated 'Important factors influencing the total dose delivered to a patient's airway include, initial fill volume, the efficiency by which nebulized aerosol is made available for patient inhalation and the amount of residual or 'dead' volume left in the nebulizer on cessation of operation. Aerosol dose is a vague concept in nebulized drug therapy. It is not common practice to prescribe a 'dose delivered to lung', but prescribers usually specify the amount of drug to be dispensed in a particular volume of nebulizer solution. Prescriptions do not normally specify the nebuliser system. The choice of nebulizer varies and is often selected by a person other than the prescriber (e.g. hospital supplies department). Nebulization therapy usually continues until the volume left in the nebulizer is so low that the nebulizer ceases to function continuously and begins to 'sputter'. This volume is typically ~1 ml, but may be as low as 0.5ml or as high as 1.5 ml. The amount left is very high compared to a typical volume fill (e.g. 2.5 ml)'.

A patient's technique was also very important in determining the amount of medicine received. Nebulisers generally produced an aerosol for the whole time the compressor was running, irrespective of whether the patient was inhaling, exhaling or not using the system. Breath-enhanced nebulisers produced an aerosol for the whole time the compressor was running, but increased the delivery during inhalation. The fact that aerosol was also produced during exhalation meant that all the medication aerosolised at this time was wasted.

Hence nebulisers were a relatively inefficient method of delivering medicine and the 'dose' a patient received was very variable. The adaptive aerosol delivery (AAD) technology used in the Prodose AAD System and its predecessor the Halolite AAD System was designed to only produce an aerosol during the first 50% of inhalation and would not deliver an aerosol if a patient stopped inhaling through the mouthpiece. The objective was to make the dose delivered to the lung more consistent than with conventional nebulisers. Because the Prodose AAD System only delivered during inhalation and little medicine was wasted spraying into the environment there was a risk of patients receiving more medicine than they would receive through a conventional nebuliser. To prevent overdosing of patients, the Prodose AAD System was programmed to only deliver 300µl of solution irrespective of the fill volume.

Spencer *et al*, referred to by Forest in point B2 below, might also be misleading as Forest did not note Kastelik *et al* (2002) in which lung deposition was assessed by planar scintigraphy to determine which type of nebuliser was optimal for individual subjects. Lung deposition of the radio-labelled saline aerosol from the Pari LC Plus nebuliser (the same nebuliser as used in the Spencer paper) (Pari Medical Ltd) and the

Halolite AAD system was measured in 10 healthy volunteers and six cystic fibrosis (CF) patients. Both nebuliser systems were filled with 3ml of normal saline containing approximately 150MBq of technitium-99m diethylenetriaminepentaacetic acid. The Halolite AAD delivered on average 2.1 times ($p=0.003$) as much aerosol to the lungs compared with Pari LC Plus. Only two subjects had higher lung deposition from Pari LC Plus than Halolite AAD System. There was marked inter-individual variation in the deposition pattern in CF patients. The aerosol deposition from Halolite AAD had higher central distribution than that obtained with the Pari LC Plus. The overall intersubject variability of the delivered dose was 56% with Pari LC Plus and 24% with Halolite AAD ($p<0.05$). The conclusion of the paper was that measurement of aerosol deposition from nebulisers could be performed using a simple and widely available methodology, and might improve nebuliser selection in CF patients.

Kastelik *et al* clearly showed a difference in the amounts of radioactivity delivered to the lungs by the Halolite AAD System, but this time it was more from the Halolite AAD System. From this study the reduced variability of dose delivered to the lung was demonstrated for the AAD system. In view of the numerous variables that occurred in trials trying to determine the amount of medicine delivered to the lung, Profile did not consider it was appropriate to use these data in promotional material as there were clear contradictions and a balanced conclusion was difficult to achieve.

The complexity of assessing nebulisers clinically had led to a recognition of a need for standard tests of nebulisers (Dennis *et al* 2001). It was clear from this paper that there was a European consensus for the need for a standard *in vitro* test of nebulisers, which would reflect the *in vivo* situation. Out of the European Respiratory Task Force the CEN 13544-1 guideline was developed and published which was used to evaluate the Prodose AAD system and determine various factors including reproducibility of dose and time taken to deliver the pre-set dose. The guideline was modified to use Promixin as opposed to the fluoride tracer and the mean delivery time was calculated to be 4 minutes and 5 seconds. Further work had been published showing that the *in vitro* testing using salbutamol correlated with the clinical situation. This was the intention of the guidelines (Silkstone *et al* 2002). Although this paper called for further correlations it was clear the CEN standard was an appropriate method for assessing nebulisers. Should Colomycin (Forest Laboratories' colistimethate sodium) be used with a Prodose AAD System in the same test, the results were likely to be the same as for Promixin.

From the above it was apparent that to talk about a 'dose' for a medicine to be administered by a nebuliser system was not particularly appropriate. Forest had stated in its complaint that the approved 'dose' of Promixin was 2 to 4ml but as Promixin was a powder presented in a vial containing 1 million international units (1MIU) this was not possible. The 2 to 4ml quoted in the SPC was the volume of diluent into which the powder was dissolved for placement in the chamber of the nebuliser – the fill volume. Promixin was approved for use in any nebuliser and the fill volume would vary depending on the nebuliser used. For the Prodose AAD system the manufacturer's recommended fill volume was 2ml, for the Ventstream, Sidestream and Pari LC Plus the fill volume was up to 4ml, hence the range of fill volumes was quoted. This was also the same range of fill volumes quoted in the SPC for Forest's Colomycin.

The Prodose AAD System had gained its CE mark for the delivery of medicines by nebulisation. The reason for the predetermined delivery volume being 300µl was based on how nebulisers were used in a domestic setting by patients.

A Prodose was charged with 2MIU of colistimethate sodium in 2ml (1MIU/mL) and a total of 0.3ml were nebulised. A Ventstream (a Ventstream was similar to the Pari LC Plus nebuliser) was charged with 2MIU of colistimethate sodium in 4ml (0.5MIU/ml) and nebulised approximately 3ml.

From this it appeared that the Prodose delivered less medicine to the lungs. Calculating the dose aerosolised gave the following:

Prodose: 0.3ml aerosolised of a 1MIU/ml solution provided 0.3MIU. (Note a further 200µl was lost in evaporation.)

Ventstream: 3ml aerosolised of a 0.5MIU/ml solution provided 1.5 MIU. (Note the amount turned into an aerosol and how much was lost in evaporation was not known.)

However, conventional nebulisers generated an aerosol cloud continuously even when the patient was exhaling (60% of the time) (Denyer *et al* 1997a). In addition with the aerosol being generated all the time, patients continued to inhale medicine at the end of inspiration, filling the dead space of the lungs with medicine which was then exhaled to the atmosphere. Hence, a lot of medicine was wasted. It was generally accepted that under ideal conditions eg in a laboratory with patients' breathing patterns supervised, a conventional nebuliser delivered approximately 10% of the nominal dose to the lungs (Zainudin *et al* 2001).

Breath-enhanced nebulisers such as Ventstream created a greater amount of aerosol during the inhalation phase and might deliver as much as 15% of the charge volume to the lungs of patients (Coates *et al* 2000). Hence, it was estimated that of the 2MIU Ventstream nominal dose, approximately 0.3MIU (15% of 2MIU) would be delivered to the lung in the laboratory setting.

The impact of poor techniques, such as nose breathing, on medicine delivery had been investigated. Denyer *et al* (1997a) found that patients breathed on the mouthpiece properly for 60% of the time. Marsden *et al* (2001) found that in treatments where the compressor was run for 7 minutes (420 seconds), when the proportion of time spent inhaling should be around 40% of the total treatment time (or 168 seconds), only 63 seconds were spent inhaling through the mouthpiece. Hence, patients only spent 37.5% of the predicted 168 seconds of inhalation time inhaling the medicine correctly. Profile noted that

patients were expected to run the compressor for 12 minutes. In addition, Monkhoff *et al* (2001) found that wearing a nose clip, forcing patients to mouth breathe, increased the inhaled dose by 113%. Hence, patient technique on the nebuliser was important and affected the dose delivered.

Looking at the theoretical 0.3MIU delivered to the lungs by a Ventstream and applying the percentages from these three papers gave a calculated dose in the home environment for Ventstream when charged with 2MIU in 4ml of 0.113MIU to 0.180MIU.

AAD technology only delivered medicine during the first 50% of inhalation and only when the patient breathed in. The result was that little medicine was wasted to the atmosphere through exhalation (3%), and 60% reached the lungs (Denyer *et al* 1997b). Hence of the 0.3ml aerosolised through the Prodose (0.3MIU), 60% reached the lungs making a lung delivered dose of 0.180MIU.

There were data in-house where the Halolite AAD System was used in a clinical trial to investigate the device technology. A total of 133 patients received their nebulised antibiotics via Halolite and 126 patients received their nebulised antibiotics via conventional nebuliser systems. Of these patients, 102 were on colistimethate sodium most of which would have been supplied from Forest as Promixin was not available at the time. There were no differences in the outcome measures (forced expiratory volume in 1 second) between the groups. This was a device trial relating to the AAD technology not the medicine and it showed the dose delivered by AAD was as effective as the dose delivered by conventional nebulisers. These data were published at the British Thoracic Society Winter Meeting in December 2002.

In clinical practice AAD had been available for over 5 years with the Halolite AAD System. The Halolite AAD System also delivered 300µl per activation and had been used with inhaled antibiotics including colistimethate sodium, (which would have been supplied by Forest Laboratories) and other antibiotics. Hence there was a lot of clinical evidence gathered in real clinical situations that the AAD System effectively delivered colistimethate sodium.

### A Claim 'An Inhaled CF Antibiotic Treatment = Promixin + AAD + 4.08 minutes'

This headline claim was referenced to data on file and a British Standard document which related to nebulizing systems and their components (CEN Standard 13544-1).

This claim appeared as the headline in the journal advertisement and on the front cover of the detail aid and the mailing.

## COMPLAINT

Forest noted that the headline in all three indicated that the dose of Promixin was delivered in 4.08 minutes. This was based on data on file. Not only was this data based on *in vitro* work but the dose delivered was only 300µl solution, whereas, according to the Promixin SPC, the full dose should be 2-4ml.

Reference was also made to respiratory therapy equipment standards. These standards related to the *in vitro* comparison of equipment, and did not seem to involve use of a candidate medicine. There was no evidence that the figure of dose delivery in 4.08 minutes related to the licensed dose nor that 300µl was clinically effective *in vivo*. Forest alleged that the claim was misleading. There were other facets of these data which were misleading which included the dissimilarity of doses used, and partial versus complete emptying of medicine reservoirs.

## RESPONSE

Profile noted that recently the international non-proprietary name (INN) for the active ingredient in Promixin had been changed from colistin sulphomethate to colistimethate sodium. The product had previously been known as colymycin, colistin, colistin methane sulphonate and sodium colistimethate.

Forest's complaint appeared to be focused on the information supplied regarding the Prodose AAD System and not to the claims relating to Promixin. The Prodose AAD System had been granted a CE mark for the purpose of delivering medicines requiring nebulisation. In line with current requirements for assessing nebuliser systems the Prodose AAD System had been evaluated using the pan-European standard CEN Standard 13544-1. It was from the work conducted in these tests that some of the data relating to the Prodose AAD System had been generated.

The Prodose AAD System was available for purchase by health authorities and patients.

With regard to the administration of Promixin, Profile noted the following from the SPC:

> **'4.2 Posology and Method of Administration**
>
> Promixin can be administered by nebulisation using a suitable nebuliser (see Section 6.6 Instructions for Use/Handling).
>
> **6.6 Instructions for Use/Handling**
>
> Promixin may be reconstituted with Water for Injections or saline or a mixture of both in order to produce an isotonic solution. When reconstituted, Promixin may be used with any conventional nebuliser suitable for delivery of antibiotic solutions.
>
> Promixin is supplied with a Prodose Disc for use with the Prodose AAD System.
>
> For instructions on the use of Promixin with a Prodose AAD System please refer to detailed instructions provided with the device.
>
> Any unused solution remaining in the nebuliser must be discarded following treatment.
>
> Conventional nebulisers operate on a continuous flow basis and it is likely that some nebulised drug will be released into the local environment. When used with a conventional nebuliser, Promixin should be administered in a well-ventilated room, particularly in hospitals where several patients

may be using nebulisers at the same time. Tubing or filters may be used to prevent waste aerosol from entering the environment.'

Profile stated that conventional nebulisers were very wasteful of medicine with as little as 10% of the dose placed in the nebulisation chamber being delivered to the lungs of patients. The Prodose AAD System had been developed with a view to improving efficiency of delivery and reducing the atmospheric pollution. From Forest's complaint there appeared to be some confusion regarding a dose and a fill volume.

Profile stated that the dose of 300µl was based on the background information supplied above and the fact that the Prodose AAD System had gained its CE mark for use as a jet nebuliser for the delivery of medicines by inhalation. The system was designed for use with all inhaled liquid medications and therefore the volume delivered was appropriate. The SPC quoted a range of volumes to dilute Promixin and was clarified with the comment to refer to the instructions for the device. Profile noted that the Colomycin SPC stated exactly the same range of volumes in which to dilute Colomycin ie 'For inhalation the required amount of powder is dissolved in 2-4ml saline, preferably, or water for injections, and poured into the nebuliser. Usually jet or ultrasonic nebulisers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of 0.5-5.0 microns when used with a compatible compressor. The instructions of the manufacturers should be followed for the operation and care of the nebuliser and compressor'.

The dose delivered would vary depending on the efficiency of the nebuliser system and the concentration of medicine used in the fill volume, and it was accepted that nebulisers were not capable of delivering the whole amount of medicine present in the chamber resulting in some residual medicine in the chamber. The use of Promixin with the Prodose AAD System was specifically referred to in the SPC hence the claims were in accordance with the SPC.

Profile noted that Forest had stated that the respiratory equipment standards reference did not refer to a medicine; this was true as they referred to a standard way of testing devices. The data on file reference used to support the nebuliser system delivering the dose did specify that Promixin was used in the tests conducted using the CEN standards using the Prodose AAD System.

Using the CEN standard the mean time taken for the Prodose AAD System to deliver the predetermined dose of Promixin was 4 minutes and 5 seconds.

Profile noted that in points B1 and B2 below Forest claimed there were no *in vivo* data to support these claims but Spencer *et al*, cited by Forest, referred to a Halolite delivery device which used Adaptive Aerosol Delivery (AAD), as did the Prodose System and the mean time for delivery was 273 seconds or 4 minutes 33 seconds but as this was a slightly different device it was not appropriate to refer to the time stated in this paper. Forest's comment that 'There are other facets of these data which are misleading which include dissimilarity of doses used and partial versus complete emptying of drug reservoirs' was vague and Profile was unable to respond. Profile did not discuss partial emptying of medicine reservoirs as this was dependent upon the nebuliser used. Nor did it refer to dissimilar doses.

## PANEL RULING

The Panel noted that the claim at issue was referenced to a footnote which read '2MIU of Promixin dissolved in 2ml of Water for Injections (WFI) took an average of 4 minutes and 5 seconds to complete delivery of dose using the standard CEN breathing pattern for assessment of nebulising systems EN13544-1'.

The Panel noted that the Promixin SPC stated that dosage was determined by several factors, including the severity and type of infection, sensitivity of causative bacteria, age and weight of the patient. Recommended doses were provided for guidance only and should be adjusted according to clinical response. For children over 2 years and adults the recommended dose was 1-2MIU twice daily. Promixin was a powder presented in a 1MIU vial for dissolution in 2-4ml of water for injections or saline for use in a nebuliser. The SPC stated that Promixin could be used with any conventional nebuliser suitable for delivery of antibiotic solutions. Promixin was supplied with a Prodose Disc for use with the Prodose AAD System and the SPC referred the reader to the detailed instructions provided with the device.

The Panel noted that the claim at issue was referenced to, *inter alia*, data on file which assessed the *in vitro* Promixin delivery treatment times from, *inter alia*, a Prodose nebuliser into a CEN breathing pattern. A fill volume of 2ml (1MIU/ml) was used and a disc was programmed to deliver a dose of 300µl at 7.8µl/sec. Prodose delivered a pre-programmed 300µl of Promixin (1MIU/ml) in an average time of 4 minutes 5 seconds. The Panel also noted that the Prodose AAD System had gained its CE mark for use as a jet nebuliser for the delivery of medicines by inhalation; the relevant British Standard formed part of the substantiation for the claim.

The Panel noted Profile's submission that to refer to a dose for a medicine to be administered by a nebuliser system was not appropriate. The Prodose AAD System had gained a CE mark and to prevent overdosing it was programmed to deliver 300µl of solution irrespective of the fill volume. The Panel noted that 2-4ml quoted in the SPC was the fill volume. Promixin was approved for use in any nebuliser and the fill volume would vary depending on the nebuliser used. The manufacturer's recommended fill volume for the Prodose AAD System was 2ml. The Panel did not consider that the claim in question was misleading with regard to dosing information as alleged. No breach of Clause 7.2 of the Code was ruled in this regard.

The Panel noted that there was some patient data which related to the predecessor of Prodose AAD System, the Halolite nebuliser (Spencer *et al*). The Panel noted Profile's submission that in the home environment the amount of medicine delivered to the lungs decreased as patients were not supervised and they adopted poor breathing techniques, (Silkstone *et al* 2002).

The Panel considered that the claim 'An Inhaled CF Antibiotic Treatment = Promixin + AAD + 4.08 minutes' gave the impression that 4.08 minutes was the delivery time obtained in patients and that was not so; there was no data in patients using the Prodose AAD System. This impression was compounded by the prominent claim 'Time matters' which appeared in the same visual field as the claim at issue on each promotional item. The Panel noted that there was some data which related to the Halolite system but considered that this alone was insufficient given the overall impression. The Panel ruled a breach of Clause 7.2 on this point.

### B Detail Aid

#### 1 Claim 'Nebulisation with Prodose AAD takes approximately 4 minutes'

This claim appeared on page 4 of the detail aid within a section headed 'Does compliance matter?' and was followed by '2MIU Promixin in 2ml'.

#### COMPLAINT

Forest noted that the data again referred to the *in vitro* experimental data which indicated that 300µl of such a solution was nebulised in 4 minutes and 5 seconds. The dose information was misleading. Similarly, there was no *in vivo* data to support these claims. Breaches of Clauses 7.2 and 7.4 were alleged.

#### RESPONSE

Profile referred to its response above at point A.

#### PANEL RULING

The Panel considered that its rulings and comments at point A in relation to both dose information and *in vitro* data were relevant here. There were differences between the present claim and that considered at point A. The claim appeared on a page headed 'Does Compliance matter?' which presented clinical data in relation to completion of started AAD doses. The Panel considered that the reference to patient compliance and clinical data strengthened the impression that the claim 'Nebulisation with Prodose AAD takes approximately 4 minutes' referred to patient data and considered the claim misleading in this regard. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted its comments and ruling in point A above regarding the dose information and considered that its ruling was relevant here. The Panel thus ruled no breach of Clauses 7.2 and 7.4.

#### 2 Adaptive Aerosol Delivery (AAD)

Page 6 of the detail aid was headed 'Does AAD matter?'

#### COMPLAINT

Forest noted that beneath the heading 'Does AAD matter?' details were given of adaptive aerosol delivery. These claims might be misleading as they ignored the *in vivo* findings of Spencer *et al* which indicated that for the delivery of colistimethate sodium by nebulisation, AAD was inferior to conventional nebulisation. Profile did not present any relevant clinical data to support its claims. Breaches of Clauses 7.2 and 7.4 were alleged.

#### RESPONSE

Profile stated that Forest's comment appeared to be focused on the nebuliser systems and not the medicine.

Spencer *et al* commented only on the level of deposition in the lung and the efficiency of the two nebulisers under study, it did not comment on the clinical effect of either delivery system. Indeed it was not possible to determine a difference in the clinical effect of the two nebuliser systems from a single dose cross-over study. Therefore, no clinical conclusions regarding the delivery of colistimethate sodium could be made from this paper. The results of this paper were at variance with Kastelik *et al* as discussed above and it was not possible to draw a balanced conclusion.

In addition the work did not make comparisons with other nebulisers to determine the range of lung deposition of medicine from all approved nebulised systems. The dose delivered to the lungs was dependent on many factors, nebuliser used, patient technique and concentration of medicine in the nebuliser system. The Prodose AAD System had been designed for delivery of inhaled liquid medications. There were no data in the paper to determine that the dose delivered by the Pari was the optimal dose for safety and efficacy.

The Prodose AAD System was approved for use and the SPC for Promixin specifically referred to the use of Prodose AAD, hence the claims were supported.

#### PANEL RULING

The Panel noted that beneath the heading 'Does AAD matter? Adaptive Aerosol Delivery (AAD)' was a series of six bullet points; 'is breath-actuated; adapts to individual breathing patterns; only delivers aerosol during inhalation phase; minimizes atmospheric contamination compared to conventional nebulisers; provides feedback to patients during treatment; signals the end of the treatment'. A graph headed 'Prodose AAD adapts to individual breathing patterns' stated that 'AAD Systems automatically pulse aerosol into the first half of each inhalation'.

The Panel considered that overall the page did not directly or indirectly compare the clinical effects of Prodose AAD System to conventional nebulisers and thus on this narrow point was not misleading as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

#### 3 'Does simplicity matter?'

Page 7 was headed 'Does simplicity matter?' and gave details as to how to use Promixin.

**COMPLAINT**

Forest alleged that the data were inconsistent with the Promixin SPC. The detail aid suggested a volume of dissolution of 2ml, but the SPC indicated 2-4ml. There was no data or information to support choosing this volume over any other. A breach of Clause 7.2 was alleged.

**RESPONSE**

Profile stated that the dissolution volume of 2ml was consistent with the SPC. Section 4.2 stated 'The Promixin powder is dissolved in 2-4ml of Water for Injections or normal saline, for use in a nebuliser attached to an air/oxygen supply'. Section 6.6 stated 'Promixin may be reconstituted with Water for Injections or saline or a mixture of both in order to produce an isotonic solution. When reconstituted, Promixin may be used with any conventional nebuliser suitable for delivery of antibiotic solutions. Promixin is supplied with a Prodose Disc for use with the Prodose AAD System. For instructions on the use of Promixin with a Prodose AAD System please refer to detailed instructions provided with the device. Any unused solution remaining in the nebuliser must be discarded following treatment'.

The detail aid related the dose to the recommendations made for use in the Prodose AAD System which were in line with the manufacturer's instructions and the Promixin SPC. For products to be administered by nebulisation it was not possible to provide data to demonstrate that a fill volume to one or other extreme of the range was more appropriate as this would depend on the nebuliser used. Profile stated that it was odd that Forest considered that there should be data on all possible fill volumes as this would be varied depending on the nebuliser system used.

**PANEL RULING**

The Panel considered that its comments and ruling about dosage and fill volume at point A above applied here and ruled no breach of Clause 7.2 of the Code.

**4 Claim 'Prodose is preferred by 80% of patients'**

This claim appeared on page 8 of the detail aid which was headed 'Does support matter?'

**COMPLAINT**

Forest recognised that the claim referred to a study covered in more detail elsewhere in the detail aid, Clause 7.2 of the Code indicated that when a comparison was made, the comparator should be referred to. In this case the comparison was unqualified.

**RESPONSE**

Profile appreciated that this was an oversight that would be amended.

**PANEL RULING**

The Panel noted that the claim was referenced to Marsden *et al* (2002) which was discussed on page five of the detail aid beneath a heading 'Does Preference Matter'. On that page was the claim 'Over 80% of the AAD group preferred it to their previous conventional nebuliser'.

The Panel noted that the claim at issue was the eighth out of ten bullet points on the final page. The sixth bullet point read 'Compliance with conventional nebulisers may be an issue'. There was no other reference to any other form of nebuliser or delivery system. The Panel considered that the bullet point 'Prodose is preferred by 80% of patients' was misleading; the comparator had not been made sufficiently clear. A breach of Clause 7.2 was ruled.

**Complaint received** **1 April 2003**

**Case completed** **19 June 2003**

CASE AUTH/1447/4/03

# HOSPITAL CHIEF PHARMACIST v SANOFI-SYNTHELABO

## Provision of free goods

**A hospital chief pharmacist complained about the provision of seventy-five packs of 10 Xatral XL (alfuzosin) tablets 10mg by Sanofi-Synthelabo which had not been requested by the pharmacy department. The complainant stated that an order form for a Xatral XL starter pack pilot scheme, which had been handed in to the pharmacy department by Sanofi-Synthelabo's representative some months earlier, was never signed by a pharmacist.**

**The complainant noted that the packs supplied were labelled 'Hospital Pack' and gave reasons as to why these packs could not be regarded as samples under the Code; on questioning the health professional concerned, it was revealed that they were intended to be given out to patients at outpatient clinics.**

**The Panel noted that each of the seventy-five packs of Xatral XL sent to the pharmacy department was labelled 'Hospital Pack 10 tablets'. Sanofi-Synthelabo stated that the packs had been supplied as free goods following a request to the local representative from a urology consultant for free stock. The representative assumed that the consultant had made the necessary arrangements with the pharmacy department. The Panel considered that it was important that companies and their representatives were clear as to the basis on which goods were supplied so that they could ensure compliance with the Code. The Panel considered that the Xatral XL packs had been supplied as free goods and not as samples and ruled no breaches of those clauses of the Code relevant to the provision of samples.**

**The Panel noted that there was no complaint about the packaging of the medicine. The free goods had been requested by the consultant urologist and therefore Sanofi-Synthelabo had not sent an unsolicited medicine. The Panel thus ruled no breach of the Code.**

**The Panel noted that an email from the consultant urologist stated that the representative, the consultant and another member of staff had discussed the provision of free goods. At this meeting it was agreed that the other member of staff would speak to the pharmacy department and ask for the 'free stock required form' to be signed and faxed to the company's head office. The company referred to a delivery note for nil charge; it made no reference to a signed free stock form received from the hospital. The email from the consultant urologist stated that the other member of staff had had ongoing discussions with one of the hospital pharmacists about this matter.**

**The Panel considered that, on the evidence before it, the hospital's requirements about the delivery of free stock were not sufficiently clear and it thus had no alternative but to rule no breach of the Code.**

**The Panel was concerned about the role of the company representative who, in its view, should have contacted the pharmacy department to clarify its requirements particularly as, some months previously, the pharmacy had declined to sign a Xatral starter pack form. The Panel considered that the representative had failed to maintain a high standard of ethical conduct. A breach of the Code was ruled.**

A hospital chief pharmacist complained about the unsolicited supply of packs of Xatral XL (alfuzosin) by Sanofi-Synthelabo Limited.

### COMPLAINT

The complainant stated that seventy-five packs of 10 Xatral XL tablets 10mg had been sent to the hospital pharmacy department by Sanofi-Synthelabo in February 2003. These samples were not requested by anyone in the department. The complainant provided a copy of an order form for the Xatral XL starter pack pilot scheme which was handed in to the pharmacy department by Sanofi-Synthelabo's representative in September 2002, and which was never signed by a pharmacist, as the department was not willing to accept these samples offered at that time either.

The complainant had consulted the Code regarding the definitions of 'samples' and the packs supplied to the hospital as 'starter packs', which, according to the Code, were for primary care prescribers to initiate treatment in emergency situations. This did not apply in the hospital situation. The packs supplied were labelled 'Hospital Pack'. If these were being supplied as 'samples', intended for the consultant to familiarise him/herself with the product, the maximum allowable was 10 per health professional per year. The Code also stated that supply must only be made in response to written requests which had been signed and dated. At no time had this been done. The complainant added that the samples were not labelled as required by the Code.

On questioning the health professional concerned, it was revealed that these packs were intended to be given out to patients at outpatient clinics. This was against pharmacy Medicines, Ethics and Practice guidelines. It was illegal to supply a prescription-only medicine (POM) from a clinic without conforming to the labelling requirements set out in the above reference.

When writing to Sanofi-Synthelabo the Authority asked it to respond in relation to the requirements of Clauses 15.2, 17.1, 17.2, 17.3, 17.5, 17.7, 17.8 and 17.10 of the Code.

### RESPONSE

Sanofi-Synthelabo stated that the local representative left an 'Order form for Xatral XL (alfuzosin) starter pack pilot scheme' with the pharmacy department on

27 September 2002. This particular order (100 packs) was not completed as the required signature of the pharmacist, as set out in the Code, was not obtained.

In February 2003 the local urology consultant asked the local representative for free Xatral XL stock. A copy of a letter from the consultant regarding the request for free stock was provided. The representative forwarded this request to Sanofi-Synthelabo's supplies department, with the assumption that the consultant had made all the necessary arrangements with the pharmacy department.

On 11 February 2003 the pharmacist informed the representative that the pharmacy department did not wish to receive samples of Xatral XL. The order for *free* stock (75 packs) requested by the hospital consultant had by then already been dispatched. The free stock was delivered to the hospital pharmacy employing standard transport procedures for POMs and was labelled as 'Hospital Pack', and not samples, and accompanied by a delivery note for nil charge.

Sanofi-Synthelabo stated that there appeared to be some confusion over two separate and unrelated events: the order form for starter packs left with the pharmacy department on 27 September 2002 but which was not followed through, as no request signature was obtained, and the request for free stock by the local consultant in February 2003.

Sanofi-Synthelabo addressed the alleged breaches of the Code referred to by the Authority:

***Clause 15.2*** The representative had complied with all relevant requirements of the Code and maintained high standards. The concerns of the complainant were a result of miscommunication within the hospital, rather than a breach in procedures relating to the provision of free stock.

***Clauses 17.1, 17.3, 17.5 and 17.7*** These clauses applied to samples and since the order was for free stock they did not apply.

***Clause 17.8*** The free stock was sent to the appropriate recipient, namely the pharmacy department. It would appear in retrospect that better co-ordination of the consultant's request and delivery of supplies to the pharmacy department might have prevented the subsequent confusion.

***Clause 17.10*** The medicines were packed and delivered as for normal despatch of POM supplies to the hospital and hence there was no breach of the Code.

This case had highlighted the need to raise the awareness of all Sanofi-Synthelabo's staff to the various issues related to sample, titration and starter packs as well as provision of free stock. A forthcoming sales meeting would be used as an opportunity to remind staff of the correct requirements and procedures.

## FURTHER COMMENTS FROM THE COMPLAINANT

Sanofi-Synthelabo's response was sent to the complainant for comment.

The complainant stated that inference of 'miscommunication within the hospital' had no bearing on the matter. Surely, there must be a single procedure in place for both samples and 'starter packs' that required a signature from the local pharmacy department? At no time did any member of the complainant's staff or the complainant agree to the receipt of free stock (other than when the goods were received).

In respect of the definition of 'starter packs' or samples, it was pedantic of Sanofi-Synthelabo to suggest there was any difference in what had been offered and supplied. The complainant stated that he could in turn be as pedantic as Sanofi-Synthelabo, the inference of a 'starter pack' was for medicines that required careful titration, however, at no point in the summary of product characteristics (SPC) for Xatral XL was there any mention of the requirement for titration of dose!

The complainant was pleased that Sanofi-Synthelabo was going to 'raise awareness' of this issue, however, he still alleged that the supply of free stock was not in accordance with ethical practice.

## PANEL RULING

The Panel noted that seventy-five packs of Xatral XL had been sent to the pharmacy department. Each pack was labelled 'Hospital Pack 10 tablets'. Sanofi-Synthelabo stated that the packs had been supplied as free goods following the request from a urology consultant for free stock. The representative assumed that the consultant had made the necessary arrangements with the pharmacy department. The Panel considered that it was important that companies and their representatives were clear as to the basis on which goods were supplied so that they could ensure compliance with the Code.

The supplementary information to Clause 17 stated that a sample was a small supply of a medicine provided to members of the health professions in order that they might familiarise themselves with it and acquire experience in dealing with it. A sample could only be provided to a health professional qualified to prescribe that particular medicine. A small sample which was provided for identification or similar purposes and which was not intended to be used in treatment could be provided to any health professional but was otherwise subject to the requirements of Clause 17. Titration packs, free goods and bonus stock provided to pharmacists and others were not samples. Neither were starter packs. This was because they were not for the purpose described above. Starter packs were defined in the supplementary information as small packs designed to provide sufficient medicine for a primary care prescriber to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable but unavoidable delay in having a prescription dispensed. The type of medicines for which starter packs were appropriate were limited to those where immediate commencement of treatment was necessary or desirable such as analgesics and antibiotics. Titration packs were described in the supplementary information to Clause 17 as packs containing various strengths of a medicine for the purpose of establishing a patient on an effective dose.

The Panel considered that as the Xatral XL packs had been supplied as free goods and not as samples there could be no breach of Clauses 17.1, 17.2, 17.3, 17.5 and 17.7 which applied only to the provision of samples and ruled accordingly.

Clause 17.10 required that medicines sent by post must be securely packaged and must not be sent unsolicited. The clause referred to medicines generally and not to samples specifically. The Panel noted that there was no complaint about the packaging of the medicine. The free goods had been requested by the consultant urologist and therefore Sanofi-Synthelabo had not sent an unsolicited medicine. The Panel thus ruled no breach of Clause 17.10 of the Code.

Clause 17.8 required that the provision of medicines and samples in hospitals must comply with individual hospital requirements. Thus the provision of free goods would be covered by this clause. The Panel noted that an email from the consultant urologist stated that the representative, the consultant and another named member of hospital staff had discussed the provision of free goods. At this meeting it was agreed that the named member of staff would speak to the pharmacy department and ask for the 'free stock required form' to be signed and faxed to the company's head office. It was unclear whether the free stock form referred to was a hospital or company document. The complainant made no reference to a free stock form. The company referred to a delivery note for nil charge; it made no reference to a signed free stock form received from the hospital. The email from the consultant urologist stated that the named member of staff had had ongoing discussions with one of the hospital pharmacists, about this matter. It appeared that there had been some discussion in the hospital pharmacy.

The Panel considered that, on the evidence before it, the hospital's requirements about the delivery of free stock were not sufficiently clear. On this basis the Panel had no alternative but to rule no breach of Clause 17.8 of the Code.

The Panel was concerned about the role of the company representative. It was incumbent upon the representative to ensure that the arrangement for the provision of free stock was in accordance with hospital policy. Sanofi-Synthelabo stated that the representative assumed that the consultant had made all the necessary arrangements with the pharmacy department. This was unacceptable. In the Panel's view the representative should have contacted the pharmacy department to clarify its requirements particularly as, some months previously, the pharmacy had declined to sign a Xatral starter pack form. The Panel considered that the representative had failed to maintain a high standard of ethical conduct. A breach of Clause 15.2 was ruled.

During its consideration of this case the Panel noted that the company had left an order form for the Xatral XL starter pack pilot scheme at the pharmacy department on 27 September 2002. The Panel noted the definition of starter packs above. Xatral XL was indicated for benign prostatic hypertrophy (BPH). In the Panel's view it was unlikely that a patient would be diagnosed with BPH in the night or at any other time when there would be an undesirable delay in having a prescription dispensed. The Panel thus queried whether Xatral XL starter packs should be provided at all and asked that Sanofi-Synthelabo be advised of its concerns in this respect.

**Complaint received** **8 April 2003**

**Case completed** **17 June 2003**

**CASE AUTH/1450/4/03**

# GENERAL PRACTITIONER v LEO PHARMA

## Gift of chocolates and umbrella

**A general practitioner complained that a monograph on psoriasis provided by Leo Pharma was badly let down by the fact that it was accompanied by two chocolates and a rather tacky umbrella. The complainant failed to see the relevance of either chocolates or an umbrella and did not consider them to be appropriate.**

**The Panel noted that the Code required that in addition to being inexpensive, any gifts in the form of promotional aids had to be relevant to the practice of the recipient's profession or employment. Leo had not provided details of the cost of the Dovobet umbrellas. However, regardless of their cost the Panel considered that umbrellas were not relevant to the practice of medicine; they had no use in the ordinary course of a doctor's professional duties. A breach of the Code was ruled.**

**The Panel noted that the representative had expected seven partners to be at a meeting which she had organized at the surgery. In the event only two turned up. As part of the hospitality for the meeting the representative had given each attendee a small cellophane bag containing two chocolates which were intended to be eaten during the event. One bag of chocolates had been left for the complainant who had not attended the meeting. The chocolates had thus been left because they were surplus to the hospitality requirements of the meeting which the complainant had been expected to attend; they had not been left as a promotional aid. In the circumstances the Panel did not consider it unreasonable for the representative to have left two chocolates for the complainant. Their value was minimal and their shelf life would be short. No breach of the Code was ruled.**

### COMPLAINT

A general practitioner complained that an excellent monograph on psoriasis, provided by Leo Pharma, was badly let down by the fact that it was accompanied by two chocolates and a rather tacky umbrella. The complainant failed to see the relevance of the chocolates or the umbrella and did not consider them to be appropriate.

The complainant appreciated that pharmaceutical companies wished to make their material attractive and easily accessible, but he did not consider that this justified what was nothing less than a stunt.

When writing to Leo, the Authority asked it to respond in relation to Clauses 9.1, 15.2, 18.1 and 18.2 of the Code.

### RESPONSE

Leo stated that its representative was invited to a practice meeting at the complainant's surgery in March. She was told that all seven partners were likely to attend but in the event only two were there.

With the permission of the two attending partners and the practice manager, the representative left a copy of Psoriasis in Practice and an inexpensive umbrella branded Dovobet for the non-attendees. In addition, a packet of two small wrapped chocolates was left for the complainant, having been provided in anticipation of his attendance at the meeting, where the attendees enjoyed their chocolates during the proceedings. It was unfortunate that the complainant had found these inappropriate but this was not the reaction that the company had generally experienced. Under the circumstances Leo did not consider that it had breached the Code.

Leo stated that it had asked its representative to visit the complainant in order to apologise to him in person.

In response to a request for further information Leo stated that the chocolates were purchased by the representative on her own initiative for the partners as hospitality provided for their practice meeting.

### PANEL RULING

The Panel noted that Clause 18.2 of the Code stated that in addition to being inexpensive, any gifts in the form of promotional aids, distributed to members of the health professions and to appropriate administrative staff, had to be relevant to the practice of the recipient's profession or employment. Leo had not provided details of the cost of the Dovobet umbrellas. However, regardless of their cost the Panel considered that umbrellas were not relevant to the practice of medicine; they had no use in the ordinary course of a doctor's professional duties. The umbrellas thus failed to meet the requirements of Clause 18.2 of the Code and were therefore in breach of Clause 18.1. A breach of that clause was ruled.

The Panel noted that the representative had expected seven partners to be at the meeting which she had organized at the surgery. In the event only two turned up. As part of the hospitality for the meeting the representative had given each attendee a small cellophane bag containing two chocolates which were intended to be eaten during the event. One bag of chocolates had been left for the complainant who had not attended the meeting. The chocolates had thus been left because they were surplus to the hospitality requirements of the meeting which the complainant had been expected to attend; they had not been left as a promotional aid.

In the circumstances the Panel did not consider it unreasonable for the representative to have left two chocolates for the complainant. Their value was minimal and their shelf life would be short. No breach of Clause 15.2 was ruled.

The Panel noted its ruling above of a breach of Clause 18.1 of the Code but nonetheless did not consider that the provision of either the umbrella or the chocolates meant that high standards had not been maintained. No breach of Clause 9.1 was ruled.

**Complaint received** **4 April 2003**

**Case completed** **15 May 2003**

CASE AUTH/1451/4/03

# AVENTIS PHARMA/DIRECTOR v MERCK SHARP & DOHME

## Cozaar journal advertisement

**Aventis Pharma complained about a journal advertisement for Cozaar (losartan) issued by Merck Sharp & Dohme. The advertisement referred to the LIFE study (cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension: a randomised trial against atenolol). Aventis drew attention to the claim that in the LIFE study, lowering blood pressure with Cozaar in high-risk hypertensive patients demonstrated 'a significant reduction in cardiovascular outcomes including a 25% reduction in stroke risk (p= 0.001)'. Aventis noted that the Panel had previously ruled, in Case AUTH/1341/7/02, that the implication that the LIFE trial results demonstrated a combination of reduction in cardiovascular and stroke risk was in breach of the Code.**

**Aventis alleged that the claim now being used was misleading. It clearly implied two distinct benefits for Cozaar patients in the LIFE study, that of cardiovascular outcomes reduction as well as a reduction in stroke risk. As was discussed in the previous case, the benefit to patients in the LIFE study was solely through a reduction in stroke risk. The current claim deliberately created confusion to imply benefits beyond those proven. Any such claim should read 'a significant reduction in cardiovascular outcomes due to stroke risk reduction' or similar, if any claims other than stroke risk reduction were to be made. Aventis alleged that Merck Sharp & Dohme was in breach for continuing to make misleading claims relating to Cozaar's cardiovascular risk reductions despite the previous ruling. As the matter involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.**

**Aventis further alleged that the use of the significance value (p=0.001) at the end of the claim was also misleading in that it could be interpreted as applying to either of the two statements made in the sentence, the stroke or cardiovascular outcomes reduction.**

**The Panel noted that in Case AUTH/1341/7/02 it had ruled that the claim 'In addition, Cozaar is the only antihypertensive to clearly demonstrate superior [cardiovascular] outcomes versus an active comparator and Cozaar showed a 25% reduction in stroke risk (p=0.001)' implied two distinct benefits and this was misleading.**

**In the present case, the Panel noted the outcomes of the LIFE study. The primary cardiovascular endpoint was defined as a composite of cardiovascular death, stroke and myocardial infarction. The differences between Cozaar and atenolol with regard to the individual endpoints of cardiovascular death and myocardial infarction did not show statistically significant differences. Only stroke had shown a statistically significant difference in favour of Cozaar and was the main driver for the reduction in the primary composite endpoint. The Panel considered that the claim gave a misleading impression of the outcome of the LIFE study. Insufficient detail had been given. A breach of the Code was ruled.**

**The Panel considered that on balance the claim at issue in this case was sufficiently different to the claim at issue in Case AUTH/1341/7/02 for it not to be covered by the undertaking given in that case. The Panel therefore made rulings of no breach of the Code in that regard, including a ruling of no breach of Clause 2.**

**With regard to the use of the significance value at the end of the claim 'a significant reduction in cardiovascular outcomes including a 25% reduction in stroke risk (p=0.001)', the Panel considered that it was not sufficiently clear that the p value given referred to the stroke risk reduction and not to the 'significant reduction in cardiovascular outcomes', particularly as the word 'significant' was used only to describe the cardiovascular outcomes. The Panel ruled a breach of the Code.**

Aventis Pharma Ltd complained about an advertisement for Cozaar (losartan) (ref 01-04CZR.02.GB.10212) issued by Merck Sharp & Dohme Limited which had appeared in Prescriber, 5 March 2003.

The advertisement was headed 'Effective blood pressure control' and included the claim 'Throw your high-risk hypertensive patients a lifeline'. The advertisement referred to the LIFE study (cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension: a randomised trial against atenolol).

### COMPLAINT

Aventis drew attention to the claim that in the LIFE study, lowering blood pressure with Cozaar in high-risk hypertensive patients demonstrated 'a significant reduction in cardiovascular outcomes including a 25% reduction in stroke risk (p= 0.001)'. Aventis noted that the presentation of these results was the subject of a previous Panel ruling, Case AUTH/1341/7/02, where the Panel ruled that the implication that the LIFE trial results demonstrated a combination of reduction in cardiovascular and stroke risk was in breach of Clause 7.2 of the Code.

Aventis alleged that the claim now being used was misleading. It clearly implied that there were two distinct benefits for Cozaar patients in the LIFE trial, that of cardiovascular outcomes reduction as well as a reduction in stroke risk. As was discussed in the previous case, Case AUTH/1341/7/02, the benefit to patients in the LIFE study was solely through a

reduction in stroke risk. The current claim deliberately created confusion to imply benefits beyond those proven. Any such claim should read 'a significant reduction in cardiovascular outcomes due to stroke risk reduction' or similar, if indeed any claims other than stroke risk reduction were to be made. A breach of Clause 7.2 was alleged.

Aventis also alleged that Merck Sharp & Dohme was in breach of Clause 22 for continuing to make misleading claims relating to Cozaar's cardiovascular risk reductions despite the previous ruling.

The presentation of the significance value (p=0.001) at the end of the claim was also alleged to be misleading in that it could be interpreted as applying to either of the two statements made in the sentence, the stroke or CV outcomes reduction. A further breach of Clause 7.2 was alleged.

Aventis stated that the advertisement and similar claims made elsewhere should be withdrawn as they misled clinicians into prescribing Cozaar thinking it provided a widespread cardiovascular event risk reduction, a benefit which was unproven.

As Aventis had alleged a breach of the undertaking and assurance given in Case AUTH/1340/7/02 this was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

When writing to Merck Sharp & Dohme the Authority invited it to respond in relation to Clause 2 of the Code in addition to the clauses cited by Aventis.

## RESPONSE

Merck Sharp & Dohme stated that similar claims to that at issue in this case had been used widely in the current Cozaar promotional campaign since September 2002, and the company noted that Aventis did not seem to consider these in breach when it wrote to the Authority in July 2002 (Case/AUTH/1340/7/02). Nonetheless, Aventis now considered that the claim was misleading.

The LIFE study demonstrated that, in hypertensive patients with left ventricular hypertrophy, treatment with Cozaar (with additional treatment if required) was better than treatment with atenolol (with additional treatment if required) at preventing adverse vascular events, as shown by:

- time to reach the first event in the primary composite endpoint cardiovascular (CV) death, myocardial infarction or stroke, reduced by 13% from 13% to 11%, p=0.021
- time to reach the first stroke, reduced by 25% from 7% to 5%, p=0.001.

There were no significant differences between the two treatments in time to reduce myocardial infarction or CV mortality, indicating that most of the reduction in the primary outcome was driven by the reduction in stroke. In order to convey these benefits, Merck Sharp and Dohme initially used the phrase '… [Cozaar] demonstrates superior CV outcomes versus an active comparator and showed a 25% reduction in stroke (p=0.001)'. This was considered to be misleading (Case/AUTH 1341/7/02) following a complaint from a doctor that the wording implied two distinct benefits. Merck Sharp and Dohme therefore changed the word 'and' to 'including' to emphasise that stroke was included in the composite of cardiovascular morbidity/mortality.

Aventis suggested that Merck Sharp & Dohme's use of words was misleading, by equating 'including' with 'as well as'. Merck Sharp & Dohme believed that its wording was as clear as it could be, faithfully representing the results of the study and was neither intended nor likely to mislead. With regard to the alleged breach of Clause 22, Merck Sharp & Dohme considered that this was inappropriate and that there was no case to answer.

Merck Sharp & Dohme disagreed that the use of the significance value (p=0.001) was misleading in that it could be interpreted as applying to either of the two statements made earlier in the sentence. The only benefit quantified in this statement was the 25% reduction in stroke risk; the p-value for this was given to enable the reader to assess the degree of confidence in this result. Had Merck Sharp and Dohme quantified the risk reduction for the composite endpoint it would also have indicated the degree of certainty in that too (eg 13% risk reduction, p=0.021). The p-value was placed in parentheses, immediately following the words '25% reduction in stroke risk', and was highly unlikely to be interpreted by doctors as relating to an endpoint earlier in the text.

## PANEL RULING

The Panel noted that in Case AUTH/1341/7/02 it had ruled that the claim 'In addition, Cozaar is the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator and Cozaar showed a 25% reduction in stroke risk (p=0.001)' implied two distinct benefits and this was misleading. Breaches of Clauses 7.2 and 7.3 of the Code had been ruled.

Turning to the case now before it, Case AUTH/1451/4/03, the Panel noted the outcomes of the LIFE study. The primary CV endpoint was defined as a composite of cardiovascular death, stroke and myocardial infarction. The differences between Cozaar and atenolol with regard to the individual endpoints of cardiovascular death and myocardial infarction did not show statistically significant differences. Only stroke had shown a statistically significant difference in favour of Cozaar and was the main driver for the reduction in the primary composite endpoint.

The Panel considered that the claim gave a misleading impression of the outcome of the LIFE study. Insufficient detail had been given. A breach of Clause 7.2 of the Code was ruled.

The Panel considered that on balance the claim at issue in this case was sufficiently different to the claim at issue in the previous case, Case AUTH/1341/7/02, for it not to be covered by the undertaking given in that case. The Panel therefore ruled no breach of Clauses 22 and 2 of the Code.

With regard to the use of the significance value at the end of the claim 'a significant reduction in cardiovascular outcomes including a 25% reduction in stroke risk (p=0.001)', the Panel considered that it was not sufficiently clear that the p value given referred to the stroke risk reduction and not to the 'significant reduction in cardiovascular outcomes' particularly as the word 'significant' was used only to describe the CV outcomes. The Panel ruled a breach of Clause 7.2 of the Code

**Complaint received** **8 April 2003**

**Case completed** **6 June 2003**

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**CASE AUTH/1452/4/03**

# NOVARTIS v FUJISAWA

## Promotion at British Transplantation Society Annual Congress

**Novartis complained about the use by Fujisawa of an article in Scrip to substantiate the claim 'Transplant Market Leader' which appeared on an exhibition stand at the British Transplantation Society (BTS) Annual Congress in London. The involvement of Fujisawa in the preparation of this article had previously been the subject of Case AUTH/1416/2/03. Novartis had not been advised of the Code of Practice Panel's rulings when it made the complaint in Case AUTH/1452/4/03. Both companies had been advised of the outcome of Case AUTH/1416/2/03 by the time Fujisawa responded to the present complaint. Novartis also complained about the provision of T-shirts at the meeting.**

**Novartis stated that it had come to its attention that Fujisawa had used the article at issue to substantiate a major claim about the market status of the company at the BTS meeting. Clearly the delegates at this meeting could be distinguished from the general readers of Scrip. The Fujisawa company stand carried the heading 'Transplant Market Leader' substantiated solely by the Scrip article. It was clear that the exhibition material had been produced following the initiation of the previous complaint and with full awareness of the issues about the article and the accuracy of the claims.**

**Novartis' concerns regarding the veracity of the information provided to Scrip in this article by Fujisawa had been made clear in Case AUTH/1416/2/03 and breaches of the Code were again alleged. Furthermore, this disregard for the Authority, and the use of information from such a questionable source to substantiate such an all embracing claim, brought discredit on the industry and Novartis therefore also alleged this activity to be in breach of Clause 2.**

**On a related issue, it had also come to Novartis' attention that Fujisawa was distributing T-shirts at the BTS meeting from its stand. It was clear that such items did not comply with the requirements of the Code that promotional aids had to be relevant to the practice of the recipient's work.**

**The Panel examined photographs of the exhibition stand. The claim 'Transplant Market Leader' appeared beneath a heading 'BTS Gold Member'. The company corporate logo appeared adjacent to the Prograf product logo in a band at the top of the panel. Another stand also featured the Prograf product logo. The Panel noted Fujisawa's submission that there was some doubt whether the phrase 'Transplant Market Leader' was within the scope of the Code. The Panel considered that as the claim was used on a promotional exhibition stand it thus had to comply with the Code.**

**The only substantiation provided by Fujisawa for the claim 'Transplant Market Leader' was the Scrip article. The claim at issue did not appear in the Scrip article which made comparative claims about, *inter alia*, the relative market share and patient capture rate. Given the Panel's comments and rulings on the information provided by Fujisawa to the Scrip journalist in Case AUTH/1416/2/03, the Panel considered that the Scrip article did not substantiate the claim in question. The graphs had been ruled to be misleading and the Panel thus ruled breaches of the Code. The Panel did not consider that the matter warranted a breach of Clause 2 of the Code which was reserved as a sign of particular censure.**

**The Code required gifts in the form of promotional aids to health professionals to be inexpensive and relevant to the practice of their profession or employment. Fujisawa had submitted that the T-shirt in question was promoting the BTS and the 2003 Congress rather than Fujisawa or any product. The Panel noted that the T-shirt was given away by the company at its promotional exhibition stand. The Panel considered that the T-shirt was not relevant to the practice of medicine. A breach of the Code was ruled.**

Novartis Pharmaceuticals Ltd complained about the use by Fujisawa Limited of an article in Scrip 20/25 December 2002 to substantiate the claim 'Transplant Market Leader' which appeared on an exhibition stand at the British Transplantation Society (BTS) Annual Congress in London. The involvement of Fujisawa in the preparation of this article had previously been the subject of Case AUTH/1416/2/03. Novartis had not been advised of the Code of Practice Panel's rulings when it made the complaint in Case AUTH/1452/4/03. Both companies had been advised of the outcome of Case AUTH/1416/2/03 by the time Fujisawa responded to the present complaint. Novartis also complained about the provision of T-shirts at the meeting.

## COMPLAINT

It had come to Novartis' attention that Fujisawa had used the article at issue to substantiate a major claim about the market status of the company at the BTS meeting held in London. Clearly the delegates at this meeting could be distinguished from the general readers of Scrip. The Fujisawa company stand carried the heading 'Transplant Market Leader' substantiated solely by the Scrip article. It was clear that the exhibition material had been produced following the initiation of the complaint, Case AUTH/1416/2/03, and with full awareness of the issues about the article and the accuracy of the claims.

Novartis' concerns regarding the veracity of the information provided to Scrip in this article by Fujisawa were made clear in Case AUTH/1416/2/03. Novartis had again brought its concerns to the attention of Fujisawa but had received a negative response to its request to discontinue this activity immediately pending the publication of the Authority's finding. Novartis alleged a breach of Clauses 7.2 and 7.4 of the Code. Furthermore, this disregard for the Authority and the use of information from such a questionable source to substantiate such an all embracing claim, brought discredit on the industry. Novartis therefore also alleged this activity to be in breach of Clause 2.

In view of the seriousness of this misinformation at such a prestigious UK meeting, Novartis requested that should the Authority subsequently find Fujisawa in breach, the company should undertake to write to each attendee at the BTS meeting correcting this blatant misrepresentation.

On a related issue, it had also come to Novartis' attention that Fujisawa was distributing T-shirts at the BTS meeting from its stand. It was clear that such items did not comply with the requirements of Clause 18.2 that promotional aids had to be relevant to the practice of the recipient's work. The issue of distribution of such items was the subject of discussion between the companies following last year's BTS meeting. At this time Novartis had received assurances from Fujisawa that this activity was a 'lapse' and would not be repeated.

## RESPONSE

Fujisawa stated that there was some doubt as to whether its use of the phrase 'Transplant Market Leader' fell within the scope of the Code. Furthermore, although the Panel's ruling in Case AUTH/1416/2/03 found Fujisawa in breach of Clauses 7.2 and 20.2 in that the information provided to the journalist was 'inadequate', no ruling had been made on the use of the phrase 'Transplant Market Leader'.

Novartis was aware that the earlier complaints made in relation to the Scrip article (Case AUTH/1416/2/03) had been vigorously defended by Fujisawa and no decision had been reached by the Authority regarding these complaints at the time of the BTS meeting. It was Fujisawa's understanding that there was no requirement under the Code to discontinue activities relating to the subject of an ongoing complaint until a judgement had been made. Indeed Fujisawa was aware of just such a set of circumstances relating to a previous complaint made by Fujisawa against Novartis where the promotional materials in question were still being used between the Panel's ruling in favour of Fujisawa and a subsequent (unsuccessful) appeal by Novartis. Therefore Fujisawa denied that its activities at the BTS meeting were in breach of Clause 2.

Fujisawa's use of the phrase 'Transplant Market Leader' on its stand was referenced to the article appearing in Scrip under the headline 'Fujisawa leads in UK transplant market'. The article was available at the stand if anyone had requested sight of it. The questions that led to the article arose spontaneously during a visit by the journalist to view the new office accommodation that had been necessitated by Fujisawa's rapid expansion over the previous two years. Although Fujisawa had provided information verbally to the journalist the article was entirely written by the staff at Scrip and Fujisawa had no other input into the contents or tone of the article. Two graphs had been provided to the journalist on request. These related to Prograf's share of the transplant market by value compared with Neoral's and had been compiled from data obtained from IMS and adjusted (by Fujisawa) to allow for the fact that the proportion of total sales reported by IMS relating to transplant patients differed for Prograf and Neoral. All assumptions on the proportion of total Neoral and Prograf sales relating to the transplant market were extremely conservative in that the proportion of total Neoral sales that related to transplant patients was certainly significantly lower than the 60% figure used in Fujisawa's calculations (even when transplantation other than kidney and liver was considered). Likewise the proportion of total Prograf sales relating to kidney and liver transplantation was likely to be higher than the 90% figure used. Fujisawa therefore had been deliberately conservative in its assumptions to avoid the dangers of introducing bias. Although the figures were based on a like for like comparison considering kidney and liver transplantation Fujisawa believed that the assumptions made were so conservative that the picture would essentially be the same if all transplant indications were included.

The graphs supplied to the Scrip journalist were provided directly from department sales charts to the journalist following a discussion initiated by the journalist. These were not fully labelled and it could be seen from the article in Scrip that these had been annotated by Scrip prior to publication. Fujisawa did not provide the graphs in publication-ready mode and no further discussion took place with Scrip regarding their inclusion in the article. Fujisawa stood by the accuracy of the data. It was made clear to the journalist that the data was based on a like for like comparison and therefore included kidney and liver transplantation only.

In relation to this allegation and others, Fujisawa submitted the information made available to the Scrip journalist was factual and presented in a balanced way. As Fujisawa had no control over the content of the published article it could take no responsibility for anything other than the information it provided to the journalist.

Subsequent to the use of the reference from Scrip at the BTS meeting the Authority had ruled that the labelling and description of the data in the graphs were 'inadequate and misleading'. Although Fujisawa made it clear to the journalist what the graphs referred to and that it had provided the graphs directly from company sales charts rather than as 'publication-ready' material, Fujisawa had accepted the findings of the Panel in relation to the inadequate labelling. However, it still believed that the claim 'Transplant Market Leaders' was accurate in relation to Prograf's share of the transplant market by value. At the time that the Scrip reference was used to support the claim Fujisawa believed that the Scrip article was an accurate reflection of the true situation and therefore was able to be used to substantiate the claim and as such Fujisawa denied any breach of Clauses 7.2 or 7.4.

In a separate complaint (but relating to the same BTS meeting) Novartis alleged a breach of Clause 18.2 in relation to the distribution of T-shirts. As Fujisawa was aware that neither the chief executive of Novartis nor his medical adviser had actually seen the item at issue, Fujisawa had sent a sample to Novartis offering the opportunity to withdraw the complaint. Fujisawa had not received a reply to its letter.

The T-shirt in question was actually promoting the BTS and the 2003 congress rather than Fujisawa or any product. The front of the T-shirt showed the British Transplantation Society's logo and the words British Transplantation Society, London 2003. On the left sleeve were the words Fujisawa BTS Gold Members. The T-shirt, and its distribution from the Fujisawa stand, had been discussed with the President of the BTS. The T-shirt was displayed prominently on the stand alongside the CD-Rom of the BTS congress (which also displayed the BTS logo and the words 'Provided by Fujisawa working in partnership with the BTS') and like the CD-Rom was available to any congress delegate. The T-shirt was a congress-specific item and was considered by delegates to be an appropriate item of apparel to wear at the more informal congress social events and during their breaks between congress activities. To suggest that this was an 'inappropriate gift' and could be regarded as an inducement to prescribe seemed rather far-fetched.

Previous correspondence concerned a different T-shirt which included the brand name Prograf. Fujisawa agreed that this was inappropriate. The issue then was the claim that this represented advertising to the general public. The T-shirt available at this year's BTS Congress could not be regarded in the same way.

Fujisawa regarded the distribution of souvenir T-shirts as part of its support for the British Transplantation Society as Gold Members (sponsors). In this sense it was similar to the distribution of congress bags to all delegates which displayed the names of four of the seven companies providing sponsorship to this meeting. Fujisawa did not believe that the purpose of Clause 18.2 was ever envisaged to refer to this sort of activity. Fujisawa therefore denied a breach of the clause and regretted that the Authority had been troubled by this trivial matter.

## PANEL RULING

The Panel noted that Case AUTH/1416/2/03 concerned a complaint by Novartis about an article headed 'Fujisawa leads in UK transplant market' which appeared in Scrip 20/25 December and discussed the relative market share of Prograf and Novartis' product, Neoral. The claim at issue in the present case, Case AUTH/1452/4/03, 'Transplant Market Leaders' was not from the Scrip article. In the previous case (Case AUTH/1416/2/03), Novartis noted that the Scrip article contained claims about Fujisawa's position as market leader, substantiated by Neoral and Prograf sales data which had been manipulated. Novartis had made a number of specific allegations about claims in the article.

***Extract from Panel Ruling in Case AUTH/1416/2/03***

The Panel noted Fujisawa's account of the circumstances of the interview. The journalist from Scrip had been invited to visit new corporate headquarters and had initiated a conversation which resulted in the article at issue. Those interviewed by the journalist had a clear recollection of what was said. No written account was made during or subsequent to the interview and other than two graphs no written material was provided to the journalist to confirm what was said.

The Panel examined the bar chart and graph provided by Fujisawa to the journalist. The bar chart was headed 'IMS Transplant Cash Market Share Hospital and Retail' and compared the percentage market share of Neoral and Prograf from October 2000 to September 2002; it was reproduced in Scrip beneath the heading 'Share of UK transplant market'. The second graph depicted the products' hospital and retail transplant cash sales for an identical period and was reproduced in Scrip beneath the heading 'Prograf/Neoral sales for transplant use (October '00 – Sept '02)'. A footnote to the graph and the bar chart in Scrip read 'hospital and retail sales. Source: Fujisawa (IMS data)'. The Panel considered that neither the graph nor the bar chart made it sufficiently clear that only data relating to the indications common to both Neoral and Prograf, ie renal and liver transplants were included. The Panel noted Fujisawa's submission that it was made clear to the journalist that the graphs featured renal and liver transplantation data only. The Panel noted that the company had no written record of what was said to the journalist about the products. The Panel considered that the written material provided to the journalist was inadequate. It was not made sufficiently clear that heart transplant data for which Prograf was not licensed was not included. The labelling and description of the data were thus inadequate and misleading. The material was not presented in a balanced way. Breaches of Clauses 7.2 and 20.2 were ruled.

In relation to the statement in the article, attributable to Fujisawa's UK President that virtually every UK liver transplant patient in the UK was put on Prograf as first choice and about 80% of kidney transplant patients, the Panel noted Fujisawa's submission that the data was based on information received from Fujisawa's sales force and related to available patients.

The Panel queried whether such data was sufficient to substantiate such claims. Fujisawa had no access to individual patient data. The Panel noted that Fujisawa had discussed the tacrolimus versus microemulsified ciclosporin in liver transplantation (TMC) study with the journalist. Fujisawa submitted that it had put the data in context. However on the evidence before it the Panel could not determine precisely what was said and how the data was thus presented. The Panel noted Fujisawa's comment that it was unclear whether a breach of the Code was alleged in relation to this. The Panel considered that the allegation was caught by the generality of the alleged breach of Clause 20.2. Given the circumstances the Panel was thus obliged to rule no breach of Clause 20.2 on this point.

In relation to comparative claims about cost effectiveness, efficacy and safety the Panel decided that in respect of each claim it was impossible for the Panel to determine precisely what was said. The Panel made rulings of no breach of the Code.

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Turning to the present case, Case AUTH/1425/4/03, the Panel examined the photographs of the exhibition stand provided by Novartis. The claim at issue 'Transplant Market Leader' appeared beneath a heading 'BTS Gold Member'. The company corporate logo appeared adjacent to the Prograf product logo in a band at the top of the panel. Another stand also featured the Prograf product logo. The Panel noted Fujisawa's submission that there was some doubt whether the phrase 'Transplant Market Leader' was within the scope of the Code. The Panel considered that as the claim was used on a promotional exhibition stand it thus had to comply with the Code. The Panel noted that the only substantiation provided by Fujisawa for the claim 'Transplant Market Leader' was the Scrip article. The claim at issue did not appear in the Scrip article which made comparative claims about, *inter alia*, the relative market share and patient capture rate. Given the Panel's comments and rulings on the information provided by Fujisawa to the Scrip journalist in Case AUTH/1416/2/03, the Panel considered that the Scrip article did not substantiate the claim in question. The graphs had been ruled to be misleading. The Panel thus ruled breaches of Clauses 7.2 and 7.4.

The Panel did not consider that the matter warranted a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

The Panel noted that Clause 18.2 required gifts in the form of promotional aids to health professionals to be inexpensive and relevant to the practice of their profession or employment. Inexpensive was defined as costing the donor company no more than £6 excluding VAT. The supplementary information to Clause 18.2, Gifts, stated that items of general utility which had been held to be acceptable gifts to doctors as being inexpensive and of relevance to work included pens, diaries, nail brushes and surgical gloves, etc. Items which were for use in the home and had no use in the ordinary course of the practice of medicine or any other health profession were unacceptable.

The Panel noted Fujisawa's submission that the T-shirt in question was promoting the BTS and the 2003 Congress rather than Fujisawa or any product. The Panel noted that the T-shirt was given away by the company at its promotional exhibition stand. The Panel considered that the T-shirt was not relevant to the practice of medicine. The Panel ruled that by not meeting the provisions of Clause 18.2 the item was in breach of Clause 18.1 of the Code.

**Complaint received** **11 April 2003**

**Case completed** **3 June 2003**

CASE AUTH/1453/4/03

# ANONYMOUS v AVENTIS PHARMA

## Lantus meetings

**An anonymous complainant wrote expressing discomfort with the organisation, and in particular the level of hospitality, of a meeting about Lantus (insulin glargine) held by Aventis Pharma in Chepstow. The complainant stated that a similar meeting had also been held in Scotland. It was established practice that anonymous complaints were accepted and dealt with in the usual way.**

**The Panel queried whether the Chepstow meeting justified two nights' accommodation as according to the documentation the meeting finished around 4pm on the Saturday and there was no educational programme for the Sunday. Aventis stated that in order to allow health professionals to meet the speakers and discuss the topics addressed during the day, dinner was offered in the evening following the meeting and hence the option of an overnight stay to follow was considered appropriate.**

**On balance the Panel considered that the impression from the documentation was that the educational programme did not justify two nights' accommodation. The Panel also considered that the informal arrangements for dinner and discussion on the Saturday evening did not justify two nights' accommodation. In the Panel's view it would have been acceptable to offer one night's accommodation given the distances attendees would be travelling. This could have been either before or after the meeting and the timings altered as appropriate. The cost might be on the limits of acceptability for some of the delegates. The hospitality offered was not in proportion to the occasion and a breach of the Code was ruled. Taking all the circumstances into account the Panel did not consider that the company had failed to maintain a high standard. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.**

**The arrangements for the meeting in Scotland were similar. The Panel considered that its rulings and comments above applied to that meeting.**

An anonymous complaint was received about a meeting concerning Lantus (insulin glargine) held by Aventis Pharma Ltd in November in Chepstow. It was established practice that anonymous complaints were to be accepted and considered by the Authority in the usual way.

### COMPLAINT

Although the meeting had been held some time ago, the complainant had been somewhat uncomfortable with the organisation and in particular the level of hospitality at this meeting. A recent national meeting with several of the complainant's colleagues, who also expressed concerns, had confirmed this.

The complainant was also aware that the company had held a similar meeting the following week in Scotland.

When writing to Aventis, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

### RESPONSE

Aventis confirmed that in November 2002 two national meetings in Chepstow and Turnberry were held to address various aspects of the management of diabetes, including the use of Lantus. The health professionals invited were either hospital doctors specialising in diabetes or diabetes specialist nurses. Each member of the Aventis sales force was able to invite a maximum of four health professionals; those whose customers resided in the South and West of the UK were invited to Chepstow, whilst those in the East and North were invited to the Turnberry meeting.

In accordance with Clause 19.1 of the Code, both meetings provided clear educational content for the benefit of the audience. A faculty of national and international speakers provided the content for a high quality agenda that addressed a variety of topics of practical interest regarding the management of diabetes. The speaker programme lasted between 10am and 4pm on both occasions.

As the speaker faculty included international members, a maximum of two meetings were possible, hence the need for them to be 'national' with invitations extended to health professionals across the UK. As many delegates travelled a considerable distance, accommodation was offered on the night before the meeting, as it would not have been possible for them to reach the venue by the start of the meeting at 10am the following day. In order to allow health professionals to meet the speakers and discuss the topics addressed during the day, dinner was offered in the evening following the meeting and hence the option of an overnight stay to follow was considered appropriate. The option to leave after the meeting closed at 4pm was of course available.

Eighty-two people attended the Chepstow meeting of which 14 attended solely as day delegates. Sixty-eight stayed at a hotel for the Friday night, whilst 25 stayed for the Saturday. The average cost per head for the venue, accommodation and meals was £272. It should be noted that the numbers quoted included the delegates, speakers and Aventis members of staff attending. Travel expenses were reimbursed separately.

Aventis was confident that the Chepstow meeting was organised within the requirements of Clause 19.1, namely that the level of hospitality was both appropriate and clearly secondary to the educational content of the meeting.

The second meeting at Turnberry conformed to the same standards. The cost per head for the venue, accommodation and meals was £318. One hundred and fifteen people attended the meeting with 112 staying for the Friday night and 110 staying for the Saturday evening. Aventis stated that the increased proportion of delegates staying overnight in

Turnberry compared to Chepstow reflected the generally greater distances travelled by delegates to the Scottish meeting. Aventis therefore refuted the complaint as regards the organisation and the level of hospitality at this meeting.

## PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The Panel noted that whilst reasonable hospitality could be provided the cost of the meetings should not exceed those which participants might normally pay. The supplementary information to Clause 19.1 stated that the provision of hospitality included the payment of reasonable, actual travel costs which a company might provide to sponsor a delegate to attend a meeting. The supplementary information further stated that it should be the programme that attracted delegates and not the associated hospitality or venue. The impression created by the arrangements was an important factor.

The Panel noted that the Chepstow meeting started at 10am and finished with summary and close at 4pm. Aventis had stated that in order to allow health professionals to meet the speakers and discuss the topics addressed during the day dinner was offered in the evening following the meeting and hence the option of an overnight stay to follow was considered appropriate. The Panel noted that there was no mention of any arrangements after 4pm in any of the documentation. The invitation, agenda and other documentation gave the impression that the meeting would finish at around 4pm.

The Panel noted that the attendees were a mixture of hospital doctors specialising in diabetes or diabetes specialist nurses. The final delegate list showed that the majority of those attending were nurses. The average cost per head of £272 plus travel expenses might be more than some of the delegates would pay if they were paying for themselves.

The Panel queried whether the meeting justified two nights' accommodation as according to the documentation the meeting finished around 4pm; there was no educational programme for the Sunday. The Panel considered that it was not necessarily unreasonable for companies to provide accommodation for the evening prior to a meeting if delegates had long distances to travel and the meeting started early in the morning. In the case in question, however, it appeared to the Panel that the second night's accommodation had been provided merely because the choice of venue meant that it might be difficult for delegates to return home on the Saturday evening. Another venue or different timings for the meetings such as an earlier start time with an earlier finish time might not have necessitated providing two nights' accommodation.

On balance the Panel considered that the impression from the documentation was that the educational programme did not justify two nights' accommodation. The Panel also considered that the informal arrangements for dinner and discussion on the Saturday evening did not justify two nights' accommodation. In the Panel's view it would have been acceptable to offer one night's accommodation given the distances attendees would be travelling. This could have been either before or after the meeting and the timings altered as appropriate. The cost might be on the limits of acceptability for some of the delegates. The hospitality offered was not in proportion to the occasion and a breach of Clause 19.1 of the Code was ruled. Taking all the circumstances into account the Panel did not consider that the company had failed to maintain a high standard and thus no breach of Clause 9.1 of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

The arrangements for the Turnberry meeting were similar. The majority of those attending were nurses. The average cost per head was £318 plus travel expenses. The Panel considered that its rulings and comments above applied to the Turnberry meeting. A breach of Clause 19.1 of the Code was ruled and no breach of Clauses 9.1 and 2 was ruled.

**Complaint received** **11 April 2003**

**Case completed** **17 June 2003**

CASE AUTH/1454/4/03

# PHARMACEUTICAL ADVISER v MERCK

## HRT guidelines used by representatives

**A pharmaceutical adviser to a primary care trust (PCT) complained that hormone replacement therapy (HRT) guidelines, which she had written for the PCT, had been amended and used by a Merck representative to promote Femseven to a community pharmacist. By defacing the original copy the representative was able to present the guidelines as a formulary. The complainant's PCT did not have an HRT formulary. Permission had not been given for the guidelines to be modified or used to promote Merck products. While the complainant realised that the PCT had very little control over guidelines once they had been sent out to the practices, she believed that it was unethical for a company to misrepresent them in this way, and to use them to promote its products.**

**The Panel noted that the original document at issue as drafted by the complainant was headed 'Guidelines for the use of HRT' and included the name of the complainant. The document used by the representative had the heading deleted but was otherwise identical. The Panel noted the allegation that the document had been presented as a formulary to a community pharmacist within the PCT. The PCT had no such formulary. The Panel also noted Merck's submission that the document had been provided to a representative by a local nurse, with the heading already deleted. That representative had passed it on to other local representatives. The document had not been through Merck's certification process.**

**The Panel considered that in the circumstances the use of the document for promotional purposes meant that the representatives had not maintained a high standard of ethical conduct and a breach of the Code was ruled. The activity was such that the company had not maintained high standards and a further breach was ruled. The Panel noted the complainant's allegation that a community pharmacist had gained a misleading impression about the nature of the document from the representative; it was presented as a formulary. The Panel also noted Merck's submission that its representatives claimed that they did not wilfully misrepresent the nature of the document. Merck stated that it could not be certain that its representative did not wrongly claim that this was a formulary document. The Panel was extremely concerned about the use of this document for promotional purposes by representatives. The Panel, however, considered that on the evidence before it, it was unable to determine precisely what was said about the document and thus had no alternative but to rule no breach in that regard.**

A pharmaceutical adviser to a primary care trust (PCT) complained about the use by a sales representative from Merck Pharmaceuticals of guidelines for the use of HRT which she had written for the PCT.

### COMPLAINT

The complainant sent the Authority a copy of a letter which she had written to Merck and provided a copy of the original guidelines which she had written for the PCT, together with an amended copy used by one of the company's representatives to promote its product Femseven. The complainant stated that by defacing the original copy the representative was able to present the guidelines as a formulary.

While the complainant realised that the PCT had very little control over guidelines once they had been sent out to the practices, she believed that it was unethical for a company to misrepresent them in this way, and to use them to promote its products.

The letter written by the complainant to Merck stated that the amended guidelines had been used to promote Femseven to a community pharmacist. The complainant's PCT did not have an HRT formulary. Permission had not been given for the guidelines to be modified or used to promote Merck products.

When writing to Merck the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1 and 15.2 of the Code.

### RESPONSE

Merck stated that the document in question had not been through the company's approval procedure and its use was not part of company policy. Merck had reiterated to its representatives that any material they used must first be approved and the seriousness of using any material not so approved.

Merck accepted that by not following procedures its representatives were in breach of Clauses 2, 9.1 and 15.2 of the Code. Concerning Clause 7.2, it appeared that the document originally supplied to one of Merck's representatives already had the headers obscured and the representatives claimed that they did not wilfully misrepresent the nature of the document. However, as Merck could not be certain that its representative did not wrongly claim that this was a formulary document, it accepted the breach of Clause 7.2.

In a letter sent to the complainant, Merck stated that it appeared that the representatives using these guidelines did so more out of naivety than malice. Apparently, a local nurse gave one of them a copy of the guideline with the header already obscured on the photocopy. They then appeared to have passed this document on to other local representatives without any instruction that they were for personal information only and had not been through Merck's approval procedure.

### PANEL RULING

The Panel noted that the original document at issue as drafted by the complainant was headed 'Guidelines for the use of HRT' and included the name of the

complainant. The document used by the representative had the heading deleted but was otherwise identical. The Panel noted the allegation that the document had been presented as a formulary to a community pharmacist within the PCT. The PCT had no such formulary. The Panel also noted Merck's submission that the document had been provided to a representative by a local nurse, with the heading already deleted. That representative had passed it on to other local representatives. The Panel noted that the document had not been through Merck's certification process.

The Panel considered that in the circumstances the use of the document for promotional purposes meant that the representatives had not maintained a high standard of ethical conduct; a breach of Clause 15.2 was ruled. Further the activity was such that the company had not maintained high standards, as required by Clause 9.1; a breach of Clause 9.1 was ruled. The Panel noted the complainant's allegation that a community pharmacist had gained a misleading impression about the nature of the document from the representative; it was presented as a formulary. The Panel also noted Merck's submission that its representatives claimed that they did not wilfully misrepresent the nature of the document. Merck also stated that it could not be certain that its representative did not wrongly claim that this was a formulary document. The Panel was extremely concerned about the use of this document for promotional purposes by representatives and noted its rulings above in this regard. The Panel, however, considered that on the evidence before it, it was unable to determine precisely what was said about the document and thus had no alternative but to rule no breach of Clause 7.2.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and was reserved for such circumstances.

**Complaint received** **11 April 2003**

**Case completed** **27 May 2003**

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**CASE AUTH/1455/4/03**

# GENERAL PRACTITIONER v PHARMACIA

## Public health educational campaign

**A general practitioner complained about Pharmacia's public health education campaign addressed to people with bladder problems. The complainant had been shown newspaper and magazine advertisements placed by the Public Health Education Campaign which some readers had assumed was a government information initiative. In fact, the Public Health Education Campaign was sponsored by Pharmacia and was not an altruistic initiative but was covert advertising hoping to increase prescription of Detrusitol. Far from being helpful, it was more likely to create anxiety in the elderly and might lead to unnecessary investigations and over-medication. Such covert advertising seemed unethical and the complainant queried its acceptability under the Code.**

**The Panel examined the materials. The advertisement was headed 'Celebration or desperation?' followed by 'Don't be shown up by a weak bladder'. The copy referred to an overactive bladder and 'sudden, strong urges to go to the loo …'. A list of possible symptoms was given which related to stress incontinence, urgency and frequency. The reader was recommended to talk to their doctor or nurse, visit the bladderzone website or call a freephone helpline. The Public Health Education Campaign and its address appeared at the bottom of the advertisement. A reply coupon featured the logos, website addresses and charity numbers of The Continence Foundation and Incontact, above the statement 'Health Education sponsored by Pharmacia'. Readers could send off for an information pack from the Public Health Education Campaign which consisted of a letter, a booklet, a symptom questionnaire to use with the doctor or nurse and a questionnaire on the campaign. A follow up questionnaire was used with people who had responded to the campaign questionnaire.**

**The information pack was sent out under a covering letter headed 'The Public Health Education Campaign'. 'Health Education sponsored by Pharmacia' appeared in small print in the bottom right-hand corner. Reference was made to the availability of 'all sorts of new treatment options'. The booklet described how the bladder worked, different types of bladder problems and how best to discuss the subject with a doctor or nurse. The materials appeared to have been sent by the Public Health Education Campaign. The letter, booklet and symptom questionnaire each stated that they were health education sponsored by Pharmacia. No such declaration appeared on the campaign questionnaire or the follow up questionnaire. Specific medicines were not mentioned.**

**The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine and no breach of the Code was ruled in that regard.**

**The Panel noted that none of the materials provided mentioned medicines. The Panel considered that the materials would increase public awareness of bladder problems and encourage people to discuss possible treatment and care options with their general practitioner. This was not necessarily unacceptable. From the information provided patients were not being encouraged to ask their doctors specifically for Detrusitol, which could be used to treat overactive bladders but was not the only product available. Patients visiting their**

**doctors as a result of seeing the campaign would not necessarily be prescribed Detrusitol and would not necessarily be suffering from a bladder problem that could be treated with it. The Panel did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of the Code was ruled.**

**The telephone helpline gave pre-recorded general information about the purpose of the information pack and enabled callers to request it. The voice-over did not state that the helpline was sponsored by Pharmacia. A breach of the Code was ruled. Further, the Panel was concerned that the home page of the website www.bladderzone.com featured the company name, Pharmacia, in logo format. There was no clear indication that Pharmacia had sponsored the website. Although a statement at the bottom of the home page referred to Pharmacia UK's copyright and Pharmacia's website usage terms and privacy statement, the Panel did not consider that the role of the company in relation to its financial sponsorship of the website had been made sufficiently clear. A breach of the Code was ruled. No declaration of sponsorship appeared on the campaign questionnaire or the follow up questionnaire. A breach of the Code was ruled in respect of each item.**

**The Panel noted that the materials at issue were aimed at the general public. The Panel noted that the telephone voice-over referred the reader to Incontact and The Continence Foundation for further information and provided contact details. The Panel considered that the failure to declare sponsorship in conjunction with the reference to two patient organisations gave a misleading impression about the generation of the campaign. Similarly, the homepage of the website featured, in a prominent position and typeface, the 'healthy bladder campaign'. The company name appeared in a less prominent colour, size and typeface on the left-hand side of the homepage beneath the site index as well as in very small print at the bottom of the page. The Panel considered that the failure to declare sponsorship in conjunction with the 'healthy bladder campaign' meant that the role of the company was not sufficiently clear. The Panel was also concerned about the failure to declare sponsorship on the campaign questionnaire. Recipients were asked to provide their name and address, in strictest confidence, if they wished to receive further educational items on this subject. The Panel noted its rulings in relation to the telephone helpline, the website and the questionnaire and considered that the failure to adequately declare sponsorship on the aforementioned items which were directed to the general public was such that Pharmacia had failed to maintain high standards. A breach of the Code was ruled.**

A general practitioner complained about Pharmacia Limited's public health education campaign addressed to people with bladder problems. Pharmacia supplied Detrusitol (tolterodine) which was indicated for the treatment of urge incontinence and/or increased urinary frequency associated with urgency as might occur in patients with unstable bladder.

## COMPLAINT

The complainant had recently been shown advertisements placed in newspapers and magazines by the Public Health Education Campaign encouraging people with bladder problems to send for an information pack which contained a short booklet and a questionnaire. The questions were such that most elderly folk would tick many of the boxes and the advice was to visit their own doctor with the completed questionnaire. The impression given was that the article was not an advertisement; some readers had assumed it to be a government information initiative. In fact, the Public Health Education Campaign was sponsored by Pharmacia and was not an altruistic initiative aiming to help the public, but was covert advertising hoping to increase prescription of Detrusitol. Far from being helpful, it was more likely to create anxiety in the elderly and might lead to unnecessary investigations and over-medication. Such covert advertising seemed unethical and the complainant queried its acceptability under the Code.

When writing to Pharmacia, the Authority asked it to respond in relation to Clauses 2, 9.1, 9.9, 20.1 and 20.2 of the Code and noted that a previous case, Case AUTH/911/8/99, had addressed similar issues but with different materials.

## RESPONSE

Pharmacia stated that the public health campaign on bladder problems was produced in conjunction with two patient support groups, The Continence Foundation and Incontact. The campaign was sponsored by Pharmacia which accepted responsibility for the materials which, whilst non-promotional, were designed to inform the public and had therefore been reviewed to ensure compliance with the Code.

The complainant had two main concerns. Firstly that the campaign was an attempt at covert advertising for Detrusitol, and secondly that the campaign was unhelpful and likely to cause anxiety to patients which might lead to unnecessary investigations and subsequent over-medication. Pharmacia's explanation drew upon a previous case, Case AUTH/911/8/99, in which Pharmacia was not ruled in breach of the Code.

Pharmacia stated that bladder problems were common in the UK with an estimated 6 million sufferers. The symptoms, which might include urinary incontinence, frequency and a strong sudden desire to void, had a profound effect on an individual's quality of life. Despite this impairment in functioning many individuals did not seek advice, having accepted the symptoms as being part of the aging process. This was further compounded by patients' embarrassment in discussing their condition.

The fundamental aim of the campaign was to raise awareness of bladder problems: to allow an individual sufferer to recognise their symptoms and

help them feel more confident in discussing them with a health professional. The campaign had gained extensive endorsement from patient support groups, carer groups as well as clinicians. In addition, Pharmacia had sought advice from the Medicines Control Agency (MCA) [now known as the Medicines Healthcare products Regulatory Agency – MHRA] when the campaign was first initiated in 1999. The material was then deemed non-promotional.

Although the campaign materials had changed over time, the overall theme was the same. Due care and consideration was applied to all the materials produced such that they were balanced, educational and non-promotional.

The present advertisement was entitled 'Celebration or desperation?' and was endorsed by the logos of The Continence Foundation and Incontact. The Public Health Education Campaign was a joint initiative fully supported by these groups. The advertisement highlighted the subjective feelings that an individual suffering from urinary incontinence might have, as well as describing other urinary symptoms. This allowed an individual to identify if they suffered from any of these. Advice was given on obtaining an information pack either through a freephone number or by filling in the coupon on the advertisement and sending it by Freepost. The information pack was also available through the web address www.bladderzone.com.

The advertisement did not mention a product and was non-promotional, nor did it raise unfounded hopes of successful treatment. The symptoms described could be relevant to a wide variety of different urological conditions. There was no covert attempt to align this material to one condition and one product.

The information pack, supplied on request, comprised a letter addressed to the individual outlining the purpose of the campaign; a booklet outlining the common types of bladder problems covering the diseases of overactive bladder, stress incontinence, mixed urinary symptoms, prostatic problems, urinary infection and other conditions; a questionnaire to help patients explain their symptoms and the impact they had upon their quality of life and two questionnaires which surveyed the usefulness of the material provided in the information pack. The materials provided used simple language to educate the public on the common disorders affecting the lower urinary tract.

Pharmacia did not consider that these materials would cause patient anxiety. Conversely, many patients were extremely anxious about their symptoms but were too embarrassed to approach their doctors. To have their condition assessed, and receive reassurance and treatment, could be a tremendous relief. This was supported by a survey of 3,280 sufferers who had seen and responded to the campaign. In this survey, 87% found the information helpful and 60% reported that it was easier to cope with their bladder problems after seeking professional help prompted by the campaign.

Further, Pharmacia considered that to suggest that the campaign would result in over investigation and over treatment discredited the medical profession. All the symptoms identified needed medical assessment and might need investigation in line with standard clinical practice. In fact, the early diagnosis of some urological conditions might be life saving. It always remained at the clinician's discretion whether or not to prescribe. Pharmacia was confident that clinicians, through appropriate communication, would be able to avoid both over-medication and over investigation.

In summary, the Public Health Education Campaign helped patients identify and assess their abnormal urinary symptoms. In doing so, patients would have greater confidence in approaching their doctors when they experienced symptoms which warranted medical assessment, and be able to express their concerns with greater clarity. Health professionals would therefore be aided in the consultation by this improved communication, facilitating appropriate diagnosis and management.

Finally, Pharmacia noted that the supplementary information to Clause 20.2 of the Code stated 'Companies may conduct disease awareness and public health campaigns provided that the purpose of these is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'.

Pharmacia had addressed this proviso of the Code in producing the public health education campaign and was confident that it had complied with Clauses 2, 9.1, 9.9 and 20.1 and 20.2.

In response to a request for further information Pharmacia stated that it had sponsored this campaign with full support from Incontact and The Continence Foundation. The campaign was established and funded by Pharmacia. Details of where the advertisement had and would appear were provided.

Pharmacia repeated that the role of the Public Health Education Campaign was to raise the awareness of bladder problems in order to help an individual sufferer recognise their symptoms and help them feel more confident in discussing them with a health professional. Pharmacia was responsible for the production of all the materials which had been reviewed for compliance with the Code.

## PANEL RULING

The Panel noted that it had considered a previous case, Case AUTH/911/8/99 where no breach of Clauses 20.1 and 20.2 of the Code was ruled in relation to a public health campaign on bladder problems. The rulings were not appealed. Paragraph 5.1 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication, it might be allowed to proceed at the discretion of the Director if new evidence was adduced by the complainant or if the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel which was not the subject of an appeal to the Code of Practice Appeal

Board. The case now at issue, Case AUTH/1455/4/03 concerned different materials and although the substance of the complaint was similar to that in Case AUTH/911/8/99, the rulings of no breach in that case had not been appealed. The Director thus decided that Case AUTH/1455/4/03 should be considered in the usual way.

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel examined the materials. The advertisement was headed 'Celebration or desperation?' followed by 'Don't be shown up by a weak bladder'. The copy referred to an overactive bladder and 'sudden, strong urges to go to the loo …'. A list of possible symptoms was given which related to stress incontinence, urgency and frequency. The reader was recommended to talk to their doctor or nurse, visit the bladderzone website or call a freephone helpline. The Public Health Education Campaign and its address appeared in the bottom left-hand corner of the advertisement. A reply coupon in the bottom right-hand corner of the advertisement featured the logos, website addresses and charity numbers of The Continence Foundation and Incontact above the statement 'Health Education sponsored by Pharmacia'. Readers could send off for an information pack from the Public Health Education Campaign which consisted of a letter, a booklet, a symptom questionnaire to use with the doctor or nurse and a questionnaire on the campaign. A follow up questionnaire was used with people who had responded to the campaign questionnaire.

The information pack was sent out under a covering letter headed 'The Public Health Education Campaign'. 'Health Education sponsored by Pharmacia' appeared in small print in the bottom right-hand corner. Reference was made to the availability of 'all sorts of new treatment options'. The booklet described how the bladder worked, different types of bladder problems and how best to discuss the subject with a doctor or nurse. The materials appeared to have been sent by The Public Health Education Campaign. The letter, booklet and symptom questionnaire each stated that they were health education sponsored by Pharmacia. No such declaration appeared on the campaign questionnaire or the follow up questionnaire. Specific medicines were not mentioned.

The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine and no breach of Clause 20.1 of the Code was ruled.

The Panel noted that one of the requirements of Clause 20.2 of the Code was that statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel noted that none of the materials provided mentioned medicines. The Panel considered that the materials would increase public awareness of bladder problems and encourage people to discuss possible treatment and care options with their general practitioner. This was not necessarily unacceptable. From the information provided patients were not being encouraged to ask their doctors specifically for Detrusitol. The Panel noted that there were a number of different treatments available for bladder problems. Not all of the treatments were medicines. Detrusitol could be used to treat overactive bladders but it was not the only product available. Patients visiting their doctors as a result of seeing the campaign would not necessarily be prescribed Detrusitol and would not necessarily be suffering from a bladder problem that could be treated with it.

The Panel while acknowledging that there was a fine distinction between education and promotion, did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of Clause 20.2 of the Code was ruled.

It could be argued that the materials were exempt from the definition of promotion given in Clause 1.2 of the Code which excluded statements relating to human health or disease provided there was no reference, either direct or indirect to specific medicines.

The Panel noted that Clause 9.9 required a clear declaration of sponsorship to appear on material relating to medicines and their uses, whether promotional or not which was sponsored by a pharmaceutical company. The only exception to this was market research material which need not reveal the name of the company involved but must state that it was sponsored by a pharmaceutical company.

The telephone helpline gave pre-recorded general information about the purpose of the information pack and enabled callers to request it. The voice-over did not state that the helpline was sponsored by Pharmacia. A breach of Clause 9.9 was ruled. Further, the Panel was concerned that the home page of the website www.bladderzone.com featured the company name, Pharmacia, in logo format. There was no clear indication that Pharmacia had sponsored the website. Although a statement at the bottom of the home page referred to Pharmacia UK's copyright and Pharmacia's website usage terms and privacy statement, the Panel did not consider that the role of the company in relation to its financial sponsorship of the website had been made sufficiently clear. A breach of Clause 9.9 was ruled. No declaration of sponsorship appeared on the campaign questionnaire or the follow up questionnaire. A breach of Clause 9.9 was ruled in respect of each item.

The Panel noted that the materials at issue were aimed at the general public. It was important that the

company's role in relation to the sponsorship of such material was made clear, in accordance with Clause 9.9 of the Code and that the material did not otherwise give a misleading impression about the role of the company. The Panel noted that the telephone voice-over referred the reader to Incontact and The Continence Foundation for further information and provided contact details. The Panel considered that the failure to declare sponsorship in conjunction with the reference to two patient organisations gave a misleading impression about the generation of the campaign. Similarly, the homepage of the website featured, in a prominent position and typeface, the 'healthy bladder campaign'. The company name appeared in a less prominent colour, size and typeface on the left-hand side of the homepage beneath the site index as well as in very small print at the bottom of the page. The Panel considered that the failure to declare sponsorship in conjunction with the 'healthy bladder campaign' meant that the role of the company was not sufficiently clear. The Panel was also concerned about the failure to declare sponsorship on the campaign questionnaire. Recipients were asked to provide their name and address, in strictest confidence, if they wished to receive further educational items on this subject. The Panel was concerned that it was not made sufficiently clear to the recipient that he/she would be providing these details in response to materials sponsored by a pharmaceutical company.

The Panel noted its rulings of breaches of Clause 9.9 in relation to the telephone helpline, the website and the questionnaire and considered that the failure to adequately declare sponsorship on the aforementioned items which were directed to the general public was such that Pharmacia had failed to maintain high standards. A breach of Clause 9.1 was ruled.

**Complaint received** **14 April 2003**

**Case completed** **20 June 2003**

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**CASE AUTH/1456/3/03**

# HOSPITAL PHARMACIST v BAXTER HEALTHCARE

## Gammagard S/D mailing

**A hospital pharmacist complained about a mailing for Gammagard S/D (Immune Globulin Intravenous (Human) Solvent/Detergent Treated) sent by Baxter Healthcare. The front page of the mailing stated that 'There's only one IVIG that's licensed…'. This was followed over the page by '… for the following neurological disorders'. This was followed by a chart comparing the licensed indications for Flebogamma, Gammagard S/D, Octagam, Sandoglobulin and Vigam. A number of neurological conditions were listed and against each was a tick for Gammagard and a cross for each of the other medicines mentioned.**

**The complainant alleged that the chart was misleading in that it suggested that Gammagard S/D had more licensed indications than the other products. However, the respective summaries of product characteristics (SPCs) did not support this point of view. It seemed to the complainant that the only way this was supported was the statement in the SPC 'Gammagard S/D can also be used to modify or control the immune response in various diseases, for example ITP [idiopathic thrombocytopenic purpura]'. However, this was too vague a statement and more specific statements were needed for licensed indications.**

**The Panel considered that the impression from the chart was that Gammagard was specifically licensed for use in all the indications mentioned and the other products were not. This was not so. The SPC for Gammagard S/D stated that it could be used as replacement therapy in primary and secondary antibody deficiency disorders and for the prevention of infections associated with these conditions. It could also be used to modify or control the immune response in various diseases, for example ITP. The comparison chart gave the impression that the licensed indications listed were specifically mentioned in the therapeutic indications sections of the Gammagard S/D SPC and that was not so. The Panel considered that the mailing was misleading in this regard and a breach of the Code was ruled.**

A hospital pharmacist complained about a mailing (ref ADV 2217) for Gammagard S/D (Immune Globulin Intravenous (Human) Solvent/Detergent Treated) sent by Baxter Healthcare Ltd.

The front page of the mailing stated that 'There's only one IVIG that's licensed…'. This was followed over the page by '… for the following neurological disorders'. This was followed by a chart comparing the licensed indications for Flebogamma, Gammagard S/D, Octagam, Sandoglobulin and Vigam. A number of neurological disorders were listed and against each was a tick in the Gammagard column and crosses in the columns for each of the other medicines mentioned.

### COMPLAINT

The complainant alleged a breach of Clause 7.2 of the Code as the chart misled prescribers by suggesting that Gammagard S/D had more licensed indications than other similar products eg Flebogamma, Octagam, Sandoglobulin and Vigam.

However, close scrutiny of the respective summaries of product characteristics (SPCs) did not support this point of view. It seemed to the complainant that the only way this was supported was the statement in the

SPC 'Gammagard S/D can also be used to modify or control the immune response in various diseases, for example ITP [idiopathic thrombocytopenic purpura'. However, this was too vague a statement and more specific statements were needed for licensed indications.

**RESPONSE**

Baxter Healthcare noted that the complaint related to a mailing that described indications for various preparations of intravenous immunoglobulin. The company did not seek to mislead prescribers and the document was created in good faith. The claims closely followed the SPC.

Support for the Gammagard S/D listed indications presented in the mailing was given in the SPC which stated 'Gammagard S/D can also be used to modify or control the immune response in various diseases, for example ITP'. However, following detailed review it was accepted that it might be possible to misinterpret the content and sense of the mailing and as a result it had been withdrawn with immediate effect.

**PANEL RULING**

The Panel considered that the impression from the chart was that Gammagard S/D was specifically licensed for use in all the indications mentioned and the other products were not. This was not so. The SPC for Gammagard S/D stated that it could be used as replacement therapy in primary and secondary antibody deficiency disorders and for the prevention of infections associated with these conditions. It could also be used to modify or control the immune response in various diseases, for example ITP. The comparison chart gave the impression that the licensed indications listed were specifically mentioned in the therapeutic indications sections of the Gammagard S/D SPC and that was not so. The Panel considered that the mailing was misleading in this regard and a breach of Clause 7.2 was ruled.

**Complaint received** **16 April 2003**

**Case completed** **21 May 2003**

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**CASE AUTH/1457/4/03**

# CONSULTANT PHYSICIAN v GLAXOSMITHKLINE

## Supplement in the journal Guidelines

**A hospital consultant complained about a supplement 'Asthma guidelines in practice – key changes for mild-to-moderate patients' included in the journal Guidelines. The supplement stated on the front page that it had been supported by an educational grant from Allen & Hanburys. An advertisement for Seretide (salmeterol/fluticasone) appeared on the back page and prescribing information was provided in the supplement for the full range of Allen & Hanburys' asthma products.**

**The complainant queried whether the supplement met the requirements for promotional material. The article in the supplement had a doctor as named author but stated that it had been produced by a named division of a named publishing group. Only products marketed by Allen & Hanburys featured in the supplement. The complainant contended therefore that the title page should have a disclaimer to the effect that this was promotional literature and not merely a statement of guidance 'Supported by an educational grant from Allen & Hanburys'.**

**The Panel noted that the supplement had been sponsored by GlaxoSmithKline. The article had been initiated by the company and it had given guidance as to the title and subject area to be covered. The author had been chosen by the agency working on behalf of GlaxoSmithKline and the agency had written the article on the author's behalf. The company had accepted editorial changes such as the author's alterations without question or adjustment. Given the company's involvement the Panel considered that the supplement was in effect promotional material for GlaxoSmithKline's asthma products. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so. The statement on the front cover 'Supported by an educational grant from Allen & Hanburys' added to this impression. A breach of the Code was ruled.**

**The Panel noted that it was stated that the article would examine the implications of the new asthma guidelines for the management of asthma in primary care, suggesting a comprehensive review of the therapy area. This impression was compounded by the title. The article, however, only detailed the use of GlaxoSmithKline's products and so was misleading in that regard. A breach of the Code was ruled.**

**The Panel also considered, given the way in which the supplement was initiated and produced, that the statement 'Supported by an educational grant from Allen & Hanburys' gave a misleading impression of the company's role. The supplement was promotional material paid for by GlaxoSmithKline. A further breach of the Code was thus ruled.**

**The Panel considered that high standards had not been maintained and that the supplement had not recognised the professional standing of the audience to which it was directed. A breach of the Code was ruled.**

A hospital consultant complained about a supplement entitled 'Asthma guidelines in practice – key changes

for mild-to-moderate patients' which had been included in the journal Guidelines. The supplement stated on the front page that it had been supported by an educational grant from Allen & Hanburys. An advertisement for Seretide (salmeterol/fluticasone propionate) (ref SFL/FPA/03/5020 – January 2003) appeared on the back page of the supplement and prescribing information was provided for the full range of Allen & Hanburys' asthma products on pages 6 and 7.

## COMPLAINT

The complainant queried whether the supplement met the requirements for promotional material. The article in the supplement had a doctor as named author but stated that it had been produced by a named division of a named publishing group. It was apparent from the article, from the references quoted and from the prescribing information, that only products marketed by Allen & Hanburys figured in the supplement.

The complainant contended therefore that the title page should have a disclaimer to the effect that this was promotional literature and not merely a statement of guidance 'Supported by an educational grant from Allen & Hanburys'.

The complainant considered that the Authority might wish to advise the company about how such partial publications should be presented in future.

When writing to GlaxoSmithKline the Authority invited it to respond in relation to Clauses 7.2, 9.1 and 10.1 of the Code.

## RESPONSE

GlaxoSmithKline stated that it had reviewed the article and with hindsight considered that the impression given might be misleading. For this reason the article might be viewed as being in breach of Clause 7.2.

However GlaxoSmithKline did not consider that the article was in breach of any other clauses of the Code. GlaxoSmithKline did not believe the article would cause offence and believed that the company's sponsorship of the article was clearly stated at the beginning and end of the item. It did not consider that promotion was disguised since sponsorship was clearly stated and prescribing information was included within the article. For these reasons GlaxoSmithKline did not consider that the article was in breach of Clauses 9.1 or 10.1.

In conclusion, on reviewing the article, GlaxoSmithKline did consider that it could be viewed as being in breach of Clause 7.2 and for this reason it was reviewing its procedures for sign off of such articles to prevent the breach re-occurring. It did not intend to re-publish the article in its current form.

In response to a request for further information GlaxoSmithKline stated that the article was initiated by a marketing manager and employee of GlaxoSmithKline and the author was selected by a named agency. The agency consulted the author, then wrote the article on his behalf. The author made alterations (documented in the job bag) which were accepted by GlaxoSmithKline which influenced the article in as much as it gave guidance as to the title and subject areas to be included. However editorial changes were accepted without question or adjustment. The reasons why, when reviewing the supplement, GlaxoSmithKline considered that it might be misleading were that the title: 'Asthma guidelines in practice – key changes for mild-to-moderate patients' implied that the article was a balanced review of the new asthma guideline. When reading the supplement now, the company considered that the content of the article might be focussed on the use of Seretide within the new recommendations. Seretide was specifically mentioned by name and this was not the case in the guideline. GlaxoSmithKline therefore considered that the title might mislead the reader. A better title might have included 'How can Seretide fit into the new guideline on asthma management'. This would have avoided any confusion.

## PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The journal supplement in question had been sponsored by GlaxoSmithKline. The article had been initiated by the company and it had given guidance as to the title and subject area to be covered. The author had been chosen by the agency working on behalf of GlaxoSmithKline and the agency had written the article on the author's behalf. The company had accepted editorial changes such as the author's alterations without question or adjustment. The article itself outlined some of the evidence that had influenced the recent changes in the British guidelines on asthma management and the implications thereof for management of asthma in primary care. Much of the ensuing discussion detailed the role of Seretide in the management of asthma although reference was also made to beclomethasone and fluticasone (GlaxoSmithKline's products Becotide and Flixotide respectively). The article concluded with the following highlighted, boxed statement 'Seretide can help practices to implement the recommendations of the new guidelines and in doing so improve the quality of life for those whose asthma is not well controlled'. Prescribing information for Seretide, Flixotide, Serevent (salmeterol) and Becotide was included on pages 6 and 7 of the supplement. The outside back cover of the supplement was an advertisement for Seretide.

The Panel considered that GlaxoSmithKline was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the document. Given the company's involvement the Panel considered that the supplement was in effect promotional material for GlaxoSmithKline's asthma products. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so. The statement on the front cover 'Supported by an educational grant from Allen & Hanburys' added to this impression. A breach of Clause 10.1 was ruled.

The Panel noted that it was stated that the article would examine the implications of the new asthma guidelines for the management of asthma in primary care, suggesting a comprehensive review of the therapy area. This impression was compounded by the title 'Asthma guidelines in practice – key changes for mild to moderate patients'. The article, however, only detailed the use of GlaxoSmithKline's products and so was misleading in that regard. A breach of Clause 7.2 was ruled.

The Panel also considered, given the way in which the supplement was initiated and produced, that the statement 'Supported by an educational grant from Allen & Hanburys' gave a misleading impression of the company's role in the generation of the supplement. The supplement was promotional material paid for by GlaxoSmithKline. A further breach of Clause 7.2 was thus ruled.

The Panel considered that high standards had not been maintained and that the supplement had not recognised the professional standing of the audience to which it was directed. A breach of Clause 9.1 was ruled.

As a consequence of its ruling in this case the Panel noted that the whole of the supplement needed to comply with the Code. Clause 7, Information, Claims and Comparisons, was particularly relevant. The Panel had not been called upon to consider any particular claims made in the supplement and its lack of comment did not mean that the content of the supplement was acceptable in that regard. The Panel requested that GlaxoSmithKline be advised of its concerns.

**Complaint received** **23 April 2003**

**Case completed** **19 June 2003**

**CASE AUTH/1458/4/03**

# HOSPITAL PHARMACIST v LUNDBECK

## Promotion of Cipralex

**A hospital pharmacist complained about two Cipralex (escitalopram) leavepieces and a journal advertisement issued by Lundbeck. Cipralex was a selective serotonin reuptake inhibitor (SSRI) for the treatment of depression. The claim 'Cipralex is significantly more effective than Cipramil in treating depression' appeared in the first leavepiece on a page headed 'Cipralex Superior efficacy and early symptom relief' and above a graph which compared the change from baseline of Montgomery Asberg Depression Rating Scale (MADRS) scores of Cipralex, Cipramil and placebo. The data was referenced to Gorman *et al* (2002). The graph showed that Cipralex produced a statistically significant reduction in MADRS scores at weeks 1 and 8 compared to Cipramil ($p<0.05$). The complainant stated that the significance referred to was statistical and probably not of a size which could be regarded as clinically significant.**

**The Panel noted that the presentation of the claim now at issue was identical to that considered in Case AUTH/1389/11/02. In the period for Lundbeck to respond to this complaint (Case AUTH/1458/4/03), Lundbeck had accepted the Appeal Board's ruling in Case AUTH/1389/11/02 that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was misleading, in breach of the Code. The Appeal Board had, *inter alia*, considered that the claim was a strong unequivocal claim and as such was not a fair reflection of the data. At week 8 the mean change from baseline in MADRS scores showed a statistically significant benefit for Cipralex compared with Cipramil (OC values) but no difference between the two if LOCF data was used as well. The Panel considered that the matter was covered by the ruling of a breach of the Code made in Case AUTH/1389/11/02; a breach of the Code was thus ruled in the present case.**

**The claim 'Cipralex As effective as an SNRI' appeared as a heading to page 3 of the second leavepiece and above a graph which compared the change from baseline of MADRS scores for Cipralex (10-20mg/day) and venlafaxine XL (Wyeth's product Efexor XL) (75-150mg/day). The data was referenced to Montgomery *et al* (2002). The graph showed that over an eight week period the reduction in MADRS scores for Cipralex and venlafaxine XL were similar. The complainant took issue with the dose of venlafaxine used; he believed that venlafaxine was a serotonin and noradrenaline reuptake inhibitor (SNRI) at doses above 150mg, but that below 150mg the main effect was that of an SSRI. As venlafaxine tended to be used in cases of depression resistant to SSRIs, and at doses of 225mg/day and higher, the claim might conceivably lead practitioners to the conclusion that Cipralex was different to other SSRIs in its efficacy with respect to that of venlafaxine.**

**The Panel noted that the claim in question was based upon the results of a comparative study of Cipralex (n=146) and venlafaxine XL (n=143) in the treatment of depression. Treatment was initiated with 10mg Cipralex or 75mg venlafaxine. The dose of either medicine could be doubled after 2 or 4 weeks of treatment if the investigator considered the clinical response inadequate. The mean daily dose at week 8 was 12.1mg for Cipralex and 95.2mg for venlafaxine XL. The Panel noted that the mean daily dose of venlafaxine XL of 95.2mg meant that the majority of patients received 75mg/day. This did not echo what was seen in practice. IMS data provided by Lundbeck showed that in secondary care 37% of venlafaxine patients received 75mg/day and 39.9% received 150mg/day.**

**The Panel noted that it had no data before it regarding the dose dependent mode of action of venlafaxine. There was no mention of this in the Efexor SPC.**

**Although the Panel had some concerns that the mean daily dose of venlafaxine XL used in Montgomery *et al* was, on average, lower than that of venlafaxine used in practice, the study had allowed doses to be increased to 150mg if the clinical response to 75mg/day had been considered inadequate. The dose regimen used in Montgomery *et al* was not inconsistent with that specified in the Efexor XL summary of product characteristics. On balance the Panel considered that the claim was not misleading with respect to the comparative efficacy of Cipralex and venlafaxine XL. No breaches of the Code were ruled.**

**The statement 'Progression from Cipramil' appeared as the headline in an advertisement in Hospital Pharmacy Europe which referred to the introduction of Cipralex. The complainant noted the use of the word 'significantly' when the significance was statistical, but where the clinicians reading it were likely to infer that the reference was to some clinical superiority.**

**The Panel noted that Hospital Pharmacy Europe was published in the UK and circulated to UK pharmacists. The Panel considered that advertisements in that journal were therefore subject to the UK Code. Although the advertisement in question had been placed by Lundbeck's parent company, Lundbeck in the UK was responsible under the Code for it.**

**The Panel noted that the advertisement included the claim 'Cipralex offers: A significantly greater efficacy compared to citalopram'. The advertisement also included the claim that compared to citalopram Cipralex offered significantly earlier symptom relief. The complainant had not stated to which use of the word significantly he objected but the Panel considered that his use of the phrase 'Here again …' implied that his complaint related to the claim for greater efficacy as in the above. The Panel noted its comments above and considered that the matter was covered by the ruling of a breach of the Code made in Case AUTH/1389/11/02; a breach of the Code was thus ruled in this case.**

A hospital pharmacist complained about the promotion of Cipralex (escitalopram) by Lundbeck Ltd. The items at issue were two leavepieces (refs

0702/ESC/525/035(889) and 0203/ESC/525/069(995)) and an advertisement in Hospital Pharmacy Europe.

When writing to Lundbeck the Authority invited it to respond to the allegations in relation to Clauses 7.2, 7.3, and 7.4 of the Code and noted similarities between this complaint and Cases AUTH/1389/11/02 and AUTH/1428/3/03.

Paragraph 5.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that if a complaint concerned matters closely similar to one which had been the subject of a previous adjudication, it might be allowed to proceed at the discretion of the Director if new evidence was adduced by the complainant or if the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which was not the subject of appeal to the Code of Practice Appeal Board.

The current complaint, Case AUTH/1458/4/03 was received after the Appeal Board had considered Case AUTH/1389/1/02 but before Lundbeck had returned its form of undertaking and assurance in acceptance of the Appeal Board's rulings. Case AUTH/1428/3/03 did not go to appeal. The Director decided that the current case, Case AUTH/1458/4/03, should thus proceed.

### 1 'Cipralex is significantly more effective than Cipramil in treating depression'

This claim appeared in the leavepiece (ref 0702/ESC/525/035(889)) on a page headed 'Cipralex Superior efficacy and early symptom relief' and above a graph which compared the change from baseline of Montgomery Asberg Depression Rating Scale (MADRS) scores of Cipralex, Cipramil and placebo. The data was referenced to Gorman *et al* (2002). The graph showed that Cipralex produced a statistically significant reduction in MADRS scores at weeks 1 and 8 compared to Cipramil ($p<0.05$).

#### COMPLAINT

The complainant stated that the significance referred to was statistical and probably not of a size which could be regarded as clinically significant.

#### RESPONSE

Lundbeck stated that the individual studies conducted as part of the clinical programme for the registration of Cipralex were not powered to determine a difference between active compounds but to observe the benefits of escitalopram over placebo. Cipramil (citalopram) was included in the studies as an active reference compound to validate the studies. The placebo response in depression studies could be very large (up to 50% of patients responding to placebo); therefore it was important to include a compound with known antidepressant activity in the studies to benchmark the placebo response and the response of the compound under investigation. In order to assess if the consistent differences between active medicine, in favour of escitalopram, observed in the individual studies were significant, and to permit sub-analysis requiring a larger sample size from similar studies, the findings were entered into a pooled analysis (Gorman *et al*) which was cited in substantiation of the claim at issue. A statistically significant benefit was observed for escitalopram over citalopram in terms of onset of symptom relief and overall magnitude of clinical effects as measured by the MADRS score. The analysis of the data showed that there were statistically significant benefits in favour of escitalopram over citalopram for MADRS change from baseline using both observed cases (OC) (weeks 1 and 8) and last observation carried forward (LOCF) (weeks 1 and 6) methodologies.

Lundbeck noted that the improvement in MADRS points score for citalopram over placebo at week 8 was 2.3 points (OC) and 1.9 points (LOCF). Treatment with escitalopram produced an improvement compared to placebo of 3.3 points (OC) and 2.6 points (LOCF). Citalopram was an effective and well-established antidepressant that was widely recommended by health professionals. There was no doubt that citalopram produced both statistically and clinically significantly improvements compared to placebo. The proportionate improvement of escitalopram over citalopram in comparison to placebo for OC was 43%, and for LOCF it was 37%. Such a degree of improvement over an established antidepressant must be considered both statistically and clinically relevant.

A further measure of a clinically relevant difference was the proportion of responders, ie the proportion of patients in whom baseline MADRS scores decreased by 50% or more at any point in the study. In the pooled analysis 59.3%, 53.4% and 41.2% of escitalopram, citalopram and placebo treated patients respectively were considered to be responders. Although only the significance values compared to placebo were included in the publication of the pooled analysis, escitalopram was also statistically significantly superior to citalopram for this parameter ($p<0.05$, data on file).

Lundbeck stated that statistical significance was a confirmation of the validity of the clinically relevant end points used in the studies (such as a reduction in MADRS score and responder rates) and Lundbeck would assert that the significant results in the pooled analysis were both statistically and clinically meaningful.

As noted, this claim was similar to one that had been ruled on (Case AUTH 1389/11/02) and Lundbeck noted that it had undertaken in that case that it would not be using the claim 'Cipralex is significantly more effective than Cipramil in treating depression' in the future.

#### PANEL RULING

The Panel noted that the presentation of the claim now at issue was identical to that considered in Case AUTH/1389/11/02. Since this complaint (Case AUTH/1458/4/03) had been received, but before Lundbeck had responded to it, Lundbeck had

accepted the Appeal Board's ruling in Case AUTH/1389/11/02 that the claim 'Cipralex is significantly more effective than Cipramil in treating depression' was misleading, in breach of Clause 7.2 of the Code. The Appeal Board had, *inter alia*, considered that the claim was a strong unequivocal claim and as such was not a fair reflection of the data. At week 8 the mean change from baseline in MADRS scores showed a statistically significant benefit for Cipralex compared with Cipramil (OC values) but no difference between the two if LOCF data was used as well.

The Panel considered that the matter was covered by the ruling of a breach of Clause 7.2 of the Code made in Case AUTH/1389/11/02; a breach of Clause 7.2 was thus ruled in the present case.

### 2 Claim 'Cipralex As effective as an SNRI'

This claim appeared as a heading to page 3 of the leavepiece (ref 0203/ESC/525/069(995)) and above a graph which compared the change from baseline of MADRS scores for Cipralex (10-20mg/day) and venlafaxine XL (Wyeth's product Efexor XL) (75-150mg/day). The data was referenced to Montgomery *et al* (2002). The graph showed that over an eight week period the reduction in MADRS scores for Cipralex and venlafaxine XL were similar.

### COMPLAINT

The complainant stated that the data presented related to a trial of Cipralex versus venlafaxine, in which they performed indistinguishably. The difficulty lay in the doses used; the complainant believed that venlafaxine was a serotonin and noradrenaline reuptake inhibitor (SNRI) at doses above 150mg, but that below 150mg the main effect was of a selective serotonin reuptake inhibitor (SSRI). As venlafaxine tended to be used in cases of depression resistant to SSRIs, and at doses of 225mg/day and higher, the claim might conceivably lead practitioners to the conclusion that Cipralex was different to other SSRIs in its efficacy with respect to that of venlafaxine.

### RESPONSE

Lundbeck noted that the complainant had stated that the data presented and referenced to Montgomery *et al* showed that '[venlafaxine and escitalopram] performed indistinguishably' and so the claim above was endorsed by the data. The complainant then went on to state that he believed that venlafaxine was only an SNRI at doses above 150mg.

Lundbeck noted that in such reference sources as Martindale, MIMS and the BNF, venlafaxine was described as an 'SNRI' or '5HT/noradrenaline reuptake inhibitor' as compared to escitalopram or other SSRIs (eg fluoxetine, paroxetine) which were described solely as SSRIs. There was no mention of differential primary mode of antidepressant action dependent on dosage in these references or in the prescribing information for venlafaxine. As to the complainant's second point that venlafaxine tended to be prescribed at doses of 225mg or higher, Lundbeck provided IMS data which it stated showed that around 80% of patients were treated in secondary care with doses of venlafaxine only up to 150mg/day. This was where patients with treatment resistant depression were most likely to be managed. The study compared venlafaxine 75-150mg/day and escitalopram 10-20mg/day and so its results were relevant to a large number of prescribers. The information presented in the leavepiece was factual, not misleading and not in breach of the Code.

### PANEL RULING

The Efexor XL (venlafaxine XL) summary of product characteristics (SPC) stated that the recommended dose was 75mg/day. If after two weeks further clinical improvement was required, the dose might be increased to 150mg/day. If needed, the dose could further be increased up to 225mg once daily. Dose increments should be made at intervals of approximately two weeks or more, but not less than 4 days. Antidepressant activity with the 75mg dose was observed after 2 weeks' treatment. Efexor XL was supplied as modified release capsules of 75mg or 150mg. The Efexor (venlafaxine) SPC showed that the dosage regimen for that product differed from Efexor XL. Efexor had the same usual starting dose, 75mg/day, in two divided doses, but physicians should wait for 'several weeks' before increasing it to 150mg/day should further clinical benefit be required. In severely depressed or hospitalised patients a starting dose of 150mg/day could be given and increased by up to 75mg every two to three days depending on response, to a maximum recommended dose of 375mg/day. The IMS data provided by Lundbeck showed that in secondary care 37% of venlafaxine treated patients received 75mg/day and 39.9% received 150mg/day but did not distinguish between venlafaxine and venlafaxine XL.

The Cipralex SPC stated that for major depressive episodes the usual dosage was 10mg daily. Depending on individual patient response, the dose might be increased to a maximum of 20mg daily.

The Panel noted that the claim in question was based upon the results of Montgomery *et al*, a comparative study of Cipralex (n=146) and venlafaxine XL (n=143) in the treatment of depression. Treatment was initiated with 10mg Cipralex or 75mg venlafaxine. The dose of either medicine could be doubled after 2 or 4 weeks of treatment if the investigator considered the clinical response inadequate. The mean daily dose at week 8 was 12.1mg for Cipralex and 95.2mg for venlafaxine XL. The Panel noted that the mean daily dose of venlafaxine XL of 95.2mg meant that the majority of patients received 75mg/day. This did not echo what was seen in practice with venlafaxine as shown by the IMS data provided by Lundbeck.

The Panel noted that in this case, Case AUTH/1458/4/03, it had no data before it regarding the dose dependent mode of action of venlafaxine. There was no mention of this in the Efexor SPC.

Although the Panel had some concerns that the mean daily dose of venlafaxine XL used in Montgomery *et al* was, on average, lower than that of venlafaxine

used in practice, the study had allowed doses to be increased to 150mg if the clinical response to 75mg/day had been considered inadequate. The dose regimen used in Montgomery *et al* was not inconsistent with that specified in the Efexor XL SPC. On balance the Panel considered that the claim was not misleading with respect to the comparative efficacy of Cipralex and venlafaxine XL. No breaches of Clauses 7.2, 7.3 and 7.4 of the Code were ruled.

### 3 'Progression from Cipramil' (Hospital Pharmacy Europe)

This statement appeared as the headline in the advertisement which referred to the introduction of Cipralex.

#### COMPLAINT

The complainant noted, here again, the use of the word 'significantly' when the significance was statistical, but where the clinicians reading it were likely to infer that the reference was to some clinical superiority. Nor would such an inference be unreasonable; to present them with the results of statistical tests, where useful clinical data were expected, might be construed as misleading.

#### RESPONSE

Lundbeck stated that it had never placed an advertisement in the journal Hospital Pharmacy Europe. From the correspondence Lundbeck assumed the complaint related to the use of the word 'significant' in relation to the effectiveness of escitalopram compared to citalopram. Lundbeck had discussed this under point 1 above and had indicated that Lundbeck would not be using a similar claim in the future.

In response to a request for further information Lundbeck repeated that it had not placed the advertisement; the company had only been made aware of it by this complaint. The advertisement was placed by Lundbeck's International Marketing Department based in Copenhagen, Denmark, the company's corporate headquarters.

The journal, Hospital Pharmacy Europe, was published by Campden Publishing Limited, London, and circulated to a number of named pharmacists with a 25% distribution in the UK and EU circulation and also Switzerland and Norway.

Lundbeck noted some deficiencies in the advertisement. The product name was not accompanied by the inverted black triangle; the cost and the legal category 'POM' were missing from the prescribing information.

Lundbeck stated that this was an international advertisement placed independently by its parent company in an international journal with 75% distribution to non-UK audiences. Having discussed the issue with its parent company, the parent company failed to understand why an international advertisement should be subject to the UK Code especially as the vast majority of the circulation was outside the UK. Lundbeck International had, however, agreed to discuss the content and layout of future advertisements with Lundbeck in the UK.

#### PANEL RULING

The Panel noted that the first issue to be decided was whether the advertisement was subject to the UK Code. The supplementary information to Clause 1.1 headed 'Journals with an International Distribution' stated that 'International journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience. It is helpful in these circumstances to indicate that the information in the advertisement is consistent with the UK marketing authorization'.

The advertisement had appeared in the journal Hospital Pharmacy Europe. The journal was published in the UK and circulated to UK pharmacists. The Panel considered that advertisements in that journal were therefore subject to the UK Code.

The advertisement was placed in the journal by the Lundbeck International Marketing Department based in Denmark. The Panel noted that it was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. The advertisement in question had been placed by Lundbeck's parent company. Lundbeck in the UK was therefore responsible under the Code for the advertisement.

The Panel noted that the advertisement included the claim 'Cipralex offers: A significantly greater efficacy compared to citalopram'. The advertisement also included the claim that compared to citalopram Cipralex offered significantly earlier symptom relief. The complainant had not stated to which use of the word significantly he objected but the Panel considered that his use of the phrase 'Here again …' implied that his complaint related to the claim for greater efficacy as in point 1 above. The Panel noted its comments in point 1 above and considered that the matter was covered by the ruling of a breach of Clause 7.2 of the Code made in Case AUTH/1389/11/02; a breach of Clause 7.2 was thus ruled in this case.

**Complaint received** **29 April 2003**

**Case completed** **7 July 2003**

**CASE AUTH/1461/5/03**

# ALCON v PHARMACIA

## Promotion of Xalacom

**Alcon complained that Pharmacia was continuing to describe Xalacom (latanoprost/timolol ophthalmic solution) as new even though the product had been available for more than a year. The materials at issue were journal advertisements, a leavepiece to which was attached a promotional aid and exhibition panels.**

**Alcon stated that Pharmacia launched Xalacom in the UK in October 2001. During November and December 2002 journal advertisements for Xalacom were still appearing with the word 'new'. More recently, at an ophthalmic meeting in March 2003, Pharmacia was still promoting Xalacom with a leavepiece, promotional aid and desk top exhibition panels containing the word 'new'.**

**The Panel noted that Pharmacia accepted that Xalacom material claiming that the product was 'new' used at the ophthalmic meeting was in breach of the Code. The Code specified that the word 'new' could not be used to describe any product which had been available for more than twelve months in the UK. A breach of the Code was ruled.**

**In relation to the advertisements the Panel noted Pharmacia's submission that an advertisement had appeared as the journal had a long lead-time for advertising and was thus unable to change the advertisement. The Panel did not consider that this was an adequate explanation. Pharmacia had wrongly used the word 'new' and a further breach of the Code was ruled.**

Alcon Laboratories (UK) Limited complained about the promotion of Xalacom (latanoprost/timolol ophthalmic solution) by Pharmacia Limited.

The materials at issue were journal advertisements, a leavepiece (ref P6609/8/01 391-0009) to which was attached a nightlight offered as a promotional aid, and representatives' exhibition panels.

### COMPLAINT

Alcon stated that Pharmacia launched Xalacom in the UK in October 2001. During November and December 2002 journal advertisements for Xalacom were still appearing with the word 'new'. On 5 December Alcon emailed Pharmacia to highlight this irregularity and to seek reassurance that advertisements and any other promotional material containing the word 'new' would not be used again. Pharmacia responded on 19 December providing reassurance that it would ensure that all material used was current.

In March 2003, at a North of England ophthalmic meeting attended by two representatives from Pharmacia, Pharmacia was still promoting Xalacom with material (the promotional aid, leavepiece and desk top exhibition panels) containing the word 'new'. Alcon alleged that the material was clearly in breach of Clause 7.11 of the Code. Alcon was particularly concerned because Pharmacia had previously provided reassurance that this would not happen. There appeared to be a breakdown in Pharmacia's internal procedures to allow such incidents to occur.

### RESPONSE

Pharmacia agreed that the material in question was used in error at the North of England ophthalmic meeting, for which it apologised.

Pharmacia's procedure for use of materials involved informing all representatives of current materials to be used in a campaign period. Following a review of this, representatives were now required to confirm that all previous materials had been returned or destroyed. Senior management had briefed all representatives, sales and product managers regarding this change and the importance of adhering to the updated procedure. This matter had also been raised with the representatives concerned and the importance of these processes re-emphasised. Pharmacia acknowledged a breach of Clause 7.11 of the Code.

Pharmacia noted that Alcon had also mentioned that a journal advertisement using the word 'new' had appeared in the later part of 2002. This occurred as the journal had a long lead-time for advertising and was unable to change the advertisement to an updated version, even though it had been informed that this was not a current advertisement. This matter was investigated and action taken to ensure that only current materials were used in advertising. Pharmacia had responded to Alcon stating that it had made the agencies aware that there was combined responsibility to ensure that only current materials appeared in publications. This clarification had resulted in improved communication with the journal, and agencies, and no further incidents. Pharmacia acknowledged this as technically in breach of Clause 7.11 but submitted that it had made all reasonable endeavours at this time to prevent this from happening.

Pharmacia noted that it was now merging with Pfizer Limited. Pfizer had procedures in place already which were very similar to those used by Pharmacia. The companies were confident that there would be no repetition during this integration period.

Pharmacia regretted the issue had occurred and undertook to ensure that this would not happen in the future.

### PANEL RULING

The Panel noted that Pharmacia accepted that Xalacom material claiming that the product was 'new', used at the North of England ophthalmic meeting, was in breach of the Code. The Code specified that the word 'new' could not be used to

describe any product which had been available for more than twelve months in the UK. A breach of Clause 7.11 of the Code was ruled in respect of each item.

In relation to the advertisements the Panel noted Pharmacia's submission that it had made agencies aware that there was combined responsibility to ensure that only current materials appeared in publication. In relation to the Code the Panel noted that Pharmacia alone had to take responsibility for the appearance of the journal advertisements notwithstanding the circumstances. The Panel also noted Pharmacia's submission that an advertisement had appeared as the journal had a long lead-time for advertising and was thus unable to change the advertisement. The Panel did not consider that this was an adequate explanation. The company had known since October 2001 that the word 'new' could be used for one year only and thus had ample time to ensure that sufficient instruction was given about the use of such advertisements and to accommodate the journal's lead time. Pharmacia had wrongly used the word 'new' and a further breach of Clause 7.11 was ruled.

During its consideration of this case the Panel considered that a night light could not be regarded as relevant to the practice of medicine as required by Clause 18.1 in relation to promotional aids offered to members of the medical profession. The Panel asked that its views on the matter be conveyed to Pharmacia.

**Complaint received** **6 May 2003**

**Case completed** **27 June 2003**

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**CASE AUTH/1464/5/03** *NO BREACH OF THE CODE*

# DIRECTOR v SCHERING HEALTH CARE

## Promotion of Levonelle-2

**The Director had received information in a previous complaint that claims in promotional material for Levonelle-2 (levonorgestrel), an emergency contraceptive marketed by Schering Health Care, might contravene the Code. It had been decided that there was no *prima facie* case to answer as the complaint concerned statements in the summary of product characteristics (SPC). As the statement at issue, and closely similar statements, were used in promotional material, not the subject of complaint in the previous case, the Director decided that their use in promotional material should be taken up as a fresh complaint.**

**The items at issue were a leaflet entitled 'A Health Professional's Guide to Emergency Contraception' and an A4 booklet entitled 'Primary Care Education Programme Regular and Emergency Contraception' and subtitled 'Focus on emergency hormonal contraception and pharmacy supply'.**

**Section 5.1, Pharmacodynamic properties, of the Levonelle-2 SPC, included the statement 'It is not effective once the process of implantation has begun'. This statement, or similar statements, appeared in Levonelle-2 promotional items. It had been alleged that there was no evidence to support the statement in the SPC. The Authority invited Schering Health Care to respond in relation to the claims in the Levonelle-2 material.**

**The Panel noted that Section 5.1 of the Levonelle-2 SPC stated that its precise mode of action was unknown. The SPC stated that at the recommended regimen it was thought to work mainly by preventing ovulation and fertilization if the intercourse had taken place in the preovulatory phase, when the likelihood of fertilization was the highest. It might also cause endometrial changes that discouraged implantation. It was not effective once the process of implantation had begun.**

**The Panel noted that additional data provided did not support a role for Levonelle-2 once implantation had occurred.**

**In relation to the leaflet, 'A Health Professional's Guide to Emergency Contraception', the claim 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work'. The claim was taken verbatim from the Levonelle-2 SPC. The Levonelle section within the booklet Primary Care Education Programme Regular and Emergency Contraception' stated that 'Levonelle stops pregnancy before it starts'. It also stated that emergency contraception 'cannot cause an abortion because it does not have an effect if used after implantation of a fertilized egg'.**

**Given the statement in the SPC and the additional data provided, the Panel considered that the relevant statements were not unacceptable. No breach of the Code was ruled in respect of both pieces.**

The present case arose from an earlier complaint which concerned a complaint made by a general practitioner about a statement 'It is not effective once the process of implantation has begun' made in Section 5.1 of the summary of product characteristics (SPC) for Levonelle-2 (levonorgestrel), an emergency contraceptive marketed by Schering Health Care Ltd. Having considered Schering Health Care's comments on the matter, the Director decided that there was no *prima facie* case for Schering Health Care to answer because SPCs were excluded from the application of the Code by virtue of Clause 1.2.

However, in view of the fact that the statement at issue and closely similar statements, were used in promotional material, not the subject of complaint, the Director decided that their use in promotional material should be taken up as a fresh complaint. The matter was taken up with the company in

accordance with Paragraph 5.1 of the Constitution and Procedure.

The items at issue were a leaflet (ref L0111032) entitled 'A Health Professional's Guide to Emergency Contraception'; and an A4 booklet (ref L0011085) entitled 'Primary Care Education Programme Regular and Emergency Contraception' and subtitled 'Focus on emergency hormonal contraception and pharmacy supply'.

## COMPLAINT

Section 5.1, Pharmacodynamic properties, of the Levonelle-2 SPC included the statement 'It is not effective once the process of implantation has begun'. This statement, or similar statements, appeared in Levonelle-2 promotional items. It had been alleged that there was no evidence to support the statement in the SPC. The Authority invited Schering Health Care to respond in relation to the claims in the Levonelle-2 material with regard to Clauses 7.2 and 7.4 of the Code.

## RESPONSE

Schering Health Care stated that the information provided within the leaflet 'A Health Professional's Guide to Emergency Hormonal Contraception', together with the similar wording used in the pharmacist training materials, that Levonelle-2 'Is not effective once the process of implantation has begun', was substantiated by the SPC. Schering Health Care submitted that it thus fulfilled the requirements of both Clauses 7.2 and 7.4 of the Code.

As stated within the SPC and the other materials, the mechanisms of action of Levonelle-2 were not fully understood, although it was recognised that its actions depended upon the stage of the menstrual cycle at application. Schering Health Care submitted that the following information supported the SPC statement at issue.

The WHO publication on Postovulatory Methods of Fertility Regulation, The Lancet (1998), showed that Levonelle exhibited an inverse relationship between efficacy and the length of time from intercourse to treatment, namely that pregnancy rates increased with time. If the action of Levonelle was in any way to disrupt an implanted zygote, the efficacy would be maintained or even increased with increased time between intercourse and treatment. Ho and Kwan (1993) found the same trend. This was a strong indication of the pre-fertilization mode of action of Levonelle and did not support the existence of the mechanism of any action after fertilization.

Further indirect evidence, which indicated that Levonelle worked prior to fertilization and thus implantation, could be found in the literature. Croxatto *et al* (2001) reviewed the mode of action of levonorgestrel and found that its administration during the luteal phase was not followed either by changes in cycle length, endometrial morphology or hormone levels. Durand *et al* (2001) did not show significant alterations in serum hormone levels during the luteal phase when Levonelle-2 was administered the day after follicular rupture and their results similarly did not support any anti-implantation effect of the preparation. Marions *et al* (2002) found that the postovulatory treatment with two doses of 75mcg levonorgestrel, 12 hours apart, resulted in a cycle pattern, hormone levels and endometrial development similar to those of the untreated cycle.

It was recognised that progesterone was necessary to maintain pregnancy and treatment of threatened miscarriage was with progesterone or progestogens. This again lent support to the premise that levonorgestrel would not act to disrupt an established pregnancy, but was conversely more likely to maintain it.

Finally, in the judicial review brought by The Society for the Protection of the Unborn Child (SPUC) against the Department of Health (where Schering Health Care was the second defendant), The Honourable Mr Justice Munby stated in his judgement that 'what is … clear … is that

i) The morning after pill … cannot cause a fertilized egg which is implanted to de-implant – that is, it cannot work after the process of implantation is complete.

ii) The morning after pill, if it is to be effective, has in any event to be taken at a time – not later than 72 hours after intercourse – when implantation will not have begun'.

## PANEL RULING

The Panel noted that Section 5.1 of the Levonelle-2 SPC stated that its precise mode of action was unknown. The SPC stated that at the recommended regimen it was thought to work mainly by preventing ovulation and fertilization if the intercourse had taken place in the preovulatory phase, when the likelihood of fertilization was the highest. It might also cause endometrial changes that discouraged implantation. It was not effective once the process of implantation had begun.

The Panel noted the additional data provided did not support a role for Levonelle-2 once implantation had occurred. The WHO Task Force on Postovulatory Methods of Fertility Regulation found that efficacy was significantly and inversely related to time since intercourse. Ho and Kwan found that pregnancy rates in patients who took the medicine within 24 hours were lower than those in patients who took it later. However, the study authors stated that probably because of the small patient numbers the difference was not statistically significant.

Croxatto *et al* reviewed research to understand how emergency contraception methods acted to prevent pregnancy. The authors stated that the fact than an entity or a process was altered by the treatment did not necessarily mean that it explained how pregnancy was prevented in real life situations. One of the complexities that researchers would have to deal with to find a thorough answer was that the mechanism might differ for the same emergency contraception treatment depending upon when it was given relative to the time of intercourse and time of ovulation. It was noted that there were few studies designed to look at the mechanism of action of levonorgestrel in emergency contraception and its exact mode of action

was unknown. Various studies were discussed; Moggia *et al* (1974) proposed that the contraceptive effect was due to changes in the endometrium that prevented transplantation. Similar comments were made in relation to Wang *et al* (1998) wherein in relation to the endometrium, preovulatory administration factors believed to be critical for implantation were changed in ways likely to alter endometrial receptivity. When appraising the possible modes of action Croxatto *et al* noted the inverse relationship between the intercourse-treatment interval and efficacy and stated that this lent support to a significant role of pre-fertilization mechanisms in its contraceptive effectiveness.

Durand *et al* assessed the mechanism of action of levonorgestrel stating that all emergency contraceptive medicines methods in use acted before implantation. The study did not support an anti-implantation contraceptive effect.

The Panel noted the statement in the Levonelle-2 SPC that the precise mechanism of action was unknown. This was reflected in the additional data provided.

In relation to the leaflet, 'A Health Professional's Guide to Emergency Contraception', the claim 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work'. The claim was taken verbatim from the Levonelle-2 SPC. The preceding paragraph in the leaflet described in general terms the mechanism of action of emergency contraception stating that it was 'thought to work mainly by delaying or preventing ovulation and fertilization …. It may also cause endometrial changes that discourage implantation'. This was referenced to the Levonelle SPC. The Levonelle section within the booklet Primary Care Education Programme Regular and Emergency Contraception' stated that 'Levonelle stops pregnancy before it starts' and described three specific modes of action. It stated that emergency contraception 'cannot cause an abortion because it does not have an effect if used after implantation of a fertilized egg'.

Given the statement in the SPC and the additional data provided, the Panel considered that the relevant statement in the booklet was not unacceptable. No breach of Clauses 7.2 and 7.4 was ruled in respect of both pieces.

**Proceedings commenced 13 May 2003**

**Case completed 10 June 2003**

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**CASE AUTH/1466/5/03**

# LILLY v PIERRE FABRE

## Navelbine leavepiece

**Lilly complained about references to its product Gemzar (gemcitabine) in a leavepiece for Navelbine (vinorelbine) issued by Pierre Fabre. The leavepiece referred to the treatment of non-small cell lung cancer and beneath the heading 'Chemoradiotherapy' detailed the results of a phase II randomised study (Vokes 2000, Lynch 1999). A table gave the results for response to, *inter alia*, GEM-CDDP* (gemcitabine-cisplatin) in relation to response rates after induction therapy and after concomitant radiotherapy. The asterisk referred to a footnote which stated '*gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC [summary of product characteristics])'.**

**Lilly noted that the Gemzar SPC stated: 'Gemcitabine should not be used concurrently with radical radiotherapy (see 'Special warnings and special precautions for use')'. The leavepiece incorrectly quoted the SPC and gave a false interpretation of it which could mislead in two ways: firstly, use of the word 'not' in uppercase implied emphasis that was not in the SPC; secondly, by omitting the word 'concurrently' the piece failed to make the distinction between concurrent use (gemcitabine given together with, or ≤ 7 days apart from radical radiotherapy) and sequential use (given > 7 days apart). Use of chemotherapy 'with' radiotherapy could mean either of these.**

**Whilst Lilly agreed that the *concurrent* use of gemcitabine and radiotherapy should only take place within the context of controlled clinical trials, the SPC stated that the data on *sequential* use did not indicate any enhanced toxicity to preclude use. Hence by omitting the word concurrently, the leavepiece could imply that gemcitabine and radiotherapy could not be given together either concurrently or sequentially.**

**The Panel considered that the statement at issue was not a fair reflection of the SPC. It was not sufficiently clear with regard to the sequential use permitted in the SPC and was misleading in this regard. The Panel noted that the word 'concurrently' did not appear in the leavepiece. The Panel ruled a breach of the Code.**

**Lilly noted that the statement at issue was linked by an asterisk to the information in the table above it. The inference of the asterisk was that the statement was supported by Vokes and Lynch which had been referenced. Vokes contained no such statement; a recent publication of the final results of this trial stated: 'Four cycles of gemcitabine, vinorelbine, or paclitaxel in combination with cisplatin can be administered at these doses and schedules'. Lynch included a commentary on the Vokes study and confirmed the use of gemcitabine with radiotherapy. Lilly alleged that there was no clear justification for the use of this data with the asterisked statement in this way, other than to mislead.**

**The Panel considered that the leavepiece was clear that the statement at issue originated from the Gemzar SPC and not from Vokes or Lynch. The Panel thus ruled no breach of the Code.**

Eli Lilly and Company Limited complained about a leavepiece (ref PF080) for Navelbine (vinorelbine) issued by Pierre Fabre Ltd. Lilly supplied Gemzar (gemcitabine).

The leavepiece referred to the treatment of non-small cell lung cancer. Page 3 included the heading 'Chemoradiotherapy' beneath which the results of a phase II randomised study (Vokes 2000, Lynch 1999) were given. A table gave the results for response to NVB-CDDP (Navelbine-cisplatin), PTX-CDDP (paclitaxel-cisplatin) and GEM-CDDP* (gemcitabine-cisplatin) in relation to response rates after induction therapy and after concomitant radiotherapy. Details of median and 1 year survival were also given. The explanation for the asterisk next to 'GEM-CDDP' was given beneath the table as a footnote which stated '*gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC)'.

### 1 Statement: '*gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC)'

#### COMPLAINT

Lilly noted that the Gemzar summary of product characteristics (SPC) stated: 'Gemcitabine should not be used concurrently with radical radiotherapy (see 'Special warnings and special precautions for use')'. The leavepiece incorrectly quoted the SPC by changing the word 'not' to upper case and omitting the word 'concurrently'. This change in the wording gave a false interpretation of the SPC and could mislead the health professional in two ways: firstly, use of the word 'not' in uppercase implied emphasis that was clearly not evident in the SPC; secondly, by omitting the word 'concurrently' the piece failed to make the distinction between the different ways that gemcitabine was given with radiotherapy in the treatment of lung cancer. As described in the SPC the use of gemcitabine 'with radiotherapy' was separated into two situations ie concurrent use (gemcitabine given together with, or ≤ 7 days apart from radical radiotherapy) or sequential use (given > 7 days apart). Use of chemotherapy 'with' radiotherapy could be interpreted in these two ways.

Whilst Lilly agreed that the *concurrent* use of gemcitabine and radiotherapy should only take place within the context of controlled clinical trials, the SPC stated that the data on *sequential* use did not indicate any enhanced toxicity to preclude use. Hence by omitting the word concurrently, the leavepiece could imply that gemcitabine and radiotherapy could not be given together either concurrently or sequentially.

Lilly stated that using the quote as it was in the leavepiece allowed a false conclusion to be drawn and misled the health professional in their thinking that gemcitabine could not be given sequentially with radical radiotherapy when the SPC stated that it could. Clearly the statement: '*gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC)' was misleading in itself and did not reflect the overall meaning of the SPC. A breach of Clause 7.2 of the Code was alleged.

#### RESPONSE

Pierre Fabre stated that the use of radical radiotherapy in the presence of gemcitabine was associated with unacceptably severe and potentially life-threatening toxicity. The warning statement regarding the use of gemcitabine in association with radical radiotherapy appeared in Section 4.2 'Posology and method of administration' of the Gemzar SPC and should therefore be considered as an instruction to any potential prescriber of gemcitabine. Further warnings appeared in Section 4.4 'Special warnings and precautions for use'.

It was clear from Section 4.4 of the gemcitabine SPC that Lilly had previously submitted the data from clinical trials in which these two technologies had been used at the same time (B9E-MC-JHDP, Vokes *et al*) to the Medicines and Healthcare products Regulatory Agency (MHRA) (formerly the Medicines Control Agency) for the partial review of the text in November 2002. It was very important to note that the UK regulatory authority had not changed or amended the important instruction in the posology section of the SPC regarding the warnings of simultaneous use of gemcitabine with radical radiotherapy. It remained a fact that radical radiotherapy must not be used when gemcitabine was present in the patient.

Pierre Fabre stated that it should be very clear from the warnings in Section 4.2 of the SPC that gemcitabine must not be used with or at the same time as radical radiotherapy. The terms 'concurrent' and 'sequential' were only later introduced in Section 4.4 of the SPC, ie after the primary warning in Section 4.2. It was clear that this terminology was not required to understand the warning in Section 4.2. It should also be noted that these terms had to be further qualified in respect to any subsequent treatment using gemcitabine. A wash-out period of 7 or more days was specified in the SPC so that any residual traces of gemcitabine were completely eliminated from the patient before any radiotherapy might be attempted. In other words, radical radiotherapy might only be attempted in the absence of, or without gemcitabine.

The Gemzar SPC, Section 4.2, Posology and method of administration, stated: 'Gemcitabine should not be used concurrently with radical radiotherapy (see 'Special warnings and special precautions for use')'. The leavepiece stated 'gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC)'. The asterisk to alert readers of the leavepiece to this fact was placed immediately adjacent to the only reference to a regimen of gemcitabine plus cisplatin. Although this was within a table of results from a clinical study, the asterisk was not referenced to the study or the study results or study conclusions.

The statement was not a direct quote from the Gemzar SPC as alleged but was clearly referenced to it. By not using quotation marks, this statement need not necessarily contain all of the same words in the

same order, but the meaning should be the same as the SPC. Pierre Fabre was confident that the substitution of the words, 'used concurrently with radical radiotherapy' by 'given with radical radiotherapy' had no impact on the overall meaning of these two statements. In this context the key words were concurrently (happening or existing at the same time, acting in union or conjunction, harmonious, contributing to the same effect) and with (in or in the company of or the relation of accompaniment, association, co-operation, harmoniousness).

Both statements drew the reader to the same conclusion that gemcitabine might not be administered at the same time as radical radiotherapy. The consequences of using these two treatments together were severe and potentially life-threatening toxicity. This warning in the SPC appeared in posology and should be considered as an instruction from the licensing authority. The emphasis on NOT was appropriate to alert the reader to the importance and seriousness of this warning.

In summary, Pierre Fabre was satisfied that the meaning of the statement was clear and in accordance with the warnings and posology specified in the SPC. In this respect, the alleged breach of Clause 7.2 was unfounded.

**PANEL RULING**

The Panel noted that the statement at issue was not presented as a quotation in the leavepiece. Section 4.2 of the Gemzar SPC stated 'Radical radiotherapy: Gemcitabine should not be used concurrently with radical radiotherapy (see 'Special warnings and special precautions for use [section 4.4]')'. Section 4.4 gave further details in sections headed 'Concurrent (given together or ≤ 7 days apart)' which referred to a single trial which showed significant toxicity and 'Sequential (given > 7 days apart)' which stated that the data suggested that gemcitabine could be started after the acute effects of radiation had been resolved or at least one week after radiation.

The Panel considered that the statement at issue was not a fair reflection of the SPC. It was not sufficiently clear with regard to the sequential use permitted in the SPC and was misleading in this regard. The Panel noted that the word 'concurrently' did not appear in the leavepiece. The Panel ruled a breach of Clause 7.2 of the Code.

**2 Inference that the statement 'gemcitabine should NOT be given with radical radiotherapy (gemcitabine SPC)' was supported by Vokes (2000) and Lynch (1999)**

**COMPLAINT**

Lilly noted that the statement at issue in point 1 was linked by an asterisk to the information in the table above it. This table displayed data from a trial where gemcitabine and cisplatin were given concurrently and sequentially with radiotherapy. The inference of the asterisk was that the statement was supported by Vokes and Lynch which had been referenced. ie that the clinical papers provided supportive evidence to preclude the use of gemcitabine with radiotherapy.

Vokes contained no such statement. A recent publication of the final results of this trial stated: 'Four cycles of gemcitabine, vinorelbine, or paclitaxel in combination with cisplatin can be administered at these doses and schedules'. Lynch included a commentary on the Vokes study and confirmed the use of gemcitabine with radiotherapy stating: 'Importantly, this study showed that gemcitabine could be given safely with radiation with an acceptable rate of oesophagitis and pneumonitis'.

Lilly alleged that there was no clear justification for the use of this data with the asterisked statement in this way, other than to mislead. Since the statement was ascribed to two authors whose meaning was clearly in contrast to the inferred meaning in the leavepiece Lilly alleged a breach of Clause 11.4 of the Code.

**RESPONSE**

Pierre Fabre stated that the asterisk was placed immediately adjacent to the only reference to a regimen of gemcitabine and cisplatin (GEM-CDDP). Although this was within a table of results from a clinical study, the asterisk was not referenced to the study, its results or its conclusions. There was no attempt to suggest that the statement was supported by these clinical papers. The source of the information was clearly indicated as the gemcitabine SPC. The alleged breach of Clause 11.4 was unfounded.

**PANEL RULING**

The Panel considered that the leavepiece was clear that the statement at issue in point 1 originated from the Gemzar SPC and not from Vokes or Lynch. The Panel thus ruled no breach of Clause 11.4 of the Code.

**Complaint received** **20 May 2003**

**Case completed** **9 July 2003**

**CASE AUTH/1467/5/03**

# MEDIA/DIRECTOR v NOVARTIS

## Promotion of Elidel

**An article entitled 'Pimecrolimus cream for atopic dermatitis' in the Drug and Therapeutics Bulletin was critical of the promotion of Elidel (pimecrolimus) cream by Novartis. In accordance with established procedure, the matter was taken up by the Director as a complaint under the Code.**

**The article criticised claims that 'When used at the first sign of redness and itch' pimecrolimus cream was 'the only treatment clinically proven to prevent progression to flare' and that 'many people using it have eliminated or reduced steroid use'. The article noted that there was no study comparing Elidel with the usual first-line therapy for mild or moderate atopic dermatitis which was stated to be a mild topical corticosteroid. The article also stated that waiting for atopic dermatitis to become severe or very severe was not a conventional way of managing a flare. The article also criticised the use of a photograph of a child aged under two given that the product was not authorized for use in children under the age of two.**

**Novartis provided two advertisements in its response. The first advertisement which contained the claims at issue, featured a woman holding a young child beneath the heading 'The suffering can stop here'. Adjacent text discussed Elidel cream stating that it could help overcome some of the limitations of conventional therapies. Readers could reassure their patients that no systemic side effects had been observed with Elidel cream. A strapline read 'New eczema control without steroid worries'.**

**The Panel considered that the advertisement highlighted that Elidel was a non-steroidal treatment for atopic eczema; it did not compare the efficacy of Elidel with conventional treatment as implied by the article. No breaches of the Code were ruled.**

**The second advertisement featured a picture of a young child, asleep. Adjacent text began 'Tiny tot Little dot Itching day and night …'. The Panel noted that Elidel cream was not for use in children under two years of age (ref summary of product characteristics (SPC)).**

**Although the child in the picture was in fact aged two years and five months the Panel considered that this was not made sufficiently clear to the reader. The impression that he was less than two was compounded by the adjacent text 'Tiny tot Little dot …' and in that regard the advertisement was misleading and inconsistent with the SPC as alleged. Breaches of the Code were ruled.**

An article entitled 'Pimecrolimus cream for atopic dermatitis' in the Drug and Therapeutics Bulletin, May 2003, was critical of the promotion of Elidel (pimecrolimus) cream by Novartis Pharmaceuticals UK Ltd. In accordance with established procedure, the matter was taken up by the Director as a complaint under the Code.

### COMPLAINT

The article criticised claims that 'When used at the first sign of redness and itch' pimecrolimus cream was 'the only treatment clinically proven to prevent progression to flare' and that 'many people using it have eliminated or reduced steroid use'. The article noted that there was no study comparing Elidel with the usual first-line therapy for mild or moderate atopic dermatitis which was stated to be a mild topical corticosteroid. The article also stated that waiting for atopic dermatitis to become severe or very severe was not a conventional way of managing a flare. The article also criticised the use of a photograph of a child aged under two given that the product was not authorized for use in children under the age of two.

When writing to Novartis, the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.3, 7.4 and 7.8 of the Code.

### RESPONSE

Novartis stated that the Drug and Therapeutics Bulletin was produced by the Consumer's Association and represented an independent review of clinical data. No promotional materials were requested or provided to the Bulletin as part of its review of Elidel and the negative comments in the final paragraph appeared to be directed at only one advertisement for the product.

The statements in the abstract of the review 'when used at the first sign of redness and itch pimecrolimus cream is the only treatment clinically proven to prevent progression to flare' and many people using it have 'eliminated or reduced steroid use' did not appear to have been presented as a complaint about promotional copy. However, these two claims appeared in an earlier, now superseded, advertisement for Elidel.

The comments about the presence or otherwise of a study comparing Elidel treatment with corticosteroids and about the management of atopic dermatitis generally, were clinical observations rather than criticisms of specific promotional items.

*Use of a photograph of a child under the age of two*

The statement in the Bulletin that the child in the Elidel advertisement was clearly under two was wrong. The child in the photograph was aged 2 years and 5 months at the time the photograph was taken; this fact was verified as part of the company's pre-selection for the models used in the advertisements to ensure compliance with the licence. A copy of the child's birth certificate was provided. It was never Novartis' intention to mislead or imply the product was authorized for use in children under two. As soon as Novartis was notified of this potential area of concern by the Medicines and Healthcare products Regulatory Agency (MHRA), the advertisement was immediately withdrawn. In addition, this image had

been removed from all Elidel materials and a corrective statement published in all journals where the advertisement appeared. The published corrective statement reiterated that Elidel was licensed for patients of 2 years and above. Novartis stressed that these actions had been taken in advance of the publication of the Drug and Therapeutics Bulletin article.

***When used at the first sign of redness and itch:***

The first signs of atopic dermatitis becoming active were generally an increase in itching and/or redness. It was at this very early stage in the potential life cycle of a flare, but before the flare had developed, that treatment with Elidel cream had been shown to be most effective in preventing relapses (development of flares).

Early intervention in the management of atopic dermatitis (eczema) was the basis for the design of the key phase III studies for Elidel. In these studies, both active and control study populations were given emollients to maintain good skin care. At the first sign of a potential relapse (increased redness and/or itch), patients used the study medication to which they had been randomly allocated ie Elidel or vehicle. If, despite these interventions the flare continued to develop, patients received topical corticosteroids. When the licence for the product was granted it included as an indication the 'intermittent long-term treatment for prevention of progression to flare' as this had been clinically proven in these phase III studies.

***The only treatment clinically proven to prevent progression to flare***

Novartis was not aware of any other products licensed specifically for the prevention of progression to flare in atopic dermatitis. The positioning of Elidel after emollients as an early intervention when the first signs of the disease becoming active appeared and ahead of the need to use steroids, presented a new approach and was the basis of the clinical development process. The summaries in the Drug and Therapeutics Bulletin outlined clinical data for the prevention of flares with Elidel in children and adults.

***Many people using it have eliminated or reduced steroid use***

Two key studies in the Elidel development programme evaluated the efficacy and safety of pimecrolimus in adults, adolescents and children with mild to moderate atopic dermatitis and looked at the need for subsequent topical steroid use.

In Meurer *et al* (2002) involving adults over a six month period, almost 50% of the pimecrolimus group did not need to use any corticosteroid throughout the study. Time to first relapse (flare) was five times longer in the pimecrolimus group compared with control. In Wahn *et al* (2002) involving children and adolescents over a twelve month period, long-term intermittent use of pimecrolimus reduced or eliminated the need for corticosteroids and prevented relapses in more than half of those treated compared to control.

Novartis considered that the following points were clinical observations rather than criticisms but provided data for the Authority's information.

***No study comparing Elidel with usual first-line therapy (a mild corticosteroid)***

Because Elidel and topical steroids were used at different stages of flare management in atopic dermatitis and because of label restrictions (topical corticosteroids were not licensed specifically for long-term prevention) it was considered inappropriate to use even mild corticosteroids as an early intervention in long-term studies in the same way as Elidel. Instead the clinical value of Elidel was assessed as an early intervention in patients with mild to moderate atopic eczema, as a means of preventing the progression of flares before it would routinely be considered appropriate to treat with repeated courses of topical corticosteroids.

Elidel was thus likely to be of greatest value in the management of atopic dermatitis when avoidance or reduction in the use of topical corticosteroids was clinically advisable. This was of particular relevance in young children and in delicate areas of skin where the clinician might wish to minimise the use of corticosteroids.

***Waiting for atopic dermatitis to become severe is not a conventional way of managing flare***

Novartis would not disagree with this statement and would not advocate waiting for the disease to become severe before initiating treatment. Elidel was licensed for mild to moderate atopic dermatitis in patients aged 2 years and over as intermittent long-term treatment for the prevention of progression to flare. In the key studies treatment with Elidel was initiated early (at the first signs of redness and itch). In many patients topical corticosteroids were not needed and early intervention with Elidel prevented flares.

In conclusion, Novartis reiterated that several of the issues mentioned in the Drug and Therapeutics Bulletin article did not represent complaints about Elidel promotional materials but rather an interpretation of the clinical data. Novartis had provided some background information on these areas. In relation to the image of the child in the advertisement, the statement in the Bulletin was wrong but, nevertheless, following discussions with the MHRA, the image was withdrawn from all materials in advance of the publication of the Bulletin.

## PANEL RULING

The Panel noted the Drug and Therapeutics Bulletin article considered the place of pimecrolimus cream in the management of atopic dermatitis. The article noted the company's claims that 'When used at first sign of redness and itch' pimecrolimus cream was 'the only treatment clinically proven to prevent progression to flare' and that many people using it had 'eliminated or reduced steroid use'. The article concluded that in relation to short-term treatment pimecrolimus had not been compared to standard therapy in children, which was brief treatment with a mild or moderately potent topical corticosteroid. The article also concluded that in relation to long-term

intermittent use to prevent progression from early symptoms and signs of atopic dermatitis to flares, Elidel had not been compared with the most appropriate conventional therapy for patients with mild or moderate disease, namely brief treatment with a mild or moderately potent topical corticosteroid commencing before the flare had become severe or very severe.

Novartis provided two advertisements in its response. The first advertisement (ref ELI02000600), which contained the claims at issue, featured a woman holding a young child beneath the heading 'The suffering can stop here'. Adjacent text discussed Elidel cream stating that it could help overcome some of the limitations of conventional therapies. Readers could reassure their patients that no systemic side effects had been observed with Elidel cream. A strapline read 'New eczema control without steroid worries'.

The Panel considered that the advertisement highlighted that Elidel was a non-steroidal treatment for atopic eczema; it did not compare the efficacy of Elidel with conventional treatment as implied by the article. No breach of Clauses 7.2, 7.3, 7.4 and 7.8 were ruled.

The second advertisement featured a picture of a young child, asleep. Adjacent text began 'Tiny tot Little dot Itching day and night …'. The Panel noted that Section 4.1 of the Elidel summary of product characteristics (SPC) stated that it was indicated in patients 'with mild to moderate atopic dermatitis (eczema) aged two years and over …'. Section 4.2, Paediatric patients, read the 'The use of Elidel in patients under 2 years of age is not recommended until further data become available'.

The Panel noted that the child depicted was 2 years and five months. The Panel considered that it was not sufficiently clear to the reader that the child depicted was over two years. The impression that the child was less than 2 was compounded by the adjacent text 'Tiny tot Little dot …' and in that regard the advertisement was misleading and inconsistent with the SPC as alleged. Breaches of Clauses 3.2 and 7.2 were ruled.

**Proceedings commenced 19 May 2003**

**Case completed 11 July 2003**

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**CASE AUTH/1471/5/03**

# HOSPITAL DOCTOR v 3M HEALTH CARE

## Unsolicited email

**A consultant respiratory physician complained about an unsolicited email which he had received from 3M Pharmaceutical. The email stated that he was on a list of people who had expressed an interest in its subject matter although he could not remember doing so.**

**The Panel noted the Code required that email must not be used for promotional purposes except with the prior permission of the recipient. The Panel noted 3M Health Care's submission that the complainant had registered on a 3M website. 3M Health Care did not identify the site at which, according to company records, the complainant had registered his details but provided the registration pages for two respiratory websites.**

**The Panel noted that although the website registration pages told readers that by clicking on a box 3M Pharmaceuticals would 'keep you informed of any updates concerning products and services, and any other offers we feel may be of interest to you. This would be by letter, telephone or e-mail', readers were not provided with sufficient information about the type of information that would be provided. It was not sufficiently clear that readers would receive promotional material. A breach of the Code was ruled. A further breach was ruled as high standards had not been maintained.**

A consultant respiratory physician complained about an unsolicited email which he had received from 3M Pharmaceuticals.

The email at issue stated:

'To [name of doctor] (Respiratory Medicine)

Subject: Our new eDetailing service puts you in control

Prescribing Information

Do you struggle to find the time to see Pharmaceutical Drug Representatives?

eRepresentative, 3M's new eDetailing Service could be the answer. eRepresentative, as you would expect from 3M is a new Innovative method for delivering information at a time and location that fits in with your busy schedule. eRepresentative is a revolutionary new way of detailing which takes place over the internet. A solution combining human interaction and rich digital media product presentation. All you need to participate in an eRepresentative session is a PC linked to the Internet and a telephone. eRepresentative meetings can be scheduled at any time on a weekday between 8.00 – 20.00, when our representative will guide you through the information remotely, using our online multimedia service.

NOTICE:
You are receiving this email because you have opted to receive information from 3M Pharmaceuticals or you have been recommended to us by a friend. If you did not opt in to receive this information then please accept our apologies. We respect your online time and privacy and pledge not to abuse this medium. If

you prefer not to receive further emails of this type from us, please reply by clicking here. If you have been forwarded this message by a friend and wish to subscribe, please reply by clicking here.

PRIVACY:
We use cookies and pixels in order to understand how you interact with the content of our emails. This helps us to understand what you like and what you don't like about our emails. This means that we can offer you more interesting and relevant content in the future. If you do not wish this to happen, please unsubscribe from our list.'

## COMPLAINT

The complainant stated that he had recently received an unsolicited email from 3M Pharmaceuticals claiming that he was on a list of people who had expressed an interest in its subject matter. The complainant had no recollection of any such expression of interest. He received enough emails anyway without extras and strongly objected to being approached in this way.

When writing to 3M Health Care Limited, the Authority asked it to respond in relation to Clauses 9.1 and 9.8 of the Code.

## RESPONSE

3M Health Care was sorry that the complainant was inconvenienced by its email and extended its apologies to him. 3M Health Care appreciated the considerable amount of material physicians received from all sources and in all formats and it was not its intention to add to this burden.

The email was intended to introduce a new eDetailing service to support Aldara (imiquimod) cream, a topical treatment for external genital warts, and to allow the physician to book a demonstration if they so wished. The eDetail would be a combination of human interaction and multi media presentation using a telephone connection and an internet link. A sales representative would telephone the physician at a predetermined time after which a dedicated internet link was established. The sales representative would guide the physician through the detail via the internet browser where visuals and data were displayed to support the discussion that was taking place. This service had not yet been launched and the detail materials were currently going through 3M Health Care's copy approval process.

3M Health Care stated that 549 physicians had received this email. 370 were contacted prior to sending the email and their consent to receive communication in this form was obtained verbally. The remaining 179 physicians, including the complainant, had registered on a 3M website.

The website registration page informed physicians wishing to register that 3M might contact them from time to time to inform them about 3M products and services. Physicians were invited to opt out if they did not wish to receive such information. The 179 physicians contacted in this instance had not elected to opt out.

3M Health Care now took the view that this was not an adequate means of determining whether a physician consented to receiving promotional emails. If the company wished to send promotional emails in future it would obtain specific consent beforehand to comply fully with Clause 9.8 of the Code.

## PANEL RULING

The Panel noted that Clause 9.8 required, *inter alia*, that email must not be used for promotional purposes except with the prior permission of the recipient. The Panel noted 3M Health Care's submission that the complainant had registered on a 3M website. 3M Health Care did not identify the site at which, according to company records, the complainant had registered his details but provided the registration pages for both its Respiratory College and Asthmaweb websites. It was unclear which site the complainant had registered on. The Panel also noted the complainant's view that the email was unsolicited; he could not recollect previously expressing an interest in the subject matter of the email.

The disclaimer on the registration pages of each website read, *inter alia*, 'In addition to facilitating your use of the [3M Asthmaweb or 3M Respiratory College] Web Site we would also like to keep you informed of any updates concerning products and services and any other offers we feel may be of interest to you. This would be by letter, telephone or e-mail. If you wish 3M to do this please click on the following box'. The Panel did not accept 3M Health Care's submission that physicians were invited to opt out if they did not wish to receive such information; the wording was such that physicians were invited to opt in.

The Panel considered that whilst the website registration pages told readers that by clicking on a box they would receive information about 3M Health Care's products, readers were not provided with sufficient information about the type of information that would be provided. It was not sufficiently clear that the reader would receive promotional material. A breach of Clause 9.8 of the Code was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

During its consideration of this case the Panel noted that information about a new eDetailing service for a topical treatment for external genital warts had been sent to a respiratory physician who, according to 3M Health Care, had registered at a site about respiratory medicine. The Panel queried whether the provision of such information met the requirements of Clause 12.1 of the Code which stated that promotional material should only be sent or distributed to categories of persons whose interest in it could reasonably be assumed. The Panel requested that 3M Health Care be advised of its views in this regard.

**Complaint received** **30 May 2003**

**Case completed** **15 July 2003**

# CODE OF PRACTICE REVIEW – AUGUST 2003

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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# PRESCRIPTION MEDICINES
# CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).