PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 43 FEBRUARY 2004

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.

Complaints in 2003 slightly up on 2002

In 2003 the Authority received 131 complaints under the Code of Practice as compared with 127 in 2002. There were 138 complaints in 2001 and 121 in 2000.

The average number of complaints received each year since the Authority was established at the beginning of 1993 is just over 125, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997 without any perceptible reason for the variations seen.

There were 122 cases to be considered in 2003, the same as in 2002. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

The number of complaints from pharmaceutical companies has again exceeded the number from health professionals, there having been fifty-eight from pharmaceutical companies (both members and non-members of the ABPI) and forty from health professionals. In the past it was generally the case that the number of complaints from health professionals exceeded the number from pharmaceutical companies but that has not been so in four out of the last five years. Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

The Medicines and Healthcare products Regulatory Agency, Social Audit, the Aspirin Foundation and SeeMe, a charity, each made a complaint. Two complaints were made by companies which did not promote medicines, two were from former pharmaceutical company employees and three were anonymous. The remaining twenty-two complaints were nominally made by the Director, eight arising from media criticism, seven from other complaints, four from voluntary admissions and three from alleged breaches of undertaking.

Non-promotional meetings

Companies are reminded that Clause 19 of the Code relating to meetings applies equally to both promotional meetings and non-promotional meetings. Thus it includes within its scope meetings of clinical trialists and the like.

This does not mean that such non-promotional meetings are covered by the generality of the Code as a meeting of clinical trialists would, for example, almost inevitably discuss unlicensed indications. What it does mean, however, is that the requirements as to the hospitality being of a reasonable standard etc, which are set out in Clause 19, apply as they do to other meetings.

Compliance with undertakings

From time to time, claims which have previously been ruled in breach of the Code pop up later in other formats, such as on a forgotten exhibition stand.

Companies are reminded that once they have accepted that a claim etc is in breach of the Code they must ensure that it is removed promptly from all promotional material in whatever form. If representative materials are involved, representatives must be given appropriate written instructions to ensure that items in breach do not continue to be used by them and that inappropriate oral statements are not made. Journal advertisements already booked must be cancelled unless it is too late to prevent their appearance, in which case full details of further appearances must be given on the form of undertaking and assurance.

On occasion, a journal advertisement found to be in breach of the Code has subsequently been published again because the agency or printer erroneously used an old film which had remained in their possession. A new dimension to this problem has arisen in recent years due to the erroneous re-use of advertisements stored in electronic form. Companies are advised to make certain that their procedures are such that they ensure that no materials which are no longer acceptable are used again, no matter how they have been stored or by whom.

The Guidelines on Company Procedures Relating to the Code of Practice (pages 40-41 of the Code booklet) states that companies are advised to keep written records of action taken to withdraw material.

Representatives bearing gifts

A medical representative who calls upon a doctor to deliver an item, such as a requested monograph or promotional aid, must not make getting to see the doctor a precondition of leaving the item.

Having indicated that he or she has called upon the doctor with a view to leaving the item, the representative must leave it even though he or she does not get to see the doctor. Taking it away in such circumstances would amount to a breach of Clause 15.3 of the Code.

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 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 date on which places remain available is:

Monday, 10 May

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.

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/1465/5/03

ROCHE v ORTHO BIOTECH

Promotion of Eprex

Roche complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech. The items at issue were a letter from a product manager which prominently displayed the Eprex brand logo and a 4 page brochure which accompanied it. Roche supplied NeoRecormon (epoetin beta).

Roche alleged that the letter discussed Eprex safety issues, made claims about the IV route of administration for erythropoietins in nephrology and disparaged the subcutaneous (SC) route. It was not a factual or accurate announcement but a covering letter that referred to an accompanying brochure and was therefore promotional in nature. No prescribing information was provided on the reverse of the letter. Roche further noted that the letter did not identify the intended recipient or their status (ie it was not addressed 'Dear Doctor'). It was possible that this could be read by an inappropriate person (eg the general public).

The Panel noted that no prescribing information was included in the letter; Ortho Biotech had acknowledged that it should have been included. A breach of the Code was ruled. The Panel did not consider that the use of 'Dear Sir or Madam' at the top of the letter meant that the letter was thus an advertisement for Eprex aimed at the general public. The letters had been addressed to health professionals. No breach of the Code was ruled.

Roche noted the statement '… a label change for Eprex, the first consequence of our emerging understanding of the relationship between the subcutaneous route of administration and PRCA [pure red cell aplasia] in nephrology' appeared in the letter and also in the mailer in a subsection headed 'Positive reasons'. Roche stated that the PRCA issue was also linked to the storage and handling of Eprex and a change in formulation. Roche alleged that the statement and the letter in general were misleading in not pointing out that the contraindication for SC use was limited only to Eprex (and not other epoetins). Roche considered that the letter and brochure were intended not only to promote IV administration but to discourage and disparage the SC route in general. Eprex had had its marketing authorization for SC use in nephrology withdrawn. There was no evidence that the SC route *per se* was a problem. The majority of UK use in nephrology for NeoRecormon was SC.

The Panel noted that the letter started by referring to the numbers of patients receiving IV Eprex. It then referred to this switch in clinical practice being prompted specifically by a label change for Eprex. This was followed by the statement at issue. The Panel considered that the aim of the letter was to inform health professionals that, following a recognition that PRCA in nephrology patients was associated with SC use of Eprex, the summary of product characteristics (SPC) had been changed and haemodialysis patients should now only be given the product IV. In that context the Panel did not consider it necessary to include information about the storage and handling of Eprex, or information about the formulation change which had occurred in 1998. Given its context the Panel did not consider that the statement at issue was misleading with regard to the SC use of other erythropoietins or that it disparaged NeoRecormon. No breach of the Code was ruled.

Roche noted that the letter and the brochure stated '… emerging information reported on the Swiss Regulatory Authorities [sic] website (www.swissmedic.ch) has shown that a number of PRCA cases have been associated with other erythropoietins also when administered via the subcutaneous route. This further reinforces the reasons to use the IV route of administration … in order to reduce the risk of developing PRCA'. Except for Eprex, there was no evidence that using the IV route reduced the risk of PRCA. No attempt was made to quantify the number of reports of PRCA with other epoetins or to put the SwissMedic statement in its proper context. A few cases of PRCA had very rarely occurred with NeoRecormon, and had been reported. However, the level of reporting was orders of magnitude smaller than Eprex, with the total suspected PRCA cases standing at 224 at end of December 2002.

Roche noted that only selective parts of the SwissMedic statement were used. For example, the SwissMedic review also stated 'The change in the mode of administration … could play a role here. It is also possible to consider other technical possibilities to explain the difference, such as wrong storage … altered excipients or cofactors which have not yet been identified'. Also the fact that the route of administration of the NeoRecormon cases was SC only, 'as far as it is known' was not made clear. In addition, the SwissMedic website did not suggest that switching all epoetins to IV would reduce the risk of PRCA. Indeed, it quoted incidences of PRCA before and after 1998 which were almost identical for NeoRecormon (0.10 vs 0.14 [per 10,000 patient years]) but which increased by a factor of 41 for Eprex (0.03 vs 1.24 [per 10,000 patient years]), suggesting that changing to SC use (a pattern which developed during the 1990s) could not possibly be the only factor to explain the increasing incidences of PRCA. The more likely explanation from these incidences was one related to Eprex's product characteristics not the route of administration.

Roche alleged that the letter and brochure were inaccurate, unbalanced, misleading and unfair and were by inference disparaging because over 90% of NeoRecormon was administered SC. Since the PRCA reference on the Swiss website was not in English it was not tailored to the intended UK audience.

The Panel considered that the phrase '… emerging information reported on the Swiss Regulatory Authorities [sic] website (www.swissmedia.ch) has shown that a number of PRCA cases have been associated with other erythropoietins also when administered via the subcutaneous route. This further reinforces the reasons to use the IV route of administration …' cast doubt upon the safety of

continuing to administer any erythropoietin subcutaneously. The Panel noted that Eprex was the only product in its class to have its licence revoked with regard to SC use in patients with renal failure. Although the Swiss Regulatory Authority had noted cases of PRCA in association with NeoRecormon, and the route of administration was, as far as was known, SC, the Panel had no evidence before it to show that switching to IV NeoRecormon would result in fewer cases of PRCA. The Panel considered that the statement was misleading as alleged and could not be substantiated and that by implication it disparaged NeoRecormon. Breaches of the Code were ruled.

The Panel did not consider that reference to a Swiss website was misleading. Some doctors would have been able to read it and those who could not could have asked Ortho Biotech for a translation. It was relevant to the audience. The Panel ruled no breach of the Code.

Roche noted that no reference was cited in support of the statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do for other very positive reasons, such as patient preference and improved compliance' which appeared in the letter. A similar statement appeared in the brochure. It was true that switching to IV was obligatory for Eprex, but the statement was all-embracing and implied all erythropoietins should be given IV because this paragraph immediately followed one in both the letter and the brochure stating that PRCA had occurred with other erythropoietins. This paragraph 'further reinforces the reasons to use the IV route' and in the brochure was adjacent to a graph headed 'The return to IV administration in haemodialysis' which purported to deal with SC erythropoietins in general. Moreover the use of 'the' ('…the right thing to do') implied it was the only choice among other alternatives. Thus the other options (eg to switch to SC NeoRecormon or darbepoetin) were ignored. It also implied that not to switch was not the right thing to do. Roche alleged that this misled the reader and failed to recognise the standing of those specialists who favoured the SC route (for those products so licensed) and might cause offence.

Roche alleged that this statement also failed to address the possible need for hospital visits and increased risks of local and systemic infection when switching to IV treatment. In addition, Kaufman *et al* (1998) cast some doubt on the claims about tolerability. Whilst a general preference for IV was expressed, a subgroup of patients who had received SC treatment for a reasonable period of time expressed a preference for that route. There was also the matter of the European and American Best Practice Guidelines that advocated SC, largely on cost grounds. Roche alleged that the claim was, therefore, not balanced.

The Panel considered that the statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do …' implied that not using the IV route was the wrong thing to do. The statement did not clearly relate only to Eprex, for which returning to the IV route was the right thing to do. The statement followed a paragraph which referred to other epoetins and so would be assumed by some readers to also apply to other erythropoietins which was not so. Erythropoietins other than Eprex could still be administered SC in renal patients, there was no requirement to administer them IV. The Panel considered that the claim was misleading as alleged and ruled a breach of the Code.

The Panel considered that the phrase 'the right thing to do' was all-embracing as it implied that everything else was the wrong thing to do. The Panel considered that by implication the statement disparaged those prescribers who legitimately continued to use another erythropoietin subcutaneously. Breaches of the Code were ruled.

The Panel did not consider that the statement constituted a comparison of Eprex with any other medicine and on that basis ruled no breach of the Code. Neither did the Panel consider that the claim was misleading with regard to the need for hospital visits and the possibility of an increased risk of infection. In the Panel's view the statement referred to benefits of IV administration but did not imply that there were no disadvantages. No breach of the Code was ruled.

Roche noted that the letter stated that 'The anticipated barriers to switching route of administration – i.e. significantly higher doses, cost, nursing resource – are, in reality, not materialising'. The brochure included the claim 'Switching to IV Eprex should not affect your budget'. The cost of switching from SC to IV was, in fact, of concern. For example, a recent publication estimated shifting all patients in Italy would increase costs from 31.1 to 46.7 million US$ per year. This might be avoided by considering a SC alternative to IV Eprex.

Roche stated that Fullerton *et al* (2002/2003) which was published in the British Journal of Renal Medicine and cited in the letter and brochure was not representative of the published information and there were reservations about the methodology used. In contrast, there were two publications reporting at a higher standard of evidence; one presented a methodologically robust parallel arm study (Kaufman *et al* 1998) and the other a meta-analysis (Besarab *et al* 2002). These two studies found that switching from IV to SC brought about a 30% dose saving. However switching SC to IV, as endorsed by Ortho Biotech, increased doses by about 50%. Hence, the cost comparisons of IV and SC in this letter and brochure were unfair and failed to consider the full body of scientific opinion.

Roche noted that the British Journal of Renal Medicine was a small circulation magazine entirely sponsored by Ortho Biotech. This was not made clear in the way the reference to Fullerton *et al* was cited in either the letter or the brochure.

The Panel noted that Fullerton *et al* reported the initial results of a systematic conversion of a large population of haemodialysis patients from SC to IV dosing of Eprex. By the end of the study there was three months' data from 135 patients. The mean dose of Eprex was increased by 6.3% from baseline

(p=0.08) over the three months. The authors noted, however, that the results would need to be confirmed through further observation of longer-term dosing and also confirmed in other UK centres.

The Panel considered that on the basis of one small, short-term study the statement in the letter and the claim 'Switching to IV Eprex should not affect your budget' had not been substantiated and were misleading in that regard. The comparison of the cost of SC Eprex vs IV Eprex was unfair. It was immaterial that Ortho Biotech was offering cost neutralisation packages. In that regard the Panel considered that the offer of such packages in itself implied that switching to IV Eprex would affect budgets. Breaches of the Code were ruled which were appealed by Ortho Biotech.

The Panel did not consider that the citation of Fullerton *et al* in the letter and the brochure needed to state that the journal was sponsored by Ortho Biotech. No breach of the Code was ruled. The Panel considered, however, that the reprint should have declared the company's sponsorship of the journal and ruled a breach of the Code in that regard. This ruling was accepted by Ortho Biotech.

Upon appeal by Ortho Biotech, the Appeal Board noted that the claim at issue in the letter, 'The anticipated barriers to switching route of administration – i.e. significantly higher doses, cost, nursing resource – are, in reality, not materialising.', was referenced to Fullerton *et al*. The Appeal Board also noted that Kaufman *et al* and Besarab *et al* had indicated that the difference in dose between IV and SC erythropoietins, not necessarily Eprex, could be closer to 30%. The letter made no reference to budgets or to cost neutralisation packages. The Appeal Board considered that on the basis of one small, short-term study the statement in the letter was misleading and had not been substantiated. The Appeal Board upheld the Panel's ruling of breaches of the Code.

With regard to the brochure, the Appeal Board noted that the claim 'Switching to IV Eprex should not affect your budget' was followed by the statement 'Talk to Ortho Biotech: we can help'. The 'help' was in the form of a cost neutralisation package. The Appeal Board noted its comments above and considered that the claim implied that switching patients from SC to IV Eprex had no cost implications which was not so. The fact that Ortho Biotech was subsidising the switch was immaterial. 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.

Roche alleged that although the letter purported to discuss safety issues, it was in fact disguised promotion of Eprex.

The Panel did not consider that the letter was disguised promotion of Eprex. The letter was signed by a product manager and featured the Eprex brand logo in the bottom right-hand corner. The Panel considered that the letter was clearly promotional. No breach of the Code was ruled.

Roche stated that it had attempted to review the 'Data on File' cited by Ortho Biotech in the letter and brochure but was told that the data was unavailable as it was held in commercial confidence.

The Panel noted in the letter and in the brochure a claim that the number of haemodialysis patients receiving IV Eprex was approaching 3,500 was referenced to data on file. Ortho Biotech had not supplied Roche with the data on file to substantiate the claim as it regarded the data as being commercially confidential. The Panel noted that it was a principle under the Code that if a claim could only be substantiated by material which a company wished to keep confidential then the claim must not be made. A breach of the Code was ruled.

Upon appeal by Ortho Bioech, the Appeal Board noted that at the time of going to press with the material in question the company could confirm that it had approximately 3,500 haemodialysis patients registered as receiving IV Eprex. The Appeal Board considered that such a reply did not provide enough information such that a recipient could be sure that the figure of 3,500 was credible. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Roche stated that the brochure distorted the issues and might confuse the reader on important matters of patient safety; it prominently displayed the Eprex brand logo, discussed Eprex safety issues, made claims about the IV route of administration for erythropoietins in nephrology and disparaged the SC route. Given the context in which the brochure was supplied, its title ' … leadership is doing the right thing' implied that 'leaders' were switching from SC to IV administration for all erythropoietins, which was not true. It also implied that if you were not switching you were neither a leader nor 'doing the right things'. This failed to recognise the professional standing of the audience. Roche also noted that there was no date on the brochure.

The Panel considered that from the title of the brochure, '… leadership is doing the right things', some readers might assume that if they were not using Eprex then they were neither leaders nor were they doing the right things. The Panel considered that the claim failed to recognise the professional standing of the audience and thus ruled a breach of the Code. The Panel further considered that the claim was exaggerated and all-embracing – using Eprex was not the only right thing to do. A breach of the Code was ruled. Ortho Biotech acknowledged that the brochure was undated and thus a breach of the Code was ruled.

Roche noted a graph on page two of the brochure showed the numbers of UK haemodialysis patients from August 2002 - February 2003 who received either IV Eprex or SC erythropoietin. The graph showed a steady rise for IV Eprex from almost zero to 3,500 in that time with SC erythropoietin falling from just over 14,000 patients in August 2002 to about 11,000 in February 2003. Roche noted that the graph was not referenced. It showed a decline in the number of patients using subcutaneous epoetins and a mirror image rise in IV Eprex, to suggest that IV Eprex was taking all the SC epoetin switches. This was misleading from Roche's understanding of the market dynamics. The reality was that there was

a general decline in the use of SC Eprex which was being compensated for by an increase in SC NeoRecormon, an increase in IV Eprex and probably an increase in mainly IV darbepoetin. Roche noted that there was no explanation how these data had been generated. Roche further alleged that the graph was not capable of substantiation in breach of the Code.

The Panel noted that the graph consisted of two converging lines labelled 'IV Eprex' and 'SC Epo' respectively. The Panel considered that the impression given was that the SC use of all erythropoietins was declining and being replaced with IV Eprex, the use of which was increasing. The graph was entitled 'The return to IV administration in haemodialysis'. The Panel noted that although haemodialysis patients on SC Eprex were having to be switched to IV Eprex there were other erythropoietins which could still be used SC. The Panel considered that the graph was misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

Roche alleged that the claim 'Patients prefer IV dosing', which appeared as a paragraph heading on page three of the brochure, failed to address the possible need for hospital visits and increased risks of local and systemic infection – especially when the maintenance and continued patency of IV access was vitally important in this patient group. In addition Kaufman *et al* cast some doubt on the claims about tolerability. Whilst a general preference for IV was expressed, a subgroup of patients who had received SC treatment for a reasonable period of time expressed a preference for that route. Roche also noted that the European and American Best Practice Guidelines advocated SC, largely on cost grounds. Roche alleged that the claim was, therefore, not balanced.

Roche noted, in contrast to page 2 of the brochure where claims were specified for haemodialysis patients, this particular claim was not. Therefore the impression was given that IV was preferred for all renal patients. There was no evidence that these patients would prefer the IV route. Roche alleged that the statement was misleading.

The Panel noted that the brochure referred to IV administration in haemodialysis on page 2, the letter also referred to haemodialysis patients. Page 3 did not refer to haemodialysis patients as such and perhaps could have been clearer in this regard, nevertheless the Panel did not consider that the page would be seen as referring to all renal patients as alleged. The Panel thus ruled no breach of the Code in this regard.

The Panel noted that Kaufman *et al* provided some data to support preference for IV dosing. In the Panel's view given that the patients were haemodialysis patients, the claim 'Patients prefer IV dosing' was not unreasonable nor unbalanced. No breach of the Code was ruled.

Roche noted that the claim 'counselling patients on self injection is therefore no longer necessary' appeared on page three of the brochure in a paragraph headed 'IV dosing has been shown to have minimal impact on nurse resource'. Roche alleged that the claim was bizarre, inaccurate and unsubstantiated.

In the Panel's view, given the context in which it appeared, the claim was self-evident, ie patients who received IV Eprex did not require counselling with regard to self injection. The Panel did not consider that the claim was inaccurate. No breach of the Code was ruled.

Roche alleged that the paragraph heading 'IV and SC doses are not substantially different' on page 3 of the brochure was confusing. Did it refer to Eprex IV and SC, which would not be in accordance with the Eprex marketing authorization as the SC route was revoked? Alternatively, was this a reference to IV Eprex and other SC erythropoietins in which case it became all-embracing. Roche alleged that the heading to page 4 of the brochure 'Switching to IV Eprex should not affect your budget' was similarly all-embracing.

The Panel considered that given the context in which the claim 'IV and SC doses are not substantially different' appeared it was clear that it referred to IV and SC doses of Eprex such that when patients were changed from SC Eprex to IV Eprex the dose would remain more or less the same. The Panel did not consider that the claim referred to all SC erythropoietins or that it promoted the use of SC Eprex in renal patients. No breach of the Code was ruled. Similarly, the Panel did not consider that the claim on page 4 of the brochure 'Switching to IV Eprex should not affect your budget' was all-embracing as alleged. In the context of the brochure it was clear that the claim referred to switching from SC Eprex to IV Eprex. No breach of the Code was ruled.

Roche noted that the statement 'Subcutaneous administration remains appropriate in all other indications, please refer to SmPC' appeared in a highlighted box beneath the prescribing information on the back page of the brochure. This constituted a claim for indications other than renal failure and so the brochure should bear prescribing information for indications other than the renal indication.

The Panel did not consider that the statement at issue constituted promotion of the non-renal indications for Eprex. No breach of the Code was ruled.

Roche alleged that Ortho Biotech's letter and brochure were part of a disreputable campaign that had been found in breach of many clauses of the Code, including Clause 2 (Case AUTH/1399/12/02). Roche alleged a breach of Clause 2.

The Panel noted its comments and rulings above and considered, on balance, that there had been no breach of Clause 2.

Roche Products Limited complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech. The items at issue were a letter from a product manager (ref 00120) dated 28 April and a 4 page brochure (ref 00119) which accompanied it. Roche supplied NeoRecormon (epoetin beta).

Roche stated that the letter and brochure represented another contribution to the campaign on which Ortho Biotech had been ruled in breach of Clause 2 of the Code (Case AUTH/1399/12/02). Roche noted that in its response to Case AUTH/1399/12/02, Ortho Biotech had stated that it had '…already taken the decision to submit **all communications regarding Eprex and PRCA** to the relevant regulators prior [emphasis added] to their circulation'. Roche would like to see evidence that Ortho Biotech had indeed done this with the brochure.

General comments from Ortho Biotech

Ortho Biotech stated that the letter and brochure represented a new campaign in which intravenous (IV) Eprex was promoted for use in a manner consistent with its summary of product characteristics (SPC) dated 11 December 2002. The letter and the brochure discussed the use of IV Eprex and also advocated the benefits of the IV route in respect to the reduction in the number of cases of pure red cell aplasia (PRCA) and other associated patient benefits. Ortho Biotech acknowledged that Eprex was the only erythropoietin to have a contraindication for subcutaneous (SC) use, but advocating the benefits of using it IV did not disparage alternative routes of administration, such as SC, which still remained available for clinicians using other erythropoietins.

Ortho Biotech stated that SC Eprex had been contraindicated since 11 December 2002, as a result of the association with this route of administration and all cases of PRCA reported with Eprex. Since this contraindication, and the conversion by some (but not all) nephrologists to using IV Eprex, it was not unreasonable to update the nephrology community as to what had occurred in the last four or five months.

In accordance with the SPC, Ortho Biotech therefore promoted IV Eprex, and in doing so it was not unreasonable to expound the benefits in relation to that route of administration that had been noted and indeed published following the recent change from using SC Eprex.

Within the remit of emerging science, the issue in respect of route of administration and the association with any reports of PRCA were pertinent to the nephrology community and the regulatory authorities (European Pharmacovigilance Working Party minutes). Roche's suggestion that PRCA was only associated with Eprex ignored the statement about PRCA which appeared in the NeoRecormon SPC and also the fact that the Swiss Regulatory Authority had stated that it had had 21 reports of PRCA in association with NeoRecormon (8 exclusively with NeoRecormon, and 13 other cases in which patients received NeoRecormon/Recormon as well as other erythropoietins prior to the loss of efficacy). The Swiss Authorities had also stated that as far as was known, for those cases associated with NeoRecormon, the route of administration was SC.

Ortho Biotech noted that Roche had pointed out that there was a difference in magnitude between the number of reports associated with Eprex and the number of reports associated with SC NeoRecormon. Ortho Biotech insisted that it had never contradicted this statement, and did not make any comparative claims between different erythropoietins in this respect in any promotional materials because it considered the appropriate manner in which to compare the incidence of adverse events was via appropriate epidemiological studies.

The Swiss Authorities had stated that reports of PRCA associated with NeoRecormon had risen since 1998 from 0.1 to 0.14 per 10,000 patient years, a rise of 40%. However, the Swiss Regulatory Authority was generous in its time span in suggesting this change had occurred over the last 5 years. Roche, in its communications to the healthcare and broader scientific community during June/July 2002, had stressed that NeoRecormon was categorically not associated with PRCA. Should this indeed have been the case, then the 21 cases reported in the SwissMedic statement up till 31 December 2002, would have meant that those cases were reported in the last 6 months of that year. This would indeed be of concern, particularly as they were all associated with the SC route.

With regard to the emerging science and clinical knowledge, the appropriate comparison within the letter in relation to the risk of developing an immune mediated case of PRCA should be the number of cases of PRCA associated with IV Eprex (the Ortho Biotech database had approximately 0.5 million patient years' experience of IV Eprex) and the number of cases of PRCA associated with other erythropoietins when administered SC. In this respect there were no cases associated with IV Eprex and 21 cases associated with SC NeoRecormon (SwissMedic statement).

Roche, in suggesting that Ortho Biotech had disparaged SC administration, had stated that 90% of NeoRecormon in the UK was administered SC and that the SC route was advocated by the European and American Best Practice Guidelines, adding that this was 'largely on cost grounds'.

As the return to the use of IV administration in the UK had only recently been advocated, and prompted specifically because of a label change for Eprex, one would not expect the European Best Practice Guidelines or indeed any UK Guidelines to have been amended yet. Also, advocating a route of administration on grounds of cost was not necessarily always appropriate, particularly when changing from SC to IV could be cost neutralised. The important element of advocating a route of administration should therefore be directed towards patient benefits and also safety. It was in this respect that there was emerging debate and also public disagreement, even between health authorities, on the importance of a change of route of administration in the reduction of the risk of immune mediated cases of PRCA occurring.

Several reputable authorities took completely different views as to the importance of the route of administration for Eprex. The Canadian Nephrology Society had stated that it believed that a recommendation to use IV Eprex was not justified and that it might precipitate more problems than it would solve, whilst the Israeli Society of Nephrology and Hypertension advocated the use of IV Eprex to

mitigate a risk of a patient developing PRCA, but furthermore, advocated that this route should be applicable to all erythropoietins.

As no cases of immune mediated PRCA had been associated with IV Eprex and 21 had been associated with SC NeoRecormon the role of the change in route of administration appeared an important issue in mitigating the risk of developing PRCA. It was therefore not unreasonable to allude to potential benefits of IV but in doing so Ortho Biotech did not disparage any particular route of administration. Further, advocating an alternative route of administration to clinicians who continued to use SC for erythropoietins, (but not for Eprex as SC use was now contraindicated), certainly did not disparage their practice nor cause offence. On the contrary, it engaged clinicians in a challenging way about maintaining the status quo of their practice. Indeed, the pharmaceutical industry had a long history of challenging the status quo in respect of clinical practice by introducing new and innovative medicines, devices and methodologies. Ortho Biotech continued in this regard as further information regarding the strongest correlations with the pathogenesis of immune mediated PRCA evolved.

1 Letter

COMPLAINT

Roche noted that the letter prominently displayed the Eprex brand logo and was signed by a product manager. The letter discussed Eprex safety issues, made claims about the IV route of administration for erythropoietins in nephrology and disparaged the SC route. It was not a factual or accurate announcement but a covering letter that referred to an accompanying brochure. It was therefore promotional in nature and came within Clause 1.2 of the Code and accordingly was a stand-alone item which should include prescribing information. Since no prescribing information was provided on the reverse of the letter, Roche alleged a breach of Clause 4.1 of the Code. Roche further noted that the letter did not identify the intended recipient or their status (ie it was not addressed 'Dear Doctor'). It was possible that this could be read by an inappropriate person (eg the general public). A breach of Clause 20.1 was alleged.

RESPONSE

Ortho Biotech accepted that prescribing information should have been on the reverse of the letter and action was being taken to ensure future compliance.

Although the letter was not personalised, the envelopes were correctly addressed to health professionals; 5% of the letters sent defaulted to Dear Sir/Madam because the database held by the mailing company was incomplete. Ortho Biotech denied a breach Clause 20.1.

Ortho Biotech noted that Roche alleged that the letter disparaged the SC route of administration in that it was not factual or accurate. The letter stated that the number of haemodialysis patients now receiving IV Eprex was approximately 3,500. This was true, and Ortho Biotech noted that no statements about other patients with chronic renal failure such as those receiving continuous ambulatory peritoneal dialysis (CAPD) or pre-dialysis patients were made. The rationale for this was that within these two patient groups the IV route was not a feasible option, with the risk:benefit ratio overwhelmingly in favour of continued use of the SC route. SC Eprex was contraindicated and so the letter specifically referred to haemodialysis patients in whom the IV route was an option.

PANEL RULING

The Panel noted that no prescribing information was included in the letter; Ortho Biotech had acknowledged that it should have been included. A breach of Clause 4.1 was ruled.

The Panel did not consider that the use of 'Dear Sir or Madam' at the top of the letter meant that the letter was thus an advertisement for Eprex aimed at the general public. The letters had been addressed to health professionals. No breach of Clause 20.1 was ruled.

The Panel noted that Roche stated that the letter disparaged the SC route. No specific clause had been cited in this regard. The Panel thus made no ruling. A similar allegation was made in point 2 below where Clause 8.1 was specifically cited.

2 Statement '... a label change for Eprex, the first consequence of our emerging understanding of the relationship between the subcutaneous route of administration and PRCA in nephrology'

This statement appeared in the second paragraph of the letter and also in the second paragraph of the mailer in a subsection headed 'Positive reasons'.

COMPLAINT

Roche noted the statement at issue and observed that the PRCA issue was also linked to the storage and handling of Eprex and a change in formulation. All three issues had been cited by Johnson & Johnson (Ortho Biotech's parent company) in recent publications. Roche alleged that the statement and the letter in general were misleading in not pointing out that the contraindication for SC use was limited only to Eprex (and not other epoetins) in breach of Clauses 7.2, 7.4 and 7.9.

Roche considered that the intention of the letter and the brochure was thus not only to promote the IV route of administration but to discourage and disparage the SC route in general. Eprex had had its marketing authorization for SC use in nephrology withdrawn. There was no evidence that the SC route *per se* was a problem. Indeed the SC route was still that recommended by the European and US Best Practice Guidelines. The only problem had been with SC Eprex. The majority of UK use in nephrology for NeoRecormon was SC and as such Roche alleged that the statement breached Clause 8.1 of the Code.

RESPONSE

Ortho Biotech submitted that the statement at issue was factual. Roche had quoted it out of context; it was the second part of a sentence, the first part of which read 'This switch in clinical practice was prompted specifically by a label change for Eprex …'. The wording **specifically by a label change for Eprex** (emphasis added) stated beyond doubt that the move towards IV use was related to Eprex only. The words 'contraindication' and 'other epoetins' in the context of this point did not exist and were the invention of Roche. This statement did not contain any comparisons, was accurate, balanced, fair, objective and unambiguous and based on the up-to-date evaluation of the evidence. The switch to IV Eprex was prompted because all cases of PRCA associated with the product were related to SC use, no cases had been reported in respect of the IV route. Consequently, in discussion with the regulatory authorities a decision was taken to contraindicate the SC use of Eprex. Since this action was taken there had been no further cases of antibody mediated PRCA reported in association with Eprex. The contributions towards the pathogenesis of antibody mediated PRCA associated with Eprex in relation to storage and handling, or the formulation changes that occurred in 1998, remained speculative and unproven.

The statement in the letter was fully substantiated (Clause 7.4) and was in relation to a side effect (PRCA) being discussed, and did not state that Eprex had no side effects, toxic hazards or risks of addiction and did not use the word 'safe' and hence was not in breach of Clause 7.9.

The letter was intended to promote IV Eprex and it did not discourage or disparage the SC route in general. Although Roche had stated that the SC route was still that recommended by the European and American Best Practice Guidelines, it was too early for these bodies to have made any public statement in respect of the IV route of administration. Ortho Biotech noted that a review of US practice, however, indicated that approximately 90% of end stage renal disease patients received IV erythropoietin. Within Europe, the UK utilised the SC route most predominantly, driven largely by cost.

Ortho Biotech submitted that it had not disparaged or denigrated SC administration, which had been used extensively in the UK for the last 10 years. Roche was wrong to state that there was no evidence that the 'SC route *per se* was a problem', and that 'the only problem had been with SC Eprex'. Although SC Eprex had a greater number of reported cases the statement that 'the only problem had been with SC Eprex' ignored the fact that SC NeoRecormon was associated with 21 cases of PRCA. Ortho Biotech submitted that highlighting within the letter that a number of PRCA cases had been associated with other SC erythropoietins did not disparage nor denigrate the SC route; it merely stated a fact. Ortho Biotech denied a breach of Clause 8.1.

PANEL RULING

The Panel noted that the letter started by referring to the numbers of patients receiving IV Eprex. It then referred to this switch in clinical practice being prompted specifically by a label change for Eprex. This was followed by the statement at issue. The Panel considered that the aim of the letter was to inform health professionals that, following a recognition that PRCA in nephrology patients was associated with SC use of Eprex, the SPC had been changed and haemodialysis patients should now only be given the product IV. In that context the Panel did not consider it necessary to include information about the storage and handling of Eprex, or information about the formulation change which had occurred in 1998. Given its context the Panel did not consider that the statement at issue was misleading with regard to the SC use of other erythropoietins or that it disparaged NeoRecormon. No breach of Clauses 7.2, 7.4, 7.9 and 8.1 was ruled.

3 Statements derived from the Swiss Regulatory Authority

COMPLAINT

Roche noted that the letter and the brochure stated '… emerging information reported on the Swiss Regulatory Authorities [sic] website (www.swissmedic.ch) has shown that a number of PRCA cases have been associated with other erythropoietins also when administered via the subcutaneous route. This further reinforces the reasons to use the IV route of administration … in order to reduce the risk of developing PRCA'. Except for Eprex, there was no evidence that using the IV route reduced the risk of PRCA. No attempt was made to quantify the number of reports of PRCA with other epoetins or to put the SwissMedic statement in its proper context. This statement further denigrated the SC route implying that patients were at risk if treated with SC NeoRecormon.

A few cases of PRCA had very rarely occurred with NeoRecormon, and had been reported. However, the level of reporting was orders of magnitude smaller than Eprex, with 224 suspected PRCA cases at the end of December 2002. Roche referred to the Eprex website.

Roche noted that only selective parts of the SwissMedic statement were used. For example, the SwissMedic review also stated 'The change in the mode of administration … could play a role here. It is also possible to consider other technical possibilities to explain the difference, such as wrong storage … altered excipients or cofactors which have not yet been identified'. Also the fact that the route of administration of the NeoRecormon cases was SC only, 'as far as it is known' was not made clear. In addition, the SwissMedic website did not suggest that switching all epoetins to IV would reduce the risk of PRCA. Indeed, it quoted incidences of PRCA before and after 1998 which were almost identical for NeoRecormon (0.10 vs 0.14 [per 10,000 patient years]) but which increased by a factor of 41 for Eprex (0.03 vs 1.24 [per 10,000 patient years]), suggesting that changing to SC use (a pattern which developed during the 1990s) could not possibly be the only factor to explain the increasing incidences of PRCA. The

more likely explanation from these incidences was one related to Eprex's product characteristics not the route of administration.

Vaguely referencing the Swiss Regulatory Authority's website failed to treat the issue in a balanced way by considering all relevant information. Roche alleged that the letter and brochure were inaccurate, unbalanced, misleading and unfair in breach of Clauses 7.2 and 7.4 and were by inference disparaging in breach of Clause 8.1 because over 90% of NeoRecormon was administered SC.

Roche stated that since the PRCA references on the Swiss website was not in English it was unreasonable to expect an English reader to be able to decipher it. Therefore, it was not tailored to the intended UK audience and Roche alleged that the use of this reference was in breach of Clauses 7.2 and 12.1 (supplementary information).

RESPONSE

Ortho Biotech noted that Roche had complained about the statement suggesting that the greater number of reports of PRCA had been associated with Eprex rather than NeoRecormon. This was correct; however, the point of the brochure was to promote the use of IV Eprex, and there had been no cases of PRCA reported with Eprex when so used. Although the return to IV administration in the UK was relatively new, in other countries IV use was more common, and it was estimated that there was approximately 500,000 patient years of experience with IV Eprex.

The appropriate comparison therefore within the letter and brochure should be the number of reports of PRCA associated with IV Eprex compared with that of other SC erythropoietins. In this respect there were no cases associated with IV Eprex, and 21 associated with the use of NeoRecormon. Therefore the statement advocating the IV route of administration in order to reduce the risk of developing PRCA was accurate.

The Swiss Regulatory Authorities had shown that a number of PRCA cases had been associated with other erythropoietins. This was fact, and moreover the association with the SC route of administration held here. The statement in the letter therefore that 'This [reports of PRCA with other erythropoietins via the SC route] further reinforces the reasons to use the IV route of administration … in order to reduce the risk of developing PRCA' again was factual. Indeed, scientific literature endorsed IV administration as being associated with the lowest immunogenic potential. That there were 21 cases of PRCA associated with SC NeoRecormon, the risk of developing PRCA could be reduced further by changing to IV Eprex, which despite over half a million patient years of exposure to date was not associated with any cases of immune mediated PRCA.

Roche stated that … 'Except for Eprex, there was no evidence that using the IV route reduced the risk of PRCA'. Ortho Biotech's letter and brochure was about promoting IV Eprex, not NeoRecormon or any other erythropoietins and in respect of lowering the risk of a patient developing antibody mediated PRCA, the lowest risk was with IV Eprex and hence Ortho Biotech advocated its use in this manner in haemodialysis patients. Again this was consistent with the SPC for Eprex.

Advocating one route of administration did not disparage another, and in respect of the above, Ortho Biotech denied a breach of Clauses 8.1, 7.2 and 7.4, in that its statements were not misleading, could be fully substantiated, and did not disparage other products, their trade marks or other companies' activities.

Ortho Biotech considered that Roche's allegation regarding the language difficulties with the Swiss website underestimated UK health professionals and their ability to have a website translated into English. Ortho Biotech would provide a translation on request. Ortho Biotech therefore did not consider it was unreasonable to quote the Swiss website as its content in relation to PRCA route of administration in general was a topic of interest. Ortho Biotech therefore denied breach of Clauses 7.2 and 12.1.

PANEL RULING

The Panel considered that the phrase '… emerging information reported on the Swiss Regulatory Authorities [sic] website (www.swissmedia.ch) has shown that a number of PRCA cases have been associated with other erythropoietins also when administered via the subcutaneous route. This further reinforces the reasons to use the IV route of administration …' cast doubt upon the safety of continuing to administer any erythropoietin subcutaneously. The Panel noted that Eprex was the only product in its class to have its licence revoked with regard to SC use in patients with renal failure. Although the Swiss Regulatory Authority had noted cases of PRCA in association with NeoRecormon, and the route of administration was, as far as was known, SC, the Panel had no evidence before it to show that switching to IV NeoRecormon would result in fewer cases of PRCA. The Panel considered that the statement was misleading as alleged and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel further considered that by implication the statement disparaged NeoRecormon. A breach of Clause 8.1 was ruled.

The Panel did not consider that reference to a Swiss website was misleading. Some doctors who accessed the site would have been able to read it and those who could not could have asked Ortho Biotech for a translation. The site, and its contents, were relevant to the audience. The Panel ruled no breach of Clauses 7.2 and 12.1 of the Code.

4 Statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do for other very positive reasons, such as patient preference and improved compliance'

This statement appeared in the letter and a similar statement appeared in the brochure.

COMPLAINT

Roche noted that no reference was cited in support of this statement. It was true that switching to IV was obligatory for Eprex, but the statement was all-embracing and implied all erythropoietins should be given IV in breach of Clause 7.10 because this paragraph immediately followed one in both the letter and the brochure stating that PRCA had occurred with other erythropoietins. This paragraph 'further reinforces the reasons to use the IV route' and in the brochure was adjacent to a graph headed 'The return to IV administration in haemodialysis' which purported to deal with SC erythropoietin in general. Moreover the use of 'the' ('…the right thing to do') breached Clause 7.10 because it implied it was the only choice among other alternatives. Thus the other options (eg to switch to SC NeoRecormon or darbepoetin) were ignored. It also implied that not to switch was not the right thing to do. This was alleged to mislead the reader in breach of Clause 7.3, it failed to recognise the standing of those specialists who favoured the SC route (for those products so licensed) and might cause offence in breach of Clause 9.1.

This statement also failed to address the possible need for hospital visits, and increased risks of local and systemic infection when switching to IV treatment – especially when the maintenance and continued patency of IV access was vitally important in this patient group. In addition, a reputable study published in the New England Journal of Medicine (Kaufman *et al* 1998) cast some doubt on the claims about tolerability. Whilst a general preference for IV was expressed, a subgroup of patients who had received SC treatment for a reasonable period of time expressed a preference for that route. There was also the matter of the European and American Best Practice Guidelines that advocated SC, largely on cost grounds. Roche alleged that the claim was, therefore, not balanced in breach of Clause 7.2.

Finally, although preferences might be of debatable value for patients on haemodialysis who had to have IV access weekly it did not apply to pre-dialysis patients who did not have to visit hospital three times weekly and who currently self-injected SC. Here, protecting IV access became critically important as future dialysis was likely.

RESPONSE

Ortho Biotech noted Roche's complaint that there was no reference supplied to support the statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do for other very positive reasons, such as patient preference and improved compliance'. At the end of the paragraph in the letter, of which this sentence was a substantial part, however, was a reference to a recently published article in a peer reviewed journal, discussing the positive benefits to patients in respect of one renal unit's change to using IV Eprex. The statement was not all-embracing as alleged by Roche, implying that it applied to all erythropoietins. The statement applied to those health professionals who had returned to using IV Eprex and who had discovered the benefits that had accrued for their patients as a result. The words 'the right thing to do' did not, as Roche alleged, imply that was the only choice, however, it was the right choice in respect of Eprex and in accord with the SPC; it was also 'the right thing to do' for the positive reasons which had been alluded to, such as patient preference and improved compliance. As such, the phrase was not exaggerated nor all-embracing and was not in breach of Clause 7.10.

By advocating IV administration, the letter did not detract from the standing of those individuals in favour of continuing to use the SC route for products so licensed, and did not breach Clause 7.3, and did not offend clinicians. Ortho Biotech did not disparage the practice of any individual by distributing this letter; it merely promoted the benefits of IV Eprex, and within the spirit of emerging science and clinical knowledge, stimulated debate as to the overall benefits of IV over SC administration in respect of PRCA in a manner which was not inconsistent with the spirit of the Code. Ortho Biotech therefore denied breaches of Clauses 7.3 and 9.1.

Ortho Biotech noted Roche's complaint that it had failed to address the possible need for hospital visits and the increase in local and systemic infection when switching to IV treatment, especially when the maintenance and continued patency of IV access was vitally important. These comments certainly applied to pre-dialysis patients where there was a need to protect IV access; Ortho Biotech would not advocate IV administration in these individuals. However, the letter very clearly stated haemodialysis patients (thus excluding CAPD patients) of which the vast majority attended hospital up to three times a week for their dialysis, whereupon they already had IV access for the purposes of dialysis and hence could receive Eprex via this route.

Clinicians and nurses in centres which used IV Eprex had found the benefits that Ortho Biotech alluded to in its statement; Ortho Biotech noted that these were expounded within a peer reviewed publication.

The Eprex SPC allowed for the promotion of IV Eprex. Within the letter there was no requirement to discuss options for other erythropoietins. Ortho Biotech submitted that its promotional position was not misleading in these respects, and did not denigrate the SC route, nor fail to recognise the standing of health professionals who wished to retain SC administration for their haemodialysis patients. Ortho Biotech therefore denied breaches of Clauses 7.3, 7.10 and 9.1.

Ortho Biotech noted that Roche had complained that in the brochure the statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do for other very positive reasons' was in breach of Clause 7.10, in that it was all-embracing and implied that all erythropoietins should be given IV because the paragraph immediately followed one stating PRCA had occurred with other erythropoietins. The statement however, stated that the return to the IV route was also the right thing to do for 'other very positive reasons'. The word 'other' implied that there were other reasons to use the IV route not specifically

related to PRCA. The brochure then progressed to expand on this theme; that the IV route was preferred by patients, that it ensured compliance and further, had a minimal impact on nurse resource. As the brochure promoted the use of Eprex within its licence, it was not unreasonable to advocate IV use and in doing so did not imply that all erythropoietins should be given IV, since this was a judgement for individual clinicians. Ortho Biotech denied a breach of Clause 7.10. Ortho Biotech also denied breaches of Clauses 7.3 and 9.1 since those clinicians who still favoured SC use for those products so licensed might continue to do so; the fact that Ortho Biotech advocated Eprex did not cause offence; it promoted Eprex in a manner consistent with its licence.

PANEL RULING

The Panel considered that the statement 'As healthcare professionals return to using the IV route, they are discovering it is also the right thing to do …' implied that not using the IV route was the wrong thing to do. The statement did not clearly relate only to Eprex, for which returning to the IV route was the right thing to do. The statement followed a paragraph which referred to other erythropoietins and so would be assumed by some readers to also apply to other erythropoietins which was not so. Erythropoietins other than Eprex could still be administered SC in renal patients, there was no requirement to administer them IV. The Panel considered that the claim was misleading as alleged and ruled a breach of Clause 7.2.

The Panel considered that the phrase 'the right thing to do' was all-embracing as it implied that everything else was the wrong thing to do. The Panel considered that by implication the statement disparaged those prescribers who legitimately continued to use another erythropoietin subcutaneously. Breaches of Clauses 7.10 and 9.1 were ruled.

The Panel noted that Roche had also alleged a breach of Clause 7.3 of the Code. Clause 7.3 related to comparisons. The Panel did not consider that the statement constituted a comparison of Eprex with any other medicine and on that basis ruled no breach of Clause 7.3.

The Panel did not consider that the claim was misleading with regard to the need for hospital visits and the possibility of an increased risk of infection. In the Panel's view the statement referred to benefits of IV administration but did not imply that there were no disadvantages. No breach of Clause 7.2 was ruled.

5 Cost of switching to SC use

COMPLAINT

Roche noted that the letter stated that 'The anticipated barriers to switching route of administration – i.e. significantly higher doses, cost, nursing resource – are, in reality, not materialising'. The brochure included the claim 'Switching to IV Eprex should not affect your budget'. The cost of switching from SC to IV was, in fact, of concern. For example, a recent publication estimated shifting all patients in Italy would increase costs from 31.1 to 46.7 million US$/year. This might be avoided by considering a SC alternative to IV Eprex.

Fullerton *et al* (2002/2003) which was published in the British Journal of Renal Medicine and cited in the letter and brochure was not representative of the published information and there were reservations about the methodology used. In contrast, there were two reputable journals reporting at a higher standard of evidence; one presented a methodologically robust parallel arm study and the other a meta-analysis. These two studies found that switching from IV to SC brought about a 30% dose saving. However switching SC to IV, as endorsed by Ortho Biotech, increased doses by about 50% – on latest MIMS prices this could represent up to a 50% cost increase. Hence, because the cost comparisons of IV and SC in this letter and brochure were unfair and failed to consider the full body of scientific opinion, the letter and brochure breached Clause 7.2. The claims on costs were also misleading in breach of Clause 7.3.

Roche noted that the British Journal of Renal Medicine was a small circulation magazine entirely sponsored by Ortho Biotech. This was not made clear in the way the reference to Fullerton *et al* was cited in either the letter or the brochure. Roche alleged that failure to declare sponsorship was in breach of Clause 9.9 in the letter, brochure and in the Journal itself.

RESPONSE

Ortho Biotech noted that Roche had alleged breaches of Clauses 7.2 and 7.3 in respect of the cost of switching from SC to IV. Indeed, the literature generally stated that there was an increase, which could be quite substantial, in the dose of an erythropoietin required to treat anaemia in patients with chronic renal failure when using the IV route compared to the SC route. When undertaking any health economic review of such costs, however, the predominant factor was the acquisition cost of the medicine. Hence, a simple health economic argument would be that if significantly more IV epoetin was used that would significantly increase costs in a proportionate manner. This, however, failed to take into account the fact that Ortho Biotech had not seen the dramatic increases in dose that would have been predicted on the basis of published literature, and had commented only on its experience of those units which had changed from SC to IV Eprex. At the time the letter was sent the majority of units had only reported slight increases in the dose of Eprex; one unit reported an increase of only 6% (Fullerton *et al*).

Additionally, the letter stated that Ortho Biotech had a wide range of clinical and commercial support that could be offered to help units switch haemodialysis patients to IV Eprex, and this included cost neutralisation, such that there would be no or minimal budgetary impact. Ortho Biotech denied breaches of Clauses 7.2 and 7.3.

Ortho Biotech was not sponsoring anything when sending the letter or mailer but promoting IV Eprex in accordance with its licence. The British Journal of Renal Medicine, although fully supported by Ortho Biotech, was managed by an independent editorial

board which maintained an independent peer review process for publication of articles. Ortho Biotech did not influence this peer review process nor exert influence over the independence of the editorial board. Ortho Biotech strongly denied any breach of Clause 9.9.

PANEL RULING

The Panel noted that in the letter the statement 'The anticipated barriers to switching route of administration – i.e. significantly higher doses, cost, nursing resource – are, in reality, not materialising' was referenced to Fullerton *et al*. Fullerton *et al* reported the initial results of a systematic conversion of a large population of haemodialysis patients from SC to IV dosing of Eprex. By the end of the study there was three months' data from 135 patients. The mean dose of Eprex was increased by 6.3% from baseline (p=0.08) over the three months. The authors noted, however, that the results would need to be confirmed through further observation of longer-term dosing and also confirmed in other UK centres.

The Panel considered that on the basis of one small, short-term study the statement in the letter and the claim in the brochure 'Switching to IV Eprex should not affect your budget' had not been substantiated and were misleading in that regard. The comparison of the cost of SC Eprex vs IV Eprex was unfair. It was immaterial that Ortho Biotech was offering cost neutralisation packages. In that regard the Panel considered that the offer of such packages in itself implied that switching to IV Eprex would affect budgets. Breaches of Clauses 7.2 and 7.3 were ruled. This ruling was appealed.

The Panel did not consider that the citation of Fullerton *et al* in the letter and the brochure needed to state that the journal was sponsored by Ortho Biotech. No breach of Clause 9.9 was ruled. The Panel considered, however, that the reprint should have declared the company's sponsorship of the journal and ruled a breach of Clause 9.9 in that regard.

APPEAL BY ORTHO BIOTECH

Ortho Biotech stated that the claim in the brochure 'Switching to IV Eprex should not affect your budget' was a factual statement based upon the experiences of those units which had converted from SC to IV Eprex. Roche had cited a publication which estimated that similarly converting all patients in Italy would increase costs from $31.1 to $46.7 million per year and suggested that such increases might be avoided by considering a SC alternative to IV Eprex (presumably NeoRecormon).

Ortho Biotech stated that this was a simplistic view of the health economics involved. In undertaking health economic evaluations of the use of erythropoietins, consistently the most sensitive element was price. If price was altered, the outcomes in terms of health gains were substantially altered in respect of the financial costs.

Ortho Biotech further considered that the health economics which might apply to Italy were not necessarily appropriate to the UK. Roche had suggested that Fullerton *et al*, was not representative of published information and that there were reservations about the methodology used. Fullerton *et al* appeared in a journal, which although sponsored by Ortho Biotech, retained its editorial independence and peer review processes. Roche also cited Kaufman *et al* and Besarab *et al* as being higher level evidence and suggested that somehow these provided the definitive answer to the question of the dose differentials that might apply when switching from SC to IV Eprex. The two papers were, however, now several years old and related to patients who had changed from IV use of erythropoietin to SC use, or patients who had been compared within a clinical study in a parallel or cross-over fashion. The methodology of these studies therefore was different from the change which might occur when converting from SC to IV Eprex. In this respect, the only paper which had so far been published in a peer review journal was Fullerton *et al* and hence it had particular relevance.

Ortho Biotech stated that it had undertaken to neutralise the impact of any dose changes that might occur as a result of a change from SC to IV Eprex. This took into account the published literature which stated that in general a higher dose of erythropoietin was needed for IV use, and also that the efficiency of the IV route compared to the SC route (in terms of dose of an erythropoietin required) had varied within the published literature.

Ortho Biotech submitted therefore, in converting patients from SC to IV Eprex it had undertaken two principal actions in respect of the health economics:

Firstly, a review of doses used historically within those units undergoing a conversion to IV Eprex such that should the dose of Eprex increase once the change to IV had occurred, this increase would be assessed and the difference returned to the unit so that there would be no overall budgetary impact to that particular unit.

Secondly, given the possible variability of a change in the dose of Eprex that might be found by an individual unit, that these changes would be assessed within the unit on an ongoing basis rather than relying on published clinical trial data, which might not be applicable to that unit. One unit, which had changed from SC to IV Eprex had reported a 6% increase in the dose of Eprex used (Fullerton *et al*). This was less than the increases quoted in the literature cited by Roche, was relevant to the nephrology community and was a genuine finding. Those nephrologists or renal specialists who might have questioned the findings of Fullerton *et al* could challenge them by means of correspondence to the author in the usual spirit of academic debate.

Ortho Biotech submitted that whilst the debate about the efficiency or otherwise of IV administration (compared to SC administration) in respect of the dose of epoetin used would continue, the fact remained that Ortho Biotech had reviewed the doses of Eprex used within the units which had converted to IV Eprex and taken steps to ensure that there was no increase in budgetary spend in those units. Therefore the claim in the brochure 'Switching to IV

Eprex should not effect your budget' was a factual statement based upon the activity which Ortho Biotech undertook with individual renal units. Ortho Biotech submitted that it had not misled the nephrology community in respect of this statement and denied breaches of Clauses 7.2 and 7.3.

COMMENTS FROM ROCHE

Roche noted that in its general comments Ortho Biotech had stated that 'Roche, in its communications to the healthcare and broader scientific community during June/July 2002, had stressed that NeoRecormon was categorically not associated with PRCA'. This statement was without any foundation and sought to mislead the Panel. Ortho Biotech had made the same statement in Cases AUTH/1399/12/02 and AUTH/1415/2/03 despite this being specifically challenged at the appeal hearings by Roche. Roche suggested that the Panel should acquire substantiation of this statement from Ortho Biotech.

Roche supplied materials extracted from the aforementioned appeals submitted by Ortho Biotech namely the Roche company statement of 19 July 2002 and Ortho Biotech's interpretation of Roche's company statement highlighting what it alleged to be Ortho Biotech's false assertions.

Roche alleged that the allusion to other regulatory authorities in Ortho Biotech's general comments seemed to cast doubt on the competence of the Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency) in the matter of withdrawing SC Eprex in nephrology and again attempted to raise concerns over the SC route for all erythropoietins.

Roche maintained that Ortho Biotech had an ongoing campaign of misinformation in these matters, to favour IV erythropoietins over its discredited SC indication in nephrology. Roche requested that the Panel ask Ortho Biotech to refrain from misrepresenting Roche in the manner outlined above.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue in the letter, 'The anticipated barriers to switching route of administration – i.e. significantly higher doses, cost, nursing resource – are, in reality, not materialising.', was referenced to Fullerton *et al* which presented data from 135 patients to show that, over a three month follow-up period, the mean dose of Eprex had increased by 6.3% from baseline (p=0.08%) when switching from SC to IV dosing. The authors commented that their results needed to be confirmed through further observation of longer-term dosing and confirmed in other UK centres. The Appeal Board also noted that two other papers (Kaufman *et al* and Besarab *et al*) had indicated that the difference in dose between IV and SC erythropoietins, not necessarily Eprex, could be closer to 30%.

The Appeal Board noted Ortho Biotech's submission that the claim at issue was substantiated by the fact that it had offered cost neutralisation packages to cover the cost of any increased dosing requirements incurred in switching from SC to IV Eprex. However, the Appeal Board noted that the letter made no reference to budgets or to cost neutralisation packages. The Appeal Board considered that on the basis of one small, short-term study the statement in the letter was misleading and had not been substantiated. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3 of the Code. The appeal on this point was unsuccessful.

With regard to the brochure, the Appeal Board noted that the claim 'Switching to IV Eprex should not affect your budget' was followed by the statement 'Talk to Ortho Biotech: we can help'. The 'help' was in the form of a cost neutralisation package. The Appeal Board noted its comments above and considered that the claim implied that switching patients from SC to IV Eprex had no cost implications which was not so. The fact that Ortho Biotech was subsidising the switch was immaterial. 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 were upheld. The appeal on this point was unsuccessful.

6 Letter alleged to be disguised promotion

COMPLAINT

Roche alleged that although the letter purported to discuss safety issues it was in fact disguised promotion of Eprex in breach of Clause 10.1. It should fail to beguile the expert, but it might confuse the non-specialist and those in training on important matters of patient safety.

RESPONSE

Ortho Biotech submitted that the letter was overtly promotional, sent by a product manager to health professionals advocating the use of IV Eprex in haemodialysis patients, in accordance with the SPC. Ortho Biotech therefore denied breach of Clause 10.1.

PANEL RULING

The Panel did not consider that the letter was disguised promotion of Eprex. The letter was signed by a product manager and featured the Eprex brand logo in the bottom right-hand corner. The Panel considered that the letter was clearly promotional. No breach of Clause 10.1 was ruled.

7 Provision of data on file

COMPLAINT

Roche stated that it had attempted to review the 'Data on File' cited by Ortho Biotech in the letter and brochure but was told that the data was unavailable as it was held in commercial confidence. Roche alleged that this was a clear breach of Clause 7.7.

RESPONSE

Roche had contacted Ortho Biotech in respect of the 'Data on File' cited in the letter; this was in respect of

the number of patients receiving IV Eprex. Ortho Biotech had responded that it closely monitored renal units where it conducted its business and therefore was able to provide a total number of patients receiving IV Eprex, though it did not give Roche its commercially confidential databases in this respect. Ortho Biotech considered that this was in keeping with standard industry practice, and having provided Roche with the information on how Ortho Biotech acquired its figures, believed this was sufficient and in keeping with the spirit of the Code. Ortho Biotech therefore denied breach of Clause 7.7.

PANEL RULING

The Panel noted that the supplementary information to Clause 7, General, stated that the application of this clause was not limited to information or claims of a medical or scientific nature. It included, *inter alia*, information or claims relating to pricing and market share. Thus, for example, any claim relating to the market share of a product must be substantiated without delay upon request as required under Clause 7.5. Clause 7.7 of the Code stated that when promotional material referred to data on file, the relevant part of that data must be provided without delay at the request of members of the health professions or appropriate administrative staff.

In the letter and in the brochure a claim that the number of haemodialysis patients receiving IV Eprex was approaching 3,500 was referenced to data on file. Ortho Biotech had not supplied Roche with the data on file to substantiate the claim as it regarded the data as being commercially confidential. The Panel noted that it was a principle under the Code that if a claim could only be substantiated by material which a company wished to keep confidential then the claim must not be made. A breach of Clause 7.7 was ruled.

APPEAL BY ORTHO BIOTECH

Ortho Biotech noted that Clauses 7.5 and 7.7 of the Code stated that substantiation of information, claims or comparisons should be provided without delay at the request of members of the health professions or appropriate administrative staff. The Code did not expound on the use of the word 'appropriate' in terms of administrative staff nor did it define 'health professionals'. Ortho Biotech submitted that these provisions were within the Code so that health professionals or their administrative staff (ie a consultant's secretary) who were involved in patient management could seek clarification on points of comparison, claims or other information put into the public domain by pharmaceutical companies. The clauses were not designed to allow pharmaceutical companies to obtain commercially sensitive information from their competitors.

Ortho Biotech submitted that no health professional working within the speciality of nephrology had made such a request to it, although had they done so Ortho Biotech would have taken them through how it obtained those figures, taking into account patient confidentiality.

Ortho Biotech did not believe that companies should use the Code to obtain commercially sensitive data from their competitors and as such appealed a breach of Clause 7.7.

COMMENTS FROM ROCHE

Roche referred to its comments at point 5 above.

APPEAL BOARD RULING

The Appeal Board noted that Ortho Biotech's submission was incorrect in that Clause 1.4 of the Code defined the term 'health professional'.

The Appeal Board noted Ortho Biotech's submission that the data on file was commercially sensitive and that it was not company practice to share information about individual business accounts outside the company. The Appeal Board noted that, in response to Roche's request to review the data on file it had been told by Ortho Biotech that it had gathered data on patient numbers receiving Eprex from all units where it conducted business with the co-operation of the clinical departments in question. At the time of going to press with the material in question the company could confirm that it had approximately 3,500 haemodialysis patients registered as receiving IV Eprex. The Appeal Board considered that such a reply did not provide enough information such that a recipient could be sure that the figure of 3,500 was credible. It was a principle under the Code that if a claim could only be substantiated by material which a company wished to keep confidential then the claim must not be made. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.7 of the Code. The appeal on this point was unsuccessful.

8 Brochure

COMPLAINT

Roche stated that the brochure distorted the issues and might confuse the reader on important matters of patient safety; it prominently displayed the Eprex brand logo, discussed Eprex safety issues, made claims about the IV route of administration for erythropoietins in nephrology and disparaged the SC route. It was therefore promotional in nature and came within Clause 1.2 of the Code.

Given the context in which the brochure was supplied, its title ' … leadership is doing the right thing' implied that 'leaders' were switching from SC to IV administration for all erythropoietins, which was not true. It also implied that if you were not switching you were neither a leader nor 'doing the right things'. This failed to recognise the professional standing of most of the audience and breached Clauses 9.1 and 7.10 (exaggerated and all-embracing claims).

There was no date on the brochure in breach of Clause 4.9.

RESPONSE

Ortho Biotech submitted that the title of the brochure, '…leadership is doing the right things', did not imply that 'leaders' were those switching from SC to IV

administration for all erythropoietins. The quotation, which was from an industry renowned performance coach, was on the front of the brochure along with the Ortho Biotech company logo and also importantly the Eprex product logo, hence it was clear that the subject matter was in regard to the promotion of Eprex. It did not imply to readers that if they were not switching to IV Eprex they were neither a 'leader' nor 'doing the right things'. Individuals made choices within the context of their own clinical practice, and as was generally accepted in medicine, there were often many different ways of achieving the same end point. 'Leadership' also meant many different things to many different individuals. Consequently, health professionals were free to conduct their clinical practice within the general constraints of the accepted norms of practice for that particular discipline, accepting that practice variations existed, though this did not diminish them in any respect should their own practice differ from that of another practitioner. The licence for Eprex in nephrology was exclusively for IV use hence it was not unreasonable to promote this route of administration. As this was a departure from the previously accepted clinical practice, challenging this paradigm (continuation of the SC route for other erythropoietins) was not out of accord with usual practices in industry.

Though the statement, '…leadership is doing the right things', was thought provoking, it did not fail to recognise the professional standing of the intended audience; market research had shown that the statement and concept were generally well accepted. Ortho Biotech therefore denied a breach of Clause 9.1 and further denied that the title was exaggerated and all-embracing in breach of Clause 7.10. The title did not make any claims in respect of Eprex but was merely a thought provoking statement.

Ortho Biotech accepted that the brochure was not dated, in breach of Clause 4.9, and had put in place action to ensure that this did not occur again.

PANEL RULING

The Panel considered that from the title of the brochure '… leadership is doing the right things' some readers might assume that if they were not using Eprex then they were neither leaders nor were they doing the right things. Nonetheless, in association with the Eprex product logo and in the context of a promotional mailing for the product the quotation appeared to be about Eprex. The Panel considered that the claim failed to recognise the professional standing of the audience and thus ruled a breach of Clause 9.1. The Panel further considered that the claim was exaggerated and all-embracing – using Eprex was not the only right thing to do. A breach of Clause 7.10 was ruled.

The Panel noted that Ortho Biotech had acknowledged that the brochure was undated. A breach of Clause 4.9 was ruled.

9 Graph entitled 'The return to IV administration in haemodialysis'

A graph on page two of the brochure showed the numbers of UK haemodialysis patients from August 2002 - February 2003 who received either IV Eprex or SC erythropoietin. The graph showed a steady rise for IV Eprex from almost zero to 3,500 in that time with SC erythropoietin falling from just over 14,000 patients in August 2002 to about 11,000 in February 2003.

COMPLAINT

Roche noted that the graph was not referenced. It showed a decline in the number of patients using subcutaneous epoetins and a mirror image rise in IV Eprex, to suggest that IV Eprex was taking all the SC epoetin switches. This was misleading from Roche's understanding of the market dynamics. Firstly, if there was a decline in the use of SC epoetin this was not the case for NeoRecormon for which SC use was increasing. The decline was probably only with Eprex although this was not clear. Secondly, it was not clear either whether SC epoetin referred only to epoetin alfa and beta or included darbepoetin. Some of the decline in epoetin use in general might be due to the use of the newer product darbepoetin. Thirdly, the title did not make clear that the so-called return to IV administration was for Eprex only. To then have one line showing a decline in SC epoetin vs an increase in Eprex was again mixing the specific with the general designed to mislead the reader into believing that there was a general reduction in the use of SC epoetin and that this was being replaced only by an increase in IV Eprex. The reality was that there was a general decline in the use of SC Eprex which was being compensated for by an increase in SC NeoRecormon, an increase in IV Eprex and probably an increase in mainly IV darbepoetin.

Roche alleged that the graph breached Clauses 7.2, 7.3, and 7.8. There was no explanation how these data had been generated. Roche further alleged that the graph was not capable of substantiation in breach of Clause 7.4.

RESPONSE

Ortho Biotech stated that the number of patients who were receiving IV Eprex was known to the company because of its careful diligence following the contraindication of SC Eprex and, as there was a relatively fixed number of haemodialysis patients within the UK, a rise in the number of patients receiving IV Eprex should be commensurate with a decrease in the number of haemodialysis patients receiving SC erythropoietins. However, the graph was in relation to IV Eprex, and Ortho Biotech acknowledged that it might well be that some patients also received other IV erythropoietins. However, Ortho Biotech, supported by Roche's contention that 90% of NeoRecormon was administered SC, understood this was a small number of patients, hence it believed the chart based on its data to be sufficiently accurate and hence denied breaches of Clauses 7.2, 7.3, 7.4 and 7.8.

Ortho Biotech noted that Roche had also stated that SC NeoRecormon use was increasing. This might well be true, however, many CAPD or pre-dialysis patients received SC erythropoietins and these markets were not available in general to Eprex, since

the use of IV erythropoietins in these patients was considered inappropriate. The graph referred to haemodialysis patients in whom the IV route was available and as shown the use of IV Eprex had been increasing since 2002. Ortho Biotech also noted that the graph did not refer to the decline in epoetin use in general but specifically the use of SC erythropoietins in haemodialysis patients. Ortho Biotech stated that the graph was specific, whereas Roche's points of contention were based on the broader nephrology market and were inappropriate to this discussion.

Roche had also suggested that the graph was designed to mislead the reader into believing that there was a general reduction in the use of SC epoetin and that this was being replaced only by an increase in IV Eprex. Ortho Biotech stated that Roche had either misunderstood the graph or deliberately misinterpreted it. Prior to the 'Dear Doctor' letters being sent by Ortho Biotech advising firstly on a recommendation to change from the SC route of administration and then secondly, contraindicating the SC route of administration, meant that although many patients were receiving Eprex IV, a number of patients who were receiving Eprex SC were now receiving other erythropoietins. This should be very clear within the graph, in that as SC Eprex was contraindicated, the difference between those patients on IV Eprex and other patients would be those receiving an erythropoietin (but not Eprex) either SC or IV, though because of the current practice in the UK, the vast majority of these patients would be receiving SC erythropoietins. Therefore the graph was not inaccurate. Ortho Biotech believed that the facts presented within the graph were fully substantiable and hence again denied breaches of Clauses 7.2, 7.3, 7.4 and 7.8.

PANEL RULING

The Panel noted that the graph consisted of two converging lines labelled 'IV Eprex' and 'SC Epo' respectively. The Panel considered that the impression given was that the SC use of all erythropoietins was declining and being replaced with IV Eprex, the use of which was increasing. The graph was entitled 'The return to IV administration in haemodialysis'. The Panel noted that although haemodialysis patients on SC Eprex were having to be switched to IV Eprex there were other erythropoietins which could still be used SC. The Panel noted Ortho Biotech's submission that the graph was 'sufficiently accurate' and 'not inaccurate' but considered that this was inadequate. The Code required all claims, comparisons etc to be accurate. The Panel considered that the graph was misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2, 7.3, 7.4 and 7.8 were ruled.

10 Claim 'Patients prefer IV dosing'

COMPLAINT

Roche alleged that the claim 'Patients prefer IV dosing', which appeared as a paragraph heading on page three of the brochure, failed to address the possible need for hospital visits and increased risks of local and systemic infection – especially when the maintenance and continued patency of IV access was vitally important in this patient group. In addition Kaufman *et al* (1998) cast some doubt on the claims about tolerability. Whilst a general preference for IV was expressed, a subgroup of patients who had received SC treatment for a reasonable period of time expressed a preference for that route. Roche also noted that the European and American Best Practice Guidelines advocated SC, largely on cost grounds. Roche alleged that the claim was, therefore, not balanced in breach of Clause 7.2. Roche noted that the European guidelines favouring SC use were co-developed and supported by Janssen-Cilag (owned by Johnson & Johnson) which had promoted Eprex prior to Ortho Biotech (also owned by Johnson & Johnson), and it then spent many years advocating these guidelines. Hence, the U-turn in approach now advocating the IV route for all epoetins (with the enforced withdrawal of Eprex's SC route) did not seem credible.

Finally, in contrast to page 2 of the brochure where claims were specified for haemodialysis patients, this particular claim was not. Therefore the impression was given that IV was preferred for all renal patients. The large group of patients not on dialysis tended to be treated by the SC route in the UK. This was also part of the expert guidance. There was no evidence that these patients would prefer the IV route. Roche alleged that the statement was misleading in breach of Clause 7.2.

RESPONSE

Ortho Biotech noted Roche had failed to recognise that the brochure related to haemodialysis patients, the vast majority of whom attended hospital for dialysis sometimes up to 3 times a week (home dialysis had been diminishing in the UK over the last decade), therefore patients would already be in hospital with IV access secured for dialysis. Patients therefore might receive IV Eprex via an existing IV portal. Under these circumstances, patients in centres where IV Eprex was now given had indicated that they had a preference for this route since they no longer had to inject themselves subcutaneously at home or collect and be responsible for supplies of Eprex.

Roche's comments in respect of hospital visits would be most appropriate for CAPD and pre-dialysis patients since, as previously stated, SC use was preferred for such patients. Ortho Biotech did not advocate IV use in these patient groups. The brochure was in respect of haemodialysis patients only.

Roche suggested that Kaufman *et al* cast some doubt on the claims about the tolerability of the IV route suggesting that a sub-group of patients who had received SC treatment for a reasonable period of time expressed a preference for that route. This in fact misquoted the study. The study, principally examined the quantity of epoetin used, SC compared with IV, and also explored patient acceptability although this was not the primary objective. At the completion of the study, the patients who had at some point

received both IV and SC epoetin (n=96) were asked to state which they preferred. 74% preferred the IV route with the remaining 26% expressing either no preference or a preference for the SC route. Furthermore, the patients that were assigned primarily to SC were more likely than those assigned to IV to have no preference or prefer the SC route, though the article did not break this subdivision down further. It was clear therefore that the majority of patients who had experienced both routes of administration preferred IV, consistent with the findings of Fullerton *et al*. Ortho Biotech therefore denied an imbalance in stating patient preferences and hence denied a breach of Clause 7.2.

Roche had also further alleged that it was not clear that the claim 'Patients prefer IV dosing' related to haemodialysis patients only. The whole point of the brochure and its accompanying letter was the return to IV administration in haemodialysis patients. Nowhere did it refer to other renal patients for whom SC was the preferred route. The nephrology community was well aware of this issue, such that Roche's suggestion that the claim was misleading in breach of Clause 7.2 was difficult to understand. Ortho Biotech therefore denied a breach of Clause 7.2 in this instance.

PANEL RULING

The Panel noted that the brochure referred to IV administration in haemodialysis on page 2, the letter also referred to haemodialysis patients. Page 3 did not refer to haemodialysis patients as such and perhaps could have been clearer in this regard, nevertheless the Panel did not consider that the page would be seen as referring to all renal patients as alleged. The Panel thus ruled no breach of Clause 7.2 in this regard.

The Panel noted that Kaufman *et al* provided some data to support preference for IV dosing. In the Panel's view given that the patients were haemodialysis patients, the claim 'Patients prefer IV dosing' was not unreasonable nor unbalanced. No breach of Clause 7.2 of the Code was ruled.

11 Claim 'Counselling patients on self injection is therefore no longer necessary'

This claim appeared on page three of the brochure in a paragraph headed 'IV dosing has been shown to have minimal impact on nurse resource'.

COMPLAINT

Roche alleged that the claim was bizarre, inaccurate and unsubstantiated in breach of Clauses 7.2 and 7.5. It would confuse a nurse in training.

RESPONSE

Ortho Biotech noted that when a haemodialysis patient received IV Eprex (or any other IV erythropoietin), there was no longer the requirement for that patient to self administer the epoetin at home subcutaneously and therefore it was not necessary to train such patients in the technique of self injection. Under these circumstances the claim 'Counselling patients on self injection is therefore no longer necessary', was true and accurate. Ortho Biotech failed to understand how Roche would deem this 'bizarre' or how such a statement would 'confuse a nurse in training'. Ortho Biotech was confident that trainee nurses in the UK would be fully able to give the appropriate advice to their patients as they progressed through their training. Ortho Biotech therefore denied breaches of Clauses 7.2 and 7.5.

PANEL RULING

The Panel noted that the claim appeared under the heading 'IV dosing has been shown to have minimal impact on nurse resource' and as part of a mailing detailing the change from SC to IV dosing for Eprex. In the Panel's view, given the context in which it appeared, the claim was self-evident ie patients who received IV Eprex did not require counselling with regard to self injection. The Panel did not consider that the claim was inaccurate. No breach of Clause 7.2 was ruled.

Roche had also alleged a breach of Clause 7.5 which required companies to provide substantiation for claims etc without delay upon request. There was no evidence before the Panel from Roche to support its allegation, ie that Roche had asked Ortho Biotech for substantiation, nor had Ortho Biotech provided details in its response. The Panel decided that it was obliged to rule no breach of Clause 7.5 of the Code.

12 Claims 'IV and SC doses are not substantially different' and 'Switching to IV Eprex should not affect your budget'

COMPLAINT

Roche alleged that the paragraph heading 'IV and SC doses are not substantially different' on page 3 of the brochure was confusing. Did it refer to Eprex IV and SC, in which case it was a breach of Clause 3.1 as the Eprex marketing authorization for the SC route was revoked? Alternatively, was this a reference to IV Eprex and other SC erythropoietins in which case it became all-embracing and a breach of Clause 7.10?

Roche alleged that the heading to page 4 of the brochure 'Switching to IV Eprex should not affect your budget' was similarly all-embracing in breach of Clause 7.10. Switching from what?

RESPONSE

Ortho Biotech noted that the brochure was about the use of IV Eprex not SC Eprex and hence Roche's suggestion of a breach of Clause 3.1 of the Code was inappropriate. It was, however, not inappropriate when changing from SC to IV to explore the impact in terms of the dose of Eprex. Such reviews were undertaken in a prospective manner and therefore in the centres where clinicians switched from SC Eprex to IV Eprex, Ortho Biotech had comparative data which suggested that the doses were not substantially different. This contradicted some of the published literature, though much of which was now

considerably out of date due to the changes in practice of iron management. By making such statements about the differences in doses following a change to IV Eprex, Ortho Biotech was not advocating the SC route for Eprex, and therefore was not in breach of Clause 3.1.

Roche's alternative suggestion for Ortho Biotech's statement was that the claim referred to IV Eprex and other SC erythropoietins as being all-embracing in breach of Clause 7.10. This was not Ortho Biotech's intention, nor was it the meaning of the statement, however, Ortho Biotech pointed out Eprex and NeoRecormon were measured and dosed in terms of international units, therefore doses of one were equivalent to doses of the other, and as such a comparison of doses here would not be an exaggerated claim and not in breach of Clause 7.10.

Roche suggested that the claim 'Switching to IV Eprex should not affect your budget' was all-embracing in breach of Clause 7.10. Roche asked the question 'switching from what?' It was quite obvious that patients who might be on a SC erythropoietin could be changed to IV Eprex, and since Ortho Biotech had a cost neutralisation programme for units converting to IV Eprex there would be no change in cost to them, hence the statement was accurate and not in breach of Clause 7.10.

PANEL RULING

The Panel considered that given the context in which the claim 'IV and SC doses are not substantially different' appeared it was clear that it referred to IV and SC doses of Eprex such that when patients were changed from SC Eprex to IV Eprex the dose would remain more or less the same. The Panel did not consider that the claim referred to all SC erythropoietins or that it promoted the use of SC Eprex in renal patients. No breach of Clauses 3.1 and 7.10 was ruled.

Similarly, the Panel did not consider that the claim on page 4 of the brochure 'Switching to IV Eprex should not affect your budget' was all-embracing as alleged. In the context of the brochure it was clear that the claim referred to switching from SC Eprex to IV Eprex. No breach of Clause 7.10 was ruled. The claim had been ruled in breach of the Code for different reasons (point 5 above).

13 Statement 'Subcutaneous administration remains appropriate in all other indications, please refer to SmPC'

COMPLAINT

Roche noted that the statement appeared in a highlighted box beneath the prescribing information on the back page of the brochure. This clearly constituted a claim for indications other than renal failure and so the brochure should bear prescribing information for indications other than the renal indication. Roche alleged a breach of Clause 4.1.

RESPONSE

Ortho Biotech submitted that the statement did not make any claims for indications outside the nephrology indication, but emphasized that the contraindication of the SC route, and hence the promotion of the IV Eprex was specific to the nephrology indication. Should readers wish to have further information they were referred to the SPC. Ortho Biotech therefore denied a breach of Clause 4.1.

PANEL RULING

The Panel did not consider that the statement at issue constituted promotion of the non-renal indications for Eprex. No breach of Clause 4.1 was ruled.

14 Alleged breach of Clause 2

COMPLAINT

Roche alleged that Ortho Biotech's letter and brochure were part of a disreputable campaign that had been found in breach of many clauses of the Code, including Clause 2 (Case AUTH/1399/12/02). Roche would like to see the Panel request that a balancing retraction statement be sent to the appropriate audience by Ortho Biotech (agreed by Roche and the Panel) to put matters straight. Roche referred to its allegation that the letter misled on important matters of patient safety (see point 6 above) and alleged a breach of Clause 2 as in its opinion the letter did nothing to retain confidence in the pharmaceutical industry.

RESPONSE

Ortho Biotech stated that it could not understand why Roche considered a letter promoting the use of Eprex according to its SPC was in breach of Clause 2. Ortho Biotech denied therefore a breach of Clause 2 in respect of the letter and other activities promoting the use of IV Eprex.

PANEL RULING

The Panel noted its comments and rulings above and considered, on balance, that there had been no breach of Clause 2 which was a sign of particular censure and reserved for such use.

Complaint received **15 May 2003**

Case completed **4 November 2003**

CASES AUTH/1470/5/03 and AUTH/1488/6/03

NORGINE and CONTINENCE NURSE SPECIALIST v SCHWARZ PHARMA

Promotion of Idrolax

Norgine (Case AUTH/1470/5/03) and a continence nurse specialist (Case AUTH/1488/6/03) complained about the promotion of Idrolax (macrogol 4000) by Schwarz Pharma. Idrolax was indicated for the symptomatic treatment of constipation in adults and children aged 8 years and above. The promotional item at issue in both cases was a leavepiece; Norgine additionally complained about a journal advertisement and a detail aid. Norgine supplied Movicol (polyethylene glycol (macrogol) 3350 plus electrolytes.

Norgine alleged that the claim 'Does not contain the dose of salts of some other macrogols' disparaged its product Movicol. There were only two macrogol products on the market, Movicol and Idrolax, and so 'other macrogols' clearly referred to Movicol. Norgine considered that Movicol had been disparaged through association with the phrase 'like a dose of salts' which had an emotive meaning and went much further than a purely factual statement.

The continence nurse specialist alleged that the claim implied that another medicine had harmful salts which could have harmful effects. She considered it a clever, though underhand, use of the well-known phrase 'a dose of salts'.

The Panel considered that the term 'dose of salts' would be seen as a general description of a laxative action not just a laxative action linked to Epsom Salts as submitted by Schwarz. The Panel considered that the term was commonly used as a derogatory term and that in the context of a leavepiece about the treatment of constipation it disparaged Movicol; a breach of the Code was ruled.

Norgine alleged that the word 'excellent' and the phrase 'first-line option' in the claim 'The clinical profile of Idrolax makes it an excellent first-line option for constipated patients who are elderly or less mobile' were superlative terms which were not substantiable. The established first-line treatment for constipation in all patients, elderly or otherwise, was advice to increase dietary fibre and fluid intake. Idrolax could not be considered a first-line option in treating constipation. The claim was also alleged to be misleading.

The continence nurse specialist stated that she would never advocate any medicine as a first-line option for constipation; the accepted practice was to start with diet, fluid and exercise.

The Panel did not consider that either 'first-line option' or 'excellent' constituted the use of a superlative and thus ruled no breach of the Code. The Panel noted the statement in the Idrolax summary of product characteristics (SPC) that the product should remain a temporary adjuvant treatment to appropriate hygienic and dietary management and considered therefore that it was not a 'first-line option' for treating constipation. The claim was misleading as alleged. The Panel ruled a breach of the Code.

Upon appeal the Appeal Board noted that the claim at issue referred to Idrolax as a first-line option [emphasis added] for constipated patients who were elderly or less mobile and considered that use of the word 'option' broadened the claim such that it referred to any intervention that might be made in the management of constipation. The Appeal Board noted that the first-line option in the management of constipation was to institute dietary and lifestyle changes. The Appeal Board noted the statement in the Idrolax SPC and considered that the description of Idrolax as a first-line option was misleading as alleged. The Appeal Board upheld the Panel's rulings.

With regard to the strapline 'the required effect', Norgine stated that the effect patients required from a laxative was to cure their constipation. Clinical studies referred to impressive rates of cure or substantial improvement but not in 100% of patients. Norgine therefore alleged that the claim was exaggerated in claiming Idrolax cured constipation. Further it misled prescribers as to the effect they might expect from Idrolax and could not be substantiated.

The Panel noted that in order to gain a marketing authorization, Idrolax would have demonstrated efficacy, quality and safety. No medicine would work for all patients. No data about the efficacy of Idrolax had been provided by either party. The Panel did not consider that the claim was exaggerated, misleading nor incapable of substantiation. No breaches of the Code were ruled.

Norgine alleged that the statement 'To avoid giving your patients the wrong macrogol (and an unnecessary dose of salts) it is important to be precise in your prescribing …' disparaged Movicol; it suggested that Movicol was the 'wrong' macrogol and by implication the other macrogol, presumably Idrolax, was the 'right' or 'correct' macrogol. Reference to the 'wrong macrogol' also disparaged health professionals as it suggested that by prescribing or dispensing Movicol they were making a 'wrong' decision.

Norgine alleged that the claim 'unnecessary dose of salts' disparaged Movicol as it clearly suggested to prescribers that the electrolyte content of Movicol was 'unnecessary'. Movicol would not have been granted a marketing authorization if it had contained 'unnecessary' ingredients. In fact in high dose or prolonged use, the electrolyte content of Movicol made a significant contribution to the safety of the product.

The continence nurse specialist asked whether there was a wrong macrogol? Would it cause her patients harm? If so, why was it licensed? However, if there was an alternative macrogol, as a professional the complainant could use her experience and judgement to choose the most appropriate product for her patient.

The Panel noted that the statement at issue appeared beneath a section headed 'How to prescribe Idrolax'. Nevertheless the Panel considered that it was disparaging to in effect refer to Norgine's product as the 'wrong macrogol' which implied that Idrolax was 'the right macrogol'. Both were licensed medicines. A breach of the Code was ruled.

The Panel considered however that the statement neither disparaged those who prescribed Movicol or who dispensed it. No breach of the Code was ruled in this regard.

Norgine alleged that the statement 'Don't 'compound' the problem', which appeared as a subheading at the foot of a page headed 'How to prescribe Idrolax?' disparaged Movicol. Norgine stated that Movicol was referred to in the Nurse Prescribers' Formulary (NPF) as 'macrogol oral powder, compound'. The use of the word 'compound' placed in inverted commas was clearly meant to refer to Movicol, and this juxtaposed with the word 'problem' implied that there was some problem with it.

The continence nurse specialist stated that the statement implied that by choosing an alternative product (namely a competitor), she was at risk of harming her patient.

In Case AUTH/1470/5/03, the Panel considered that the statement would be seen as a reference to Movicol (a compound) being a problem. This was reinforced by the other meaning of the word compound: add to, increase, complicate especially in relation to difficulties. In the Panel's view the statement disparaged Movicol and a breach of the Code was ruled.

In Case AUTH/1488/6/03, the Panel noted the continence nurse specialist alleged that the statement at issue implied that she was at risk of harming her patient. This point had not been alleged by Norgine. Schwarz responded to this additional point stating that there was no reference to clinical effects on a patient. The Panel decided that its ruling in Case AUTH/1470/5/03 was nonetheless relevant. A breach of the Code was ruled.

The continence nurse specialist noted that the claim 'Delete the word 'compound' and make sure your patients only get the required effect' appeared as part of the text beneath the subheading the subject of the point above. The nurse alleged that this claim implied that using macrogol oral powder compound medicine would not give her patient the required effect of relieving their constipation. This would only be achieved with Idrolax.

The Panel considered that its ruling in the point above was relevant. Further the claim implied that only patients on Idrolax got the required effect. The Panel considered that the claim disparaged Movicol and thus a breach of the Code was ruled.

The continence nurse specialist alleged that the leavepiece implied that by advising the use of a macrogol compound powder she was in danger of harming her patients by using the wrong medicine. She found the tone very patronising.

The Panel considered that the leavepiece had gone further than simply addressing confusion about Idrolax prescriptions. It had ruled that claims and statements used in the leavepiece were disparaging. The Panel considered that the material failed to maintain a high standard and to recognize the professional standing of the audience. The Panel thus ruled a breach of the Code.

Norgine alleged breaches of the Code regarding some of the claims above which also appeared in a journal advertisement and a detail aid.

The Panel considered that its rulings with regard to the claim 'the required effect' in the leavepiece also applied to the journal advertisement and to the leavepiece. No breach of the Code was ruled.

The Panel considered that its rulings with regard to the claim 'dose of salts' in the leavepiece also applied to the detail aid. Breaches of the Code were ruled respectively.

Norgine was extremely concerned about the number of breaches of the Code contained in the leavepiece and detail aid, but it was particularly concerned about the attempts to seriously disparage Movicol in the eyes of the medical and nursing professions. Norgine alleged a breach of Clause 2 in respect of this deliberate knocking copy directed towards its product.

The Panel noted its rulings above. The Panel considered that the circumstances did not warrant such a ruling and therefore ruled no breach of Clause 2.

Norgine Limited (Case AUTH/1470/5/03) and a continence nurse specialist (Case AUTH/1488/6/03) complained about the promotion of Idrolax (macrogol 4000) by Schwarz Pharma Limited. The promotional item at issue was a leavepiece (ref IDR2488a/FEB03). Norgine also complained about a journal advertisement which had appeared in MIMS, May 2003, and a detail aid (ref IDR/2427/FEB03). Norgine supplied Movicol (polyethylene glycol (macrogol) 3350 plus electrolytes).

Idrolax was indicated for the symptomatic treatment of constipation in adults and children aged 8 years and above.

A Idrolax leavepiece (IDR2488a/FEB 03) headed 'Why prescribe Idrolax?'

1 Claim 'Does not contain the dose of salts of some other macrogols'

The claim was referenced to the Idrolax summary of product characteristics (SPC) and appeared on the front page of the leavepiece as the fourth of four bullets points beneath the heading 'Why prescribe Idrolax?'

Case AUTH/1470/5/03

COMPLAINT

Norgine submitted that the phrase 'dose of salts' was chosen deliberately. There were only two macrogol

products on the market, Movicol and Idrolax, so the reference to 'other macrogols' was clearly meant to refer to Movicol.

Norgine alleged that the claim was unjustified knocking copy designed to disparage Movicol by connecting the electrolyte (salts) content of Movicol with the well known phrase 'like a dose of salts'. This was not a factual statement as the phrase had an emotive meaning which went much further than a purely factual statement. Norgine alleged a breach of Clause 8.1 of the Code.

RESPONSE

Schwarz stated that the phrase 'dose of salts' was a statement of fact in reference to Idrolax not containing electrolytes ('dose of salts') that might be contained within other macrogol-based products. Any macrogol possessing electrolytes (as salts) as an active ingredient by definition included a 'dose of salts'. The claim was thus factual, accurate and capable of substantiation and not in breach of Clause 8.1.

The allegation that the phrase had an emotive meaning beyond being a purely factual statement was misplaced. The expression 'like a dose of salts' implied a laxative effect and seemed to originate from the use of Epsom Salts as a laxative. Any perceived association between this expression and Movicol seemed to confer further benefits, with these 'salts' being laxative in action. However, the phrase originated from the use of Epsom Salts as a laxative and would be associated with magnesium sulphate, which was not listed as an active ingredient in Movicol. No direct comparison was made or implied with Epsom Salts for Idrolax or Movicol, and any association was entirely related to the 'play on words'.

Norgine's statement that there were only two macrogol products on the market was only true with regard to constipation. Norgine did not specifically relate its point to macrogols for constipation and Schwarz noted that another macrogol with electrolytes was available for bowel cleansing.

PANEL RULING

The Panel did not accept Schwarz's submission that the reference to 'dose of salts' would be associated with magnesium sulphate (Epsom Salts) and not the salts sodium chloride, potassium chloride and sodium bicarbonate which were constituents of Movicol. The term 'dose of salts' would be seen as a general description of a laxative action not just a laxative action linked to Epsom Salts. The Panel considered that the term was commonly used as a derogatory term.

The Panel considered the phrase 'dose of salts', in the context of a leavepiece about the treatment of constipation disparaged Movicol and a breach of Clause 8.1 of the Code was ruled.

Case AUTH/1488/6/03

COMPLAINT

The continence nurse specialist alleged that this implied that another medicine had harmful salts which could have harmful effects. She considered it a clever, though underhand, use of the well-known phrase 'a dose of salts'.

RESPONSE

Schwarz's response was similar to its response to Case AUTH/1470/5/03.

PANEL RULING

The Panel decided that its ruling of a breach of Clause 8.1 in Case AUTH/1470/5/03 also applied to Case AUTH/1488/6/03.

2 Claim 'The clinical profile of Idrolax makes it an excellent first-line option for constipated patients who are elderly or less mobile'

This claim appeared as the final statement on the front page of the leavepiece immediately above the product logo.

Case AUTH/1470/5/03

COMPLAINT

Norgine alleged that the word 'excellent' and the phrase 'first-line option' were superlative terms which were not substantiable, in breach of Clause 7.10. The established first-line treatment for constipation in all patients, elderly or otherwise, was advice to increase dietary fibre and fluid intake. Idrolax could not be considered to be a first-line option in treating anyone with constipation. No practitioner would consider Idrolax as a first-line option for the treatment of constipation. The claim was also alleged to be misleading in breach of Clause 7.2.

RESPONSE

Schwarz stated that 'excellent' and 'first-line option' were clearly qualified in context by reference to the entire sentence. The actual phrase was 'an excellent first-line option'. This clearly suggested there were other excellent first-line options, so could not be misconstrued as a superlative phrase. The words in context did not suggest special merit, quality or properties. Therefore, there was no breach of Clause 7.10 as the phrase was explained in context and represented a summary of the important preceding points contained in the leavepiece.

Dietary fibre and fluid intake might equally be considered lifestyle measures, accepted by health professionals to be a first-line option in the management of constipation. It was accepted standard practice to recommend dietary fibre and fluid intake, and other lifestyle measures, in the management of constipation. Such measures were often instituted by patients before consulting a health professional. However, the leavepiece gave information about a laxative for prescription at a point when a health professional would understand such an option referred to the need for a laxative,

having considered the lifestyle measures. It disparaged health professionals' knowledge and training to assume they were not clear in the context of such lifestyle measures and deciding on an option, first-line or otherwise, of additional therapeutic measures. As such, the claim was not misleading and was not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the Idrolax summary of product characteristics (SPC) stated that:

> 'An organic disorder should have been ruled out before initiation of treatment. Idrolax 10g should remain a temporary adjuvant treatment to appropriate hygienic and dietary management of constipation, with a maximum 3-months treatment course in children. If symptoms persist despite associated dietary measures, an underlying cause should be suspected and treated'.

The Panel did not consider that either the phrase 'first-line option' or the word 'excellent' constituted the use of a superlative prohibited by Clause 7.10. The Panel thus ruled no breach of Clause 7.10 of the Code with regard to the phrase 'an excellent first-line option'.

The Panel considered that, given the statement in the SPC that Idrolax was not a 'first-line option' for treating constipation, the claim was misleading as alleged. The Panel ruled a breach of Clause 7.2 of the Code.

Case AUTH/1488/6/03

COMPLAINT

The continence nurse specialist stated that she would never advocate any medicine as a first-line option for treating constipation; the accepted practice was to start with diet, fluid and exercise.

RESPONSE

Schwarz noted that the complainant would never advocate any medicine as a first-line option for constipation. Firstly, 'never' was all-embracing and could only reflect their personal opinion. It was accepted in clinical practice that there was no such concept as 'never' and that 'the exception proved the rule'. The phrase was clearly related to the context of prescribing a laxative, Idrolax in this case, as it appeared on a page entitled 'Why Idrolax is prescribed'. However, the statement did not suggest that it was the only first-line option, nor did it preclude the use of lifestyle measures. This clearly suggested there were other excellent first-line options, which might be conservative lifestyle measures and/or medicines.

Dietary fibre, fluid intake and exercise might equally be considered lifestyle measures, accepted by health professionals to be a first-line option in the management of constipation. It was accepted standard practice to recommend dietary fibre and fluid intake, and other lifestyle measures in the management of constipation. However, Schwarz noted that the evidence base for such measures as fluid intake and exercise remained unclear. Such measures were often instituted by patients prior to consulting a health professional. However, the leavepiece gave information regarding a laxative for prescription at a point when a health professional would understand such an option referred to the need for a laxative, having considered the lifestyle measures. It would be disparaging of the generally accepted wisdom to assume the distinctions were not clear in the context of such lifestyle measures and deciding on an option, first-line or otherwise, of additional therapeutic measures. The appearance of the statement in a section entitled 'Why Idrolax is prescribed' clearly related the situation to the context of prescribing. It did not negate the consideration of lifestyle measures, which would be considered prior to prescribing Idrolax. As such, the claim was not misleading and was not in breach of Clause 7.2.

PANEL RULING

The Panel decided that its ruling of a breach of Clause 7.2 in Case AUTH/1470/5/03 also applied to Case AUTH/1488/6/03. These rulings were appealed by Schwarz.

Cases AUTH/1470/5/03 and AUTH/1488/6/03

APPEAL BY SCHWARZ PHARMA

Schwarz submitted that when the claim 'The clinical profile of Idrolax makes it an excellent first-line option for constipated patients who are elderly or less mobile' was considered in its entirety 'first-line option' was qualified by 'an excellent', clearly implying that other excellent options existed, not limited to prescription laxatives. However, the sentence itself was in the context of the page entitled 'Why Idrolax is prescribed'. It was, therefore, clear that the point at which Idrolax would be a first-line option was when a prescriber had already decided that prescription of a laxative might be necessary. When a prescriber considered a laxative option, patients had usually initiated the lifestyle measures.

Schwarz submitted that the leavepiece and the appearance of the phrase, in context of the complete sentence as should be the consideration, was consistent with the SPC when related to the consideration of prescribing a laxative. Therefore, the phrase 'first-line option' was not misleading. There was no statement in the SPC that contradicted the possibility of considering Idrolax as a first-line option. The stage at which a medicine was prescribed might be defined under specific clinical situations eg anti-epileptic medicines where it might be stated such were adjunctive to other anti-epileptic medicines. No such requirement was placed upon Idrolax other than to state 'adjuvant treatment'. The phrase related to an 'option' rather than a requirement.

Schwarz noted that Idrolax could be sold in pharmacies. According to the patient information leaflet, Idrolax might be used for 'occasional constipation': 'This medicine can be helpful in the

treatment for occasional short-term constipation. This can often be connected with a recent change in lifestyle (for example, travel)'.

Schwarz submitted that the claim did not preclude the use of Idrolax as a first-line option and remained in line with the marketing authorization in this context. The appeal focused on the fact that Idrolax was referred to as 'an excellent first-line option' in a section clearly entitled 'Why Idrolax is prescribed'. At the point of prescribing a laxative, Idrolax was therefore 'an excellent first-line option' as could be the case for alternative laxatives.

Case AUTH/1470/5/03

COMMENTS FROM NORGINE

Norgine noted Schwarz's statement that: 'At the point of prescribing a laxative, Idrolax was therefore an 'excellent first-line option' as could be the case for alternative laxatives'.

Norgine alleged that laxatives were not first-line options in treating constipation, but for the sake of the specific points made by Schwarz in its appeal, Norgine assumed that the prescriber had tried non-laxative interventions which had failed, and had made the decision to prescribe a laxative. The question then was, could Idrolax be considered a 'first-line option' in this situation when a decision to prescribe had been made? The answer was no. The macrogol laxatives in general were not used first-line to treat constipation but as second- or third-line treatments after fibre supplements like ispaghula, or other cheaper laxatives like senna or lactulose had failed. Norgine noted that this was supported by a Health Technology Assessment (Petticrew *et al* 1997) which stated: 'Where possible therefore, constipation should be managed by a 'stepped care' approach, with the first step (after exclusion of co-morbidity) being advice about dietary improvement. If this fails, patients could then be prescribed the cheapest laxative treatment and, if this also fails, other laxative preparations could be given'. Norgine noted that this systematic review specifically referred to the use of laxatives in the elderly, exactly the group in which Schwarz specifically claimed that Idrolax should be used as a first-line option. Norgine submitted that current medical opinion therefore supported its assertion that it was misleading to refer to Idrolax as a 'first-line' treatment, excellent or otherwise.

Case AUTH/1488/6/03

COMMENTS FROM THE COMPLAINANT

The continence nurse specialist had no further comments.

Cases AUTH/1470/5/03 and AUTH/1488/6/03

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue referred to Idrolax as a first-line **option** (emphasis added) for constipated patients who were elderly or less mobile and considered that use of the word 'option' broadened the claim such that it referred to any intervention that might be made in the management of constipation. The Appeal Board did not accept Schwarz's submission that the heading 'Why prescribe Idrolax' meant that the claim at issue was solely in the context of a health professional making a prescribing decision. The Appeal Board noted that the first-line option in the management of constipation was to institute dietary and lifestyle changes. The Idrolax SPC stated that the product 'should remain a temporary adjuvant treatment to appropriate hygienic and dietary management of constipation …'. The Appeal Board considered that the description of Idrolax as a first-line option was misleading as alleged. The Appeal Board upheld the Panel's rulings. The appeal on this point was thus unsuccessful.

3 Strapline 'the required effect'

The strapline appeared beneath the brand logo in the leavepiece.

Case AUTH/1470/5/03

COMPLAINT

Norgine stated that patients who were constipated would like to take a medicine that cured their constipation. In other words the effect they required from a laxative was to cure them. The clinical studies published with Forlax (Idrolax) referred to impressive rates of cure or substantial improvement in the patient's constipation, but not in 100% of patients. There was therefore a percentage of patients who did not get 'the required effect' from Idrolax. Norgine therefore alleged that the claim was exaggerated in claiming Idrolax as a cure for constipation, in breach of Clause 7.10. Further it misled prescribers as to the effect they might expect from Idrolax in breach of Clause 7.2 and could not be substantiated in breach of Clause 7.4.

Norgine noted that in Case COP 1085/1/92 the strapline 'Gives them the bladder control they want' was ruled in breach on the basis that only 70% of patients treated with the medicine in question were cured or substantially improved; at least 30% of patients, therefore, did not get the bladder control they wanted. As a result the claim was ruled as being exaggerated and misleading. Norgine submitted that the claims 'the required effect' and 'the bladder control they want' were sufficiently close for this precedent to apply in this case.

RESPONSE

Schwarz stated that Norgine referred to the fact that patients who were constipated would like to take a medicine that cured their constipation and associated this with a percentage of patients who did not get 'the required effect from Idrolax'. This claim was not directed at patients and was relevant only to health professionals with the requisite training and knowledge to contextually comprehend the phrase.

Prescribers were undoubtedly aware that medicines such as laxatives might not 'cure' constipation in 100% of cases. Norgine had ascribed the term 'cure' and association with 100% to this phrase. The phrase was consistent with any evaluation of benefit-risk that was inherent in the marketing authorization granted by regulatory authorities. A medicine must produce the required effect for it to be granted approval. This did not equate to being effective in 100% of patients. It would seem that the alleged breach implied that a medicine licensed for, and therefore effective in constipation should be further qualified with 'but not in all cases'. This would again disparage health professionals' knowledge and training. Therefore, the claim was neither exaggerated nor misleading with respect to the effect a prescriber would expect.

The use of the word 'the' in the strapline did not imply special merit or quality in the treatment of constipation. The required effect clearly related to Idrolax, with no reference to any other product. It was expected that the use of a laxative in the treatment of constipation produced 'the' required effect, as opposed to 'an' effect, which could therefore be unrelated to the desired therapeutic need. 'The required effect' could equally be applied to any other licensed medicine, without suggesting a special merit or property. Without having 'the required effect' a medicine would not be considered effective and would unlikely be approved for marketing.

Idrolax was licensed for 'the symptomatic treatment of constipation in adults' and therefore was considered to possess 'the required effect'. It would be a nonsense to suggest any product had 'a required effect', as this might imply a spectrum of efficacy outcomes not immediately related to the desired therapeutic outcome. Use of the word 'the' in this context was, therefore, not in breach of Clause 7.4 as a consequence of the marketing authorization granted for Idrolax in the symptomatic treatment of constipation.

PANEL RULING

The Panel noted that Idrolax was indicated for the symptomatic treatment of constipation. The leavepiece included a photograph of a lock on a toilet door with the word 'Result' appearing where 'vacant' or 'engaged' would usually appear.

In order to gain a marketing authorization, Idrolax would have demonstrated efficacy, quality and safety. No medicine would work for all patients. No data about the efficacy of Idrolax had been provided by either party. The Panel did not consider that the claim was exaggerated, misleading nor incapable of substantiation. No breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

4 Statement 'To avoid giving your patients the wrong macrogol (and an unnecessary dose of salts) it is important to be precise in your prescribing …'

The statement appeared on page 2 of the leavepiece beneath the heading 'How to prescribe Idrolax'.

Case AUTH/1470/5/03

COMPLAINT

Norgine alleged that the phrase 'the wrong macrogol' disparaged Movicol in breach of Clause 8.1, as it suggested that Movicol was the 'wrong' macrogol and by implication the other macrogol product available, presumably Idrolax, was the 'right' or 'correct' macrogol.

Reference to the 'wrong macrogol' also disparaged health professionals who elected to prescribe Movicol, suggesting that by doing so they were making a 'wrong' decision. A breach of Clause 8.2 was alleged.

A further breach of Clause 8.2 was alleged as the statement also disparaged pharmacists who dispensed Movicol as it implied that by dispensing Movicol they were dispensing the 'wrong' macrogol.

The claim 'unnecessary dose of salts' was alleged to be unjustified knocking copy intended to disparage Movicol in breach of Clause 8.1, as it clearly suggested to prescribers that the electrolyte content of Movicol was 'unnecessary'. Movicol had a marketing authorization granted by the licensing authority which would not grant a marketing authorization to a product that contained 'unnecessary' ingredients. In fact in high dose or prolonged use, the electrolyte content of Movicol made a significant contribution to the safety of the product.

Also the phrase 'dose of salts' was repeated again which was alleged to be disparaging in breach of Clause 8.1 (point A1 above).

RESPONSE

Schwarz noted that this statement appeared in a clearly delineated section entitled 'How to prescribe Idrolax'. The use of the word 'wrong' was in the context of ensuring prescribers, who had already decided to prescribe Idrolax, actually produced a prescription with the intended proprietary product, Idrolax. It was apparent that there had been confusion from prescribers and dispensers over various representations of macrogols on prescriptions (handwritten or computer-generated), especially when presented generically.

The decision as to which laxative was prescribed was based on the health professional determining the clinical needs of the patient, whether this required the addition of electrolytes would depend on the needs and indications being treated. It did not disparage Movicol as it did not suggest Movicol might be the 'wrong' macrogol or imply that Idrolax was the 'correct' or 'right' macrogol. The context was clear when taken in completeness of the section 'How to prescribe Idrolax'. It was assumed that context and layout were perceived as a whole rather than inappropriately focussing on phrases that were potentially misconstrued when read out of context. There was no breach of Clause 8.1 in this respect.

Reference to the 'wrong macrogol' was not disparaging to health professionals who elected to prescribe Movicol, suggesting they were making a 'wrong' decision. The section in which this appeared,

'How to prescribe Idrolax', clearly reflected the situation that a prescriber had already determined that Idrolax was their selected medicine. As such, it could not be disparaging to health professionals who had elected to prescribe Movicol. It was clear that the prescriber had made their decision based on consideration of the licensed indications and needs of the patients. The item gave important information to ensure that the technical process of generating a prescription was sufficiently clear to ensure no confusion as to how Idrolax might appear on the prescription. This was, therefore, not in breach of Clause 8.2.

The statements in the leavepiece were equally valid to dispensers who had also been confused by the variations on prescriptions that seemed to occur in prescribing macrogols. However, the leavepiece was directed at prescribers, and Schwarz had a distinct leavepiece for addressing dispensers over the confusion. The information ensured that dispensers were aware of the correct interpretation of a prescription for a macrogol (Idrolax or any other). This was, therefore, not in breach of Clause 8.2 as related to pharmacists.

There had been confusion regarding the descriptions of the macrogols in sources such as the BNF, MIMS and the Drug Tariff. The leavepiece attempted to clarify the issue as it related to Idrolax. The industry should strive to ensure prescribers and dispensers were clear on what, how and when to prescribe its products.

Where the decision had been made to prescribe Idrolax, it would be inappropriate for any other macrogol to be dispensed. It seemed that confusion had arisen through the variations in representation of Idrolax on data systems used by primary care and pharmacists. Inputting 'macrogol' into some systems did not necessarily produce a list of both laxatives. Idrolax might appear as PEG 4000, Macrogol 4000 or macrogol oral powder. The leavepiece informed health professionals of the possible presentations of Idrolax on a prescription once they had made the decision to prescribe Idrolax. Similarly, it informed dispensers of the variations on a prescription that equated to Idrolax.

The context of 'unnecessary dose of salts' followed this argument. If Idrolax was the selected therapy, the inadvertent prescribing or dispensing of Movicol would result in an 'unnecessary dose of salts'. This reference to an 'unnecessary dose of salts' was therefore not in breach of Clause 8.1. It could not disparage Movicol when it referred to Idrolax, which did not require electrolytes for its licensed use in constipation and not faecal impaction where it was presumed Norgine was referring to the use of high doses of Movicol.

Schwarz referred to its response to point A1 above with regard to the phrase 'dose of salts'.

PANEL RULING

The Panel noted Schwarz's submission regarding the confusion about what in effect amounted to generic prescribing of macrogols.

The Panel noted that the statement at issue appeared beneath a section headed 'How to prescribe Idrolax'. Nevertheless the Panel considered that it was disparaging to in effect refer to Norgine's product as the 'wrong macrogol' which implied that Idrolax was 'the right macrogol'. Both were licensed medicines. A breach of Clause 8.1 of the Code was ruled.

The Panel considered that the statement was critical of the product. It was neither disparaging to health professionals who elected to prescribe Movicol nor to pharmacists dispensing Movicol. No breach of Clause 8.2 of the Code was ruled in this regard.

The Panel considered that the reference to an 'unnecessary dose of salts' was disparaging of Movicol as alleged. The Panel noted its ruling in point A1 above. A breach of Clause 8.1 of the Code was ruled.

Case AUTH/1488/6/03

COMPLAINT

The complainant asked whether there was a wrong macrogol? Would it cause her patients harm? If so, why was it licensed? However, if there was an alternative macrogol, as a professional the complainant could use her experience and judgement to choose the most appropriate product for her patient.

RESPONSE

Schwarz stated that this statement appeared in a clearly delineated section entitled 'How to prescribe Idrolax'. The use of the word 'wrong' was in the context of ensuring prescribers, who had decided to prescribe Idrolax, actually produced a prescription with the intended proprietary product, Idrolax. It was apparent that there had been confusion from prescribers and dispensers over various representations of macrogols on prescriptions (hand-written or computer-generated), especially when presented 'generically'.

The decision as to which laxative was prescribed was based on the health professional determining the clinical needs of the patient, whether this required the addition of electrolytes would depend on the needs and indications being treated. It did not disparage another macrogol as it clearly did not suggest such might be the 'wrong' macrogol and imply Idrolax was the 'correct' or 'right' macrogol. The context was clear when taken in completeness of the section 'How to prescribe Idrolax', as presented in the leavepiece. It was assumed that context and layout were perceived as a whole rather than inappropriately focussing on phrases that were potentially misconstrued when read out of this context.

Reference to the 'wrong macrogol' did not disparage another macrogol, suggesting there was a 'wrong' macrogol or that it caused harm to patients for whom it was prescribed according to the SPC. The section in which this appeared was 'How to prescribe Idrolax', which clearly reflected the situation that a prescriber had already determined that Idrolax was their

selected medicine. It was clear that the prescriber had based their decision as to which laxative to prescribe on consideration of the licensed indications and needs of the patients. This conformed with the complainant's view that 'If there is an alternative macrogol, as a professional I can use my experience and judgement to choose the most appropriate product for my patient'. The context had no other interpretation. Depending on the indication, there were two alternative macrogols. The item gave important information to ensure that the technical process of generating a prescription was sufficiently clear to ensure no confusion as to how Idrolax might appear on the prescription once the decision had been made to prescribe it.

There had been confusion regarding the descriptions of the macrogols in sources such as the BNF, MIMS and the Drug Tariff. The leavepiece attempted to clarify the issue as it related to Idrolax. The industry should strive to ensure prescribers and dispensers were clear on what, how and when to prescribe its products.

Where the decision had been made to prescribe Idrolax, it would be inappropriate for any other macrogol to be dispensed. It seemed that confusion had arisen through the variations in representation of Idrolax on data systems utilised by primary care and pharmacists. Inputting 'macrogol' into some systems did not necessarily produce a list of both laxatives. Idrolax might appear as PEG 4000, Macrogol 4000 or macrogol oral powder. The leavepiece informed health professionals the possible representations of Idrolax on a prescription once they had made the decision to prescribe Idrolax. Similarly, it informed dispensers of the variations on a prescription that equated to Idrolax.

The patient, in receiving a prescription from a health professional, was owed a duty of care. This extended to the prescription containing the appropriate information regarding the medicine that was to be prescribed. Patients to whom the prescriber intended to treat with Idrolax were required to receive Idrolax. Computer-based prescribing systems and reference material had the potential to confuse this issue, and as such, the information was relaying this situation to the prescriber and dispenser clearly in the context that the prescriber had assessed the needs of the patients and decided to prescribe Idrolax.

The context of 'unnecessary dose of salts' followed this discussion. If Idrolax was the selected therapy, the inadvertent prescribing or dispensing of another macrogol might result in an 'unnecessary dose of salts'. It could not be disparaging another macrogol when it was referring to Idrolax, which did not require electrolytes for its licensed indication. The salts in other macrogols were listed as active ingredients, and the decision having been made by the prescriber based on the indication, dosage and other considerations listed in the SPCs had already determined the need or not for these salts.

In view of these points, the statement did not disparage another macrogol and was not in breach of Clause 8.1.

PANEL RULING

The Panel noted its rulings in Case AUTH/1470/5/03 and decided that its ruling in that case also applied to the present case, Case AUTH/1488/6/03.

5 Statement 'Don't 'compound' the problem'

The statement appeared as a heading to a paragraph at the foot of page 2. The page was headed 'How to prescribe Idrolax'.

Case AUTH/1470/5/03

COMPLAINT

Norgine stated that Movicol was referred to in the Nurse Prescribers' Formulary (NPF) as 'macrogol oral powder, compound'. The use of the word 'compound' placed in inverted commas was clearly meant to refer to Movicol, and this juxtaposed with the word 'problem' in this sentence implied that there was some problem with macrogol oral powder, compound. Norgine alleged that this disparaged its product Movicol in breach of Clause 8.1.

RESPONSE

Schwarz stated that Norgine correctly pointed out that Movicol was referred to as 'macrogol oral powder, compound' in the NPF. A 'compound' in this context was defined as having more than one active constituent. Therefore, Idrolax was not classified as a compound, and the use of the term 'compound' in the heading was appropriate to this context. As potential prescribers of macrogol-based laxatives, this was an important group (nurse prescribers) requiring the information already provided in the context to which they might be referred ie NPF presentation as macrogol oral powder for Idrolax or macrogol oral powder, compound for Movicol. The only other distinction provided in the NPF for discerning the macrogols was by weight ie 10g for Idrolax and 13.125g for prescribing generically. The leavepiece addressed the actual confusion that had been caused by highlighting the various representations of Idrolax on a prescription.

Schwarz stated that the section at issue was beneath the subheading 'How Idrolax is prescribed'. 'Problem' referred to the overall subject of the prescribing of Idrolax. This was an important informative section ensuring that prescribers and dispensers were aware of all the generic variations that might occur on prescriptions for Idrolax. The decision as to which macrogol was prescribed was dependent on factors already discussed. The issue clearly referred to there being a 'problem' in the representation of Idrolax on the prescription, and highlighted the variation based on the NPF entries. The use of the word 'compound' did not refer to Movicol being the 'problem', but of the problem of attempting to prescribe Idrolax in its generic form. It did, however, represent a well-executed creative brief. This was, therefore, not a breach of Clause 8.1.

PANEL RULING

The Panel noted that the statement at issue appeared on the page headed 'How to Prescribe Idrolax' and not 'How Idrolax is prescribed' as submitted by Schwarz. The Panel considered that the statement would be seen as a reference to Movicol (a compound) being a problem. This was reinforced by the other meaning of the word compound: add to, increase, complicate especially in relation to difficulties. In the Panel's view the statement disparaged Movicol and a breach of Clause 8.1 of the Code was ruled.

Case AUTH/1488/6/03

Beneath the heading was stated: 'Your system may automatically enter 'macrogol oral powder, compound'. This is NOT Idrolax. It is a different product which contains Na+ and K+. Delete the word 'compound' and make sure your patients only get the required effect'.

COMPLAINT

The continence nurse specialist stated that this heading implied that by choosing an alternative product (namely a competitor), she was at risk of harming her patient.

RESPONSE

Schwarz repeated its response given in Case AUTH/1470/5/03 and further noted that there was no reference to potential clinical effects on a patient, and therefore did not imply alternative products might cause harm. Any such considerations were purely based on the prescriber's judgement and consideration of each patient's requirements, acknowledging the contents of the SPC. This was therefore not a breach of Clause 8.1.

PANEL RULING

The Panel noted its ruling on this claim in Case AUTH/1470/5/03.

Turning to the present case, Case AUTH/1488/6/03, the Panel noted that the complainant alleged that the statement at issue implied that she was at risk of harming her patient. This point had not been alleged in the previous case. Schwarz responded to this additional point stating that there was no reference to clinical effects on a patient.

The Panel decided that its ruling in the previous case, Case AUTH/1470/5/03, was nonetheless relevant. A breach of Clause 8.1 was ruled.

6 Claim 'Delete the word 'compound' and make sure your patients only get the required effect'

This claim appeared as part of the text beneath the heading the subject of point 5 above.

Case AUTH/1488/6/03

COMPLAINT

The continence nurse specialist alleged that this claim implied that using a macrogol oral powder compound medicine would not give her patient the required effect of relieving their constipation. This would only be achieved with Idrolax.

RESPONSE

Schwarz stated that the section to which the complainant referred remained in the context of 'How Idrolax is prescribed' as a subheading. This related to the overall subject of the prescribing of Idrolax. This was an important informative section ensuring that prescribers and dispensers were aware of all the 'generic' variations that might occur on prescriptions of Idrolax. This claim referred to a situation in which the prescriber had decided to prescribe Idrolax. The potential appearances of entering a 'generic' macrogol into a data system included 'macrogol oral powder, compound'. It would be inappropriate by all clinical standards for this to be prescribed as the prescriber had decided this was the product appropriate in a given situation. However, some data systems did not have the facility for the prescriber to adapt the representation. The only option was to delete the extraneous word where the alternative representations of Idrolax were not available. Again, to re-iterate, this was purely in the context of 'How Idrolax is prescribed', and this could only refer to a situation where the prescriber had made that decision. This was, therefore, not a breach of Clause 8.1.

PANEL RULING

The Panel noted that this claim had not been the subject of an allegation in Case AUTH/1470/5/03. It considered that its ruling in point 4 above was relevant. Further the claim implied that only patients on Idrolax got the required effect. The Panel considered that the claim disparaged Movicol and thus a breach of Clause 8.1 of the Code was ruled.

7 Patronising tone

Case AUTH/1488/6/03

COMPLAINT

The continence nurse specialist alleged that the leavepiece implied that by advising the use of a macrogol compound powder she was in danger of harming her patients by using the wrong medicine. She found the tone very patronising.

RESPONSE

Schwarz stated that by ensuring consideration of the points in the context of the leavepiece, where it was clear that statements regarding how Idrolax was prescribed had followed the prescriber's consideration of the patient needs, the leavepiece addressed a need to clarify the appearances on prescriptions of Idrolax. It could not be patronising when the situation had occurred, and continued to occur, where prescribers and dispensers were unclear as to the numerous representations of Idrolax on a prescription. By addressing this need, the material ensured that high standards were maintained in

clinical practice, and the material itself was of an appropriate and high standard. It was targeted at an identified need and was appropriate to the audience, which was experiencing the need for this information. Therefore, the material was not in breach of Clause 9.1.

PANEL RULING

The Panel considered that the leavepiece had gone further than simply addressing confusion about Idrolax prescriptions. It had ruled that claims and statements used in the leavepiece were disparaging. The Panel considered that the material failed to maintain a high standard and to recognize the professional standing of the audience. The Panel thus ruled a breach of Clause 9.1 of the Code.

Case AUTH/1470/5/03

B Idrolax advertisement, MIMS May 2003

Strapline 'the required effect'

COMPLAINT

Norgine noted that the strapline 'the required effect' also appeared in journal advertising for Idrolax such as an advertisement in MIMS, May 2003. Its comments about the use of this strapline in point A3 above also applied to the journal advertisements. Norgine alleged that the journal advertisements also breached Clauses 7.2, 7.10 and 7.4 in respect of the use of an exaggerated and misleading claim that could not be substantiated.

RESPONSE

Schwarz referred to its response in point A3.

PANEL RULING

The Panel considered that its ruling in point A3 above also applied here. No breach of Clauses 7.2, 7.4 and 7.10 of the Code was thus ruled.

C Idrolax detail aid IDR247/FEB 03

1 Strapline 'the required effect'

This appeared on every alternate page of the detail aid.

COMPLAINT

Norgine stated that this claim appeared on the front and most of the other pages of this detail aid wherever the Idrolax brand name appeared. As for point A3 above Norgine alleged a breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Schwarz referred to its response in A3.

PANEL RULING

The Panel considered that its ruling in point A3 above also applied here. No breach of Clauses 7.2, 7.4 and 7.10 of the Code was thus ruled.

2 Page headed 'An osmotic laxative without the dose of salts'

COMPLAINT

Norgine referred to point A1 above and alleged that the phrase 'dose of salts' was deliberately chosen to be derogatory towards Movicol.

RESPONSE

Schwarz referred to its response to point A1.

PANEL RULING

The Panel considered that its ruling in point A1 above also applied here. A breach of Clause 8.1 of the Code was thus ruled.

3 Claim 'Does not contain the dose of salts of some other macrogols'

COMPLAINT

Norgine noted that this claim, which appeared on the back cover of the detail aid, was the same as that at issue in point A1 above.

RESPONSE

Schwarz referred to its response to point A1 above.

PANEL RULING

The Panel considered that its ruling in point A1 above also applied here. A breach of Clause 8.1 of the Code was thus ruled.

D Alleged breach of Clause 2

COMPLAINT

Norgine was extremely concerned about the number of breaches of the Code contained in the leavepiece and detail aid, but it was particularly concerned about the attempts to seriously disparage Movicol in the eyes of the medical and nursing professions. Norgine alleged a breach of Clause 2 in respect of this deliberate knocking copy directed towards its product.

RESPONSE

Schwarz stated that the context of the claims at issue regarded the need to ensure the prescriber was confident that their desire to prescribe Idrolax was borne out by the dispensing of the appropriate active agent. Statements regarding 'dose of salts' clearly related to a factual comparison of macrogols. They related to the fact that Idrolax did not possess electrolytes / salts as an active ingredient (ie 'dose of salts'). Claims at issue remained in the context of addressing confusion over prescribers generating Idrolax prescriptions from a multitude of systems that represented Idrolax in numerous ways. It would be inappropriate for the patient to receive a medicine not

intended by the prescriber. This had significant implications over prescriber and dispenser liabilities. As highlighted, Idrolax might appear in a number of presentations on prescription generating and dispensing systems, some of which might be similar to 'generic' representations of Movicol. The objective was to raise awareness of this issue and ensure prescribers and dispensers were able to identify and represent appropriately their desired selection for the patient.

Schwarz noted that a proportion of the alleged breaches were repeated appearances of statements at issue rather than new allegations of breaches. The allegation of attempts to seriously disparage Movicol in the eyes of the medical and nursing professions was unfounded and Norgine's misrepresentations of the factual information in the context (content and layout) of prescribing Idrolax inappropriate.

Statements regarding a 'dose of salts' (electrolytes) were clearly within the context of the prescriber having determined an individual patient's requirements. There were situations that would require a laxative with additional electrolytes, and the inclusion in licensed products demonstrated the therapeutic benefit in such circumstances. Equally, there would be situations in which addition of electrolytes to laxative therapy was not necessary, and this was also borne out by laxatives without additional electrolytes being licensed for use in such circumstances. Where a laxative without electrolytes was required, the leavepiece and detail aid were designed to facilitate the patient receiving Idrolax therapy once the prescriber had made their decision.

Schwarz submitted that there was no breach of Clause 2.

PANEL RULING

The Panel noted its rulings above. Any breach of the Code was a serious matter. The Panel considered that the circumstances did not warrant a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and was reserved for such use. The Panel therefore ruled no breach of the Clause 2. It might be argued that Schwarz had failed to maintain a high standard but there was no allegation in that regard.

Complaints received:	**15 May 2003**
Case AUTH/1470/5/03	**21 May 2003**
Case AUTH/1488/6/03	**30 June 2003**
Cases completed	**3 November 2003**

CASE AUTH/1477/6/03

BRISTOL-MYERS SQUIBB and SANOFI-SYNTHELABO v NOVARTIS

Promotion of Diovan

Bristol-Myers Squibb and Sanofi-Synthelabo complained jointly about the promotion of Diovan (valsartan) by Novartis. The materials at issue were a detail aid, a leavepiece and a product monograph. Diovan was an angiotensin-II receptor antagonist (AIIRA) indicated for the treatment of hypertension. Bristol-Myers Squibb and Sanofi-Synthelabo co-marketed Aprovel (irbesartan), also an AIIRA. Aprovel was indicated for the treatment of essential hypertension.

Page 10 of the detail aid included the heading 'Does the class reduce microalbuminuria?' and a graph showing a 47% reduction in urinary albumin excretion rate (UAER) in hypertensive, type 2 diabetics when treated with Diovan. Bristol-Myers Squibb and Sanofi-Synthelabo noted that the hypertensive subgroup of the Microalbuminuria Reduction with Valsartan (MARVAL) study to which the graph referred clearly stated that the reduction in microalbuminuria was a 'blood pressure-independent effect'. Although the hypertensive subgroup was presented, the benefits claimed did not relate to blood pressure control, as per the licence, but to other independent merits. Irrespective of the patients studied this claim for reduction in microalbuminuria was alleged to be outside the marketing authorization for blood pressure lowering. Bristol-Myers Squibb and Sanofi-Synthelabo further noted that the heading 'Does the class reduce microalbuminuria?' suggested a class effect in reduction in microalbuminuria. Only Aprovel had a marketing authorization for this indication.

The Panel noted that Diovan was an AIIRA of which there were six on the UK market. All of the AIIRAs were licensed for the treatment of hypertension but Aprovel was additionally licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen. Cozaar (losartan) was additionally licensed for renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria).

The Panel noted that the MARVAL study concluded that valsartan had a blood pressure independent antiproteinuric effect.

The Panel was concerned that the page at issue bore the heading 'Does the class reduce microalbuminuria?' and claims such as 'Reduction in microalbuminuria' and 'The significant effect of Diovan on microalbuminuria makes it an appropriate choice for hypertensive patients with type 2 diabetes'. In respect of the second claim the Panel noted that although the patient characteristics had been defined the reason for giving Diovan, ie to reduce blood pressure, had not. Diovan was not licensed for its effects on microalbuminuria; its only licensed indication was to lower blood pressure. Some other medicines in the same class had broader licences to encompass renal disease. In the Panel's view the effects of Diovan on microalbuminuria had been given undue emphasis and had not been placed sufficiently within the context of treating hypertension such that the material appeared to promote the product for reduction of microalbuminuria. A breach of the Code was ruled which was appealed.

With regard to the question 'Does the class reduce microalbuminuria?', the Panel noted that reductions for losartan, irbesartan and candesartan were mentioned on the page. Aprovel did not have a specific indication for the reduction of microalbuminuria although Aprovel and Cozaar had additional licensed indications to that for Diovan which was only licensed for the treatment of hypertension. The Panel considered that the page gave the impression that the class reduced microalbuminuria and that the products were similar in this regard. The Panel noted its rulings above and considered that it was misleading to imply similarities in relation to Diovan, Aprovel and Cozaar with regard to reductions in microalbuminuria. This was inconsistent with the summary of product characteristics (SPC) for Diovan and the Panel ruled a breach of the Code which was appealed.

The Panel noted that Novartis was not promoting irbesartan, losartan or candesartan and thus ruled no breach of the Code in that regard. This ruling was not appealed.

Upon appeal by Novartis, the Appeal Board noted that albuminuria was a recognised surrogate marker for diabetic nephropathy. Microalbuminuria was not, however, a recognised surrogate marker in hypertension. Although microalbuminuria occurred in hypertension it was a function of blood pressure; lowering blood pressure with an antihypertensive would reduce microalbuminuria. Reduction in microalbuminuria, however, was not an indicator of successful antihypertensive therapy. Blood pressure was used to assess the efficacy of an antihypertensive. The Appeal Board noted that the subgroup of patients from the MARVAL study, although hypertensive, type 2 diabetics, had a UAER of 20-200µg/min which was less than that required for a diagnosis of diabetic nephropathy.

The detail aid referred to the reduction of microalbuminuria in type 2 diabetics and the Appeal Board considered that by association readers would assume that Diovan was indicated for use in diabetic nephropathy. This impression was strengthened by the reference to irbesartan and losartan, both of which were licensed to treat diabetic renal disease. The Appeal Board considered that the presentation of the data in relation to Diovan, losartan and irbesartan and their effects on microalbuminuria was such as to imply, by association, that Diovan was licensed for the management of diabetic nephropathy which was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code.

With regard to the question 'Does the class reduce microalbuminuria?' the Appeal Board noted its comments above and again upheld the Panel's ruling of a breach of the Code.

Bristol-Myers Squibb and Sanofi-Synthelabo noted that page 2 of a four page leavepiece was headed 'Diovan delivers BP control in practice' followed by the claim that Diovan was an appropriate choice 'after your first ACE-inhibitor has fallen short because:', which was followed by three claims. The third claim being 'Diovan is effective in reducing microalbuminuria in hypertensive patients with type 2 diabetes'. Beneath the product logo on the facing page, and also on page one, was the strapline 'Evolutionary antihypertensive therapy'.

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that for the reasons given above the claim '… effective in reducing microalbuminuria in hypertensive patients with type 2 diabetes' constituted promotion outside the marketing authorization. It appeared from this and the detail aid that Novartis was encouraging its representatives to proactively promote Diovan for an unlicensed indication.

The Panel considered that the leavepiece clearly set the effects of Diovan on reducing microalbuminuria in the context of treatment of hypertension, the heading to the page in question was 'Diovan delivers BP control in practice'. The Panel considered that the leavepiece was different to the detail aid in this regard. No breach of the Code was ruled.

With regard to the representatives the Panel noted that no evidence was provided as to what the representatives had said. Taking all the circumstances into account the Panel ruled no breach of the Code.

Bristol-Myers Squibb and Sanofi-Synthelabo noted that page 20 of the product monograph featured a bar chart showing the reduction in UAER in hypertensive type 2 diabetics treated either with valsartan (–47%) or amlodipine (–11%) ($p<0.001$). The complainants stated that the data again referred to a study that claimed a reduction in microalbuminuria beyond blood pressure lowering. The monograph clearly stated 'Blood pressure reductions were comparable in both treatment groups'. The claim that valsartan reduced microalbuminuria to a greater extent than amlodipine was therefore claiming that this effect was blood pressure independent. As above this was not part of the marketing authorization for Diovan.

The Panel noted that the page in question referred to a subset of hypertensive patients and this was followed with a description of the results from the MARVAL study. The comparison between Diovan and amlodipine was shown graphically. It was not clearly stated that the patients were treated with Diovan for hypertension. The Panel considered that the results had not been set sufficiently in the context of the licensed use of Diovan.

The Panel noted that the second half of page 20 referred to reductions in microalbuminuria observed with the other AIIRAs.

The Panel noted its comments above with regard to the differences in the licences of the various products. The Panel considered that where the benefits of treatment were licensed indications for some members of a class but not others, then companies must take particular care to ensure that health professionals were not misled into assuming that the licence for a product was broader than it actually was. On balance the Panel considered that the page did not meet the requirements of the Code and ruled accordingly.

Upon appeal by Novartis, the Appeal Board considered that the reference to a recognised marker of diabetic nephropathy and to other AIIRAs which had either been licensed separately for renal protection in type 2 diabetics with nephropathy, or licensed for treatment of renal disease in hypertensive type 2 diabetic patients, as part of an antihypertensive drug regimen, implied by association that Diovan was similarly licensed which was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Bristol-Myers Squibb Pharmaceuticals Ltd and Sanofi-Synthelabo Ltd complained jointly about the promotion of Diovan (valsartan) by Novartis Pharmaceuticals UK Ltd. The materials at issue were a detail aid (ref DIO 02000282), a leavepiece (ref DIO 02000532) and a product monograph (DIO 02000536). Diovan was an angiotensin-II receptor antagonist (AIIRA) indicated for the treatment of hypertension. The detail aid and leavepiece were withdrawn from use in March 2003. The product monograph was still in use.

Bristol-Myers Squibb and Sanofi-Synthelabo co-marketed Aprovel (irbesartan), also an AIIRA. Aprovel was indicated for the treatment of essential hypertension. It was also indicated for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

A Detail Aid

Page 10 of the detail aid included the heading 'Does the class reduce microalbuminuria?' and a graph showing a 47% reduction in urinary albumin excretion rate (UAER) in hypertensive, type 2 diabetics when treated with Diovan.

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo noted that valsartan was licensed for the treatment of essential hypertension. The hypertensive subgroup of the Microalbuminuria Reduction with Valsartan (MARVAL) study to which the graph referred clearly stated that the reduction in microalbuminuria was a 'blood pressure-independent effect'. Although the hypertensive subgroup was presented, the benefits claimed did not relate to blood pressure control, as per the licence, but to other merits independent of blood pressure lowering. Irrespective of the group of patients studied this claim for reduction in microalbuminuria was alleged to be outside the marketing authorization for blood pressure lowering.

The Authority had previously ruled that a licence was required in order to make claims that were independent of blood pressure lowering (Case AUTH/1268/12/01). The companies alleged a breach of Clause 3.2 of the Code.

The heading on page 10 'Does the class reduce microalbuminuria?' suggested a class effect and the conclusion was strongly suggestive of a class effect in reduction in microalbuminuria. As only Aprovel had a marketing authorization for this indication the companies alleged that these claims were also in breach of Clause 3.2 of the Code.

RESPONSE

Novartis stated that the data presented showed the reduction in microalbuminuria that was achieved with valsartan in the hypertensive subgroup in the MARVAL study. Novartis noted the bullet point at the top of the page stated 'Microalbuminuria is a strong predictor of total cardiovascular premature mortality and morbidity in hypertensive patients with type 2 diabetes'. This statement made it very clear that the data presented with respect to reductions in microalbuminuria were in the context of treating hypertensive type 2 diabetic patients with Diovan and that microalbuminuria was a strong predictor of cardiovascular disease in this population. This was of relevance to the management of hypertension since:

- Microalbuminuria occurred in between 5% and 40% of hypertensive patients and was therefore not an infrequent finding in this patient group (Rosa and Palatini 2000).
- Microalbuminuria in hypertensive patients was associated with an increased risk of cardiovascular events (Campese *et al*).
- Hypertensive patients with type 2 diabetes were at an increased risk of cardiovascular disease compared to the 'general' hypertensive population (UKPDS 1998).
- Studies had demonstrated that a reduction in blood pressure in hypertensive patients with type 2 diabetes reduced microalbuminuria. As this had been achieved with agents from various antihypertensive classes it had been concluded that the simple haemodynamic effect of reducing blood pressure reduced microalbuminuria (Maki *et al* 1995).
- The different classes of antihypertensive medicines reduced blood pressure by different mechanisms. Classes that reduced blood pressure by acting on the renin-angiotensin system (ACE inhibitors and AIIRAs) had been repeatedly shown to reduce microalbuminuria to a greater extent than other classes. It had been suggested that this was due to their specific mode of action which also reduced blood pressure locally within the kidney. It appeared therefore that, in contrast to other antihypertensive classes, the ACE inhibitors and AIIRAs (including Diovan) reduced microalbuminuria through the haemodynamic improvement achieved through systemic blood pressure reduction and local effects within the kidney (Odama Bakris).

As a consequence the effect of Diovan on microalbuminuria in hypertensive diabetic patients was of interest and relevance to customers managing these patients. Novartis disagreed with the position of the complainants in that any claims relating to the effects of Diovan on microalbuminuria were clearly placed in the context of treating hypertensive type 2 diabetics. This was in accordance with the terms of the marketing authorization for Diovan and consistent with the summary of product characteristics (SPC). Consequently the claims did not breach Clause 3.2 of the Code.

Novartis noted that in Case AUTH/1340/7/02 Aventis Pharma had complained that Merck Sharp & Dohme was making claims for Cozaar which were not consistent with the SPC and which constituted promotion outside the licensed indications. This complaint was in relation to the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study where Cozaar was compared to atenolol in high risk hypertensive patients. The conclusion of this study was that losartan prevented more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and was better tolerated; losartan seemed to confer benefits beyond reduction in blood pressure. Aventis alleged that claims relating to event reduction with losartan were in breach of Clause 3.2 of the Code as losartan was only licensed for the treatment of hypertension at that time. The Panel noted that Cozaar was indicated for the treatment of hypertension and that there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The Panel did not raise any concerns regarding the blood pressure-independent beneficial effects of losartan in this study. In the Panel's view the promotional material must make it clear that Cozaar was used to treat hypertension in high risk patients and all references to the LIFE study results must be set in that context. In the light of these comments the claims for Diovan with respect to microalbuminuria reduction, despite being blood pressure independent, were clearly set in the context of its licensed indication (ie treating hypertensive type 2 diabetic patients) and described the benefits of treating the condition with Diovan. All claims relating to microalbuminuria reduction were capable of substantiation as they were based on the findings of the MARVAL study which was published in the peer reviewed journal, Circulation.

Furthermore within the same case claims made by Merck Sharp & Dohme that losartan 'reduced the risk of onset of diabetes (–25%, p=0.001)' were not found to be in breach of Clause 3.2 of the Code since the claim was set within the context of lowering blood pressure with losartan-based therapy. When this was compared to the current case it was apparent that all claims for reduction in microalbuminuria were within the context of treating hypertensive type 2 diabetics. Page 10 of the Diovan detail aid included an opening bullet point to this effect as well as a prominent red box at the bottom of the page which stated 'The significant effect of Diovan on microalbuminuria makes it an appropriate choice for hypertensive patients with type 2 diabetes'.

The complainants cited Case AUTH/1268/12/01 as supporting evidence for the complaint. However, it was clear that a breach of Clause 3.2 of the Code was ruled in that case because supporting data presented came from a study (Muirhead *et al*) that included both normotensive and hypertensive subjects. Furthermore the page of the detail aid at that time did not make it clear that Diovan should only be used in hypertensive diabetic patients. Since Diovan was licensed only for the treatment of hypertension, claims relating to normotensive subjects were outside the marketing authorization and a breach of Clause 3.2 was ruled. As a consequence of this ruling Novartis had ensured that all data presented in promotional materials related to hypertensive subjects and page 10 of the detail aid as well as the graph in question were clearly labelled as such. Consequently the complainants' citing of this case was not relevant.

The complainants also had concerns over the header on page 10 which posed the question 'Does the class reduce microalbuminuria?'. This question by its very nature was not a definitive statement and therefore suggested a class effect *per se* with respect to microalbuminuria. However, it was again important to appreciate the context of the page in that microalbuminuria was discussed in the setting of treating hypertensive type 2 diabetics. In such patients microalbuminuria was an important predictor of cardiovascular risk and there was evidence that the angiotensin receptor blockers reduced the level of this risk marker in hypertensive type 2 diabetics. The SPC for irbesartan stated that it was licensed for the treatment of essential hypertension and the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicine regimen. Irbesartan itself did not have a specific indication for the reduction of microalbuminuria and since all claims relating to the effects of Diovan on microalbuminuria were in the context of treating hypertensive type 2 diabetics no breach of Clause 3.2 of the Code had occurred. Novartis noted that irbesartan was indicated for the treatment of renal disease in hypertensive type 2 diabetics; however no claims were made with respect to any renoprotective effect of Diovan.

Hence the data presented did not breach Clause 3.2 of the Code.

PANEL RULING

The Panel noted that Diovan was licensed for the treatment of hypertension. Diovan was an AIIRA of which there were six on the UK market. All of the AIIRAs were licensed for the treatment of hypertension but Aprovel (irbesartan) was additionally licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen. Cozaar (losartan) was additionally licensed for renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria).

The Panel noted that the MARVAL study concluded that valsartan had a blood pressure independent antiproteinuric effect. The authors stated that 'The observation that valsartan reduced microalbuminuria by >40% both in the hypertensive and particularly the normotensive subgroups is very important.'. The authors also stated that the study was short-term and could not establish whether the correction of microalbuminuria by valsartan would be translated into clinical benefit. Several studies in patients with and without diabetes had shown a clear relation between proteinuria reduction and slowing of renal disease progression.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The Panel was concerned that the page at issue used the heading 'Does the class reduce microalbuminuria?' and claims such as 'Reduction in microalbuminuria' and 'The significant effect of Diovan on microalbuminuria makes it an appropriate choice for hypertensive patients with type 2 diabetes'. In respect of the second claim the Panel noted that although the patient characteristics had been defined the reason for giving Diovan, ie to reduce blood pressure, had not. The detail aid referred to the treatment of hypertension on previous pages. Nevertheless the Panel noted that Diovan was not licensed for its effects on microalbuminuria; its only licensed indication was to lower blood pressure. The Panel noted that some other medicines in the same class had broader licences to encompass renal disease. In the Panel's view the effects of Diovan on microalbuminuria had been given undue emphasis and had not been placed sufficiently within the context of treating hypertension such that the material appeared to promote the product for reduction of microalbuminuria. A breach of Clause 3.2 of the Code was ruled. This ruling was appealed.

With regard to the question 'Does the class reduce microalbuminuria?', the Panel noted that reductions for losartan, irbesartan and candesartan were mentioned on the page. Aprovel did not have a specific indication for the reduction of microalbuminuria although Aprovel and Cozaar had additional licensed indications to that for Diovan which was only licensed for the treatment of hypertension. The Panel considered that where the benefits of treatment were licensed indications for some members of a class but not others particular care must be taken to ensure that health professionals were not misled into assuming that the licence for a product was broader than it actually was. The Panel considered that the page gave the impression that the class reduced microalbuminuria and that the products were similar in this regard. The Panel noted its rulings above and considered that it was misleading to imply similarities in relation to Diovan, Aprovel and Cozaar with regard to reductions in microalbuminuria. This was inconsistent with the SPC for Diovan and the Panel ruled a breach of Clause 3.2 of the Code. This ruling was appealed.

With regard to the information on irbesartan, cosartan and candesartan, the Panel noted that Clause 3.2 of the Code stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization. Novartis was not promoting irbesartan, losartan or candesartan therefore Clause

3.2 did not apply. The Panel thus ruled no breach of Clause 3.2 of the Code. This ruling was not appealed.

APPEAL BY NOVARTIS

Novartis noted that the page in question was within a detail aid dedicated to the treatment of hypertension. The front cover was subtitled 'Diovan Evolutionary antihypertensive therapy'. The four double page spreads, leading up to page 10, all clearly referred to the treatment of hypertensive patients. In the bottom right hand corner of every double page spread was the bold heading 'Diovan For BP control after a patient's 1st ACE inhibitor'. As the detail aid was designed for representatives to use sequentially, page by page, the emphasis was on the treatment of hypertension.

Novartis submitted that the central theme of page 10 was the treatment of hypertension. The page was headed 'Microalbuminuria is a strong predictor of total cardiovascular premature mortality and morbidity in hypertensive patients with type 2 diabetes'. The red highlighted take-home-message box at the foot of the page stated 'The significant effect of Diovan on microalbuminuria makes it an appropriate choice for hypertensive patients with type 2 diabetes'. The data presented for Diovan was that for the hypertensive subgroup of the MARVAL study and this was clearly stated in the first-line of the appropriate legend. Also on the adjacent page the title 'Diovan For BP control after a patient's 1st ACE inhibitor' further emphasised that Diovan was for the treatment of hypertensive patients. Novartis denied a breach of Clause 3.2 of the Code.

Novartis submitted that both irbesartan and losartan were licensed to treat patients with degrees of renal dysfunction. However, the use of the microalbuminuria data on page 10 was completely in the context of microalbuminuria being a cardiovascular risk factor, not a marker of progressing renal disease. This was stressed by the first bullet point on the page, 'Microalbuminuria is a strong predictor of total cardiovascular premature mortality and morbidity in hypertensive patients with type 2 diabetes', and reinforced by the repeated reference to the patients involved being hypertensive.

Novartis submitted that it was fair to illustrate the additional benefit on an established cardiovascular risk factor (microalbuminuria) in hypertensive patients for whom Diovan was licenced. This page was consistent with the Diovan SPC and thus not in breach of Clause 3.2 of the Code.

COMMENTS FROM BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

Bristol-Myers Squibb and Sanofi-Synthelabo noted that the statement 'Microalbuminuria was a strong predictor of total cardiovascular premature mortality in hypertensive patients with type 2 diabetes' was widely accepted and supported by scientific evidence. The important word in the sentence was 'predictor' as microalbuminuria had been demonstrated to be an independent risk factor for cardiovascular disease in both diabetic and non-diabetic hypertensive patients and recent guidelines suggested screening all hypertensive patients for microalbuminuria. Patients in whom microalbuminuria was detected should be offered comprehensive risk factor management. What was not proven or known was whether reducing microalbuminuria alone reduced cardiovascular risk. The data presented on page 10 of the detail aid demonstrated that AIIRAs were effective in reducing microalbuminuria but as yet there was no evidence to suggest that reductions in morbidity and mortality would result purely based on this effect. The page therefore misled doctors by implying that treatment with AIIRAs, and Diovan in particular, would lead to a morbidity and mortality benefit in hypertensive type 2 diabetics. This was not substantiable and Diovan was not licensed to support this assertion, hence the page was in breach of Clause 3.2.

The companies submitted that it was irrelevant that the microalbuminuria data were presented in the context of hypertension. The three trials presented on page 10 of the detail aid had not studied the effects of blood pressure lowering. The blood pressure targets were the same for patients in each arm of the trials with the objective of studying treatment effects that were unrelated to blood pressure lowering.

The companies noted that, by contrast, however, microalbuminuria was a marker for diabetic renal disease and was used to diagnose and monitor its progression. Irbesartan was the only AIIRA to be granted a licence for renal protection in type 2 diabetics with microalbuminuria (early stage renal disease). This was supported by the results of Parving *et al* (2001), presented on page 10 of the detail aid, which demonstrated a 70% reduction in progression to diabetic nephropathy for the 300mg dose. This study had not assessed impact on overall cardiovascular risk reduction. There were trial data for both losartan (Brenner *et al* 2001) and irbesartan (Lewis *et al* 2001) to demonstrate a reduction in the combined end point of doubling of serum creatinine, progression to end stage renal disease or death in hypertensive type 2 diabetics with established nephropathy. The licences clearly focused on renal protection and not overall cardiovascular risk reduction.

The companies alleged that the reason that doctors were familiar with data studying renal markers, such as microalbuminuria for irbesartan and losartan in hypertensive type 2 diabetics, was in connection with renal protection. The question 'Does the [AIIRA] class reduce microalbuminuria?' followed by the statement 'Microalbuminuria is a strong predictor of total cardiovascular premature mortality in hypertensive patients with type 2 diabetes' encouraged doctors to link Diovan to the data and the irbesartan and losartan licences for renal protection in hypertensive type 2 diabetics. It was unlikely to be coincidence that these two AIIRAs had been selected for comparison on page 10 of the detail aid which implied superiority for Diovan. If it was not such an attempt, why specifically had hypertensive type 2 diabetic patients been selected rather than the wider hypertensive population? The companies considered that this was a clear attempt to promote outside the hypertension licence for Diovan. As in Case AUTH/1262/12/01 which related to a previous detail

aid promoting Diovan for reduction in microalbuminuria, the Appeal Board had ruled that 'there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition'. [Case AUTH/1262/12/01 concerned the promotion of Cozaar.]

The companies questioned whether the final statement on page 10 of the detail aid 'The significant effect of Diovan on microalbuminuria makes it an appropriate choice for hypertensive patients with type 2 diabetes' would raise safety concerns. Doctors might prescribe Diovan in hypertensive type 2 diabetics with diabetic nephropathy, ie significant renal impairment. Clinical trials of Diovan in patients with diabetic nephropathy had not been conducted and safety data were therefore not available. The companies noted that Diovan required dose adjustment in renal impairment unlike irbesartan. It might be preferable for this statement to limit use to hypertensive type 2 diabetics with early stage renal disease. In addition to misleading doctors and promoting outside of licence there might also be genuine patient issues relating to page 10 of the detail aid.

The companies noted Novartis had substantiated its claim that page 10 of the detail aid did not unduly emphasise the effect of Diovan on microalbuminuria by stating that the detail aid was dedicated to the treatment of hypertension. The companies alleged that this was not entirely the case as pages 8 and 9 were dedicated to the effect of Diovan on left ventricular hypertrophy and two pages were dedicated to the effect of Diovan on microalbuminuria. The companies also considered that each page of the detail aid should stand alone with regard to the Code. The companies noted that Novartis stated that the detail aid was designed to be used sequentially. In Case AUTH/1268/12/01 the Panel had ruled that individual pages of a Diovan detail aid which had given undue emphasis to reduction in microalbuminuria were in breach of Clause 3.2 of the Code. In light of the fact that the emphasis of the page was clearly on the treatment of microalbuminuria and not hypertension, the companies continued to allege a breach of Clause 3.2 of the Code consistent with the Panel's ruling in Case AUTH/1268/12/01. The companies alleged that in this context it could be argued that Novartis was in breach of a previous undertaking.

The companies noted that Novartis also claimed emphasis on hypertension by having a bold heading 'Diovan For BP control after a patient's 1st ACE inhibitor'. This statement was included in the bottom right-hand corner of each double page. Furthermore, it was printed in the smallest font on the page except for the graph legend and the references. This did not therefore constitute a heading but a footnote.

The companies alleged that despite the comments made by Novartis, they had not altered their opinion and considered that page 10 of the detail aid constituted a breach of Clause 3.2.

APPEAL BOARD RULING

The Appeal Board noted that albuminuria was a recognised surrogate market for diabetic nephropathy. Diabetic nephropathy was independent of blood pressure. Microalbuminuria in a type 2 diabetic, irrespective of blood pressure, gave an indication of impending nephropathy. Microalbuminuria was not, however, a recognised surrogate marker in hypertension. Although microalbuminuria occurred in hypertension it was a function of blood pressure; lowering blood pressure with an antihypertensive would reduce microalbuminuria. Reduction in microalbuminuria, however, was not used as an indicator of successful antihypertensive therapy. Blood pressure was used to assess the efficacy of an antihypertensive. The Appeal Board noted that the subgroup of patients from the MARVAL study, although hypertensive, type 2 diabetics, did not have microalbuminuria such that they would have been diagnosed as having diabetic nephropathy and be treated for it *per se*. Patients were included in the MARVAL study if they had a urinary albumin excretion rate (UAER) of 20-200µg/min which was less than that required for a diagnosis of diabetic nephropathy.

The detail aid referred to the reduction of microalbuminuria in type 2 diabetics and the Appeal Board considered that by association readers would assume that Diovan was indicated for use in diabetic nephropathy. This impression was strengthened by the reference to irbesartan and losartan both of which were licensed to treat diabetic renal disease. The Appeal Board considered that the presentation of the data in relation to Diovan, losartan and irbesartan and their effects on microalbuminuria was such as to imply, by association, that Diovan was licensed for the management of diabetic nephropathy which was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2 of the Code. The appeal on this point was thus unsuccessful.

With regard to the question 'Does the class reduce microalbuminuria?' the Appeal Board noted its comments above and again upheld the Panel's ruling of a breach of Clause 3.2 of the Code. The appeal on this point was unsuccessful.

B Leavepiece

Page 2 of a four page leavepiece was headed 'Diovan delivers BP control in practice' followed by the claim that Diovan was an appropriate choice 'after your first ACE-inhibitor has fallen short because:', which was followed by three claims. The third claim being 'Diovan is effective in reducing microalbuminuria in hypertensive patients with type 2 diabetes'. Beneath the product logo on the facing page, and also on page one, was the strapline 'Evolutionary antihypertensive therapy'.

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that for the reasons given above the claim '… effective in reducing microalbuminuria in hypertensive patients with type 2 diabetes' constituted promotion outside the marketing authorization in breach of Clause 3.2 of the Code. It appeared from this and the detail aid that Novartis was encouraging its

representatives to proactively promote valsartan for an unlicensed indication. A further breach of Clause 3.2 was alleged.

RESPONSE

Novartis repeated that all references made to reduction in microalbuminuria were in the context of treating hypertensive type 2 diabetic patients and that the reduction in microalbuminura represented a benefit of treating hypertension in these patients with Diovan. The leavepiece itself focused on treating hypertension with Diovan with statements such as 'Diovan is highly effective in reducing BP'. Its response with regard to the detail aid (point A) above was relevant here and supported Novartis' submission that these claims were not in breach of Clause 3.2 of the Code.

Novartis strongly refuted the complainants' suggestion that it was encouraging its representatives to proactively promote valsartan for an unlicensed indication, Novartis ensured that at all times its promotional activities were in accordance with the Code and that claims relating to the effects of Diovan on microalbuminuria in hypertensive type 2 diabetic patients were in accordance with the marketing authorization.

PANEL RULING

The Panel considered that the leavepiece clearly set the effects of Diovan on reducing microalbuminuria in the context of treatment of hypertension, the heading to the page in question was 'Diovan delivers BP control in practice'. The Panel considered that the leavepiece was different to the detail aid in this regard. No breach of Clause 3.2 of the Code was ruled.

With regard to the representatives the Panel noted that no evidence was provided as to what the representatives had said. The detail aid had been ruled in breach of the Code (point A above). Taking all the circumstances into account the Panel ruled no breach of Clause 3.2 of the Code.

C Product Monograph

Page 20 of the product monograph featured a bar chart showing the reduction in UAER in hypertensive type 2 diabetics treated either with valsartan (–47%) or amlodipine (–11%) ($p<0.001$).

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated the data again referred to a scientific study that claimed a reduction in microalbuminuria beyond blood pressure lowering. The monograph clearly stated 'Blood pressure reductions were comparable in both treatment groups'. The claim that valsartan reduced microalbuminuria to a greater extent than amlodipine was therefore claiming that this effect was blood pressure independent. As above this was not part of the marketing authorization for Diovan and a breach of Clause 3.2 of the Code was alleged.

RESPONSE

Novartis stated that the page at issue appeared in the section entitled 'Management of hypertensive patients with type 2 diabetes'. This section described the importance of treating hypertensive diabetic patients and presented the National Institute for Clinical Excellence (NICE) guideline recommendations for the management of hypertensive patients with type 2 diabetes. These guidelines recommended angiotensin receptor blockers as first-line therapy in low and high coronary risk patients and as alternatives to ACE-inhibitors in patients with microalbuminuria or proteinuria. In this context of treating hypertensive type 2 diabetic patients where microalbuminuria was an important predictor of cardiovascular risk the previously mentioned data from the hypertensive subgroup of the MARVAL study was presented. Blood pressure reductions in both the Diovan and amlodipine groups were comparable, whilst a significantly greater reduction in microalbuminuria was observed with Diovan. This data described the benefits of treating hypertensive patients with Diovan and therefore did not constitute a breach of Clause 3.2 of the Code.

Novartis referred again to Case AUTH/1340/7/02 as supportive evidence for its position.

PANEL RULING

The Panel noted its comments in point A above.

The Panel noted that the page in question referred to a subset of hypertensive patients and this was followed with a description of the results from the MARVAL study. The comparison between Diovan and amlodipine was shown graphically. It was not clearly stated that the patients were treated with Diovan for hypertension. The Panel considered that the results had not been set sufficiently in the context of the licensed use of Diovan.

The Panel noted that the second half of page 20 referred to reductions in microalbuminuria observed with the other AIIRAs.

The Panel noted its comments at point A above with regard to the differences in the licences of the various products. The Panel considered that where the benefits of treatment were licensed indications for some members of a class but not others then companies must take particular care to ensure that health professionals were not misled into assuming that the licence for a product was broader than it actually was.

On balance the Panel considered that the page did not meet the requirements of Clause 3.2 of the Code and ruled accordingly. This ruling was appealed.

APPEAL BY NOVARTIS

Novartis submitted that the data presented on page 20 of the product monograph clearly related to the use of Diovan in the treatment of hypertension. The nature of the document was such that a single page would not be used in isolation. The product monograph was titled 'The Evidence – Diovan – Evolutionary antihypertensive therapy'. The section in which page

20 appeared was titled 'Management of hypertensive patients with type 2 diabetes'. Pages 18 and 19 summarised the guidelines issued by NICE for the management of hypertension in type 2 diabetics.

Novartis noted that at the top of page 20 was a description and representation of the results of the hypertensive subgroup of patients in the MARVAL study. Novartis submitted that the text emphasised that all the patients referred to were hypertensive and that they were treated with Diovan to a blood pressure target of 135/85mmHg. Therefore, these patients were treated with Diovan for their hypertension. The study was designed such that if a patient's blood pressure was <135/85mmHg they did not receive a titration of their antihypertensive treatment.

In addition, the legend under the graph restated that the patients represented were all hypertensive and that they received antihypertensive treatment depending on blood pressure control.

Novartis submitted that taken as a whole, these references focused on the use of Diovan for the treatment of hypertension and that the representation of the microalbuminuria data was a fair description of the benefits of treating this condition with Diovan.

Novartis noted that the Panel had considered that reference to other AIIRAs on the second half of page 20 suggested that Diovan was indicated for use in patients beyond hypertension. Novartis submitted that for the same reasons as its appeal in point A above, it considered that reference to the effects of AIIRAs on microalbuminuria, an established cardiovascular risk factor, was reporting the additional benefits of treating these patients with hypertension.

Novartis submitted that this was not in breach of Clause 3.2 of the Code.

COMMENTS FROM BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

Bristol-Myers Squibb and Sanofi-Synthelabo noted Novartis' submission that page 20 of the product monograph clearly related to the use of Diovan in the treatment of hypertension. However, nowhere on the page was there a heading to suggest this. The only heading stated 'AT1 receptor blockers – reductions in microalbuminuria', and the most prominent aspect of the page was a graph entitled 'Effect on levels of UAER' and a graph depicting the results of the MARVAL study. Again the Panel had previously considered that an individual page in a previous Diovan detail aid had unduly emphasised microalbuminuria and ruled a breach of Clause 3.2 of the Code (Case AUTH/1268/12/01).

The companies noted that the section to which Novartis claimed page 20 was related was the double page spread on pages 18 and 19. Page 20 was over the page and laid out in a different manner suggesting that the two sections were independent. The title 'Management of hypertensive patients with type 2 diabetes' appeared across pages 18 and 19 and was not repeated on page 20 further reinforcing the impression that the two sections were unrelated.

The companies noted Novartis' suggestion that the patients in the MARVAL study were treated for hypertension. Clearly this was not the case as hypertension was not an inclusion criteria and failed control of hypertension was explicitly not an exclusion criteria. Blood pressure was to be controlled to the same level in both arms of the MARVAL study in order to eliminate it as a factor in any difference in effects observed between the amlodipine and valsartan arms on microalbuminuria. The objective of the MARVAL study was to detect changes in urinary albumin excretion rate and not to control hypertension. In Case AUTH/1262/12/01 the Appeal Board had expressed concern over the use of data from a trial designed to treat microalbuminuria and not hypertension.

The final paragraph of the page contained the unqualified statement 'Valsartan 80-160mg has shown a 47% reduction in microalbuminuria over 6 months in hypertensive patients with type 2 diabetes'. The companies again noted that Diovan was not licensed for reduction of microalbuminuria in patients with type 2 diabetes and hypertension. This was clearly placing undue emphasis on microalbuminuria and, as in Case AUTH/1268/12/01, was in breach of Clause 3.2 of the Code.

The companies alleged that it was misleading to promote reduction in microalbuminuria in the context of cardiovascular risk reduction. Whilst microalbuminuria was known to be an independent risk factor for cardiovascular events data was not yet available to demonstrate that reducing microalbuminuria alone resulted in a reduction in cardiovascular morbidity and mortality. Diovan was not licensed for the reduction of microalbuminuria and cardiovascular risk independently of blood pressure lowering in hypertensive type 2 diabetics.

The companies considered that in addition to Case AUTH/1268/12/01 there were also similarities to Case AUTH/1262/12/01 which concerned the promotion of Cozaar in relation to benefits beyond blood pressure lowering in hypertensive type 2 diabetics before a renal protection licence was granted. It was clearly considered by both the Panel and the European Medicines Evaluation Agency that a licence was required for benefits beyond blood pressure lowering.

The companies stated that in the light of the above and their previous complaint, they continued to consider that Novartis was promoting Diovan outside its marketing authorization in breach of Clause 3.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that its comments at point A above were relevant. The reference to a recognised marker of diabetic nephropathy and to other AIIRAs which had either been licensed separately for renal protection in type 2 diabetics with nephropathy, or licensed for treatment of renal disease in hypertensive type 2 diabetic patients, as part of an antihypertensive drug regimen, implied by association that Diovan was similarly licensed which was not so. The Appeal Board upheld the Panel's

ruling of a breach of Clause 3.2 of the Code. The appeal on this point was unsuccessful.

Complaint received **11 June 2003**

Case completed **31 October 2003**

CASE AUTH/1484/6/03

PFIZER v GILEAD SCIENCES

Promotion of AmBisome

Pfizer complained about the promotion of AmBisome (liposomal amphotericin B) by Gilead Sciences. The items at issue were a leavepiece and a detail aid; both were entitled 'Killer Instinct'. Pfizer supplied Vfend (voriconazole).

The claim 'AmBisome shown to be superior to voriconazole in a comparative study' appeared as a heading in both the leavepiece and the detail aid. The claim was referenced to a letter published in the issue of the New England Journal of Medicine which also reported the results of Walsh *et al* (2002). Walsh *et al* had compared AmBisome and Vfend as empirical antifungal therapy in patients with neutropenia and persistent fever. Beneath the claim a graph depicting the results of the study was accompanied by three stabpoints the first two of which referred to the study results; the third one read 'Voriconazole is not indicated in Europe for the empirical treatment of pyrexia of unknown origin'.

Pfizer stated that this claim implied overall superiority of AmBisome over Vfend. However the only study cited in support of the claim compared the use of Vfend and AmBisome as empirical antifungal therapy in patients with neutropenia and persistent fever. A stabpoint beneath the claim stated that voriconazole was not licensed in Europe for empirical treatment of febrile neutropenia which Pfizer stated contradicted Gilead Sciences argument that Vfend 'is a medicine that is intended for the same purpose as AmBisome and that the comparison is 'justifiable'.' Pfizer also noted Walsh *et al* used Vfend at a maintenance intravenous (IV) dose of 3mg/kg twice daily, which was lower than the licensed IV maintenance dose of 4mg/kg twice a day. This was not mentioned anywhere in the piece.

Gilead Sciences had noted that Walsh *et al* was in the public domain and that it would not draw undue attention to the potential use of Vfend in empirical therapy. Pfizer agreed that the data were of interest to health professionals but in line with the Code, use in a promotional context by either Gilead Sciences or Pfizer would be inappropriate. Pfizer therefore alleged that the claim was an unfair comparison based on a lower than approved dose of Vfend and an indication for which Vfend was not licensed.

The Panel noted Gilead Sciences submission that both AmBisome and Vfend were used by specialist physicians, all of whom were well aware of treatment indications for products in this therapeutic area, and that off-label use was commonplace and as such Vfend was frequently used to treat neutropenic patients with fever where infection was not confirmed ie empiric treatment of systemic fungal infection. Walsh *et al* had recently published a study in the New England Journal of Medicine comparing AmBisome and Vfend as empirical antifungal therapy in patients with neutropenia and persistent fever.

The Code required, *inter alia*, that 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. A comparison was only permitted if, *inter alia*, it was not misleading and medicines for the same needs or intended for the same purpose were compared. The Panel noted that there were difficulties in comparing medicines where the competitor product was being used outside its marketing authorization. The Panel queried whether comparing products using unlicensed doses and/or indications of a competitor product met the requirements of the Code. Readers might be misled as to the approved use of the competitor product and the company with the competitor product could not counter the arguments as it would be open to accusations of promoting an unauthorized indication. The Panel noted Gilead Sciences' submission that Vfend was frequently used for the empiric treatment of febrile neutropenia notwithstanding the fact that it was not so authorized. There was a relevant published paper comparing AmBisome and Vfend and such information might be of practical and clinical relevance.

The Panel considered that the headline claim in both the detail aid and the leavepiece 'AmBisome shown to be superior to voriconazole in comparative study' implied overall superiority of AmBisome as alleged. It was irrelevant that the reference cited in support of the claim, the graph below it and the accompanying bullet points referred to empirical therapy. Readers would gain the misleading impression that in all ways AmBisome was better than voriconazole. The Panel further considered that it was not immediately clear to the reader that voriconazole was not licensed for use in the empirical therapy of febrile neutropenia. The third bullet point that 'Voriconazole is not indicated in Europe for the empirical treatment of pyrexia of unknown origin' was not sufficient in that regard. Breaches of the Code were ruled.

The Panel noted that the dose of voriconazole used by Walsh *et al*, although not referred to in the detail aid or the leavepiece, was 3mg/kg twice daily which was less than the licensed maintenance dose of 4mg/kg twice daily. Given that there was not a

licensed dose of voriconazole in the empiric treatment of febrile neutropenia and that 3mg/kg twice daily was the dose of voriconazole used by Walsh *et al* the Panel did not consider that failure to note the difference in dose in the promotional material was misleading as alleged. No breach of the Code was ruled on that narrow point.

Upon appeal by Pfizer, the Appeal Board noted that the Code stated, *inter alia*, that a comparison was only permitted in promotional material if it was not misleading and that medicines for the same needs or intended for the same purpose were compared.

Although it was not licensed for such, voriconazole was nonetheless used for the empirical treatment of febrile neutropenia. Walsh *et al* had used 3mg/kg twice daily and at this dose voriconazole did not fulfil the protocol defined criteria for non-inferiority to liposomal amphotericin B with respect to overall response. On the basis of Walsh *et al* the FDA did not grant Vfend an indication for empirical use. Vfend was however licensed at a dose of 4mg/kg twice daily for the maintenance treatment of confirmed infection.

The Appeal Board considered that although voriconazole *per se* was used for the empirical treatment of febrile neutropenia, voriconazole 3mg/kg twice daily was not intended or licensed for such use. The Appeal Board thus considered the comparison unfair and ruled a breach of the Code.

The claim 'AmBisome is significantly less nephrotoxic than Amphotericin B' appeared only in the detail aid and was referenced to the AmBisome summary of product characteristics (SPC) and Prentice *et al* (1997). Beneath the claim a graph showed the percentage of patients, none of whom were taking concomitant nephrotoxic medicines, with nephrotoxicity on conventional amphotericin B or AmBisome 1mg/kg and 3mg/kg.

Pfizer noted that the graph presented only a subgroup of those patients from Prentice *et al* who were not on concomitant nephrotoxic drugs. This subgroup comprised less than one third of the total patients in the study and this was not stated explicitly. The use of this subgroup did not reflect clinical practice in this therapeutic area. As in this study, the majority of patients who received antifungal therapy were on concomitant nephrotoxic medications. Nephrotoxicity in this group of patients was therefore clearly relevant as this group was more representative of true clinical practice.

The graph gave the impression that AmBisome 1mg/kg had no nephrotoxicity. This was misleading because if the total population in the study had been depicted, the adult nephrotoxicity rate would have been 12%. The graph would therefore have looked very different (graphs were provided for comparison which had been drawn with what Pfizer considered an appropriate scale of 0-100% on the y axis compared to the scale of 0-30% as represented by Gilead Sciences). The graph presented data in adults, children and the total population and visually implied a difference between the conventional amphotericin B group and both AmBisome groups for adults, children and the total population as stated. The page and the graph however failed to mention that the difference in children between conventional amphotericin B and AmBisome was not significant at any dose and regardless of concomitant nephrotoxic medications. This was therefore misleading.

The Panel did not consider that it was misleading *per se* to compare the nephrotoxicity of AmBisome with that of conventional amphotericin B, in a subset of patients who were not, at the same time, taking other nephrotoxic medicines. However, although the graph at issue described the patient group the headline claim above it, 'AmBisome is significantly less nephrotoxic than Amphotericin B' did not. The impression given was that in all patients and in all circumstances AmBisome was significantly less nephrotoxic than amphotericin B and that was not so. Breaches of the Code were ruled.

The graph showed that no nephrotoxicity occurred in those patients taking AmBisome 1mg/kg, but not concomitant nephrotoxic medicines. While this was a true reflection of Prentice *et al*, the Panel did not consider that it reflected the balance of the evidence. It was tantamount to stating that AmBisome 1mg/kg did not cause nephrotoxicity. That was not so, the SPC stated that AmBisome might be nephrotoxic despite being tolerated significantly better than other amphotericin products. The SPC also stated that nephrotoxicity occurred to some degree with conventional amphotericin in most patients receiving the medicine IV and that in two studies the incidence of nephrotoxicity with AmBisome was approximately half of that reported for conventional amphotericin B or amphotericin B lipid complex. Breaches of the Code were ruled.

With regard to the y axis the Panel did not consider it misleading to have it only extended to 30%. The y axis was clearly labelled. No breach of the Code was ruled in that regard.

The Panel noted its comments above with regard to the headline claim 'AmBisome is significantly less nephrotoxic than amphotericin B'. The graph gave no indication that there was no statistically significant difference in the incidence of nephrotoxicity in children treated with either AmBisome or conventional amphotericin B. Visually the graph suggested otherwise and such an impression was strengthened by the headline claim. A breach of the Code was ruled.

The claim 'Nephrotoxicity in the C-AMB [conventional amphotericin B] arm was not influenced by the use or absence of concomitant nephrotoxic agents' appeared as the second of three stabpoints beneath the claim and graph considered above. The claim was referenced to Prentice *et al*. The third bullet point read 'In contrast nephrotoxicity was significantly less in the AmBisome arm in patients not receiving other nephrotoxic medication (23% v 3%)'.

Pfizer alleged that the claim did not reflect the balance of evidence and was misleading. Whilst the claim was supported by Prentice *et al* which involved approximately 300 patients, Walsh *et al*

(1999), a much larger study involving over 700 patients showed this not to be the case.

The Panel noted that Prentice *et al*, in a comparison of liposomal and conventional amphotericin B for the empirical treatment of neutropenic patients with persistent fever, showed that the incidence of nephrotoxicity in all patients receiving conventional amphotericin B was 24%. In patients who were not also taking concomitant nephrotoxic medicines the incidence was 23% and in those who were also taking nephrotoxic medicines the incidence was 26%. Thus the concomitant use or otherwise of nephrotoxic medicines with conventional amphotericin B did not appear to influence the incidence of nephrotoxicity. Walsh *et al* (1999) similarly compared liposomal and conventional amphotericin B and showed that in patients taking the conventional preparation together with either none or one nephrotoxic medicine the incidence of nephrotoxicity was 15.2%. This incidence rose to 40.5% and 45.4% if patients were also taking 2 or more or 3 or more concomitant nephrotoxic medicines respectively. Thus the incidence of nephrotoxicity appeared to increase as the number of concomitant nephrotoxic medicines increased.

The Panel considered that although the claim 'Nephrotoxicity in the [conventional amphotericin B] arm was not influenced by use or absence of concomitant nephrotoxic agents' reflected the results of Prentice *et al*, it did not take into account the results of Walsh *et al* (1999). The Panel considered that the claim was thus misleading and ruled a breach of the Code.

Pfizer Limited complained about the promotion of AmBisome (liposomal amphotericin B) by Gilead Sciences Limited. The items at issue were a leavepiece (ref 104/UK/02-05/JB290) and a detail aid (ref 104/UK/02-05/JB291); both were entitled 'Killer Instinct'. Pfizer supplied Vfend (voriconazole). Contact between the companies had failed to resolve the issues.

1 Claim 'AmBisome shown to be superior to voriconazole in a comparative study'

This claim appeared as a page heading in both the leavepiece (page 2) and the detail aid (page 2). The claim was referenced to a letter published in the issue of the New England Journal of Medicine which also reported the results of Walsh *et al* (2002). Walsh *et al* (2002) had compared AmBisome and Vfend as empirical antifungal therapy in patients with neutropenia and persistent fever. Beneath the claim a graph depicting the results of the study was accompanied by three stabpoints the first two of which referred to the study results; the third one read 'Voriconazole is not indicated in Europe for the empirical treatment of pyrexia of unknown origin'.

COMPLAINT

Pfizer stated that this claim implied overall superiority of AmBisome over Vfend. However the only study cited in support of the claim compared the use of Vfend and AmBisome as empirical antifungal therapy in patients with neutropenia and persistent fever (Walsh *et al* 2002). Vfend was only licensed for the treatment of invasive aspergillosis, fluconazole-resistant Candida infections and for the treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

Pfizer noted that a stabpoint beneath the claim stated that voriconazole was not licensed in Europe for empirical treatment of febrile neutropenia and stated that this contradicted the defensive argument put forward by Gilead Sciences during the consultation process that Vfend 'is a medicine that is intended for the same purpose as AmBisome and that the comparison is 'justifiable'.'

Pfizer also noted that the study involved the use of Vfend at a maintenance intravenous (IV) dose of 3mg/kg twice daily, which was lower than the licensed IV maintenance dose of 4mg/kg twice a day. This was not mentioned anywhere in the piece.

Gilead Sciences had noted that Walsh *et al* (2002) was in the public domain and that it would not draw undue attention to the potential use of Vfend in empirical therapy. Pfizer agreed that the data were of interest to health professionals but in line with the Code, use in a promotional context by either Gilead Sciences or Pfizer would be inappropriate.

Pfizer therefore alleged that the claim was in breach of Clauses 7.2 and 7.3 of the Code; it was an unfair comparison based on the lower than approved dose of Vfend and for use in an indication for which Vfend was not licensed.

RESPONSE

Gilead Sciences stated that the Code did not prohibit the use in promotional material of clinical papers where the comparator product or products were not used squarely within the terms of the licensed indication(s). Such data frequently substantiated statements that appeared in summaries of product characteristics (SPCs) and might properly be discussed, provided that was not done in a misleading way. As an example of this Gilead Sciences noted that Section 4.8 of the AmBisome SPC stated: 'In two, double-blind studies, the incidence of nephrotoxicity with AmBisome … is approximately half of that reported for conventional amphotericin B or amphotericin B lipid complex'. In both of the studies the comparator products were used as empirical treatment of neutropenic fever unresponsive to antibiotic treatment, despite the absence of an approved indication for empiric treatment. Gilead Sciences stated that it was entitled to refer to such studies not just because they were referred to in the SPC, but because they contained important scientific knowledge that was not invalidated simply because the data were derived from usage outside an approved indication.

Gilead Sciences therefore submitted that a proper interpretation of the Code was that it was acceptable to make use of such data in promotional material if it was relevant in the context of the promotion and appropriately presented. The test was not whether the comparator was licensed for the treatment

discussed, but rather whether the comparison drawn was unfair or misleading.

In this case there was no question that the promotion would mislead doctors that Vfend was indicated for empirical treatment. The fact that the product was not licensed for such treatment was stated in the third bullet point which was given the same prominence as the other two.

Whether a comparison was unfair depended upon background circumstances and the particular facts. Both AmBisome and Vfend were used by specialist physicians all of whom were well aware of treatment indications for products in this therapeutic area. Gilead Sciences estimated that about 3000 patients received empiric antifungal treatment for neutropenic fever in the UK every year. Most of these were patients with haematological malignancies that had become neutropenic due to cancer treatment and a significant proportion would have undergone bone marrow transplants. Treatment of such patients by non-specialists simply did not arise.

In such specialities, off-label use was commonplace. Consistent with this, Vfend was frequently used off-label to treat neutropenic patients with fever where infection was not confirmed (ie empiric treatment for systemic fungal infection). Indeed the Vfend SPC might be viewed as encouraging this as Section 5.1 (Microbiology) stated 'Therapy may be instituted before the results of cultures and other laboratory studies are known; however once these results become available, anti-infective treatment should be adjusted accordingly'. The fact that there was significant off-label use was further evidenced by the antifungal treatment protocol currently in operation at a major UK teaching hospital. A confidential copy was provided.

It was, in fact, Pfizer's intent that Vfend be used for empirical therapy and the data from Walsh *et al* (2002), which was supported in part by a grant from Pfizer Global Research and Development, was submitted to the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) in 2001 in support of such an indication. Indeed, it was the pivotal study for the licence application. The conclusion of the study authors that 'Voriconazole is a suitable alternative to amphotericin B preparations for empirical antifungal therapy in patients with neutropenia and persistent fever' further supported the view that Vfend was a suitable comparator. The authorization was not granted because the data were not viewed as supportive, but the transcript from the FDA Committee referred to the fact that since the first studies were conducted addressing the question of empirical antifungal treatment 20 years ago, empirical therapy had become the standard of practice in neutropenic patients if they remained febrile after a period of antibacterial treatment.

Accordingly, given the extent of use of Vfend for empirical therapy Gilead Sciences considered that it was fair to make the comparison in its materials and draw doctors' attention to the comparative efficacy in what was the only study directly comparing the two products. Pfizer's suggestion that only a comparison between AmBisome and placebo was allowed in these circumstances (despite acceptance that the data were 'of interest to health professionals') was misconceived. This was a therapeutic field where active comparators were required and as only AmBisome was currently approved for empirical treatment, Gilead Sciences would be unreasonably restricted if it could not refer at all to available literature. Moreover, if Pfizer was correct it would mean that, even in specialist fields, the studies that companies sponsored with a view to demonstrating favourable comparisons with products already authorized for a given indication, but which turned out to be 'negative', could not thereafter be given any publicity by competitors. That was not consistent with the overarching aim of the Advertising Directive that advertising to health professionals should contribute to the information available to such persons and encourage rational use of products. Gilead Sciences considered that it was in the interest of physicians and patients that information from this pivotal study be shared. This also ensured that the favourable conclusions of the authors of the study were more critically considered by physicians.

Gilead Sciences acknowledged that Clause 7.3 of the Code only permitted a comparison to be made between two products in promotional material if the medicines were being compared for the same needs or intended for the same purposes. Pfizer asserted that it was contradictory for Gilead Sciences to state, on the one hand, that Vfend was not approved for empirical treatment, but, on the other hand, to imply that Vfend was for the same needs. In the context of the particular promotion and the reference to Walsh *et al* (2002), Gilead Sciences did not consider the statements were contradictory. What mattered in this context was the actual purpose for which Vfend was used in the research to which attention was drawn. The reference to medicines used for the same needs, pre-supposed that they might not, in fact, be indicated in a regulatory sense for the same purpose. If that were not the case, the reference to 'same needs' would not be required.

This was also supported by consideration of the rationale underpinning the requirements in Clause 7.3 of the Code. The conditions for permitting comparative advertising set out in Clause 7.3 were intended to reflect the terms of the Control of Misleading Advertisements Regulations 1988 as amended. The Regulations in turn implemented the Comparative Advertising Directive (97/55). It was clear from the Directive that the requirement that goods be for the same needs or intended for the same purposes in order to be compared was designed to ensure that comparisons were only made between products that in practice competed. As described above, the reality was that voriconazole and AmBisome did compete, irrespective of the exact wording of the SPCs.

Gilead Sciences noted that dosing information was not included on the graph for either AmBisome or voriconazole. It was disingenuous of Pfizer to suggest that it was unfair and/or misleading not to state that the dose of Vfend used in Walsh *et al* (2002) was lower than the dose indicated for use of Vfend in confirmed

infection. There was no reason why the dose used in empirical treatment should be the same as the dose used when treating a confirmed infection.

In empirical treatment, inevitably some patients were treated that were not suffering from mycoses and accordingly the severity of side-effects which was acceptable tended to be less than for patients with confirmed infection. The side-effect profile at a dose of 3mg/kg was likely to be more favourable than that at a dose of 4mg/kg. This was presumably the very reason why Pfizer chose the dose of 3mg/kg rather than 4mg/kg for this study which was used to support its registration dossier for empirical treatment.

Accordingly, it was misleading for Pfizer now to imply that the poorer efficacy results for Vfend were the result of using a dose that was too low and, therefore, the comparison was inappropriate. This was the dose chosen by Pfizer as an appropriate dose when treating empirically. This was really only an extension of the issue of the allegation that only data relating to the licensed indications of a competitor could be mentioned. Gilead Sciences submitted that this allegation was without merit and that the comparison it made must faithfully report data derived from the dose used by Walsh *et al* (2002).

Gilead Sciences noted that companies had previously been ruled in breach of the Code where they referred to studies with the comparator product that included patients titrated to a dose higher than the licensed dose and then used for the comparison a dose that was not consistent with that actually licensed for the comparator in the indication which was the subject of the comparison made in the promotion. But this was not the case here. There had been no inappropriate selection of dose by Gilead Sciences and the fact that Vfend was not approved in the EU for empirical treatment was not buried away in a footnote or small print, but was very prominently declared. The dose for Vfend used in Walsh *et al* (2002) was 3mg/kg. Pfizer itself was of the view that for an appropriate comparison the dose for such therapy should be 3mg/kg. The mere fact of referring to data derived from unlicensed use, where this fact was clearly stated did not mislead physicians as to the efficacy or safety of the competitor product for its licensed uses.

PANEL RULING

The Panel noted Gilead Sciences submission that both AmBisome and Vfend were used by specialist physicians all of whom were well aware of treatment indications for products in this therapeutic area. Gilead Sciences had also submitted that off-label use was commonplace and as such Vfend was frequently used to treat neutropenic patients with fever where infection was not confirmed ie empiric treatment of systemic fungal infection. Walsh *et al* had recently published a study in the New England Journal of Medicine comparing AmBisome and Vfend as empirical antifungal therapy in patients with neutropenia and persistent fever.

Clause 7.2 of the Code required, *inter alia*, that 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 7.3 stated that a comparison in promotional material was only permitted if, *inter alia*, it was not misleading and medicines for the same needs or intended for the same purpose were compared. The Panel noted that there were difficulties in comparing medicines where the competitor product was being used outside its marketing authorization. The Panel queried whether comparing products using unlicensed doses and/or indications of a competitor product met the requirements of the Code. Readers might be misled as to the approved use of the competitor product and the company with the competitor product could not counter the arguments as it would be open to accusations of promoting an unauthorized indication.

The Panel noted Gilead Sciences' submission that Vfend was frequently used for the empiric treatment of febrile neutropenia notwithstanding the fact that it was not so authorized. There was a relevant published paper comparing the AmBisome and Vfend and such information might be of practical and clinical relevance.

The Panel noted the headline claim in both the detail aid and the leavepiece 'AmBisome shown to be superior to voriconazole in comparative study' and considered that this implied overall superiority of AmBisome as alleged. It was irrelevant that the reference cited in support of the claim, the graph below it and the accompanying bullet points referred to empirical therapy. Readers would gain the misleading impression that in all ways AmBisome was better than voriconazole. The Panel further considered that it was not immediately clear to the reader that voriconazole was not licensed for use in the empirical therapy of febrile neutropenia. The third bullet point that 'Voriconazole is not indicated in Europe for the empirical treatment of pyrexia of unknown origin' was not sufficient in that regard. Breaches of Clauses 7.2 and 7.3 were ruled. These rulings were accepted by Gilead Sciences.

The Panel noted that the dose of voriconazole used by Walsh *et al* (2002), although not referred to in the detail aid or the leavepiece, was 3mg/kg twice daily which was less than the licensed maintenance dose of 4mg/kg twice daily. Given that there was not a licensed dose of voriconazole in the empiric treatment of febrile neutropenia and that 3mg/kg twice daily was the dose of voriconazole used by Walsh *et al* (2002) the Panel did not consider that failure to note the difference in dose in the promotional material was misleading as alleged. No breach of Clauses 7.2 and 7.3 of the Code was ruled on that narrow point. Pfizer appealed the ruling of no breach of Clause 7.3.

APPEAL BY PFIZER

Pfizer noted that in its ruling the Panel had noted 'Clause 7.3 stated that a comparison in promotional material was only permitted if, *inter alia*, it was not misleading **and** [emphasis added by Pfizer] medicines for the same needs or intended for the same purpose were compared'. Vfend was not licensed for use in

the empirical treatment of febrile neutropenia and so a comparison with AmBisome could not be justified.

Pfizer stated that the wording of Clause 7.3 did not allow for the latitude of interpretation of the Panel in this instance. Pfizer could not and did not promote in this indication and so the submission of third party endorsement of such off-label usage was irrelevant here and could not be used to justify a re-interpretation of Clause 7.3, whose meaning was absolutely unequivocal on this point.

The Panel appeared to take the position that it was acceptable to compare AmBisome in this situation with Vfend (3mg/kg) which was unlicensed in this indication on the grounds that, in practice, clinicians used Vfend empirically. Thus it might be implied that a comparison was fair and helpful and in the best interests of the patient. This argument might be acceptable to a certain extent except that, at least three specialist centres in the UK, from whom Pfizer had sought confirmation, used Vfend, off-licence, empirically at 4mg/kg, the dose at which it was licensed for its licensed indications. Comparative data generated from use at a lower dose than that which was used in practice were unlikely to be helpful to clinicians in these circumstances.

Walsh *et al* contained important data on voriconazole which Pfizer would wish to use in its promotional materials; the company would welcome clarification on its ability to do this. Were Gilead Sciences permitted to continue to use these data in this way, and there was a possibility that Pfizer could not, the company argued that this would put it at an unacceptable disadvantage commercially.

COMMENTS FROM GILEAD SCIENCES

Gilead Sciences noted that the breach which Pfizer had appealed was limited to the narrow point of whether it was inappropriate for Gilead Sciences not to make clear in the promotion that the dose of voriconazole used in Walsh *et al* in empiric treatment (for which Pfizer did not have an approved indication) was less than the licensed maintenance dose for Vfend in confirmed infection (for which Pfizer had an approved indication). The Panel ruled that it was not misleading because the presentation did not mislead as to nature of results of the study and, in any event, there was no licensed dose for empiric use of Vfend.

Gilead Sciences stated that the points raised by Pfizer went beyond this narrow point and it was seeking a ruling from the Appeal Board on the broader issue of whether it was acceptable for Gilead Sciences ever to refer to Walsh *et al* in its promotion of AmBisome, even though Pfizer accepted that Vfend was frequently used off-label for empiric antifungal therapy, and the results of Walsh *et al* (which Pfizer sponsored) were relevant, important and would be of interest to health professionals. Gilead Sciences noted that, on this aspect of the original complaint, Pfizer's concern would, seemingly be met by the inclusion of a statement pointing out that the dose of Vfend approved for the licensed indications was different. Pfizer did not put its complaint to the Panel so broadly on this point as it did now. Nevertheless, Gilead Sciences would address both the point of principle and the issue of whether a qualifying statement was necessary in the particular circumstances.

Gilead Sciences stated that it was common ground that in the therapeutic field at issue only AmBisome was approved for use in the UK for empiric therapy of fever of unknown origin, but that other products and, in particular, Vfend were commonly used off-label by oncologists and haematologists for this purpose. In consequence, Gilead Sciences submitted that, in principle, there were good scientific and medical reasons for allowing the dissemination of relevant comparative data generated from the use of the products as empiric therapy and no good public policy reasons for forbidding this, provided that the presentation of the data in question was unlikely to mislead.

Gilead Sciences stated that the Code should be interpreted consistently with the relevant European advertising law. This did not prohibit a company engaged in the promotion of a product for its licensed indication from referring to data developed with a product being used in a study for the same indication, simply because the second product had not been approved in the Member State for that indication or gained it at a different recommended dose or in a different pharmaceutical form. Indeed, European law was premised on the belief that pharmaceutical advertising could be of benefit because it increased knowledge about products. The central aim of the European controls was to avoid the dissemination of misleading statements and to promote rational use of products.

Moreover, as with all European law, there was an overarching requirement that the interpretation of controls should recognise the right of companies to be free to disseminate information about their products to health professionals, unless there were sound reasons based upon other public policy considerations for restricting that freedom. A real and identifiable risk that the promotion would mislead and constitute a risk to public health must, therefore, exist to justify forbidding the dissemination of accurate information to health professionals about studies conducted using a particular product.

There was nothing in the Code that could properly be interpreted as forbidding such a reference to comparator data. Rather, the central issue under Clause 7.2 was whether the presentation of those data, in context, was misleading and, therefore, undermined the basic aims of the Code and in particular the protection of public health. The data would not mislead if presented accurately and objectively. A related issue raised by Clause 7.3 was whether a comparison was fair in all the circumstances. Gilead Sciences contended that the use of relevant data should be treated as fair, in circumstances of this type, if they were presented accurately and objectively.

Gilead Sciences submitted that the Panel was right to conclude that, in relation to the distinction between the dose used in the study and the licensed dose for Vfend, there was no requirement to qualify the presentation because, as it stood, it was a fair

reflection of the study methodology and results and would not lead to irrational use of the medicines concerned.

In the current case, the Panel had found that there was a potential for certain identified aspects of the presentation to mislead and Gilead Sciences had not appealed that finding and would remedy the perceived defects. However, Gilead Sciences contended that the Panel was right to conclude that, in relation to the distinction between the dose used in the study and the licensed dose for Vfend, there was no requirement to qualify the presentation because, as it stood, it was a fair reflection of the study methodology and results and would not lead to irrational use of the medicines concerned.

Gilead Sciences submitted that about 3,000 patients underwent empiric antifungal treatment for neutropenic fever in the UK every year. Most of these patients suffered from haematological malignances that had become neutropenic due to cancer treatment and a significant portion would have undergone bone marrow transplant. This was a highly specialised area of practice where off-label use by oncologists and haematoligists was commonplace.

Although AmBisome was the only product in the UK approved to treat neutropenic patients with fever where infection was not confirmed (ie empiric treatment for systemic fungal infection) Vfend was also frequently used off-label as empiric treatment. Indeed, although the approved indications did not include such use, the Vfend SPC was somewhat ambiguous as it stated 'Therapy may be instituted before the result of cultures and other laboratory studies are known; however once these results become available, anti-infective treatment should be adjusted accordingly' (see Section 5.1. (microbiology)).

Gilead Sciences had supplied evidence to the Panel of significant off-label use in the form of one example of an antifungal treatment protocol currently in operation at a major UK teaching hospital that was provided to it in confidence. This presented the option of using voriconazole in such patients. Pfizer itself stated that it knew of at least three specialist centres in the UK that used Vfend off-label empirically, although it stated that the three from whom it had sought confirmation used the product at 4mg/kg (which was the same dose as was approved for its licensed indications).

Walsh *et al* was supported in part by a grant from Pfizer Global Research and Development and the data was submitted to both the FDA and the EMEA in 2001 in support of an application for an extension of the indications to cover use as empirical therapy. Walsh *et al* was the pivotal study for the licence application. Despite the conclusion of Walsh *et al* that 'voriconazole is a suitable alternative to amphotericin B preparations for empirical antifungal therapy in patients with neutropenia and persistent fever' the authorization was not granted because the data were not treated as substantiating the efficacy claim. Gilead Sciences noted that the transcript from the FDA Committee referred to the fact that since the first studies were conducted addressing the question of empirical antifungal treatment twenty years ago, empirical therapy had become a standard of practice in neutropenic patients, if they remained febrile after a period of antibacterial treatment.

Gilead Sciences contended that in these circumstances it was beyond dispute that the data were highly relevant to the use of AmBisome and whether its licensed use in empirical therapy might reasonably be preferred over the unlicensed use of Vfend. Gilead Sciences considered that it was legitimate for it to draw health professionals' attention to the evidence on comparative efficacy derived from the only study directly comparing the two products. Pfizer too had accepted that the data were of interest to health professionals but sought to restrict Gilead Sciences ability to disseminate the results on the basis that it was restricted in its ability to refer to the data because Vfend was not licensed in the UK for empirical therapy.

Gilead Sciences noted that its interpretation of the Code was consistent with the language and aims of the Pharmaceutical Directive on Advertising, as well as the balancing of interests that was required under the Convention on Human Rights. It would be difficult in law to justify an interpretation of the Code that went beyond the restrictions imposed by European law and indeed the Code expressly stated that it sought to reflect the principles of the Advertising Directive.

Directive 92/28/EEC noted in its recitals that the advertising of medicinal products to health professionals 'contributes to the information available to such persons' but that it should be carefully monitored. It was noted that the protection of public health required a prohibition on 'excessive and ill-considered' advertising. Article 2 of the Directive reflected the overriding aim of ensuring that advertising did not mislead and should 'encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties'.

The UK's implementation of the Directive in the Advertising Regulations reflected this aim. Neither the Directive nor the Regulations would seemingly forbid the presentation of the data from Walsh *et al*, provided the presentation was not misleading and did not promote Vfend for an unlicensed indication. Pfizer had in the past suggested that Gilead Sciences' references to Walsh *et al* might draw attention to unapproved use and thereby promote Vfend for an unlicensed indication. This rather artificial proposition appeared to have been dropped. Plainly, Gilead Sciences was promoting the efficacy of its own product in the relevant indication and the most likely effect of its promotion was a reduced use of Vfend for the unlicensed indication in question. The central issue was, therefore, whether the use of such data was automatically misleading.

Article 10 of the Human Rights Convention concerned freedom of speech and the need for restrictions to be properly justified by counter-balancing public interests (of which the protection of public health was clearly one) and proportionate having regard to risks from which the public could properly expect protection. Directives must be interpreted consistent

with those principles and national rules in the UK must also be interpreted consistent with these principles. The Convention was now independently part of English law.

Gilead Sciences contended that there was nothing in Clauses 7.2 and 7.3 of the Code that should be interpreted as only allowing references in promotion to comparator data, derived from properly conducted studies, where those data concerned a product that was or had subsequently been approved in the UK for the same use and in the same dose and pharmaceutical form. Nor would such a restriction be a natural result of the Code's aims.

The introduction to the Code stated that it was 'vital … that the pharmaceutical industry keeps the medical profession informed about its products and promotes their rational use'. The aim of the Code was stated to be to ensure that the promotion of medicines was carried out in a 'responsible, ethical and professional manner'. Gilead Sciences contended that references to comparative data that concerned use of another product that had not subsequently been approved in the UK for the same use (although it might have been in other countries) or in the same doses were not intrinsically wrong. Rather the particular circumstances and the particular presentation of the data should determine whether the promotion was acceptable.

Consistent with the aims of the Code, Clause 7.2 required claims and comparisons to be presented in a way that did not mislead either directly or by implication. Clause 7.3 stated that comparisons were only permitted if certain conditions were met. These were principally aimed at ensuring fairness between companies and included a requirement that the medicines being compared were 'for the same needs or intended for the same purpose'. In citing data from a legitimate comparative study, where the administration was for the same purpose in both arms, this condition was met. There was no requirement that the products being compared were both licensed in the UK for the purpose for which the investigators administered the products in the study.

The fact that clinical studies might refer to comparator products that were not being used squarely within the terms of the licensed indication for the comparator did not mean that those data could never be referred to by a company to whose product they related and where that product was authorized for the indication in question. Such data were frequently included in the relevant sections of a product's SPC and might properly be discussed, provided that this was not done in a misleading fashion. Section 4.8 of the AmBisome SPC stated 'In two, double-blind studies, the incidence of nephrotoxicity with Ambisome … is approximately half of that reported for conventional amphotericin B or amphotericin B lipid complex'.

In both of these two studies the comparator products were being used as empirical treatment of neutropenic fever unresponsive to antibiotic treatment, despite the absence of an approved indication for empiric treatment. Gilead Sciences was entitled to refer to such studies, not just because they were referred to in the SPC, but because they contained relevant scientific information that was not invalidated simply because the data were derived from usage outside an approved indication for the comparator. Indeed there were several examples of medicines that had been promoted in the UK with data derived from studies done against unlicensed but commonly used and generally accepted comparators.

Gilead Sciences did not consider that it was inconsistent to accept that Vfend was not approved for empirical treatment, but to state that, in the context of a comparative study, Vfend was being used for the same needs. Good science and fairness dictated that where a comparison was made the actual medical purpose for which the two products were being used was the same. This was the case in relation to Walsh *et al*. It also appeared that if the reference in Clause 7.3 to medicines being used for the same needs, referred not just to whether this was true factually, but also that products were approved for this same purpose, the reference to products being used for the 'same needs' would add nothing to the statement that the comparison should be of two products 'intended' for the same purpose. Gilead Sciences considered that the Panel was right to treat the reference to 'same needs' as a reference to administration for the same needs as a matter of fact rather than as a requirement that both products had approved indications for those needs.

This conclusion was also supported by the law that underpinned what was acceptable in terms of comparative advertising. The conditions for permitting comparative advertising, as set out in Clause 7.3, would have had regard to the terms of The Control of Misleading Advertisements Regulations 1988, as amended. These Regulations in turn implemented the Comparative Advertising Directive (97/55/EEC). The requirement that goods be for the same needs or intended for the same purposes was designed to ensure that comparisons were only made between products that competed in practice. As stated above, the reality was that AmBisome and Vfend did compete as products used for empirical treatment.

Gilead Sciences noted that Pfizer had suggested that Gilead Sciences' use of the data from Walsh *et al* was unfair because Pfizer was thereby put at 'an unacceptable disadvantage commercially'. The gist of this argument was that while Pfizer agreed that the data were 'of interest to health professionals' and contained 'important data on voriconazole' which Pfizer would wish to use in its promotional materials, for Pfizer to use the data would be inappropriate under the Code. Pfizer did not make clear how it would wish to use the Walsh *et al* data. To the extent that Pfizer faced commercial disadvantages in using Walsh *et al*, these derived from the restriction that such use should not amount to promoting the product for an unlicensed indication. That was a necessary disadvantage and was not one that should be balanced by forbidding Gilead Sciences from referring to the data when promoting its product for its licensed indication.

Pfizer had not put forward any cogent case that the use of Walsh *et al* would mislead as to the quality,

safety or efficacy of the products concerned when used as they were used in the study. Indeed its appeal submission made no reference to Clause 7.2 and developed a case only in relation to Clause 7.3. However, there was nothing intrinsically unfair to Pfizer in Gilead Sciences drawing attention to the fact that this comparative study provided evidence that AmBisome had potential advantages over voriconazole when used empirically in such patients. Pfizer had sponsored Walsh *et al* with a view to using the data for a regulatory submission to obtain an extension of the licensed indications for Vfend to cover the indication already approved for AmBisome, but found that the data was not sufficiently supportive to justify such an extension. Gilead Sciences considered that it was in the interests of both physicians and patients that information from Walsh *et al* be shared. This also ensured that the favourable conclusions were more critically analysed by physicians.

Both Gilead Sciences and Pfizer had pointed to a high level of off-label use of Vfend in the UK and Pfizer conceded that the information from the study was relevant and indeed that the data were 'of interest to health professionals'. It might be somewhat galling for Pfizer to find that the data did not support its proposed regulatory initiative. However, Gilead Sciences believed that the Appeal Board should be slow (as clearly were the Panel) to interpret Clause 7.3 in a way that would have the effect of stifling the dissemination of these results to those who would be most likely to find them of interest. This would conflict with the objective the Code because it would not be conducive to promoting rational use of medicines and it would be unfair to Gilead Sciences. It was important that if a product appeared to have a better efficacy or safety profile than one commonly used to meet the same clinical needs, the Code should promote dissemination of this information. Off-label use was common in certain therapeutic fields such as haematology and oncology, and it could not be right that a company without an approved indication was in a better position to avoid the increased scrutiny and transparency in relation to adverse study results that came from competitor promotional and informational activities than a company with an approved indication.

Gilead Sciences noted the current pressure upon companies to conduct studies with active comparators or to disseminate information about such studies conducted by third parties, so that health professionals had a clearer picture of the relative benefits and risks of using particular products. As AmBisome was the only product in the UK authorized for the indication in question, any prohibition on references to Walsh *et al* would cut against the prevailing view that the results of comparator studies were highly relevant to prescription. Pfizer had stated, in inter-company discussions, that AmBisome should only be promoted by reference to placebo controlled studies or its SPC, but placebo controlled studies were not ethical in this indication and were not conducted. Furthermore, the AmBisome SPC included results of studies conducted against medicines not licensed for empiric therapy. Gilead Sciences, therefore, contended that the dissemination of the data from Walsh *et al* was not only consistent with the aims of the Code, but that any general prohibition would be disproportionate and unfair to the company. To the extent that the dissemination of the Walsh *et al* data led to a reduction in the off-label use of Vfend, for the indication in question, that was not a matter of which Pfizer could legitimately complain.

Gilead Sciences did not accept that the presentation of Walsh *et al* was misleading and/or unfair within the meaning of Clause 7.3 unless the presentation noted that the dose used (3mg/kg twice daily) was less than the maintenance dose used in the indications for which Vfend was approved and which Pfizer suggested was the normal dose when the product was used off-label for empirical treatment (4mg/kg twice daily).

Gilead Sciences did not accept that Vfend was only used off-label at the dose of 4mg/kg twice daily and, in any event, considered that as it was reasonable for Gilead Sciences to refer to Walsh *et al*, there was no reason to refer to the licensed dose for Vfend for its use in different indications. Gilead Sciences had faithfully referred to the dose used in Walsh *et al* and to the fact that there was no licensed dose of Vfend for empiric treatment of febrile neutropenia. Dosing information was not included on the graph for either AmBisome or voriconazole. The absence of a reference to the licensed dose for Vfend for its licensed (but different) indications did not render the presentation of Walsh *et al* non-objective.

Nor did it render the presentation confusing as there was no reason why the dose used in empirical treatment should be the same as the dose used when treating a confirmed infection. Pfizer took this view when selecting the 3mg dose for Walsh *et al*. This was entirely justified because in empirical treatment it was inevitable that some patients who were treated would turn out not to be suffering from mycoses and the severity of side-effects which was acceptable for such patients was likely to be viewed as less than for patients with confirmed infection. The side-effect profile at a dose of 3mg/kg was likely to be more favourable than that at a dose of 4mg/kg. Pfizer's choice of the lower dose for Walsh *et al* was rational. What Pfizer seemed to be implying was that the poorer efficacy results for voriconazole might be the result of using a dose that was too low and, therefore, the comparison was inappropriate. However, Gilead Sciences must faithfully report the data derived from the dose actually used in the study that it relied upon and was under no obligation to note that this dose differed from the dose approved for a different indication.

Gilead Sciences was aware that companies had previously been ruled in breach of the Code where they referred to studies with a comparator product that included patients titrated to a dose higher than the licensed dose and then used in a comparative presentation a dose that was not consistent with the dose actually licensed for the comparator in the UK. However, the current case was entirely different because there had been no inappropriate selection of dose by Gilead Sciences. Gilead Sciences had merely reported the best evidence available relating to a

comparison of the two products used for empirical treatment. Gilead Sciences therefore considered that the Panel was right to rule that the failure to note the difference in dose in the promotional material was not misleading.

FURTHER COMMENTS FROM PFIZER

Pfizer stated that it considered that the licensed indications as approved by the relevant UK and European regulatory authorities were the only acceptable grounds on which to reasonably assess the purpose for which medicines were intended and therefore promoted. Should a medical professional decide to prescribe a product 'off-licence', then that was a risk/benefit decision that they must make based on their own training and knowledge, and certainly should not result from 'off-licence' promotion by pharmaceutical companies. Pfizer did not accept that pharmaceutical companies or the Panel should be able to decide whether or not promotion of unlicensed indications for medicines was permissible.

Gilead Sciences' observations in relation to European law (including the Convention on Human Rights) and the interpretation of domestic law did not address the real issue, which was compliance with Clauses 7.2 and 7.3 of the Code. Whilst the Code reflected European law, as stated in the introduction of the Code, it also extended well beyond the legal requirements controlling the advertising of medicines. Therefore, the fact that a certain activity was not prohibited at European level or appeared to be in line with the interpretation of European law did not mean that it would not breach the Code, nor did it mean that the Code should be interpreted to the effect that such activity was permitted.

Pfizer did not consider that Gilead Sciences had addressed its comment abut the dosage of voriconazole used in clinical practice. Walsh *et al* discussed the use of 3mg/kg bd. In practice, however, the usual dose was the same as the dose for its licensed indications which was 4mg/kg bd. Thus it seemed difficult to justify the use of Walsh *et al* as support for the efficacy of AmBisome. Moreover, Gilead Sciences only cited the superiority of the composite endpoint. Composite endpoints were notoriously difficult to interpret. The editorial in the New England Journal of Medicine in the same edition as Walsh *et al* acknowledged the case for the use of clinical endpoints such as prevention of fungal infection and related death in future studies.

The other simpler endpoints used in the study were of obvious clinical importance, and most of these, namely breakthrough fungal infections, severe infusion-related reactions, nephrotoxicity and the reduction in duration of hospitalization as a result of the change from parenteral to oral voriconazole were significantly in favour of voriconazole. Gilead Sciences was being selective in not mentioning these. Moreover, if Gilead Sciences was to be credible in its use of data comparing AmBisome with those unlicensed in the specific indication, it should also include the findings of Walsh *et al* (2003) which showed that when used as empirical antifungal therapy to treat persistently febrile neutropenic patients caspofungin was as effective as AmBisome and was better tolerated.

In conclusion, Pfizer considered that Gilead Sciences was in breach of Clause 7.3 as it was comparing its product with one that was 'not intended for the same purpose ...'.

APPEAL BOARD RULING

The Appeal Board noted that Clause 7.3 of the Code stated, *inter alia*, that a comparison was only permitted in promotional material if it was not misleading and that medicines for the same needs or intended for the same purpose were compared.

The Appeal Board noted that although it was not licensed for such, voriconazole was nonetheless used for the empirical treatment of febrile neutropenia. Walsh *et al* had used a dose 3mg/kg twice daily and at this dose voriconazole did not fulfil the protocol defined criteria for non-inferiority to liposomal amphotericin B with respect to overall response. On the basis of Walsh *et al* the FDA did not grant Vfend an indication for empirical use. Vfend was however licensed at a dose of 4mg/kg twice daily for the maintenance treatment of confirmed infection.

The Appeal Board considered that although voriconazole *per se* was used for the empirical treatment of febrile neutropenia, voriconazole 3mg/kg twice daily was not intended or licensed for such use. The Appeal Board thus considered the comparison unfair and ruled a breach of Clause 7.3 of the Code. The appeal on this point was successful.

2 Claim 'AmBisome is significantly less nephrotoxic than Amphotericin B'

This claim appeared only in the detail aid (page 5) and was referenced to the AmBisome SPC and Prentice *et al* (1997). Beneath the claim was a graph showing the percentage of patients, none of whom were taking concomitant nephrotoxic medicines, with nephrotoxicity on conventional amphotericin B or AmBisome 1mg/kg and 3mg/kg.

COMPLAINT

Pfizer noted that the graph presented only a subgroup of those patients from Prentice *et al* who were not on concomitant nephrotoxic drugs. This subgroup comprised less than one third of the total patients in the study and this was not stated explicitly. The use of this subgroup did not reflect clinical practice in this therapeutic area. As in this study, the majority of patients who received antifungal therapy were on concomitant nephrotoxic medications. Nephrotoxicity in this group of patients was therefore clearly relevant as this group was more representative of true clinical practice. Pfizer alleged breaches of Clauses 7.2 and 7.3.

Pfizer noted that the graph gave the impression that AmBisome 1mg/kg had no nephrotoxicity. This was misleading because if the total population in the study had been depicted, the adult nephrotoxicity rate would have been 12%. The graph would therefore

have looked very different (graphs were provided for comparison which had been drawn with what Pfizer considered an appropriate scale of 0-100% on the y axis compared to the scale of 0-30% as represented by Gilead Sciences). Pfizer alleged breaches of Clauses 7.2 and 7.3.

The graph presented data in adults, children and the total population and visually implied a difference between the conventional amphotericin B group and both AmBisome groups for adults, children and the total population as stated. The page and the graph however failed to mention that the difference in children between conventional amphotericin B and AmBisome was not significant at any dose and regardless of concomitant nephrotoxic medications. This was therefore misleading and Pfizer alleged a breach of Clause 7.3 of the Code.

RESPONSE

Gilead Sciences stated that its aim was to examine the relative nephrotoxicities of two forms of amphotericin B, conventional and liposomal. The only 'clean' way to do this was to compare incidence rates in circumstances where nephrotoxicity could not arise as a result of concomitant medication. Examination of subgroup data was an accepted technique in clinical trial data analysis. The graph was clear that the incidence rates shown related to a situation where no concomitant medication had been used and the number of patients involved was shown. The data shown were not misleading, they were reflective of the relevant results from the total study population.

Pfizer argued that in clinical practice the majority of patients received concomitant medication and it was, therefore, misleading to show the low nephrotoxicity rates for patients treated with AmBisome alone. At face value this suggested that it was impermissible to seek to remove potentially confounding factors encountered in clinical practice when analysing research data. In fact, of course, the opposite was true – every attempt must be made to separate the effect of the product from the potential effect of other factors and exposures. To say that nephrotoxicity would have been 12% with AmBisome if the confounders had been left in missed the point. The suggestion that by including data for AmBisome 1mg/kg, Gilead Sciences sought to argue that its product had no nephrotoxicity was to pluck out one part of the graph and suggest it would be viewed by health professionals in isolation. This was entirely unjustified in context, particularly when the main heading did not claim 'no toxicity', but only 'significantly less toxicity'.

Gilead Sciences accepted that in clinical practice patients were often receiving concomitant nephrotoxic medicines, but the point of using the data from Prentice *et al* was to examine whether the nephrotoxicity observed when patients were treated with AmBisome was more likely than with other products to be caused by concomitant medication rather than by AmBisome itself. The data from Prentice *et al* confirmed the approved information in the SPC, that AmBisome was 'tolerated significantly better than other amphotericin products'.

Gilead Sciences noted that Pfizer had alleged that it was inappropriate to use a scale of 0-35% rather than 0-100% for the y-axis of the graph. However, in the study the highest percentage of patients experiencing nephrotoxicity in any group was 29% therefore there was no reason to extend the y axis to 100%. If one adopted Pfizer's logic, companies would have to represent data on a scale from 0-100% irrespective of the percentage level of the results, in other words, where all percentages were less than 1% the results would be depicted on a graph with a scale extending to 100%. This was clearly unjustified.

The Code did not prohibit the truncating of axes on a graph provided the end result did not mislead. Gilead Sciences had used the same scale for the results from both conventional amphotericin and AmBisome and there was, therefore, no question of the comparison being misleading.

Gilead Sciences noted that Pfizer had also objected to the fact that the graph did not indicate that the difference in nephrotoxicity in children between conventional amphotericin and AmBisome was not significant. The graph did not quote the significance level for either subgroup even though the p value for the adult group was 0.05 which was the standard level of significance used to justify a claim of statistically significant. The graph clearly stated that the p value quoted of $p<0.01$ was in respect of the total incidence and this was emphasised in the first bullet point beneath the graph. If the significance of the effect on the total population was accurately recorded, the results did not become misleading simply because the individual significance levels for subgroups, which necessarily contained smaller numbers, were not reported.

PANEL RULING

The Panel did not consider that it was misleading *per se* to compare the nephrotoxicity of AmBisome with that of conventional amphotericin B, in a subset of patients who were not, at the same time, taking other nephrotoxic medicines. However, although the graph at issue described the patient group the headline claim above it, 'AmBisome is significantly less nephrotoxic than Amphotericin B' did not. The impression given was that in all patients and in all circumstances AmBisome was significantly less nephrotoxic than amphotericin B and that was not so. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the graph showed that no nephrotoxicity occurred in those patients taking AmBisome 1mg/kg, but not concomitant nephrotoxic medicines. While this was a true reflection of Prentice *et al* the Panel did not consider that it reflected the balance of the evidence. It was tantamount to stating that AmBisome 1mg/kg did not cause nephrotoxicity. That was not so, the SPC stated that AmBisome might be nephrotoxic despite being tolerated significantly better than other amphotericin products. The SPC also stated that nephrotoxicity occurred to some degree with conventional amphotericin in most patients receiving the medicine IV and that in two studies the incidence of nephrotoxicity with AmBisome was approximately half of that reported

for conventional amphotericin B or amphotericin B lipid complex. Breaches of Clauses 7.2 and 7.3 were ruled.

With regard to the y axis the Panel did not consider it misleading to have it only extended to 30%. The y axis was clearly labelled. No breach of Clauses 7.2 and 7.3 were ruled in that regard.

The Panel noted its comments above with regard to the headline claim 'AmBisome is significantly less nephrotoxic than amphotericin B'. The graph gave no indication that there was no statistically significant difference in the incidence of nephrotoxicity in children treated with either AmBisome or conventional amphotericin B. Visually the graph suggested otherwise and such an impression was strengthened by the headline claim. A breach of Clause 7.3 was ruled.

3 Claim 'Nephrotoxicity in the C-AMB [conventional amphotericin B] arm was not influenced by the use or absence of concomitant nephrotoxic agents'

This claim appeared as the second of three stabpoints beneath the claim and graph considered at point 2 above. The claim was referenced to Prentice *et al*. The third bullet point read 'In contrast nephrotoxicity was significantly less in the AmBisome arm in patients not receiving other nephrotoxic medication (23% v 3%)'.

COMPLAINT

Pfizer alleged that the claim did not reflect the balance of evidence and was misleading in breach of Clause 7.2 of the Code. Whilst the claim was supported by Prentice *et al* which involved approximately 300 patients, Walsh *et al* (1999), a much larger study involving over 700 patients showed this not to be the case.

RESPONSE

Gilead Sciences noted that claim appeared beneath the main heading that AmBisome was 'significantly less nephrotoxic than Amphotericin B'. The point being made in the second and third bullet points beneath the graph was that nephrotoxicity observed with conventional amphotericin treatment was more likely to be associated with the medicine itself rather than with concomitant medication, whereas this was not the case with AmBisome. The claim at issue was a faithful representation of the study result. Moreover, this finding was not inconsistent with the approved comparative statement in the AmBisome SPC and the evidence on which that was based, including Walsh *et al* (1999) cited by Pfizer. All such sources indicated that liposomal amphotericin was less nephrotoxic than conventional amphotericin. The fact that the extent of influence of concomitant nephrotoxic agents with conventional amphotericin B varied from study to study did not invalidate the critical clinical point, which was the overall direction of the evidence.

No health professional would sensibly treat a reference to this study finding in support of a statement on **relative** nephrotoxicity, as a claim that concomitant medication never had an influence on nephrotoxicity. That would be to deny a basic pharmacological tenet of treatment that applied to both types of amphotericin. Pfizer's complaint would only be justified if the statement was made in the context of promotion that viewed overall was a claim that concomitant treatment with other nephrotoxic agents was irrelevant to overall nephrotoxicity. That was plainly not the case here.

PANEL RULING

The Panel noted that Prentice *et al*, in a comparison of liposomal and conventional amphotericin B for the empirical treatment of neutropenic patients with persistent fever, showed that the incidence of nephrotoxicity in all patients receiving conventional amphotericin B was 24%. In patients who were not also taking concomitant nephrotoxic medicines the incidence was 23% and in those who were also taking nephrotoxic medicines the incidence was 26%. Thus the concomitant use or otherwise of nephrotoxic medicines with conventional amphotericin B did not appear to influence the incidence of nephrotoxicity.

Walsh *et al* (1999) similarly compared liposomal and conventional amphotericin B and showed that in patients taking the conventional preparation together with either none or one nephrotoxic medicine the incidence of nephrotoxicity was 15.2%. This incidence rose to 40.5% and 45.4% if patients were also taking 2 or more or 3 or more concomitant nephrotoxic medicines respectively. Thus the incidence of nephrotoxicity appeared to increase as the number of concomitant nephrotoxic medicines increased.

The Panel considered that although the claim 'Nephrotoxicity in the [conventional amphotericin B] arm was not influenced by use or absence of concomitant nephrotoxic agents' reflected the results of Prentice *et al* it did not take into account the results of Walsh *et al* (1999). The Panel considered that the claim was thus misleading and ruled a breach of Clause 7.2 of the Code.

Complaint received **25 June 2003**

Case completed **11 November 2003**

CASE AUTH/1486/6/03

FORMER REPRESENTATIVE v ASTRAZENECA

Failure to adequately train representative

A former respiratory products sales representative and member of AstraZeneca's Vitex sales team complained about the way in which she had been required to promote Nexium (esomeprazole), a gastrointestinal product, during the course of her employment.

The complainant alleged that her manager gave her a detail aid and asked her to sell Nexium second line and then to ultimately get practices to 'switch' patients over or to agree to a gastrointestinal patient review programme (GIPRP). The complainant achieved examples of both. The complainant stated that she was not given any training to sell Nexium and did not receive any bonus for doing so as the company was unaware that she was actively selling Nexium as a second line product. According to the complainant after a heated discussion with her manager in June 2002 she told him that she should not be selling Nexium because she had not been trained; at this point he told her that if she did not do what he said she would be 'managed' out. The complainant stated that she and others had witnessed this first hand so she complied, as she did not want to lose her job. In November 2002 she went on sick leave and reported her manager to human resources and commenced a grievance procedure. The grievance procedure was exhausted and even though the company was aware of the complainant's concerns as detailed above it condoned this unethical behaviour and so the complainant felt she had no other choice than to complain under the Code.

The Panel noted the complainant's allegation that she had been provided with a Nexium detail aid and asked to promote it second line and persuade practices to switch from their existing product to Nexium or to agree to a GIPRP. The complainant stated that she had received no training to sell Nexium. The complainant referred to a response from the company's national sales manager which stated that for her to effectively support the GIPRP appropriate training would have been of benefit. The complainant stated that she was given targets to achieve switches or audits. Further, that whilst she actively detailed Nexium second line at every call, she purposely did not record the calls and could not remember doing so.

The Panel noted AstraZeneca's submission that while the complainant had not been provided with a Nexium detail aid or asked to sell Nexium, she herself had suggested that she pass on details of specific requests from her GP practices for the GIPRP to the AstraZeneca GI nurse and GI sales team; this was accepted by her manager. AstraZeneca stated that the complainant received informal training at her request on Nexium materials from her manager. The company stated that she was not set any formal targets for obtaining GIPRP requests. In this regard the Panel queried whether she received informal targets. The position was not clear. AstraZeneca accepted that 16 calls relating to Nexium were logged by the representative from March to November 2002 on its electronic territory management system.

The Panel noted that the parties' accounts differed. A judgement had to be made on the available evidence. The printouts of calls logged by the representative showed that she was making separate calls in relation to Nexium. The Panel further noted the complainant's submission that she was also detailing Nexium second line at every call. The Panel did not accept AstraZeneca's submission that the complainant's role was limited to forwarding information of those practices who had requested the GIPRP and that all sales activity was provided by her Nexium sales colleagues. The Panel considered that the calls logged by the representative showed that her role went beyond merely referring unsolicited information to the Nexium team and that she had an active and continuing role in relation to the audit programme, subsequent product switches and the promotion of Nexium.

In the Panel's view the complainant ought to have received formal training on Nexium and the GIPRP. It was unacceptable to state that the complainant's training on the Asthma Patient Review Programme procedure was sufficient in this regard. The Panel noted the company's submission that the complainant had, at her own request, been taken through the Nexium materials by her manager. This did not constitute formal training. The complainant made reference to a statement from the national sales manager which referred to her 'continued involvement in cross therapeutic work'. There was thus official recognition by the company that she was not confining her activities to the respiratory area. The Panel considered that the representative had not been provided with adequate training and a breach of the Code was ruled.

The Panel further considered that the call details recorded by the representative were such that the company was aware of her role in relation to the GIPRP and the promotion of Nexium and despite such knowledge took no steps to suspend such activity or otherwise provide her with training. In the Panel's view if representatives were to be involved in cross therapeutic work then they must be adequately trained in each therapeutic area in which they were to be active. The Panel considered that the conduct of the company was such that it had failed to maintain high standards; the circumstances were such that the company had brought discredit upon and reduced confidence in the pharmaceutical industry. Breaches of the Code, including Clause 2, were ruled.

Upon appeal of all of the Panel's rulings by AstraZeneca, the Appeal Board noted the company's submission that the complainant had previously worked in the Asmatec sales team and was trained to promote and detail Nexium third line from the Nexium launch in September 2000 until her transfer to the Vitex sales team in June 2001. The Appeal Board noted AstraZeneca's documentation indicated that the complainant had completed one quiz as part of her Nexium distance learning assessment but was

on holiday for a second. No evidence had been provided by AstraZeneca to show that the complainant had attended the product training or the mop up training.

The Appeal Board noted that the Nexium Incentive Bonus Summary for quarter 4, 2000 listed the complainant. The complainant stated that the sales figures next to her name would have represented those for the territory. She had not detailed Nexium during this period. The complainant pointed out that the detail priorities for all one-to-one calls were to include two product details as a minimum. She only promoted Oxis and Pulmicort.

The Appeal Board considered that there was evidence to show that the complainant had received some training on Nexium in 2000 but not enough to show that she had been fully trained. The Appeal Board noted AstraZeneca's submission that regardless of any Nexium training received by the complainant in 2000 further training would have been required to detail Nexium in 2002.

The Appeal Board noted AstraZeneca's submission that although the complainant had not been provided with a Nexium detail aid, it could not rule out that the complainant might have a copy of one. The Appeal Board noted that the complainant had produced her copy of the detail aid at the appeal hearing. According to the company the complainant herself had suggested that she pass on details of specific requests from her GP practices for the GIPRP to the AstraZeneca GI nurse and GI sales team which was accepted by her manager. This was denied by the complainant. The Appeal Board noted in its original response to the complaint AstraZeneca had stated that 'The complainant received informal training at her request on Nexium materials from her manager'. At the appeal hearing, when questioned, the complainant's manager denied that any such training had occurred and stated that he had not seen AstraZeneca's response to the Panel. The company explained that this response was based on documents and information obtained during the grievance procedure. AstraZeneca therefore withdrew the statement. The Appeal Board expressed concern as to the validity therefore of AstraZeneca's other submissions.

The Appeal Board noted that the parties' accounts differed. A judgement had to be made on the available evidence. The Appeal Board considered that there was evidence that the representative was promoting Nexium. AstraZeneca had stated that having reviewed the latest evidence, in particular customer statements, it was difficult to rule out that the complainant might have been promoting Nexium. The company's submission regarding the training on Nexium materials had changed. The Appeal Board noted that the format of Nexium detail aids had changed in 2002 such that they did not have a unique identifying number. The complainant was not aware of this change. The complainant had a copy of the 2002 Nexium detail aid which she truly believed was her manager's numbered copy. The Appeal Board did not accept AstraZeneca's submission that the complainant's role was limited to forwarding information regarding GIPRP and that all sales activity was provided by her Nexium sales colleagues. The Appeal Board considered that the representative's role went beyond this. Further it would be difficult to try to persuade practices to sign up for a GIPRP without discussing Nexium. It appeared that the complainant's manager was aware that the complainant was discussing GIPRP with health professionals and others.

In the Appeal Board's view despite any previous training that might have taken place in 2000, the complainant should have received formal training on Nexium and the GIPRP in 2002. The Appeal Board considered that the complainant would have to be prepared to answer any questions the GPs might ask. The complainant's training on the APRP procedure was insufficient in this regard. The complainant made reference to a statement from the national sales manager which referred to her 'continued involvement in cross therapeutic work'. There was thus official recognition by the company that the representative was not confining her activities to the respiratory area. The Appeal Board considered that the representative had not been provided with adequate training in relation to the promotion of Nexium as required by the Code.

The Appeal Board further considered that the detail recorded by the representative on the LAZER system, the representative's emails and the customer statements were such that her manager and others were aware of her role in relation to the GIPRP and the promotion of Nexium. No steps were taken to stop such activity or otherwise provide the appropriate training. The Appeal Board considered that the conduct of the company was such that it had failed to maintain high standards and that the circumstances were such that the company had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld all the Panel's rulings of breaches of the Code including Clause 2.

A former respiratory products sales representative and member of AstraZeneca UK Limited's Vitex sales team, complained about the way in which she had been required to promote Nexium (esomeprazole), a gastrointestinal product, during the course of her employment.

This case was considered under the 2001 edition of the Code and the Constitution and Procedure.

COMPLAINT

The complainant stated that her manager gave her a detail aid and asked her to sell Nexium second line and then to ultimately get practices to 'switch' patients over or get them to agree to a gastrointestinal patient review programme (GIPRP). The complainant achieved examples of both and had the evidence. The complainant stated that she was not given any training to sell this product and did not receive any bonus for doing so as the company was unaware that she was actively selling Nexium as a second line product. After a heated discussion with her manager on a field visit in June 2002 the complainant told him that she should not be selling Nexium because she

had not been trained. It was at this point that he allegedly told the complainant that she worked for him and if she did not do what he said she would be 'managed' out. The complainant stated that she and others had witnessed this first hand so she complied, as she did not want to lose her job. In November 2002 she went on sick leave and reported her manager to human resources and commenced the grievance procedure route. The grievance procedure was exhausted and even though the company was aware of the complainant's concerns as detailed above it chose to condone this unethical behaviour so consequently the complainant felt she had no other choice than to report this matter to the Authority.

The complainant gave examples of the responses to her complaint.

'Stage 1

[sales manager]

I have conflicting information from [the complainant's manager] and yourself as to whether you were specifically asked to detail Nexium to GPs. You have recorded 16 Nexium calls on GPs over a period of 8 months, which is much less than I would expect if you had been requested to detail Nexium as a major part of your role. I do however acknowledge that it would be difficult for you to effectively support GIPRPs without having a good knowledge of Nexium and that appropriate training would have been of benefit, I suggest that I review your continued involvement in cross therapeutic work on your return to work and if you wish to continue and it is appropriate from a business prospective, I will ensure that appropriate training is provided.'

The complainant's answer to this was that she should not have been given a detail aid or given targets from [her manager] to achieve GI switches or audits, and whilst she actively detailed Nexium second line at every call, she purposely did not record the calls and could never remember doing so.

'Stage 2

[head of primary care]

From my investigations I have concluded that you were asked to use the good relationships you had with certain GPs and your track record of obtaining asthma patient review programmes to persuade the GPs to sign up to a GI audit. I confirm that I support [the National Sales Manager's] decision as set out to you in [a] letter of 4 March 2003 but do not uphold this aspect of your grievance as set out above.'

The complainant stated that she had documented evidence of GPs actively changing patients over to Nexium in practices where they had not agreed to have a GI audit.

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.1 of the Code.

RESPONSE

AstraZeneca stated that the complainant's role was to detail and sell the company's respiratory products (Symbicort, Pulmicort and Oxis). She was also responsible for passing details to the relevant AstraZeneca asthma nurse of those practices who had requested a clinical audit of their asthma patients using the Asthma Patients Review Programme (APRP). The APRP was a patient review programme that was undertaken by specifically trained AstraZeneca nurses in practices that requested it.

At a team meeting in early 2002, the complainant raised the fact that she had excellent working relationships with her GP practices who had requested the APRP. As a result of this, she volunteered to pass details of requests she might receive from her GP practices for a similar GIPRP to the relevant AstraZeneca GI nurse and her sales colleagues who worked with Nexium. The idea was accepted by her manager. The GIPRP reviewed current therapies in patients who suffered from symptomatic gastro-oesophageal reflux disease. The service was such that an AstraZeneca GI nurse identified patients who were not optimally controlled on their current therapy. However, it was ultimately the practice GP who made the final decision as to what treatment was received by all patients involved in the review process.

The complainant was given full training on the APRP procedure, and therefore did not need training on the GIPRP process as the procedures were identical apart from the fact they were for different therapy areas. At no time was the complainant given a Nexium detail aid, nor asked to detail or sell Nexium to any customers by her manager, but only to pass information of those practices which had requested the GIPRP services. The complainant requested to be taken through Nexium materials for her own information, which her manager did. However this was not regarded as formal Nexium training and there was never any intention for her to sell Nexium. All sales activity around Nexium was provided by her sales colleagues.

AstraZeneca emphasized that all AstraZeneca representatives were trained to a very high standard on the Code. AstraZeneca did not condone representatives to detail or sell a company product without appropriate training in the disease area and the product as it was fully aware that such activity was not compliant with the Code. Furthermore this practice would not allow it to meet the high standards expected of AstraZeneca representatives by its customers. The complainant was not provided with any training on Nexium because she was not at any time asked to detail or sell the product by her manager. She was not set any formal fixed targets for obtaining GIPRP requests by her manager. Furthermore AstraZeneca emphasised that no incentive schemes were paid to her for getting practices to participate in the GIPRP.

The complainant had noted that the relationship between herself and her manager was strained. This was as a result of a number of issues relating to her performance. The complainant went on sick leave in November 2002, shortly after one of her performance reviews. Soon after going on sick leave, she raised a grievance against her manager. As part of her grievance, she alleged that she was being asked to work in breach of the Code by her manager. It was of

note that she alleged that she was asked to do this from March 2002, but did not make her complaint until November 2002. This was the first occasion that AstraZeneca was aware of the complainant's concerns.

All of the matters raised in the grievance had been thoroughly investigated under the company's grievance procedure, which was completed in April 2003. AstraZeneca concluded that the complainant was not asked to work in a manner that breached the Code. The complainant was due to return from her sick leave in June 2003, but resigned from the company the day before she was due back at work.

All sales calls were logged by the sales representatives on to a company electronic territory management system (LAZER), on which they entered the nature and the outcome of each call. The only departments that could access the system were the sales information team and customer information team. Each territory area sales manager also spent a minimum of three days a week monitoring field force activity by accompanying representatives they managed on their field visits to keep track of their progress. AstraZeneca was informed by the complainant's manager that at no time when he accompanied the complainant on her field visits did she detail or sell Nexium.

The LAZER system showed that the complainant logged 16 calls related to Nexium during the period from March 2002 to November 2002 with comments for each of those calls. AstraZeneca believed that because only 16 calls were logged in the space of eight months, and the comments for each call indicated that they were related to the GIPRP and not around sales activity for Nexium, it was very unlikely that the complainant was asked to detail or sell Nexium. If she was asked to sell Nexium, she would have been expected to log many more Nexium calls than 16; the LAZER system showed that she logged 1099 calls relating to Symbicort for the same period of time. Therefore AstraZeneca considered that the 16 Nexium calls logged on the LAZER system related to the instances where she received specific requests from her GP practices for a GIPRP.

AstraZeneca therefore denied that the complainant was requested to detail or sell Nexium and as such it had not got any record of product specific training given to the complainant with regard to Nexium. Furthermore the complainant was not requested to get GP practices to 'switch' patients to Nexium, but only to pass on information of those practices who had requested the GIPRP services. AstraZeneca therefore denied breaching Clauses 2, 9.1 and 15.1 of the Code.

PANEL RULING

The Panel noted that Clause 15.1 of the Code required that representatives be given adequate training and have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines which they promoted.

The Panel noted the complainant's allegation that she had been provided with a Nexium detail aid and asked to promote it second line and persuade practices to switch from their existing product to Nexium or to agree to a GIPRP. The complainant stated that she had received no training to sell Nexium. The complainant referred to a response from the company's national sales manager which stated that for her to effectively support the GIPRP appropriate training would have been of benefit. The complainant stated that she was given targets to achieve switches or audits. Further, that whilst she actively detailed Nexium second line at every call, she purposely did not record the calls and could not remember doing so.

The Panel noted AstraZeneca's submission that the complainant had not been provided with a Nexium detail aid nor asked to sell Nexium at any time. According to the company the complainant herself had suggested that she pass on details of specific requests from her GP practices for the GIPRP to the AstraZeneca GI nurse and GI sales team; this was accepted by her manager. The complainant received informal training at her request on Nexium materials from her manager. The company stated that she was not set any formal targets for obtaining GIPRP requests by her manager. In this regard the Panel queried whether she received informal targets. The position was not clear. AstraZeneca accepted that 16 calls relating to Nexium were logged by the representative from March to November 2002 on its electronic territory management system.

The Panel noted that the parties' accounts differed. A judgement had to be made on the available evidence. The Panel examined the printouts of calls logged by the representative in relation to both Symbicort and Nexium. These showed that the representative was making separate calls in relation to Nexium. The Panel further noted the complainant's submission that she was also detailing Nexium second line at every call. The Panel did not accept AstraZeneca's submission that the complainant's role was limited to forwarding information of those practices who had requested the GIPRP and that all sales activity was provided by her Nexium sales colleagues. The Panel considered that the calls logged by the representative showed that the representative's role went beyond merely referring unsolicited information to the Nexium team and that she had an active and continuing role in relation to the audit programme, subsequent product switches and the promotion of Nexium. The recorded call comment stated, *inter alia*, 'called to see if the Nexium switch was going okay. No problems to date', 'using Nexium instead of Lans' 'has initiated 35 script of Nexium so far' and 'happy to sign scripts for Nexium'. The next call objectives stated, *inter alia*, 'needs plenty of activity until completion', 'present cost savings to him'. It was unclear whether these objectives were to be met by the complainant herself or the Nexium representative.

In the Panel's view the complainant ought to have received formal training on Nexium and the GIPRP. It was unacceptable to state that the complainant's training on the APRP procedure was sufficient in this regard. The Panel noted the company's submission that the complainant had, at her own request, been taken through the Nexium materials by her manager.

This did not constitute formal training. The complainant made reference to a statement from the national sales manager which referred to her 'continued involvement in cross therapeutic work'. There was thus official recognition by the company that the representative was not confining her activities to the respiratory area. The Panel considered that the representative had not been provided with adequate training as required by Clause 15.1 and a breach of that clause was ruled.

The Panel further considered that the detail recorded by the representative on the logged call system was such that the company was aware of the representative's role in relation to the GIPRP and the promotion of Nexium and despite such knowledge took no steps to suspend such activity or otherwise provide the representative with training. In the Panel's view if representatives were to be involved in cross therapeutic work then they must be adequately trained in each therapeutic area in which they were to be active. Representatives were often a customer's primary point of contact with a company and as such were relied upon to be knowledgeable about the products or therapy areas with which they were involved. The Panel considered that the conduct of the company was such that it had failed to maintain high standards and that the circumstances were such that the company had brought discredit upon and reduced confidence in the pharmaceutical industry. Breaches of Clauses 9.1 and 2 were ruled.

APPEAL BY ASTRAZENECA

AstraZeneca refuted that the complainant was asked to promote Nexium or to be involved in the GIPRP to any degree that required brand knowledge.

AstraZeneca submitted that it was not aware of the complainant's alleged involvement in any activity directly associated with Nexium, as opposed to the GIPRP, until after she entered into a grievance procedure.

Alleged instruction to promote Nexium

AstraZeneca submitted that the complainant's manager denied that he had ever instructed her to sell Nexium. The complainant's manager stated that the complainant had volunteered to use her relationships with existing customers to create opportunities around audit for her colleagues. The complainant was already involved in the APRP and it was understood that she would ask these customers if they would like a similar audit to be carried out on their GI patients.

Evidence from LAZER

AstraZeneca submitted that the Panel might have misinterpreted the customer logging system used by the sales force (LAZER) for the Nexium calls made by the complainant. It was important to note that because of the way the software for LAZER had been designed, it was only possible to log a call by first assigning an AstraZeneca promoted brand eg Nexium, or one of two branded information services. There was no option to log an audit as APRP or GIPRP and so a general call regarding audit activity would have had to be assigned to a brand such as Symbicort or Nexium. This could have given the misleading impression to the Panel that a Nexium call was actually associated with activity promoting or discussing that brand.

AstraZeneca submitted that when using the term 'Nexium call', it was not referring to promotion of Nexium. AstraZeneca submitted that however, for ease of reference it would refer to these as Nexium calls for the purpose of the appeal.

AstraZeneca submitted that between March and November 2002 the complainant logged 1099 calls for Symbicort but only 16 for Nexium. These 16 calls had consisted of calls on only 10 different GPs or practice managers, as some were called on more than once. On a quantitative basis alone, 16 Nexium calls was a very small number compared to 1099 Symbicort calls (1.4%). However, when the calls were looked at in more detail it was clear that the complainant was not making direct Nexium sales calls. Rather, the majority of the calls and interactions with those health professionals appeared in line with the type of impromptu discussion one would have with someone with whom one had a good professional relationship eg 'Checked to see if GI clinic had gone well. Very pleased with outcome'.

AstraZeneca noted that neither it or the complainant's manager condoned the comments the complainant had made within the LAZER call comments field. AstraZeneca submitted that the framework for the GIPRP had been explained in its response to the complaint.

AstraZeneca GI representatives had been involved in initiating GIPRP activity with some of the customers that the complainant logged in LAZER as Nexium calls. It appeared that in most instances she was merely mentioning GIPRP in passing to customers who had agreed to undergo audits due to interactions with other AstraZeneca representatives and recording the details for the benefit of colleagues working in the same practice. AstraZeneca provided an analysis of the 16 calls logged as Nexium by the complainant.

Evidence from customer statements

AstraZeneca had tried to contact some of those customers logged as Nexium calls by the complainant, and had obtained a statement from one of them. The practice manager at a health centre confirmed that the purpose of the complainant's call was to inquire if the practice was interested in undergoing a GI audit and then referred the practice to a nurse specialist. It was confirmed that the complainant had no further involvement with that audit.

Provision of Nexium detail aid

AstraZeneca noted that the complainant alleged that she was asked to promote Nexium and that she was given a Nexium detail aid.

AstraZeneca submitted that its grievance procedure had not found any evidence that the complainant had ever been given a Nexium detail aid but that her

manager had taken her through some Nexium sales material at her own request.

AstraZeneca did not believe that the complainant was ever asked to promote Nexium, since it did not believe she had ever had a Nexium detail aid and was never given any formal training. It also believed she would not have been able to promote Nexium. Finally, as the complainant was never given an incentive to promote Nexium, AstraZeneca had not believed that she would have any inclination to promote it.

AstraZeneca noted the requirements of Clause 15.1 and submitted that the complainant was never asked to promote Nexium and would not have required an in-depth knowledge of Nexium. Her involvement in cross therapeutic work was to be limited to referring customers to a colleague if they had expressed an interest in a GI patient audit. AstraZeneca therefore denied any breach of Clause 15.1.

Alleged company awareness of complainant's activity

AstraZeneca submitted that the Panel had made a ruling of a breach of Clause 9.1 and Clause 2 because it considered that the conduct of the company was such that it had failed to maintain high standards and that the circumstances were such that the company had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel considered that the company was aware of the complainant's role in relation to the GIPRP and the promotion of Nexium and despite such knowledge it had not taken steps to suspend such activity or otherwise provide the representative with training.

AstraZeneca was not aware of the complainant's alleged promotion of Nexium

AstraZeneca denied that it was aware of the complainant's alleged promotion of Nexium. However, the complainant's manager was aware that she was using established relationships with respiratory audit customers to create audit opportunities for her GI colleagues; he was not aware that she was allegedly promoting Nexium until the start of the grievance procedure in November 2002.

AstraZeneca submitted that it would have been very difficult for the complainant's manager to be aware of any inappropriate behaviour as she had not logged calls on a regular basis, a performance issue that was being addressed by her manager. The LAZER system had to be specially opened up twice to allow the complainant to catch up on the backlog of calls.

AstraZeneca submitted that the primary purpose of the call comment field was for the representatives to make notes for themselves or for colleagues working within the same territory. The LAZER system was typically used by managers to generate standard reports relating to call rate, time in territory and coverage and frequency on target customers. The first two standard reports would not reveal any specific brand activity. The third report could reveal brand activity and call comments but only for the specific brand entered by the manager creating the report.

The complainant was a respiratory representative and was not expected or requested to sell any other brands therefore her manager would have only searched under respiratory brands. Even if he had looked under Nexium the low frequency of calls was such that they would have been unlikely to be picked up. As previously stated, the complainant was involved in passing on requests for GI audit work. The activities of all the representatives, including the complainant, in relation to tracking the audit activities was discussed at regular weekly meetings in which they were joined by one of the AstraZeneca nurses involved in the audits.

The complainant's manager was vigilant in his performance tracking of her and went on frequent visits with her (at least once every fortnight) and on none of those occasions had she promoted Nexium.

Comments from grievance procedure documentation

AstraZeneca submitted that the excerpts of letters written by the national sales manager and the head of primary care and provided by the complainant had been taken out of the context in which they should be set ie within a very complex grievance procedure of which alleged Nexium promotion without training was a comparatively small part. The investigation conducted as part of the grievance procedure had not established that the complainant had been asked to actively participate in GIPRP other than as described above ie to use good relationships already established to refer customers to suitable GI representatives or nurses. The complainant's manager had given her a target of making successful referrals for 5 patient review programmes per month which would have included her work on asthma audits. This was in line with targets set for other representatives within the territory. The investigation conducted within the grievance procedure had not found that the complainant had been offered a bonus for specifically meeting GIPRP targets.

AstraZeneca training requirements

AstraZeneca submitted that it had rigorous training programmes for its representatives to ensure that high standards were maintained in all customer contact. This involved 14 days on brand training after which they were assessed and needed to pass a customer validation before they could commence work on that brand. Representatives were not expected to detail brands they had not received training on.

Summary

AstraZeneca submitted that it had not become aware of the allegations made by the complainant until November 2002, when she formally entered the grievance procedure. The company could only act on what it was aware of. As soon as AstraZeneca had become aware of this matter a full investigation was carried out in accordance with the grievance procedure. AstraZeneca submitted that every care and due diligence had been taken in investigating this matter and in exercising reasonable judgment in

reaching the decision in the grievance procedure. AstraZeneca submitted that Clause 2 was a sign of particular censure which was not warranted in this case.

In summary, AstraZeneca denied the alleged breaches of Clause 9.1, 15.1 and Clause 2 and therefore appealed the Panel's rulings.

COMMENTS FROM THE COMPLAINANT

Alleged instruction to promote Nexium

The complainant stated that at no time did she volunteer to use her relationships with existing customers around audit for her colleagues.

The complainant stated that, as in her original complaint, she actively had not recorded her Nexium calls. Although she believed that senior management might not have been aware of her involvement in the promoting of Nexium, nevertheless when made aware no action was taken.

The complainant alleged that her manager had bullied and harassed her into selling Nexium and any calls that were recorded were by pure chance. At no time were the calls an impromptu discussion, as a professional representative, her purpose for seeing GPs was always to promote products, ie respiratory officially and GI unofficially.

Evidence from customer statements

The complainant alleged that AstraZeneca had not thoroughly investigated her complaint with reference to the breach of the Code. Although she had produced documented evidence and colleagues were interviewed to substantiate her involvement, at no time was this ever acknowledged or action taken.

The complainant provided statements from a GP and a practice manager at the health centre referred to by AstraZeneca. The complainant also provided documentation for the audit at the health centre together with copies of the GIPRP agreement with the health centre.

The complainant stated that a colleague, a GI representative, had gained agreement from the GP to have a GI audit done by a third party company AstraZeneca provided. The audit was completed, however the GP decided that he would reduce the doses of lansoprazole and likewise reduce the dose of Losec. The GP had not wished to change any of his patients to Nexium. When the complainant's manager had found out about this he was absolutely furious. The complainant stated that it was at this point that she had become involved in the GI therapy area. The complainant alleged that her manager had insisted that she called to see the GP to try to persuade him to change his patients over to Nexium. The complainant had told her manager that she did not know anything about Nexium so he arranged to meet her to give her his own detail aid. The complainant stated that her manager had not gone through the clinical data with her so she had to use her own judgement and experience to use the detail aid in a professional manner. After going through the clinical data with the GP he agreed to allow one of AstraZeneca's GI nurses to recall these patients and change them to Nexium 20mg. The complainant stated that she had returned a few days later with the nurse and the relevant forms were signed. The complainant alleged that it was the success of this call that had given her manager the idea that she should actively sell Nexium second line to try to gain commitment from the GPs to either agree to a 'switch or a GIPRP'. The complainant provided further statements from another GP and practice manager which referred to patients being switched to Nexium as a result of the presentation of clinical data referring to the advantages of Nexium compared with lansoprazole. The complainant provided part of an email she had sent to AstraZeneca's sales director which referred to visits the complainant had made to two GPs to talk about the clinical advantages of Nexium compared to lansoprazole. According to her email one of the GPs had agreed to a 'controlled GIPRP' and the other had switched patients to Nexium.

Provision of Nexium detail aid

The complainant stated that AstraZeneca was told that she had a Nexium detail aid. The human resources officer had requested it but the complainant declined and said she would produce the detail aid at her grievance hearing. The complainant had taken the detail aid to that meeting but was never asked to produce it.

With regard to AstraZeneca's statement regarding her manager's vigilance, that he would not have given her his own detail aid unless he intended her to use it, the complainant stated that AstraZeneca was correct in saying that she had not been given an incentive to promote Nexium. The fact that she had a detail aid and documented evidence should question why she had promoted Nexium. The complainant's reason for doing so was that she was bullied and harassed into doing so by her manager.

The complainant produced the original detail aid at the appeal hearing.

AstraZeneca was not aware of alleged promotion of Nexium

The complainant stated that throughout her grievance procedure, AstraZeneca had never intimated that it had found evidence of any inappropriate behaviour. On the contrary AstraZeneca had referred to her using her relationships with existing customers to create opportunities around audit for her colleagues.

The complainant stated that her team had a meeting every Friday to discuss the progress of any switches, GIPRPs or APRPs, the whole team was aware of her detailing Nexium. The complainant stated that her manager was vigilant in his performance tracking so he was well aware of her detailing Nexium as a second line product at every call. The complainant stated that whilst her manager had telephoned daily to have an update on her progress, it would have been impossible for him to accompany her every fortnight as stated by AstraZeneca. By AstraZeneca's

own admission the complainant's manager had spent three days a week in the field so with a team of nine representatives it would have been an impossibility to do so.

The complainant provided a copy of her agreed objectives with her manager together with those agreed for two other representatives. The complainant noted that her target was higher than those of two colleagues who were both selling Nexium first line. Even though this was documented proof of her having to achieve higher targets than her colleagues her manager had said that everyone's target should have been five and AstraZeneca had accepted that. An email sent by a GI representative on 30 September was also provided. This referred to the need to increase the Nexium coverage figure which was down and the need to 'pull out all the stops to do this'. Various representatives were listed under product names. The complainant's name appeared under 'Nexium'.

The complainant provided IT fault records to explain why she could not log her calls into LAZER.

AstraZeneca's training requirements

The complainant provided a statement by a colleague who had also just completed a grievance procedure with reference to the complainant's manager. This representative's statement referred to the complainant's manager wanting the representative to sell Symbicort, she was given promotional material for Symbicort but was not trained on it. This had been raised by the representative as part of an internal grievance procedure, the outcome of which was not discussed.

The complainant referred to an email from a GI representative and noted that the email was dated 6 November 2002, which was five days before the complainant went off sick and began the grievance procedure. The email referred to APRP and GIPRP and stated in relation to two GIPRPs that 'we really need the Nx [Nexium] Scripts to make the difference for the year end'. Her manager was copied in on this email and the complainant alleged that the email showed that the pressure on her activities was predominately on the GI side.

Summary

AstraZeneca had not become aware of the complainant's allegations of Code breaches until November 2002. The complainant noted however even when AstraZeneca was aware of the details and had been given documented evidence, it still chose to believe her manager. The complainant stated that she was reluctant to report AstraZeneca to the PMCPA, however in her view senior management had whitewashed the whole incident. The complainant stated that she could no longer work for a company which had so little regard for the Code; consequently she had no other choice than to resign from the company and put in a formal complaint.

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AstraZeneca was concerned that the complainant's response to the appeal provided new information.

Taking all the circumstances into account the Chairman of the Appeal Board decided that AstraZeneca should have the opportunity to comment on the complainant's response to the appeal and that these comments should be sent to the complainant for further comment.

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FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that as the complainant had raised new evidence, it had conducted a new investigation into this matter. The external affairs and strategic planning director, who was appointed to lead this investigation, was experienced in hearing late-stage grievances and other appeals and was independent of the sales directorate. This new investigation entailed a review of the relevant parts of the grievance process documentation as well as a fresh interview with the complainant's manager.

AstraZeneca concluded that having reviewed the latest evidence, in particular the statements from health professionals, it was difficult to rule out that the complainant might have been promoting Nexium (and might even have used a Nexium sales aid). AstraZeneca did not, however, accept this was anything more than a marginal activity and was probably limited to the small number of customers from which statements were obtained. AstraZeneca submitted that this activity was neither sanctioned nor requested by management. The complainant had centred on the allegation that she was not given sufficient training in order to promote Nexium. As it had never asked her to promote Nexium it did not accept a ruling of Clause 15.1. As stated in previous correspondence the complainant had been asked to use her relationships with existing customers to elicit interest from practices for GI audits. This was deemed to be a simple task that would not require further training, as the complainant was very experienced in working with services of this nature already. Training on Nexium was not required, as the product being offered was a service to medicine and not a brand related service.

Further investigation concluded that the complainant's manager did not ask her to promote Nexium. The external affairs and strategic planning director concluded that the complainant's manager was wholly credible and consistent when confronted with the latest evidence from the complainant. AstraZeneca therefore denied it had failed to uphold high standards and had brought discredit upon and reduced confidence in the pharmaceutical industry, and appealed the rulings of breaches of Clauses 9.1 and 2. AstraZeneca submitted additional points for its appeal in response to the new material presented by the complainant.

Alleged instruction to promote Nexium

AstraZeneca noted the complainant's statement 'At no time did I 'volunteer' to use my relationships with existing customers around audit for my colleagues'. The external affairs and strategic planning director

had specifically addressed this point in his investigation. The statement seemed at variance with the fact that she accepted helping with the GI audits from the end of 2001 and raised no documented objection for some time; with what one would expect from a normal working relationship and with statements taken from other AstraZeneca staff.

AstraZeneca submitted that in terms of being instructed to sell Nexium, the external affairs and strategic planning director's investigation and review of the grievance documentation found the following:

'[the complainant] says that she was first told to sell Nexium at a field visit on 19th June 2002 (Grievance Note, 11/12/02) but this appears at variance with how I have read the e-mail traffic which is contemporaneous. E-mail traffic (enclosed) of 20-24th June 2002 (following a performance review on 19th June 2002), and which [the complainant] appears to have validated as accurate records, show no reference to selling of Nexium or to training to sell Nexium. There are references to [the complainant] having a role in starting-up (but note, not continuing) GIPRPs. As documentation that appears to be agreed between [the complainant's manager] and [the complainant], I believe that appreciable weight can be placed on this'.

AstraZeneca submitted the above excerpt was particularly important evidence that the complainant was not instructed to sell Nexium by her manager. Additionally in a fresh interview the complainant's manager clearly remembered the complainant offering to use her 'brilliant' relationships with some customers to elicit opportunities or leads to be passed to the GI representative.

AstraZeneca noted that the complainant admitted she was not given a bonus or incentive to sell Nexium, her manager had confirmed that this was so and in the email traffic of 20-24 June 2002 he confirmed that the complainant would have qualified for rewards from the motivational fund which were small motivational rewards for meeting targets, such as a bottle of champagne.

AstraZeneca noted that the complainant stated that she did not record her Nexium calls which seemed strange since she would then have had no documentation to demonstrate to her manager that she was carrying out what she says he allegedly asked her to do. AstraZeneca stated that it did take action when eventually informed of the complaint and this was part of the grievance procedure.

AstraZeneca questioned if the complainant had not actively recorded calls how could she have recorded calls by pure chance? One of the main reasons to record calls was to inform team members; therefore if the complainant was performing properly she should have recorded impromptu discussions which would have been helpful intelligence for colleagues. She should certainly have recorded details of contacts or leads regarding audit discussions. AstraZeneca stated that there was no evidence that the complainant's manager bullied or harassed her into selling Nexium.

AstraZeneca submitted that the grounds of the complainant's grievance had changed throughout the grievance process. Details were provided.

AstraZeneca submitted that it was part of the company's ethos that all employees took personal responsibility for their own training and development plans; hence if the complainant had identified a personal development requirement, it was strange and contrary to expectation that this would not be raised for almost a year.

Evidence from customer statements

AstraZeneca was unable to refute the statements made by the customers and could not provide comparable evidence to counter what was said in the statements. The complainant's manager denied ever asking her to promote Nexium. The external affairs and strategic planning director's investigation had concluded that 'the evidence did not support the allegation that [the complainant's manager] 'forced' or in some way compelled [the complainant] to sell Nexium whether against her will or not'. The evidence reviewed included statements from the complainant's colleagues.

AstraZeneca submitted that the alleged Nexium calls would have been made between 10 and 15 months before customer statements were obtained and there were a considerable number of representatives, including representatives selling Nexium, calling on these practices. It was conceivable that the identity of representatives could be confused, however AstraZeneca conceded that taken in isolation these customer statements appeared to indicate that the complainant was promoting Nexium.

AstraZeneca noted that the complainant said that she was first asked to sell Nexium on 19 June 2002. Her manager ceased to be in that role from 8 October 2002 due to promotion and therefore the customer statements would need to relate to her activities occurring precisely between these two dates for any weight to be attached to them. There were no specific dates identified in these customer statements.

AstraZeneca submitted that the allegation that the complainant's manager became furious about the outcome of one GP audit was absolutely refuted by him.

AstraZeneca questioned the complainant's motivation to sell Nexium; it could only speculate that it might have been a step taken independently by her to increase the number of patient referral programmes as she was not achieving her targets otherwise. AstraZeneca had never condoned such behaviour.

AstraZeneca submitted that it could not be discounted that the complainant was raising the grievance in anticipation of disciplinary action against her (see 'General comments' later).

Provision of detail aid

AstraZeneca did not believe that the complainant's manager gave his detail aid to the complainant. The most recent investigation carried out by the external affairs strategic planning director had revealed that the complainant's manager was able to produce his Nexium detail aid at short notice for inspection. This was a critical finding and appeared to cast serious

doubt on a central platform of the complainant's case; if the complainant's manager had his detail aid then the complainant would not also have it. Further AstraZeneca's witness statements generally stated that the witnesses did not know whether the complainant's manager had given the complainant a detail aid. AstraZeneca submitted that the one exception was a statement given by a medical representative during the grievance procedure, who was a colleague of the complainant during the time frame of the allegations. AstraZeneca submitted that, in additional notes which the same representative added after her initial interview, she stated that she knew of the complainant selling Nexium and of having a detail aid, however she had openly admitted to being a friend of the complainant and it could not be discounted that she was only recounting what she had been told by the complainant. AstraZeneca submitted that there was no corroboration of the complainant's claim that her manager had handed over his detail aid to her.

AstraZeneca submitted that there was no evidence that the detail aid that the complainant claimed to have in her possession was the original allegedly given to her by her manager. Furthermore, the external affairs and strategic planning director concluded that there 'was only the most vague chronology about the alleged handing-over of [the complainant's manager's] detail aid'.

AstraZeneca submitted that it would have been relatively easy for the complainant to obtain a Nexium detail aid from a colleague or from someone leaving the company. By failing to volunteer the detail aid at the time of the Stage 2 and 3 Grievance AstraZeneca submitted that the complainant had significantly reduced the weight of this evidence. Even if the complainant was now in possession of a detail aid, there was no evidence that she was in possession of it at the time of the alleged conflict with the Code. AstraZeneca had therefore concluded that the complainant's manager did not hand over his Nexium detail aid to her.

AstraZeneca was not aware of alleged promotion of Nexium

AstraZeneca submitted that evidence had demonstrated that the complainant had indeed voluntarily used her contacts to get GI audits.

AstraZeneca submitted that the document referred to by the complainant as 'Agreed Objectives with Manager' was actually an action plan drawn up by another representative on the territory with duties delegated to her by the complainant's manager. This document had contained some elements of targets agreed between the complainant and her manager. AstraZeneca submitted that this document, however, appeared to show a clear sequence from 'prospective practices' which had the complainant's name alone alongside them to 'agreed' practices all (but one) of which had the name of an AstraZeneca nurse alongside them. This would seem to support the contention that the complainant's role was to elicit interest from practices known to her and then to hand them over to a nurse. The complainant was not expected to have sold these customers Nexium. This would have been the duty of the various Nexium representatives who had called on those practices such as those cited in the spreadsheet enclosed with the response to the complaint.

AstraZeneca submitted that, contrary to the complainant's submission, her manager would have been able to go on fortnightly field visits with her, as he would have concentrated on those he regarded as under-performing. The complainant was regarded as under-performing (email traffic 20-24 June 2002 was provided) and fortnightly meetings were eminently achievable. The objectives agreed between the complainant and her manager in the GI area were only for GIPRPs. AstraZeneca submitted that the email (dated 30 September 2002) from the GI representative was potentially misleading; he was questioned during the new investigation and stated that the email had reflected cross functional working. In those lists when a representative saw a doctor to sell their brand they would help the other representative selling a different brand by using their good relationships to create call back opportunities.

AstraZeneca submitted that the targets for patient review programmes were set individually for representatives, alongside other responsibilities and dependent on experience therefore variation should not be unexpected.

AstraZeneca submitted that the LAZER evidence of downtime was for a very short period of time (approximately 3-4 weeks). As explained before, the system was opened up to allow the complainant the opportunity to retrospectively enter details of the calls she should have logged.

AstraZeneca's training requirements

AstraZeneca submitted that the statement from another representative who had completed a grievance procedure did not support the complainant's case as she stated that the complainant had 'sold Symbicort 'and only' Symbicort' in the grievance procedure interviews.

AstraZeneca submitted that the email dated 6 November 2002 from a GI representative referred to a need for Nexium scripts but this appeared in the context of GIPRPs, as there was a perceived and urgent need to get more 'clinics' (ie audit clinic) set up. There was no instruction for the complainant to sell Nexium. It should also be noted that this email was between representatives and not a manager to representative exchange.

AstraZeneca submitted that the complainant's manager had confirmed that 'need' for Nexium prescriptions meant those representatives for whom Nexium was their lead product, thereby excluding the complainant. The complainant's manager had ceased to be in his role at this time as he had been promoted.

General comments

AstraZeneca submitted that the grounds of the complainant's grievance changed throughout the grievance process. Some points were not presented at the outset which had made the process difficult and complex.

AstraZeneca submitted that it had gone to very considerable lengths to investigate this matter, and resolve the situation to the satisfaction of the complainant. This included a meeting of the complainant and the sales director, after completion of the grievance procedure in May 2003, where great efforts were made to help her return to work with AstraZeneca.

AstraZeneca submitted that it was pertinent to advise that an employment tribunal was also underway regarding this and other matters raised by the complainant, separate to those in this complaint. AstraZeneca's aim here was to address those points raised by the complainant with regard to the Code. There was a large volume of documentation relating to the grievance procedure. AstraZeneca submitted that where appropriate it had presented summaries of the relevant documentation to provide focus for the appeal and not deflect from the salient points within this complaint.

The complainant's manager was a medical sales professional with 14 years' experience, he was very mindful of the Code and had stated that he would not tolerate staff breaching the Code. During an interview he had cited, without any prompting, an example where he was required to cancel promotional meetings set up by representatives in his previous company because they were potentially in breach of the Code. He was an experienced manager focussed on delivery. On joining AstraZeneca he had noted a number of shortcomings in terms of performance within the team he managed and had tried to improve this performance by using tactics such as getting the representative to be more productive in the afternoon when appointments could be difficult. It was conceivable that a representative operating within their comfort zone could have been unsettled by this new manager.

AstraZeneca submitted that the complainant was a representative of long-standing who had been used to a much more lenient and less delivery focused style of management from the manager's predecessor. The complainant's manager considered that the complainant was not performing to the required standard, issues with which she had appeared to agree. When the complainant had submitted her grievance, her manager confirmed that he was about to initiate disciplinary proceedings against her. As stated before, the complainant appeared to have made some of her potential grievances public and shared them with customers. That said, the complainant was very experienced and would therefore have had a good understanding of the requirements of the Code. AstraZeneca continued to be unclear as to why the complainant had not reported the alleged breaches of the Code at the time they allegedly took place.

In summary, based on some of the new evidence AstraZeneca submitted that it could not rule out that the complainant had promoted Nexium although the company had never asked her to do so. AstraZeneca did not accept a ruling of a breach of Clause 15.1 as the complainant would not have required training or scientific knowledge on Nexium if she had restricted her activities to those instructed by the company. AstraZeneca also appealed the rulings of breaches of Clause 9.1 and Clause 2. AstraZeneca had conducted a formal grievance procedure immediately the allegations were made. The balance of evidence at the time was such that AstraZeneca had found the complainant's allegations with regard to the Code to be unsubstantiated. A further independent review together with the other investigations had concluded that the complainant's manager had never instructed her to sell Nexium. AstraZeneca submitted that it could not have known about the complainant's activities regarding this matter because as she herself admitted, she had not documented it or reported it to anyone until the grievance procedure in November 2002. The company did not condone this behaviour.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant referred to a signed statement from a practice manager who was also the wife of the GP. AstraZeneca's stance and defence of the complainant's manager was based on the unsubstantiated fact that he was unaware she was promoting Nexium.

The complainant submitted that on a call in early March 2002 with the GP an agreement was made to do a switch from lansoprazole to Nexium. At this meeting the GP requested some Nexium samples. The complainant stated that as a respiratory representative she had no access to Nexium samples. The complainant alleged that she had informed her manager of the agreed switch and the GP's request for Nexium samples. Approximately a week later the complainant and her manager had taken the requested Nexium samples on a field visit to the GP's surgery. At a meeting with the practice manager, the complainant and her manager, the complainant had handed over the samples. The complainant asked the Appeal Board to reflect on what, if any weight could be placed on all of her manager's statements regarding 'No knowledge of [the complainant] promoting Nexium' or to quote the external affairs and strategic planning director 'I believe that appreciable weight can be placed on this'.

The complainant stated that if AstraZeneca had conducted a thorough and unbiased investigation into her original complaints, the single statement from the practice manager would have at the very least cast serious doubt on her manager's credibility.

The complainant noted AstraZeneca's conclusion that '… it is difficult to rule out that the complainant might have been promoting Nexium (and may even have used a Nexium sales aid)'. The complainant stated that far from being difficult, it was impossible! The manager had given her his detail aid as previously stated, which she would produce at the appeal hearing. The complainant alleged that numerous doctors and practice managers had signed statements that not only did she promote Nexium (under duress) she also used the said detail aid and supplied samples of Nexium.

The complainant noted that AstraZeneca believed she had promoted Nexium to a marginal amount of customers. The complainant alleged that AstraZeneca had not stated how many GPs she would have had to detail to before it was considered a breach of the Code.

AstraZeneca had contacted a number of GPs and practice managers as part of its further investigation. The complainant asked the Appeal Board to draw its own conclusions as to why AstraZeneca had chosen not to provide any of the responses. Two documents were provided by the complainant. Firstly, a letter from a GP dated 7 October 2003. The letter was addressed to a head office AstraZeneca employee and stated that the complainant was professional in her manner and her knowledge of Nexium was good. She had used a detail aid to promote the product and was arranging an audit in the practice looking at prescribing proton pump inhibitors and possible switches to Nexium. Secondly, a statement from a practice manager which referred to a lunchtime meeting when the complainant had asked doctors to swap patients onto Nexium and offered support to assist. The practice said that it was not keen to do this. The statement described the complainant as being very stressed, 'under pressure' and 'she had never reacted in this way when discussing chest medicine, she seemed desperate'. One of the GPs was able to talk to AstraZeneca if required. The complainant believed that AstraZeneca had therefore failed to uphold high standards, with reference to Clause 2 of the Code and had undoubtedly brought discredit upon and reduced confidence in AstraZeneca.

The complainant believed that the first practice manager's signed statement alone was sufficient to prove breaches of Clauses 2, 9 and 15.1 and cast serious doubt on her manager's credibility.

The complainant responded in full to AstraZeneca's 'new investigation' even though she felt that the content gave no additional documented evidence and was both repetitious and slanderous.

Alleged instruction to promote Nexium

With regard to the complainant's statement that she did not volunteer to use her relationship with existing customers for arranging audits for her colleagues and AstraZeneca's view that this was at variance with the fact that she accepted helping with the GI audits from the end of 2001 and raised no documented objection for some time, the complainant stated that she had witnessed her manager bullying and harassing another representative. The complainant did not want to suffer the same fate so she merely complied. The complainant stated that no one in her team was allowed to disagree without the threat of disciplinary action, save the few employed by her manager from his previous company. The complainant referred to her statement for the representative's grievance hearing.

With regard to AstraZeneca's view that the statement was also at variance with what one would expect from a normal working relationship, the complainant stated that her role as a Vitex representative was to sell respiratory products only. There were sixty other Vitex representatives in the company with exactly the same remit.

The complainant stated that she was unable to comment upon AstraZeneca's view that the statement was also at variance with the statements taken from other members of the AstraZeneca staff as AstraZeneca had not disclosed any signed statements from colleagues or medical professionals.

AstraZeneca was wrong to state that the complainant was first told to sell Nexium at a field visit on 19 June 2002. The complainant stated that 19 June 2002 was when she had had the heated discussion with her manager and not when she was first told to sell Nexium.

With regard to AstraZeneca's statement that 'As documentation that appears to be agreed between [the complainant's manager] and [the complainant], I believe that appreciable weight can be placed on this', the complainant stated that the said 'agreement' was under the threat of being 'managed 'out. Either the external affairs and strategic planning director had chosen to ignore the complainant's statement or had been misinformed.

With regard to AstraZeneca's statement that '… the above excerpt from [the external affairs and strategic planning director's] report is particularly important evidence that [the complainant] was not instructed to sell Nexium by [her manager]', the complainant referred to the first practice manager's statement.

The complainant noted that the external affairs and strategic planning director had referred to her manager clearly remembering her offering to use her 'brilliant ' relationships with some customers to elicit opportunities or leads to be passed on to the GI representative. If the external affairs and strategic planning director had referred to previous evidence submitted, he would have noted that on the contrary, it was because of the GI representative that she had initially become involved in the GI therapy area when the GP had agreed to an audit but decided not to prescribe Nexium.

The complainant also referred to her response to AstraZeneca's initial appeal under the heading 'Evidence from customer statements' with regard to the GP.

With regard to the fact that the complainant was not given a bonus or incentive to sell Nexium, the complainant questioned why she would, as an experienced respiratory representative, even contemplate promoting a product she was not trained to sell. The complainant stated that the answer was simple, her only reward was that if she complied she would not be 'managed out' to use her manager's favourite colloquial term.

With regard to AstraZeneca's view that it was strange that the complainant did not record her Nexium calls since she would not have had documentation to demonstrate to her manager that she was carrying out what he allegedly asked her to do, the complainant stated that there was no need to record any of her Nexium calls as her team met each Friday and any APRPs GIPRPs and switches were updated. Additionally whilst her manager was not out on a field visit with her every fortnight, nevertheless he had rung every member of the team daily for a progress update. The complainant noted that AstraZeneca had found that she had recorded sixteen Nexium calls and decided to take no action.

With regard to AstraZeneca's comment that if the complainant did not record calls how could she have

recorded calls by pure chance? and that she should have recorded impromptu discussion, the complainant referred to her first response to AstraZeneca's appeal regarding the reasons why she had not actively recorded her Nexium calls. In addition she could only state that any calls that were recorded were done so subconsciously whilst under a great deal of stress.

The complainant stated that the grounds of her grievance had not changed. Reference was made to an email to the head of primary care, 2 December 2002 and grievance statement stage 1: formulated by the human resources officer.

The complainant agreed with AstraZeneca that employees should take personal responsibility for their own training and development plans. However, the complainant alleged that she had asked for training from her manager on several occasions and yet he had not contacted anyone in the training department to give any formal training.

Evidence from customer statements

The complainant stated that AstraZeneca could not refute the customer statements enclosed previously. It had withheld even more evidence from customers to substantiate her complaint.

AstraZeneca conducted its grievance hearings behind closed doors so she was unable to comment or refute any statements from colleagues.

The complainant submitted that all statements submitted by customers or colleagues were accurate and true and had not been influenced by her. The complainant noted that as she had been a magistrate for some 13 years she was well aware of the implications of submitting, interfering with or withholding evidence.

The complainant did not doubt that her manager denied being furious about the outcome of the GP's audit, especially when this would mean that this was another breach of the Code, Clause 18.1. He also denied any knowledge of her promoting Nexium. The complainant referred again to the practice manager's statement.

The complainant noted that as a successful medical representative she had earned a very good salary and with the exception of one year she had achieved full bonus, she really loved her job and wished to stay with AstraZeneca until she retired. That was until she was bullied in to breaching the Code.

The complainant alleged that in defending her manager AstraZeneca was publicly condoning unethical behaviour.

In response to AstraZeneca's comment that the grievance was raised in anticipation of disciplinary action against her, the complainant noted that the national sales manager upheld her complaint at stage 1 of her grievance procedure regarding unfounded threats of disciplinary action.

The complainant stated that the reasons for instigating the grievance procedure were solely based on ethical and moral grounds and not as a second line defence against any threats of unfounded disciplinary action.

Provision of detail aid

The complainant noted that her manager would have access to Nexium samples and Nexium promotional materials. The complainant therefore had no doubt that her manager was able to produce another Nexium detail aid.

The complainant alleged that AstraZeneca had seen a photocopy of her detail aid (No NEX DET 9646) before and could not understand why, if it was not her manager's, had AstraZeneca not been able to verify whose it was when every detail aid had to be signed for? The complainant found it disturbing that her manager should be carrying an obsolete detail aid 'just in case'. If the necessary investigation had been carried out, this would have been a 'critical finding'. The detail aid she had was the one she was given by her manager. The complainant noted either she or her manager was lying, and it was for the Appeal Board to reach a conclusion.

AstraZeneca was not aware of alleged promotion of Nexium

The complainant stated that her manager was AstraZeneca and he was not only aware, he had instigated her role in the promoting of Nexium.

The complainant stated that whilst another representative might have drawn up the document setting out the agreed objectives the complainant's manager had given the targets and parameters. The complainant stated that at her appraisal in August 2002, her manager decided that her target should be two and a half times greater than any other member of the team and in fact two and a half times greater than any other member of the whole of the AstraZeneca sales force.

The complainant stated that she had produced an abundance of evidence to prove that she had indeed striven to achieve such unrealistic targets by detailing Nexium and ultimately getting practices to agree to a GI switch or a GIPRP based on the clinical data she presented.

The complainant stated that her manager had not attended fortnightly field visits. At no time was she an underachiever, this was verified at stage 1 of her grievance, and she was also made an AstraZeneca Academy Award Winner for 2002 which meant that she was one of the company's top 10% sales representatives.

The complainant alleged that the targets set for the northern team were her manager's targets and not targets set by head office.

The complainant referred to the IT fault records previously submitted as evidence showing the reason why she could not record her calls.

AstraZeneca training requirements

The complainant stated that the statement from the representative who had also undergone a grievance procedure was submitted to substantiate the point that being asked to sell a product without training was not an isolated case.

With regard to AstraZeneca's comments on the email dated 6 November 2002, the complainant noted that it would be impossible to get a GP to agree to a GIPRP without selling the clinical benefits of a product. The nursing service was a non-promotional service. Therefore it was imperative that the GP was convinced of the clinical benefits of a product before agreeing to a GIPRP. The complainant noted that her manager was copied in on all emails from representatives.

The complainant alleged that her manager was very specific about the need for Nexium prescriptions; his bonus unlike hers depended upon it. The complainant alleged that she was bullied into selling Nexium for one purpose only and that was to convert GPs' prescribing to Nexium. The complainant stated that she did not receive any training to sell Nexium and there was no formal training to set up APRPs until November 2002, as far as she was aware there was still no formal guidance on setting up GIPRPs. The complainant referred to one page of a field force briefing document for APRP.

Response to AstraZeneca's general comments

The complainant stated that contrary to AstraZeneca's claims, her grievance had not changed throughout the process, she might have added other grievances at stage 2 and 3 combined, however this was merely an addition and not a change. Relevant documents were provided.

The statements the complainant presented from the GPs were accounts of factual events, and the statements omitted by AstraZeneca were also statements of events.

The complainant alleged that AstraZeneca had not gone to extensive lengths to investigate her complaint. It was only after she had written to AstraZeneca's chief executive, in desperation with concerns about the breach of the Code and the AstraZeneca code that she was invited to a meeting to discuss her concerns. At the meeting her concerns were not addressed and she was told that as far as the company was concerned the Code of Practice issue was concluded. The complainant had tried hard to sort this matter out in-house.

The complainant stated that whilst she did not think it pertinent for AstraZeneca to state that an employment tribunal was also underway regarding the matters raised in the complaint and other matters raised by the complainant, the implication of AstraZeneca choosing to believe her manager's version of events was that her statements were false. The complainant stated that as a magistrate and a conscientious medical representative, she was left in the untenable position of clearing her name. Thus she had made application to the employment tribunal.

The complainant resigned from her job on 23 June 2003 for ethical reasons and made her complaint under the Code. The complainant noted that she had not been given any guarantees that this type of behaviour would not happen again; consequently she could not continue to work for AstraZeneca. The complainant filed her case to the employment tribunal on 5 September 2003.

With regard to AstraZeneca's comments about her manager's career record and approach, the complainant stated that her manager was mindful of the Code, however as AstraZeneca had stated he was very focused on delivery at any cost, she had no idea why he would compromise AstraZeneca's position in relation to the Code.

The complainant stated that she found AstraZeneca's insinuations that her previous managers were less delivery focused than the manager in question very distasteful and offensive, especially when three of them were still employed by AstraZeneca.

With regard to AstraZeneca's statement that when the complainant submitted her grievance, her manager was about to initiate disciplinary procedures and that the complainant had made some of her potential grievances public and shared them with customers, the complainant noted that however repetitive, as stated previously her grievance of threats of disciplinary were upheld by the national sales manager. The complainant's manager was currently on a disciplinary, he had also denied the allegations made against him in the said proven case, despite the evidence against him. AstraZeneca ruled against the other representative's grievance at stages 1and 2. It was not until stage 3 that AstraZeneca upheld the grievance. The said representative no longer worked for AstraZeneca and had settled out of court, signing a 'Non disclosure contract'.

In response to AstraZeneca's statement that it was unclear why the complainant did not report the alleged breaches of the Code at the time they allegedly took place, the complainant stated that she wished she had been as brave as one of the other representatives and reported the breach of the Code straightaway, unfortunately she was not.

General comments

The complainant noted that AstraZeneca had asked for more time to investigate the new evidence she had produced in response to its appeal. To date, AstraZeneca had not produced a single document to refute her claim. AstraZeneca's entire defence was based around a new interview with her manager. The complainant stated that AstraZeneca's further letter was both repetitious and slanderous and contained limited new material.

AstraZeneca had contacted several GPs and practice managers, conducted taped interviews, received written statements, and then decided to omit them all from its final report.

The complainant noted that her manager denied all knowledge of her promoting Nexium. The complainant alleged that the practice manager's statement supported the fact that not only was he aware of her actions, he also accompanied her on a field visit and supplied Nexium samples for a GP who had requested them on a previous call.

The complainant stated that AstraZeneca was well aware of her manager's bullying and harassment, he was already on a disciplinary and AstraZeneca had and indeed was currently investigating other

grievances submitted by experienced representatives and managers.

The complainant alleged that several of AstraZeneca's statements had been inaccurate and misleading. The complainant noted that AstraZeneca had also stated that the complainant's role was to merely pass leads over to a GI colleague. Statements from the GP and practice manager were quite clear that her involvement in the GI therapy in this instance was a role reversal.

The complainant noted that AstraZeneca had insinuated that some of the doctors and practice managers might have confused her with other medical representatives. All the doctors and practice managers, who voluntarily gave statements, did so without prejudice and on the understanding that they might have to sign an affidavit or appear in court.

The complainant noted that all the detail aids were numbered and had to be signed for. As the detail aid she had was the one she was given by her manager then clearly either she or her manager was lying.

The complainant noted that AstraZeneca had stated that there was no evidence of bullying and harassment, but continued to question why an experienced medical representative would promote a product that she was not bonused to sell. The complainant found it hard to believe that AstraZeneca did not know the answer to this question!

The complainant noted that AstraZeneca had insinuated that she was an underachiever and then alluded to her brilliant relationships with customers. The complainant questioned if she was such an underachiever why was she given targets that were two and a half times greater than anyone else's in the whole of the AstraZeneca field force and why was she made an Academy member for her outstanding performance in 2002?

Conclusion

The complainant posed a question that if AstraZeneca truly believed that she promoted Nexium without any directorate from her manager, then why was she not disciplined? As AstraZeneca had stated that it would never condone such behaviour.

The complainant had asked herself on a number of occasions why had AstraZeneca's senior management actively condoned her manager's aggressive management techniques and apparent disregard for both the Code and company code of practice?

The complainant believed that the answer lay in the management structure of AstraZeneca and the grievance procedure. It was a simple case of the police, policing themselves. The people, who interviewed, employed and subsequently promoted her manager were the same people who investigated her grievance, thus by trying to whitewash over her grievance they would exonerate themselves from employing a maverick manager.

The complainant noted that she had made every effort to resolve the Code breaches within AstraZeneca and she had never intended to get to this stage. The complainant stated that the internal grievance procedure was never thoroughly investigated.

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The following information and documentation was received shortly before the appeal hearing.

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ASTRAZENECA'S LETTER OF 11 NOVEMBER 2003

AstraZeneca submitted that it now had evidence that the complainant had previously worked in the AstraZeneca Asmatec sales team and was trained to promote Nexium in third line detail position from the Nexium launch in September 2000 until her transfer to the Vitex sales team in June 2001 when Symbicort was launched – a period of about 8 months.

AstraZeneca submitted that this documentation had emerged as part of its ongoing preparation for the employment tribunal concerning the complainant. It had not come to light earlier because:

- In the grievance procedure a much wider range of complaints, pertaining to the period March to November 2002, was being addressed other than solely the Code of Practice issues.
- In the additional investigation conducted by the external affairs and strategic planning manager, concerning Code of Practice matters only, it was not possible to interview the complainant in the time available, had she consented.
- Throughout the grievance and Code of Practice complaint the complainant had made very strong statements that she had not been trained to sell Nexium. AstraZeneca submitted that at the onset of the grievance procedure, it had no reason to doubt her statement that she had not been trained to sell Nexium. The additional investigation had focused on the period in 2002 when the complainant reported to the manager in question. However, on the basis of its ongoing internal investigations AstraZeneca investigated the complainant's previous employment history in more depth, and this was the reason for this latest evidence to emerge.

AstraZeneca submitted that it fully understood that in normal circumstances new evidence should not be presented at the appeal. AstraZeneca felt strongly that the documentation it provided was highly significant and of pivotal importance to the appeal and must be considered.

The accompanying documentation gave the detailing priorities, incentive scheme and training for the respiratory team in quarter 4, 2000 until June 2001. AstraZeneca submitted that the documentation confirmed the active part that the respiratory sales team had in promoting Nexium from launch.

The first document was a memo dated 3 August 2000 to Wilmington representatives and others (including FSMS and ASMS [which were taken to mean field sales managers and area sales managers]) which gave the selling priorities after the Orlando sales conference. The Asmatec team was to detail Oxis, Pulmicort and Nexium as first, second and third detail respectively.

The second document was a report of the Nexium distance learning assessment headed 'Therapy Area Respiratory' which listed the complainant as obtaining 75% in quiz 1 and being on holiday for quiz 2. The Asmatec team would receive Nexium training on 9-11 August, with mop up training on 11-15 September. A memo dated 9 May 2000 sent to fieldforce teams including Asmatec, stated 'All of you are involved in the launch programme be it in first, second or third line detail position' and that the training team would ensure that '… you have everything you need to sell Nexium'.

The third document was headed 'Nexium Bonus Summary – Quarter 4, 2000'. The complainant had not achieved a bonus for selling Nexium. Territory sales in the complainant's territory were less than required for a Level 1 bonus. AstraZeneca submitted that this document indicated that the complainant was eligible for the Nexium Incentive Scheme.

The fourth document comprised an extract from a document and was described by AstraZeneca as a communication to future respiratory sales force highlighting priorities for 2000 post Nexium launch meeting. This referred to Nexium being the third detail for respiratory representatives.

The fifth document comprised one page of a larger document and gave the detail priorities for early 2001. Prelaunch of Symbicort the detail priorities were Oxis, Pulmicort and Nexium (in that order). Post Symbicort launch the detail priorities were Symbicort followed by a 'Snappy detail on Pulmicort'.

The sixth document confirmed the respiratory primary care representatives' detail priorities (Jan-June 2001) as Oxis, Pulmicort and Nexium (in that order for quarters 1 and 2) and stated that 'All 1:1 calls to include 2 product sell as a minimum'. The meeting priorities were for respiratory products.

The seventh and final document confirmed the changes in detail priorities in June 2001 for the Vitex team. AstraZeneca submitted that the complainant moved from selling Nexium to focus entirely on Symbicort.

COMPLAINANT'S RESPONSE TO ASTRAZENECA'S LETTER OF 11 NOVEMBER

On the morning of the appeal hearing the complainant provided further information in response to AstraZeneca's letter of 11 November. The complainant provided two emails dated 12 and 13 November 2003 from a former AstraZeneca representative. In the email of 12 November addressed to the complainant, the former representative stated that as far as he was aware he did not promote Nexium third line. He did not recall a time when he had a three product portfolio which included Nexium. In an email to the Authority regarding Nexium training the former representative stated that 'Though I completed some training, like [the complainant] I missed the final part of the training which was held between 9-11 Aug 2000' as he was on leave and that no 'mop up' training was held for him.

An email dated 11 November 2003 from a current AstraZeneca representative, stated that to the best of her knowledge the complainant had not received Nexium training. The representative was the complainant's study partner.

The complainant provided documentation to support the submission that she was on annual leave in connection with her house purchase at the time of the Nexium training.

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Page 15 of the addendum to AstraZeneca's slide presentation was a memorandum dated 11 November 2003 from an AstraZeneca area sales manager that had not been previously submitted. The memo gave the area manager's recollection of the complainant's training to sell Nexium at its launch in 2001 [sic]. The memo referred to distance learning materials and quizzes run at local meetings. The complainant's training had been interrupted by a holiday but was brought back on course. The complainant was able to take part in key Nexium sessions at the launch conference. The memo concluded that although there had been a two year gap he was confident that the complainant's training had been completed and she was fully capable of promoting Nexium at launch.

APPEAL BOARD RULING

The Appeal Board noted AstraZeneca's late submission that the complainant had previously worked in the Asmatec sales team and was trained to promote and detail Nexium third line from the Nexium launch in September 2000 until her transfer to the Vitex sales team in June 2001. The Appeal Board noted AstraZeneca's documentation indicated that the complainant had completed one quiz as part of her Nexium distance learning assessment but was on holiday for a second. No evidence had been provided by AstraZeneca to show that the complainant had attended the product training on 9-11 of August or the mop up training.

The Appeal Board noted that the complainant had stated that she could not recall ever doing a Nexium quiz and she certainly would have remembered the intensive training had she done it. The complainant submitted that she could not have done the training arranged for 9-11 August because she had been in the process of buying a house and had thus taken annual leave. The Appeal Board noted the two emails dated 12 and 13 November from the former AstraZeneca representative, in which he stated that as far as he was aware he 'did not promote Nexium at third line' and with regard to Nexium training he said 'Though I completed some training, like [the complainant] I missed the final part of the training which was held between 9th-11th Aug 2000', 'I recollect that no 'mop up' training was held for me'.

The Appeal Board noted that the Nexium Incentive Bonus Summary for quarter 4, 2000 listed the complainant. The complainant stated that the sales figures next to her name would have represented those for the territory. The complainant stated that she had not detailed Nexium during this period. The complainant pointed out that the detail priorities for January-June 2001 stated that all one-to-one calls were to include 2 product details as a minimum. She only promoted Oxis and Pulmicort.

The Appeal Board noted that the complainant had attended the Nexium product launch in Orlando in 2000 and that product training would have been part of the programme. The Appeal Board considered that there was evidence to show that the complainant had received some training on Nexium in 2000. In the Appeal Board's view there was insufficient evidence to show that the complainant had been fully trained on the product in 2000 when she was a member of the Asmatec sales team. The Appeal Board noted AstraZeneca's submission that regardless of any Nexium training received by the complainant in 2000 further training would have been required to detail Nexium in 2002. The Appeal Board noted AstraZeneca's submission that any evidence that the complainant had received Nexium training in 2000 did not change its grounds for appeal.

The Appeal Board noted AstraZeneca's submission that the complainant had not been provided with a Nexium detail aid. AstraZeneca, however, conceded that it could not rule out that the complainant might have a copy of the detail aid. The Appeal Board noted that the complainant had produced her copy of the detail aid at the appeal. According to the company the complainant herself had suggested that she pass on details of specific requests from her GP practices for the GIPRP to the AstraZeneca GI nurse and GI sales team which was accepted by her manager. This was denied by the complainant. The Appeal Board noted in its original response to the complaint AstraZeneca had stated that 'The complainant received informal training at her request on Nexium materials from her manager'. At the appeal hearing, when questioned, the complainant's manager denied that any such training had occurred and stated that he had not seen AstraZeneca's response to the Panel. The company explained that this response was based on documents and information obtained during the grievance procedure. AstraZeneca therefore withdrew the statement. The Appeal Board expressed concern as to the validity therefore of AstraZeneca's other submissions.

AstraZeneca stated that the complainant was not set any formal targets for obtaining GIPRP requests by her manager. In this regard the Appeal Board queried whether she received informal targets. The position was not clear. AstraZeneca accepted that 16 calls relating to Nexium were logged by the representative from March to November 2002 on LAZER (the electronic territory management system). AstraZeneca pointed out that 1099 Symbicort calls were logged. There was no incentive for the complainant to promote Nexium. The parties disputed the events relating to the visit to deliver Nexium samples.

The Appeal Board noted the various emails which referred to Nexium calls and agreed objectives. It noted AstraZeneca's response that although these documents referred to target health professionals and establishing GIPRPs they were sent for the purpose of keeping all members of the territory, regardless of which products they promoted, up to date about activities and were not instructions to promote Nexium *per se*. The Appeal Board noted one email (dated 6 November 2002) however, was sent only to the complainant by a representative and copied to the manager in question. It was headed 'Actions from today – Priorities'. This email referred to APRP / GIPRP and stated 'WE REALLY NEED THE NX SCRIPTS TO MAKE THE DIFFERENCE FOR YEAR END'. In the Appeal Board's view this appeared to indicate that the complainant was expected to generate Nexium prescriptions. The complainant's manager had been promoted in October 2002 but still received copies of emails after his promotion.

The Appeal Board noted that the parties' accounts differed. A judgement had to be made on the available evidence. The Appeal Board considered that there was evidence that the representative was promoting Nexium. AstraZeneca had stated that having reviewed the latest evidence, in particular the customer statements, it was difficult to rule out that the complainant might have been promoting Nexium. The company's submission regarding the training on Nexium materials had changed. The Appeal Board noted that the format of Nexium detail aids had changed in 2002 such that they did not have a unique identifying number. The complainant was not aware of this change. The complainant had a copy of the 2002 Nexium detail aid which she truly believed was her manager's numbered copy. The Appeal Board did not accept AstraZeneca's submission that the complainant's role was limited to forwarding information regarding GIPRP and that all sales activity was provided by her Nexium sales colleagues. The Appeal Board considered that the representative's role went beyond this. Further it would be difficult to try to persuade practices to sign up for a GIPRP without discussing Nexium. It appeared that the complainant's manager was aware that the complainant was discussing GIPRP with health professionals and others.

In the Appeal Board's view despite any previous training that might have taken place in 2000, the complainant should have received formal training on Nexium and the GIPRP in 2002. The Appeal Board considered that the complainant would have to be prepared to answer any questions the GPs might ask. It was unacceptable to state that the complainant's training on the APRP procedure was sufficient in this regard. The complainant made reference to a statement from the national sales manager which referred to her 'continued involvement in cross therapeutic work'. There was thus official recognition by the company that the representative was not confining her activities to the respiratory area. The Appeal Board considered that the representative had not been provided with adequate training in relation to the promotion of Nexium as required by Clause 15.1 of the Code. The Appeal Board upheld the Panel's ruling of a breach of Clause 15.1 of the Code. The appeal was unsuccessful.

The Appeal Board further considered that the detail recorded by the representative on the LAZER system, the representative's emails and the customer statements were such that the complainant's manager and others were aware of the complainant's role in relation to the GIPRP and the promotion of Nexium. No steps were taken to stop such activity or otherwise

provide the appropriate training. The Appeal Board considered that the conduct of the company was such that it had failed to maintain high standards and that the circumstances were such that the company had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's rulings of breaches of Clauses 9.1 and 2. The appeal was unsuccessful.

Complaint received **25 June 2003**

Case completed **15 December 2003**

CASES AUTH/1490/7/03

PRIMARY CARE TRUST MEDICINES MANAGEMENT PROGRAMME DIRECTOR v AVENTIS PASTEUR MSD

Promotion of Viatim

A primary care trust medicines management director complained about two successive statements which appeared beneath a reference to Viatim (combined Vi polysaccharide typhoid and inactivated hepatitis A vaccine) in a booklet on Aventis Pasteur MSD's range of vaccines for UK travellers. The statements read 'The Department of Health recommends: 'If any course of immunisation is interrupted, it should be resumed and completed as soon as possible" and 'Therefore, if a patient presents later than the recommended 12 months for the booster dose, there is no need to restart the course from the first dose'.

The complainant noted that with respect to Hepatitis A, the Green Book and the Viatim summary of product characteristics (SPC) stated 'In order to provide long-term protection against infection caused by the hepatitis A virus, a booster injection of an inactivated hepatitis A vaccine should be given 6 to 12 months later. It is predicted that HAV antibodies persist for many years (at least 10 years) after the booster'. The complainant interpreted this as meaning that if a booster was not given 6-12 months after the first dose, then the course would need to be restarted. Therefore the complainant alleged that the second statement in the booklet was misleading and should be withdrawn.

The Panel noted that Viatim was indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus and should be given in accordance with official recommendations. The Viatim SPC stated that initial protection was achieved with one single dose of Viatim and that in order to provide long-term protection against hepatitis A a booster injection should be given 6 to 12 months later. The SPC did not give any guidance on what to do if a booster injection had not been given 6-12 months after the primary dose. The Panel's interpretation of the SPC was that if no booster injection had been given 6-12 months after the primary dose, then long-term protection had not been provided.

The Panel considered that the statements in the booklet were misleading. 'If any course of immunisation is interrupted it should be resumed and completed as soon as possible' appeared in Chapter 11 of the Green Book that appeared to give general advice about childhood immunisation schedules, not travel vaccine schedules. The definition of resume as 'begin again, recommence, go on again with, continue' (ref The New Shorter Oxford English Dictionary (1993)) did not assist matters.

The Panel noted that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in the SPC. Regardless of any statement in the Green Book the Panel considered that it was misleading to state in promotional material for Viatim that '… if a patient presents later than the recommended 12 months for the booster dose, there is no need to restart the course from the first dose'. This was tantamount to stating that the advice in the SPC to give a booster injection 6-12 months after the first injection could be ignored. The Panel ruled a breach of the Code.

Upon appeal by Aventis Pasteur MSD, the Appeal Board noted the statements in the SPC regarding initial immunization and booster doses and accepted that many patients presented late for their hepatitis A booster dose and that this situation was not addressed in the SPC. The Appeal Board further noted that expert opinions provided by Aventis Pasteur MSD were inconsistent with regard to the acceptable time interval between first vaccination for hepatitis A and the booster dose. The Appeal Board also noted the submission of the company representatives at the appeal that there was some uncertainty in this area.

The Appeal Board considered that the claim '… if a patient presents later than the recommended 12 months for the booster dose there is no need to restart the course from the first dose' was a strong, open-ended claim; it implied that there was no limit to the time interval after which a booster dose could be given. This was inconsistent with the SPC statement about long-term protection. The Appeal Board considered that within the context of promotional material the claim was misleading and it upheld the Panel's ruling of a breach of the Code.

A primary care trust medicines management programme director complained about the entry for Viatim (combined Vi polysaccharide typhoid and inactivated hepatitis A vaccine) in a booklet (ref 2685)

on Aventis Pasteur MSD Ltd's range of vaccines for UK travellers.

COMPLAINT

The complainant referred to two successive statements in the booklet which appeared beneath a reference to Viatim:

'The Department of Health recommends: 'If any course of immunisation is interrupted, it should be resumed and completed as soon as possible'.

Therefore, if a patient presents later than the recommended 12 months for the booster dose, there is no need to restart the course from the first dose.'

The complainant considered that the second statement was misleading. With respect to hepatitis A, the Green Book and the Viatim summary of product characteristics (SPC) stated 'In order to provide long-term protection against infection caused by the hepatitis A virus, a booster injection of an inactivated hepatitis A vaccine should be given 6 to 12 months later. It is predicted that HAV antibodies persist for many years (at least 10 years) after the booster'. The complainant interpreted this as meaning that if a booster was not given in this 6-12 month period after the first dose, then the course would need to be restarted. Therefore the complainant alleged that the statement in the booklet was misleading and should be withdrawn.

When writing to Aventis Pasteur MSD, the Authority invited it to respond in relation to Clauses 7.2 and 7.3 of the Code.

RESPONSE

Aventis Pasteur MSD stated that in its view as no comparison was made in the statement at issue Clause 7.3 did not apply. It therefore responded in relation to Clause 7.2.

A course of inactivated hepatitis A vaccine, providing long-term protection, consisted of a primary dose followed by a booster. For Viatim it was recommended that the latter was given 6-12 months after the former. Therefore, the Viatim SPC stated: 'In order to provide long-term protection against infection caused by the hepatitis A virus, a booster injection of an inactivated hepatitis A vaccine should be given 6 to 12 months later'.

This was quoted correctly by the complainant. The Green Book statement was however, slightly different (page 87): 'The primary course produces anti-HAV antibodies which persist for at least one year and antibody persistence can be prolonged by administration of a booster dose of vaccine 6-12 months after the initial course'.

However, the Green Book also provided generic guidance about how to proceed when a vaccine course was interrupted (page 45): 'If any course of immunisation is interrupted, it should be resumed and completed as soon as possible'.

Aventis Pasteur MSD's position, and the stance taken in the booklet, was therefore as follows: The company recommended that, to ensure long-term protection against hepatitis A, a booster dose of inactivated hepatitis A vaccine should be administered 6-12 months after receipt of Viatim. This was consistent with the SPC. In the event that a patient failed to return within the recommended timeframe, the SPC provided no guidance. In this case it was generally accepted to follow the Department of Health guidance given in the Green Book. Since this situation was not covered by the SPC, this guidance was not inconsistent with it.

In order to address the issue further, Aventis Pasteur MSD had sought independent advice from TRAVAX a leading web-based provider of independent travel health information to the NHS. It stated: 'Immunologically you can almost invariably lengthen intervals indefinitely (unless the recipient has some immuno compromise problem) between doses and get at least a similar (often better) response'.

In terms of restarting a course, even if the interval between primary and booster doses was more than three years, TRAVAX stated: 'This is almost certainly unnecessary'.

Advice was also sought from the National Travel Health Network and Centre (NaTHNaC), an organisation funded by the Department of Health to provide advice on travel medicine. It concurred with the Green Book advice based upon data that existed for a competitor hepatitis A vaccine which it stated it would extrapolate to other inactivated hepatitis A vaccines.

In conclusion, Aventis Pasteur MSD did not accept that the statement was in breach of the Code, in particular Clause 7.2. In the event of a patient not returning for a booster during the recommended period, the SPC did not apply. In such a situation, it was accepted practice to follow national guidance issued by the Department of Health. This guidance was clear in stating that an interrupted course need not be restarted and this position was supported by experts in the field.

PANEL RULING

The Panel noted that Viatim was indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus and should be given in accordance with official recommendations. The Viatim SPC stated that initial protection was achieved with one single dose of Viatim and that in order to provide long-term protection against infection caused by hepatitis A virus a booster injection of inactivated hepatitis A vaccine should be given 6 to 12 months later. The SPC did not give any guidance on what to do if a booster injection had not been given 6-12 months after the primary dose. The Panel's interpretation of the SPC was that if no booster injection had been given 6-12 months after the primary dose then long-term protection had not been provided.

The Panel considered that the statements in the booklet were misleading. 'If any course of immunisation is interrupted it should be resumed and completed as soon as possible' appeared in Chapter 11 of the Green Book that appeared to give general

advice about childhood immunisation schedules not travel vaccine schedules. The Panel also noted the definition of resume was given as 'begin again, recommence, go on again with, continue' (ref The New Shorter Oxford English Dictionary (1993)). This did not assist matters.

The Panel noted that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in the SPC. Regardless of any statement in the Green Book the Panel considered that it was misleading to state in promotional material for Viatim that '… if a patient presents later than the recommended 12 months for the booster dose, there is no need to restart the course from the first dose'. This was tantamount to stating that the advice in the SPC to give a booster injection 6-12 months after the first injection could be ignored. The Panel thus ruled a breach of Clause 7.2 of the Code. This ruling was appealed.

APPEAL BY AVENTIS PASTEUR MSD

Aventis Pasteur MSD noted that the Panel had considered that Chapter 11 of the Green Book provided advice solely about childhood immunisation and not travel vaccine schedules. Aventis Pasteur MSD disagreed with this interpretation on the grounds that immediately after section 11.7, which contained the disputed statement, section 11.8 read 'The schedule for routine immunisation is given below. Details of the procedure for each vaccine are given in the relevant chapters and should be consulted'. Thereafter, the immunisation schedule was laid out beginning with childhood immunisation but finishing with adult vaccination including hepatitis A. There was no section beyond 11.8 and the chapter ended at this point. Thus, it was clear that hepatitis A vaccination was mentioned in Chapter 11. In fact, it was mentioned in the very next section after the disputed statement.

Aventis Pasteur MSD also noted that the Panel had discussed the various definitions of the word 'resume' as laid out in the New Shorter Oxford Dictionary; these included one possible interpretation that 'resume' might mean 'begin again'. Aventis Pasteur MSD did not believe that the vast majority of clinicians would ever begin a course of vaccination again [from the beginning] because a patient presented late for one dose. Aventis Pasteur submitted that with regard to hepatitis A, this was certainly contrary to the advice it had so far received.

Finally, Aventis Pasteur MSD disagreed with the Panel's view that the statement in the booklet was 'tantamount to stating that the advice in the SPC to give a booster injection 6-12 months after the first injection could be ignored'. In the two places in the booklet where the disputed wording was used, it was immediately preceded by advice about the timing of the booster dose, which was in accordance with the SPC. Therefore, when taken in context, the material had stated the guidance about the timing of booster doses in accordance with the SPC. The pragmatic and realistic advice was given to cover the not uncommon situation in which a patient presented late for a booster dose. Aventis Pasteur MSD could readily accept that, had the statement at issue been used on its own, as an alternative to a proper statement about when the booster dose was to be given, then the Panel would be right to have considered this as tantamount to stating that the SPC could be ignored. However, when the statement was used after, and in addition to one that had clearly reflected the SPC, then it was clearly not being used to encourage health professionals to ignore the SPC, but to provide pragmatic advice in relation to a common problem.

COMMENTS FROM THE COMPLAINANT

The complainant noted that both he and the Panel had considered that Chapter 11 of the Green Book referred to childhood immunisation. Section 11.8 only listed schedules for childhood vaccines: hepatitis A was mentioned at the end under adults in high risk groups, but not in the context of travel vaccines. Furthermore, there was no information in Chapter 17 Hepatitis A regarding interrupted courses. The complainant thus considered that the Green Book was not particularly helpful and should not be used as a reference source in this scenario. The complainant noted from the TRAVAX website that 'manufacturers do not consider it necessary to 're-start' the course unless more than 3 years has elapsed since the first dose'. The complainant noted that the statement at issue about presentation after 12 months for the booster dose did not mention this 3 year deadline.

The complainant acknowledged that the information provided by TRAVAX and NaTHNaC would be very useful to a health professional seeking advice on immunisation after an interrupted course. The complainant noted that whilst this advice was pragmatic and realistic, it was not referenced as such and not provided in the SPC. The complainant noted that the basis of his complaint was promotion outwith particulars stated in the SPC, as found by the Panel.

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Aventis Pasteur MSD was given permission to present further data.

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FURTHER COMMENTS BY AVENTIS PASTEUR MSD

Aventis Pasteur MSD provided the opinion of a number of experts in the field of travel medicine in order to summarise its views on the following three issues:

1 Whether the statement 'If any course of immunization is interrupted it should be resumed and completed as soon as possible', which appeared in Chapter 11 of the Green Book, gave advice pertaining only to the childhood immunization schedule, or whether this applied more generally to other vaccines including those used in travel medicine?

2 Whether the word 'resume' as it was used in the statement should be interpreted to mean re-

starting the course of vaccination where it was left off, or whether it could / should be interpreted as re-starting the course of vaccination from the beginning, ie to repeat all the doses previously given and then continue to completion?

3 How to manage a patient who had been given an initial dose of Avaxim or Viatim who then returned for a hepatitis A booster dose later than the recommended 6 to 12 months after the primary dose. In particular should the patient be made to restart the course of vaccination against hepatitis A from the beginning or should she / he be given the booster without repeating the original dose?

Aventis Pasteur MSD submitted that, on balance, the views expressed by the experts supported its appeal.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant considered that the expert opinions sought by Aventis Pasteur MSD had lent considerable weight to its position that there would be no need to re-start the course if more than 12 months had elapsed since the first vaccination. The complainant noted, as previously, that this was very useful information for a health professional dealing with a patient re-presenting after an interrupted course. The complainant alleged, however, that this would be outside the product licence and the crux of the complaint was that this was promotion outside of the terms of the SPC and misleading to potential users of the product, especially when no time-frame was mentioned.

FURTHER COMMENTS BY AVENTIS PASTEUR MSD

Aventis Pasteur MSD provided further expert opinion on the interpretation of the Green Book recommendations and on the timing of boosters from NaTHNaC. NaTHNaC was funded by the Department of Health to promote clinical standards in travel medicine. Aventis Pasteur MSD submitted that the response from NaTHNaC was important as the ruling on this matter might result in fundamental changes in the guidance that organizations which provided travel health advice might feel comfortable to give.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant considered that the material provided further reassurance to a health professional dealing with a patient re-presenting after an interrupted course. The complainant alleged however that it still did not change the fact that the leaflet had promoted use outside of the terms of the SPC.

APPEAL BOARD RULING

The Appeal Board noted that Viatim was indicated for simultaneous active immunisation against typhoid fever and hepatitis A virus and should be given in accordance with official recommendations. The Viatim SPC stated that initial protection was achieved with one single dose of Viatim and that in order to provide long-term protection against infection caused by hepatitis A virus, a booster injection of inactivated hepatitis A vaccine should be given 6 to 12 months later. The Appeal Board accepted that many patients presented late for their hepatitis A booster dose and that this situation was not addressed in the SPC.

The Appeal Board noted that the expert opinions provided by Aventis Pasteur MSD were inconsistent with regard to the acceptable time interval between first vaccination for hepatitis A and the booster dose. The Appeal Board also noted the submission of the company representatives at the appeal that there was some uncertainty in this area.

The Appeal Board considered that the claim '… if a patient presents later than the recommended 12 months for the booster dose there is no need to restart the course from the first dose' was a strong, open-ended claim; it implied that there was no limit to the time interval after which a booster dose could be given. This was inconsistent with the SPC statement about long-term protection. The Appeal Board considered that within the context of promotional material the claim was misleading and it upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

Complaint received **3 July 2003**

Case completed **17 November 2003**

CASE AUTH/1491/7/03

NOVARTIS v FUJISAWA

Promotion of Protopic

Novartis complained that Fujisawa had promoted Protopic (tacrolimus) ointment to a wider group of physicians than allowed by its product licence. The company cited market research data and referred to a leavepiece which took the form of a CD wallet.

Novartis noted that the Protopic summary of product characteristics (SPC) stated that the product 'should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy'. The existence of the restriction indicated that the authorities considered that significant experience in the use of such immunomodulators in the treatment of atopic dermatitis (eczema) was required if health professionals were to prescribe Protopic. This appeared to place its use outside the remit of the majority of GPs who would not have the experience required.

Novartis stated that independent market research showed clear evidence of the promotion of Protopic by Fujisawa in primary care; in the months January to April 2003 The Medical Promotion Index (MPI) recorded a figure of between 3 and 9 contacts for tacrolimus in each month from a sample of 200 GPs. In addition another audit, conducted by a separate research organisation, confirmed evidence of promotion of Protopic to some 21 GPs between January and May 2003. A further analysis of this data by geographical region demonstrated that this promotion was nationwide. Novartis considered that to find such evidence of promotion from a sample of GPs strongly suggested promotion of Protopic outside of its licence by Fujisawa representatives.

Novartis noted from the treatment algorithm under the heading 'Using Protopic' contained in the leavepiece that the product had been positioned for initiation in primary care following moderate/potent corticosteroid instead of referral to a hospital specialist. This appeared to place the use of Protopic clearly in primary rather than secondary care. The licence restriction on the use of the product to dermatologists and those physicians with extensive experience of the use of immunomodulating therapy did not appear with this algorithm. Novartis alleged that the item was intended to promote the use of Protopic to GPs in general and not to those to whom the licence referred.

The Panel noted that both strengths of Protopic ointment, 0.1% and 0.03%, were indicated for the treatment of moderate to severe atopic dermatitis in adults who were not adequately responsive to or were intolerant of conventional therapies. Additionally the lower strength ointment was indicated for the treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies. Protopic was thus a second-line therapy for use in patients who had 'failed' on topical corticosteroids either in terms of efficacy or tolerability. In the Panel's view these patients were likely to be referred to a dermatologist for further treatment. The Panel noted the statement in the Protopic SPC.

The Panel did not accept Fujisawa's submission that 'extensive experience … with immunomodulating therapy' included experience with topical corticosteroids. Although topical steroids did affect the immune system the Panel considered that in the context of dermatology the term 'immunomodulators' was assumed to refer to medicines other than topical steroids. In the Panel's view if 'immunomodulators' encompassed topical corticosteroids then any doctor with experience of treating atopic dermatitis would be able to prescribe Protopic given that topical corticosteroids were a mainstay of therapy. If that were the case then the cautionary SPC statement would be superfluous.

The Protopic GP Briefing Document (January 2003) referred to each representative's Protopic GP target list. Representatives were told that they could introduce and promote Protopic to other GPs by asking them if they would be interested to know about a new treatment for moderate to severe atopic dermatitis. If the GP questioned the appropriateness of the discussion with them, as they could not prescribe it due to the licensed indication, then the representatives were advised to refer to the SPC statement. The briefing document stated that both Fujisawa and a named consultant dermatologist considered that topical steroids were immunomodulating therapies. The representative was told that if the GP agreed with this, and was happy to hear about Protopic, then the discussion should continue. The briefing document continued by setting out a concise outline of who could prescribe Protopic. The Panel noted that neither the Protopic positioning statement nor the key communications messages referred to the cautionary SPC statement.

The briefing document referred to the Protopic GP sales aid from which it appeared that the product was to be presented as an alternative to the use of a potent topical corticosteroid or hospital referral. The leavepiece was to be left with customers after every call. The front cover stated 'Atopic dermatitis not responding to topical corticosteroids? … now there is a non-steroidal alternative'. A treatment algorithm showed that Protopic was to be used where moderate/potent topical corticosteroids had failed or were inappropriate, as an alternative either to hospital referral or the use of very potent corticosteroids. On the back cover of the leavepiece Protopic was described as 'a real alternative to steroids in the treatment of atopic dermatitis'. Reference to 'dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' appeared in the prescribing information.

The Panel considered that the limitations on who could prescribe Protopic were not adequately described in the leavepiece; the prescribing information was not sufficient in this regard.

Although there would be some GPs who met the conditions stated in the SPC, clinical assistants in dermatology and the like, in the Panel's view their numbers would be limited. The company had a target list of 4,000 GPs which included those with a special interest in dermatology and those who were high prescribers of topical corticosteroids within each territory. With regard to the latter group the Panel noted its comments above about corticosteroids and immunomodulators. Representatives could also promote Protopic to GPs other than those on the target list. Overall the Panel considered that Protopic was being promoted to more GPs than just those 'with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' as specified in the SPC. The promotion of Protopic to this audience was thus not in accordance with the terms of its marketing authorization and inconsistent with the particulars listed in its SPC. Breaches of the Code were ruled.

Upon appeal by Fujisawa the Appeal Board's view was that the statement in the Protopic SPC was a note of caution and, for the same reasons as the Panel, it did not accept Fujisawa's submission that 'extensive experience … with immunomodulating therapy' included experience with topical corticosteroids. In addition the Appeal Board noted Fujisawa's submission that GPs who prescribed at least two and a half times the national average of topical steroids were considered to be those with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy. The Appeal Board did not consider that volume of prescribing alone was a sound basis on which to make such a judgement.

The Appeal Board noted that although each representative was given a list of target GPs, identified as the highest prescribers of topical steroids on each territory and with an interest in dermatology, up to 20 other GPs could be added to this list by the representative. It appeared that they were added on the basis of their interest in a new treatment for moderate to severe atopic dermatitis. With regard to whether that doctor had 'extensive' experience was a matter for the individual practitioner to decide.

The Appeal Board considered that the limitation stated in the SPC with regard to who could prescribe Protopic was not adequately described in the leavepiece; to only include such information in the prescribing information was not sufficient.

Overall the Appeal Board considered that Protopic was being promoted to more GPs than just those 'with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' as specified in the SPC. The promotion of Protopic to such a wide audience was thus not in accordance with the terms of the product's marketing authorization and inconsistent with the particulars listed in its SPC. The Appeal Board noted that following the inadequate instructions from the company meant that the representatives had failed to comply with the Code. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Novartis Pharmaceuticals Ltd complained that Fujisawa Limited had promoted Protopic (tacrolimus) ointment outside of its product licence. The company cited market research data and referred to a leavepiece (ref 86/02/D/WBR) which took the form of a CD wallet.

COMPLAINT

Novartis noted that the Protopic summary of product characteristics (SPC) contained the statement 'Protopic should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy'. No recent amendments had removed this restriction.

Novartis noted that the British National Formulary (BNF) classified medicines affecting the immune system in dermatology in section 13.5.3. This section contained information on azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, pimecrolimus and tacrolimus as medicines which affected the immune system and were for use in eczema. The section did not contain information on topical corticosteroids which were contained in section 13.4.

Novartis stated that it was clearly not party to the thought processes involved in the approval of the wording of the Protopic licence by the authorities. However the existence of the restriction indicated that the authorities considered that significant experience in the use of such immunomodulators in the treatment of atopic dermatitis (eczema) was required if health professionals were to prescribe Protopic. This appeared to place its use outside the remit of the majority of GPs who would not have had such 'extensive experience of immunomodulating therapies'. Novartis considered that to find evidence of promotion from a sample of GPs in the independent market research audits referred to below strongly suggested promotion of Protopic outside of its licence by Fujisawa representatives. Breaches of Clauses 3.2 and 15.2 of the Code were alleged.

The topical management of atopic dermatitis was a new therapeutic area for Novartis. The company was thus currently reviewing in some detail feedback on the levels of awareness amongst health professionals of the various treatment options. Novartis' own product Elidel (pimecrolimus) was the main focus of this research but clearly the company also obtained feedback on the other available products including Protopic.

Novartis explained that The Medical Promotion Index (MPI) audit involved approximately 1,800 GPs in the UK who were mailed on a monthly basis to take part in market research. GPs who agreed to respond completed a diary for one calendar month recording information on all contacts with pharmaceutical company sales representatives and the products discussed. GPs were asked to record details of all such contacts which would include in-surgery discussions and contacts that occurred at external meetings, exhibitions and conferences. Two hundred completed GP diaries were used in the audit each month. A GP who had completed a diary for one month would not be invited to participate again for a

further 12 months. The 200 GPs included in the sample group were designed to be a representative sample of the GP population in the UK. This market research audit showed clear evidence of the promotion of Protopic by Fujisawa in primary care; in the months January to April of this year a figure of between 3 and 9 contacts for tacrolimus in each month had been recorded from a sample of 200 GPs.

The Detail Monitor audit, conducted by a separate research organisation collected information on a GP's recollection of discussions that took place with pharmaceutical company representatives during the previous week. Eight hundred to nine hundred GPs were mailed each week and invited to record information on the previous week's contacts with representatives. A minimum of 1,250 completed questionnaires were incorporated into the final market research in each 3 month period. The completed questionnaires returned by GPs participating in this audit in 2003 confirmed evidence of promotion of Protopic to some 21 GPs between January and May 2003. A further analysis of this data by geographical region demonstrated that this promotion was a nationwide issue. Some of the verbatim responses included indicated that GPs were confused about the licence for Protopic. One GP recalled being informed that the product 'Used to be consultant only prescription, now can be prescribed by GPs', and commented that it was 'useful to have alternative to steroids in eczema now allowed to prescribe'.

Novartis stated that in addition to the data obtained from market audit, there was also evidence from Protopic promotional materials that Fujisawa was positioning the product in the management of atopic dermatitis in primary care. Novartis noted from the treatment algorithm under the heading 'Using Protopic' contained in the leavepiece that the product had been positioned for initiation in primary care following moderate / potent corticosteroid instead of (represented by a broken arrow) referral to a hospital specialist. This appeared to place the use of Protopic clearly in primary rather than secondary care. The licence restriction on the use of the product to dermatologists and those physicians with extensive experience of the use of immunomodulating therapy did not appear with this algorithm. Novartis alleged that the item was intended to promote the use of Protopic to GPs in general and not to those to whom the licence referred.

Novartis stated that in conclusion, the results of two independent audits highlighted that Fujisawa representatives were talking about Protopic to GPs thereby promoting the product to health professionals, who as a result of a restriction to the product licence should not prescribe it. In addition, promotional materials clearly suggested that Fujisawa was positioning Protopic in primary rather than secondary care as stated in the licence. It appeared that this activity was leading to some misleading impressions and confusion amongst GPs about the exact licence status of Protopic.

RESPONSE

Fujisawa noted that Novartis had interpreted the sentence 'Protopic should be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' suggesting that Protopic use was outside the remit of the 'majority of GPs'. Novartis therefore suggested that evidence of Fujisawa's activities within primary care implied promotion beyond the Protopic licence.

Fujisawa's interpretation of the phrase chosen by the European Medicines Evaluation Agency (EMEA) ie 'physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' was supported by a massive body of evidence from the world literature and clinical and academic opinion in the UK. Novartis based its interpretation on a highly misleading representation of the relevant section of the BNF regarding the classification of topical corticosteroids.

Fujisawa noted that Novartis' product Elidel, was a very similar agent to Protopic and was used as topical treatment for atopic dermatitis. Tacrolimus and Elidel varied to a minimal degree at the molecular level. According to the Elidel SPC, Elidel 'should be prescribed by physicians with experience in the topical treatment of atopic dermatitis'.

It was clear from the wording chosen by the EMEA for the Protopic SPC that it was anticipated that Protopic would be prescribed by doctors other than dermatologists (ie … and physicians etc). Other than paediatricians (and a decision was made not to limit prescription to dermatologists and paediatricians) there were not really any other classifications of doctors other than various types of primary care physicians (GPs in the UK) that this more general wording could have been envisioned to include. As the marketing authorization for Protopic was obtained centrally it was important to use a phrase that would be applicable to all EC countries.

Fujisawa stated that the difference of opinion between it and Novartis concerned the proportion of GPs who could be considered to fulfil the description of having extensive experience in the treatment of atopic dermatitis with immunomodulating treatment. Novartis had indicated that in its view this would exclude 'the majority of GPs' (but not all). Fujisawa had interpreted this differently.

Fujisawa noted Novartis' comment that the section of the BNF classifying medicines affecting the immune system in dermatology (section 13.5.3) did not contain information on topical corticosteroids. This gave the very misleading impression that topical corticosteroids were not considered to be medicines 'affecting the immune system'. The truth was somewhat different.

Between the March 2002 (43) and September 2002 (44) editions of the BNF, and continued in the current edition, a crucial change was made to the structure of Chapter 13: Skin. This corresponded to the inclusion of the first reference to Protopic. A new section 13.5.3 was added entitled 'Drugs affecting the immune response'. The introductory passage described the use of ciclosporin, azathiopine, mycophenolate mofetil, hydroxycarbamide, methotrexate, tacrolimus (and in March 2003 edition, pimecrolimus) and importantly included a final sentence 'For the role of

corticosteroids in eczema see section 13.5.1 and for comment on their limited role in psoriasis see section 13.4'. Section 13.5.1 discussed preparations for eczema including topical steroids but not systemic steroids. Inclusion of the sentence referring to the use of topical steroids in eczema in the section dealing with medicines affecting the immune response seemed to suggest that in the view of those compiling the BNF, that topical corticosteroids were 'drugs affecting the immune response' in other words 'immunomodulators or immunosuppressants'. The only reason for not including them in section 13.5.3 was that they had already been described in an earlier section. Novartis' use of the phrase 'extensive experience in the use of **such immunomodulators**' would be in danger of being misleading with regard to the status of topical steroids.

Fujisawa submitted that the decision of the EMEA to refer to immunomodulating therapy rather than immunosuppressant therapy was an attempt to broaden the category beyond only the systemically acting immunosuppressant agents and as a result broaden the types of prescribers considered appropriate. However, 'immunomodulating therapies' was not a recognized category in any of the reference books generally available. In the Merck directory although a classification of immunomodulators was listed it appeared that none of the listed medicines had an application to atopic dermatitis. Therefore there was no 'official' description of an immunomodulating therapy used in the treatment of atopic dermatitis. The dictionary definition of modulate referred to a calming down. Immuno- referred to the immune system, which included the non-specific and specific pathways. Steroids had their anti-inflammatory action as a consequence of their activity against inflammatory elements of the immune system. Therefore steroids could be said to be immunomodulating agents. Equally, the description of steroids as immunosuppressants was also appropriate.

The reason for suggesting that physicians should have extensive experience in the use of immunomodulating therapy specifically in **atopic dermatitis** (emphasis added) was because Protopic was indicated for moderate to severe atopic dermatitis in 'adults who are not adequately responsive to or are intolerant of conventional therapies' (for 0.1% and 0.03%) and 'in children (2 years of age and above) who failed to respond adequately to conventional therapies' (for 0.03% only). Thus, in order to judge when a patient had not responded adequately to treatment a doctor would require experience in treating atopic dermatitis with these conventional therapies. This included many, and probably a majority of, GPs.

To support the view of the BNF that topical steroids acted via an immunosuppressive/immunomodulating effect there was an extensive list of supporting material. It was tempting to suggest that the recognition of the use of corticosteroids as an essential component of immunosuppressive regimens in organ transplantation for 40 years should not necessitate any further discussion regarding the appropriateness of referring to corticosteroids (including topical corticosteroids) as immunosuppressive or immunomodulating therapies. As early as 1951 locally applied corticosteroids were shown to have a genuinely local immunosuppressive effect, ie the effect was not due merely to the absorption of cortisone into the circulation.

Eichenfield *et al* (2002) which referred to 'topical steroids (as being) the mainstay of therapy for atopic dermatitis, **owing to their broad immunosuppressant and anti-inflammatory effects**' (emphasis added) was published in the Journal of the American Academy of Dermatology and included amongst its authors three employees of Novartis Pharmaceuticals.

Marsland *et al* had stated that 'many dermatological conditions are benefited by treatment with **immunomodulating** (emphasis added) drugs. Indeed for the past fifty years, topical or systemic glucocorticords have been the mainstay of immunosuppressive therapy'. The second author on this paper was one of the foremost UK experts in the field of academic dermatology and had an international reputation for his clinical trials work.

In clinical practice too, the idea of topical corticosteroids having their effect via immunosuppressive effects, as described in 1951, seemed to be well-established. The mechanisms of action, in particular their immunosuppressive effect, and role of topical corticosteroids in skin disease was described by Coulson (1996). Fujisawa provided copies of five papers which gave further similar supporting evidence and stated that a further 46 publications could be provided if required.

Further evidence for the general acceptance of corticosteroids as immunomodulators or immunosuppressants came from the testimony of senior academic figures in the UK regarding established opinion as taught to medical students. A letter from a professor of dermatology at a medical school was provided. The professor's statement that 'we would certainly expect doctors we train to view the overall effects of steroids as being similar in principle to those of topical calcineurin antagonists' was particularly telling. Discussions with other senior academics and clinicians within the fields of dermatology and immunology indicated that an even larger dossier of evidence could be obtained if necessary.

There was also support in general practice for the above interpretation. In the journal Update (28 November, 2002), which was widely read by GPs, with regard to the wording in the Protopic licence, Henderson stated that 'this covers any GP who prescribes topical steroids, which are non-selective immunomodulators'.

Under the circumstances it might be possible to agree that topical corticosteroids could rightly be regarded as 'immunomodulating therapy'. Therefore as topical corticosteroids were regarded as conventional treatment in atopic dermatitis, GPs experienced in the treatment of patients with atopic dermatitis clearly fell within the scope of the description contained in the Protopic SPC.

Fujisawa noted that Novartis had included evidence from two market research audits to show that

Protopic had been promoted to GPs. The first by MPI included 200 GPs in the final sample. Three to nine contacts where tacrolimus was discussed were recorded per month (Jan-April) ie a maximum of 4.5% of GPs in any one month. In the second survey Detail Monitor considered a minimum of 1,250 completed questionnaires in each 3 month period (no figure on exact number used) recording information on the previous week's contacts with representatives. Twenty-one GPs between January and May 2003 recalled contact ie 0.33% per month in this 5 month period. This rather low level of contact with a small minority of GPs in the UK was entirely in keeping with Fujisawa's stated policy regarding promoting to GPs. A total of 40 part time product specialists for the whole of the UK focused on GPs with a special interest in dermatology and those identified as particularly high prescribers of topical corticosteroids. However, as atopic dermatitis was one of the most common reasons for consulting with a GP this 'target group' clearly represented a small proportion of those GPs who could rightly be described as having 'extensive experience' of immunomodulating therapies in atopic dermatitis.

Fujisawa provided a confidential copy of the Protopic GP Briefing Document which it stated clearly described the target list of GPs which included GPs with a special interest in dermatology and the highest prescribers of topical steroids. A mechanism was described for adding up to 20 GPs to a product specialist's target list after discussion with the regional sales manager. In the course of a visit to a 'target' GP there was a possibility of contact being made with GPs not on the target list. For instance, a presentation at a lunchtime meeting would likely bring the product specialist into contact with a number of additional GPs. In recognition of this practicality and in keeping with the knowledge that the majority of GPs would in any case have a large experience in the treatment of atopic dermatitis a section was included in the briefing document describing precautions to be taken in this situation.

The GP would be first of all asked if (s)he would be interested to know about a new treatment for moderate to severe atopic dermatitis. If the GP wanted further information then the product specialist would go on to discuss Protopic. Issues regarding the appropriateness of prescribing Protopic in general practice would be addressed by referring to the statement in the SPC and explaining the view of senior dermatologists regarding the explanation of immunomodulating therapies and the inclusion of topical corticosteroids in this group. Importantly, further information would only be provided to the general practitioner if (s)he agreed that description was appropriate to them.

The briefing notes also contained a full explanation of the difficulties caused by the inclusion by the EMEA of the phrase 'immunomodulating therapy'.

Fujisawa noted that Novartis had indicated that at least one GP in the population sampled appeared confused 'about the licence for Protopic'. Fujisawa submitted that from the briefing document it had taken every step to resolve any confusion which more likely originated in the wording chosen by the EMEA, than as a result of any of Fujisawa's activities.

Fujisawa denied breaches of either Clause 3.2 or Clause 15.2.

Fujisawa noted that in the leavepiece at issue, under a clinical algorithm entitled 'Using Protopic' three arrows issued from a decision box which considered 'on treatment failure or where [moderate / potent] topical corticosteroid treatment is inappropriate'. The options at this stage were given as referral to hospital specialist, Protopic ointment or very potent corticosteroid. The arrows to 'referral to hospital specialist' and 'very potent corticosteroid' were broken to indicate that the preferred option was 'Protopic ointment'. This description of the second-line use of Protopic was in accordance with the licensed indication stated in the SPC. Prescribing information was included on the leavepiece and this included full details of the Protopic licence. The argument regarding initiation in primary care had already been made above. Fujisawa denied a breach of Clause 3.2.

The management of patients receiving Protopic was, if anything, more straightforward than managing those treated with topical steroids who would often have restrictions on the length of time they could continue to 'safely' use steroids, due to their known potential side effects. No additional monitoring was required when treating a patient with Protopic rather than a topical steroid. Therefore the only logical reason for including the phrase 'extensive experience in the treatment of **atopic dermatitis** (emphasis added) with immunomodulating therapy' was to ensure that the treating physician had sufficient experience to diagnose the condition and to recognize when steroid treatment was failing.

In summary, Fujisawa considered that the issue regarding the classification of topical corticosteroids was clear cut and supported by a huge volume of published materials and expert opinions. Indeed, it appeared to be standard teaching in medical schools. In Fujisawa's view this matter could have been settled by direct dialogue with Novartis and it was disappointed not to have been afforded that opportunity.

PANEL RULING

The Panel noted that Protopic ointment was available in two strengths – 0.1% and 0.03%. Both preparations were indicated for the treatment of moderate to severe atopic dermatitis in adults who were not adequately responsive to or were intolerant of conventional therapies. Additionally the lower strength ointment was indicated for the treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies. Protopic was thus a second-line therapy for use in patients who had 'failed' on topical corticosteroids either in terms of efficacy or tolerability. In the Panel's view these patients were likely to be referred to a dermatologist for further treatment. Section 4.2 of the Protopic SPC stated that the product should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy.

The Panel did not accept Fujisawa's submission that 'extensive experience … with immunomodulating therapy' included experience with topical corticosteroids. Although topical steroids did affect the immune system the Panel considered that in the context of dermatology the term 'immunomodulators' was assumed to refer to medicines other than topical steroids. In the Panel's view if 'immunomodulators' encompassed topical corticosteroids then any doctor with experience of treating atopic dermatitis would be able to prescribe Protopic given that topical corticosteroids were a mainstay of therapy. If that were the case then the cautionary SPC statement would be superfluous.

The Panel noted that Fujisawa had referred to the similarity between Protopic and Novartis' product Elidel (pimecrolimus). Elidel, however, was indicated as a first-line therapy for use in mild to moderate atopic dermatitis (Protopic was a second-line therapy for use in moderate to severe atopic dermatitis). The Elidel SPC stated that the product 'should be prescribed by physicians with experience in the topical treatment of atopic dermatitis'. There were thus some significant differences in the practical use of the two products.

The Protopic GP Briefing Document (January 2003) referred to each representative's Protopic GP target list. Representatives were told that they could introduce and promote Protopic to other GPs by asking them if they would be interested to know about a new treatment for moderate to severe atopic dermatitis. If the GP questioned the appropriateness of the discussion with them, as they could not prescribe it due to the licensed indication then the representatives were advised to refer to the SPC statement 'Protopic should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapies'. The briefing document stated that both Fujisawa and a named consultant dermatologist considered that topical steroids were immunomodulating therapies. The representatives were told that if the GP agreed with this, and was happy to hear about Protopic, then the discussion should continue. The briefing document continued by setting out a concise outline of who could prescribe Protopic. The Panel noted that neither the Protopic positioning statement nor the key communications messages referred to the cautionary SPC statement.

The briefing document referred to the Protopic GP sales aid from which it appeared that the product was to be presented as an alternative to the use of a potent topical corticosteroid or hospital referral. The leavepiece was to be left with customers after every call. The front cover stated 'Atopic dermatitis not responding to topical corticosteroids? … now there is a non-steroidal alternative'. A treatment algorithm showed that Protopic was to be used where moderate / potent topical corticosteroids had failed or were inappropriate, as an alternative either to hospital referral or the use of very potent corticosteroids. On the back cover of the leavepiece Protopic was described as 'a real alternative to steroids in the treatment of atopic dermatitis' that was, *inter alia*, 'Well-tolerated' with 'Simple and convenient administration'. Reference to 'dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' appeared in the prescribing information.

The Panel considered that the limitations on who could prescribe Protopic were not adequately described in the leavepiece; the prescribing information was not sufficient in this regard. Although there would be some GPs who met the conditions stated in the SPC, clinical assistants in dermatology and the like, in the Panel's view their numbers would be limited. The company had a target list of 4,000 GPs which included those with a special interest in dermatology and those who were high prescribers of topical corticosteroids within each territory. With regard to the latter group the Panel noted its comments above about corticosteroids and immunomodulators. Representatives could also promote Protopic to GPs other than those on the target list. Overall the Panel considered that Protopic was being promoted to more GPs than just those 'with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' as specified in the SPC. The promotion of Protopic to this audience was thus not in accordance with the terms of its marketing authorization and inconsistent with the particulars listed in its SPC. Breaches of Clauses 3.2 and 15.2 were ruled.

APPEAL BY FUJISAWA

Fujisawa noted that Novartis had complained that Protopic had been promoted beyond the terms of its licence. Novartis' interpretation of the wording of the licence (as contained in the SPC) was that the **majority** of GPs would not have had sufficient experience to meet the requirements of the licence. However no evidence was presented to suggest that Protopic was promoted to anything other than a relatively small subgroup of GPs.

Fujisawa noted that the Panel had suggested that as Protopic 'was a second-line therapy for use in patients who had 'failed' on topical corticosteroids either in terms of efficacy or tolerability' patients fulfilling this description would be likely to be referred to a dermatologist for further treatment. Fujisawa submitted that this confused second-line treatment with referral to secondary care. For many conditions these two concepts might be quite separate. For atopic dermatitis it was very common for a GP to try several different treatments prior to hospital referral. In the NICE referral guidelines for atopic eczema in children one reason for referral was 'the disease is severe and has not responded to **appropriate** therapy in primary care'. This implied that patients with less severe disease (eg moderate for whom Protopic was licensed) should not necessarily be referred. Furthermore Protopic was indeed 'appropriate' therapy and this should be tried in moderate and severe patients in primary care before referral to secondary care if the GP had sufficient experience in the treatment of atopic dermatitis with topical steroids.

Fujisawa noted that the Panel had agreed that topical steroids affected the immune system in a way that

was variably described as immunosuppressing or immunomodulating. However, despite the views of two professors of dermatology in the UK and a representative of the Primary Care Dermatology Society that 'many dermatological conditions are benefited by treatment with **immunomodulating** drugs…….topical or systemic glucocorticoids have been the mainstay of immunosuppressive therapy' and that medical students were taught that 'the overall effects of steroids …(are)…very similar in principle to those of topical calcineurin antagonists' and 'topical steroids …are non-selective immunomodulators', the Panel considered that in the 'context of dermatology the term immunomodulators was assumed to refer to medicines other than topical steroids'. Fujisawa was surprised at this conclusion in the face of the experts' evidence presented to the Panel, and suggested that it was the wording of the licence, as represented in the SPC, which was important in assessing the promotional activities at issue. Fujisawa submitted that it was not the Panel's role to speculate on or attempt to second-guess what might have been in the minds of the EMEA when the wording of the licence was agreed. Fujisawa's interpretation of the wording within the SPC was reasonable.

Fujisawa submitted that the Panel had justified its interpretation based on a misquotation of the Protopic licence. In arguing that 'if immunomodulators encompassed topical corticosteroids then any doctor with experience of treating atopic dermatitis would be able to prescribe Protopic given that topical corticosteroids were a mainstay of therapy', the Panel went on to state that 'if that were the case then the cautionary statement would be superfluous'. Crucially the word 'extensive' was omitted in the Panel's reference to the wording of the licence. The wording of the SPC indicated that 'extensive' experience was required before prescribing Protopic and this would relate to only a proportion of GPs.

Fujisawa questioned that only if the relevant phrase in the SPC had **not** related to topical steroids would the cautionary statement be superfluous. If immunomodulating therapy used in the treatment of atopic dermatitis was not considered to include topical steroids and only referred to medicines such as systemic steroids and ciclosporin and therapies such as UV irradiation it could be asked who this description referred to other than dermatologists, in which case the additional phrase would indeed be superfluous.

Fujisawa repeated that 'extensive experience' was specified to ensure that the treating physician had sufficient experience to diagnose the condition and to recognise when treatment with steroids was failing.

Fujisawa submitted that by identifying a list of GPs with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy it had taken a very responsible approach. By identifying GPs whose use of topical steroids was at least two and a half times the national average, a target group of around 10% of all GPs in the UK was selected. The market research figures provided by Novartis confirmed the fact that only a select group of GPs would have met with Fujisawa's product specialists. It was likely that this target group would not include all of the GPs who would qualify according to the description in the licence.

Fujisawa therefore strongly denied that it had promoted Protopic to more GPs than just those 'with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' as claimed by the Panel.

COMMENTS FROM NOVARTIS

Novartis noted that the Protopic SPC clearly stated that the product should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy.

Novartis supported the Panel's position that topical corticosteroids had effects on the immune system, but that in the context of dermatology the term 'immunomodulators' in the SPC referred to medicines other than topical steroids. Indeed in this context the term immunomodulator would be unlikely to mean topical steroids and was more likely to refer to a very different group of medicines used in the management of dermatological conditions eg methotrexate and cyclosporine.

Novartis noted that Fujisawa had incorrectly interpreted the company's point regarding the sections 13.4 and 13.5.3 of the BNF which related to the above. Novartis had not stated or implied that topical steroids had no immune system effects and agreed with Fujisawa's lengthy supporting summary of the effects on the immune system of topical steroids. Novartis had highlighted the different classification of medicines in these two sections of the BNF to indicate their different mechanisms of action, efficacy, tolerability profiles and hence their different indications and posologies.

Novartis alleged that the BNF had clearly differentiated the licence restrictions on the prescribing of Protopic from that of other topical agents through the inclusion of statements such as 'treatment with tacrolimus should normally be initiated by a specialist' and 'specialist use only' in relation to the product.

Novartis alleged that the scientific and clinical reasons for the inclusion of the restrictive wording in the Protopic SPC was elaborated upon by the European Product Assessment Report (EPAR)(CPMP/3447/01) Scientific Discussion Document (SDD). This public document was part of the regulatory documentation for this centrally approved product. As such the EPAR/SDD had not presented new material, but provided clarification on the licence position for Protopic.

Novartis stated that the SDD had confirmed that the prescribing of tacrolimus was restricted due to the risk of systemic exposure and subsequent immunosuppression. Novartis alleged that for this reason Protopic should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy, who were able to fully evaluate the risk/benefit profile of the product. This

position was further supported by the following statements from parts 4 and 5 of the SDD.

Part 4 – Clinical Aspects – Clinical Safety – Discussion on clinical safety:

- 'The main issue regarding the safety of this product is the potential effect on Immunocompetence'
- 'Pharmacokinetic data suggest the possibility of systemic exposure to tacrolimus with resulting potential immunosuppressant effect'

Part 5 – Overall conclusions, benefit / risk assessment and recommendation – Benefit / risk assessment:

- '…However, a concern remains regarding tacrolimus ointment potential for immunosuppression.'
- 'In view of the systemic absorption of tacrolimus, albeit minimal, and the potential for systemic immunosuppression, it is recommended that tacrolimus ointment should be reserved for the treatment of adult patients who are not adequately responsive to or are intolerant of conventional therapies (such as moderately potent topical steroids)'.
- 'The treatment will also be restricted to dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy, because tacrolimus represents a new option (an immunomodulator) for a chronic disease to be used intermittently over long periods with the potential for immunosuppression'.

Novartis alleged that it thus appeared that the specific restrictions in the licence were intended to protect the non-specialist physician from the inappropriate use of a new immunomodulator, and the patient from potential systemic immunosuppression. It was clearly not, as Fujisawa had suggested, to address a lack of physician experience in the general routine management of atopic dermatitis which might result in a failure to recognise a lack of response to topical steroids. This particular restriction appeared to be specific for Protopic and had not appeared in the SPC of any other topically administered immunomodulator or topical steroid.

Novartis alleged that the extent of the concerns regarding the clinical impact of systemic absorption of tacrolimus was not shared with pimecrolimus. This difference was clearly reflected by the difference in the licence statements for the two products as acknowledged by the Panel in its ruling.

Novartis maintained that the promotion of Protopic had been inconsistent with the restrictions in the product licence. Clear evidence had been provided that the extent of promotion by Fujisawa had exceeded that permitted by the product licence. Fujisawa's response had failed to address these concerns and the company had failed to provide any clear rationale for its stated selection criteria for GPs. Fujisawa was targeting around 10% of UK GPs, but Novartis thought it unlikely that this many would consider themselves as having extensive experience of the treatment of atopic dermatitis with immunomodulating therapy.

Nor had any evidence been provided to support the assertion that 'prescribing rates of 2.5 times the national average for topical steroids' fulfilled the criteria of having extensive experience with immunomodulating therapy.

Novartis stated that in relation to the Protopic leavepiece at issue, it supported the Panel's ruling that there had been inadequate emphasis on the limitations of the product licence. This, together with the other elements of Fujisawa's response, suggested that it had been designed for use with a wider group of physicians than those defined by the licence.

Novartis noted that Fujisawa had suggested that the inter-company discussion route had not been explored in relation to this issue. However the positioning of Protopic had been the subject of previous discussions between the companies last year though clearly such discussion did not prove successful.

In conclusion Novartis alleged that there was clear evidence of the promotion of Protopic outside of its product licence and it fully supported the ruling to this effect by the Panel in relation to this case.

APPEAL BOARD RULING

The Appeal Board noted that the Protopic SPC stated 'Protopic should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy'. In the Appeal Board's view this statement was a note of caution.

The Appeal Board did not accept Fujisawa's submission that 'extensive experience … with immunomodulating therapy' included experience with topical corticosteroids. Although topical steroids did affect the immune system the Appeal Board considered that in the context of dermatology the term 'immunomodulators' was assumed to refer to medicines other than topical steroids. In the Appeal Board's view if 'immunomodulators' encompassed topical corticosteroids then any doctor with experience of treating atopic dermatitis would be able to prescribe Protopic given that topical corticosteroids were a mainstay of therapy. If that were the case then the cautionary SPC statement would be superfluous.

The Appeal Board noted Fujisawa's submission that GPs who prescribed at least two and a half times the national average of topical steroids were considered to be those with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy. The Appeal Board did not consider that volume of prescribing alone was a sound basis on which to make such a judgement.

The Appeal Board noted that although each representative was given a list of target GPs, identified as the highest prescribers of topical steroids on each territory and with an interest in dermatology, up to 20 other GPs could be added to this list by the representative. It appeared that they were added on the basis of their interest in a new treatment for moderate to severe atopic dermatitis. With regard to whether that doctor had 'extensive' experience was a matter for the individual practitioner to decide.

The Appeal Board considered that the limitation stated in the SPC with regard to who could prescribe Protopic was not adequately described in the leavepiece; to only include such information in the prescribing information was not sufficient.

Overall the Appeal Board considered that Protopic was being promoted to more GPs than just those 'with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy' as specified in the SPC. The promotion of Protopic to such a wide audience was thus not in accordance with the terms of the product's marketing authorization and inconsistent with the particulars listed in its SPC. The Appeal Board noted that following the inadequate instructions from the company meant that the representatives had failed to comply with the Code. The Appeal Board upheld the Panel's rulings of breaches of Clauses 3.2 and 15.2. The appeal on this point was unsuccessful.

Complaint received **14 July 2003**

Case completed **12 December 2003**

CASE AUTH/1492/7/03

WYETH/DIRECTOR v NOVO NORDISK

Breach of undertaking

Wyeth alleged that two Kliovance (estradiol plus norethisterone acetate) leavepieces, issued by Novo Nordisk, contained claims previously ruled in breach in Case AUTH/1417/2/03. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with an undertaking. This accorded with advice previously given by the Code of Practice Appeal Board.

When this complaint, Case AUTH/1492/7/03, was received the previous case, Case AUTH/1417/2/03, had been considered by the Code of Practice Panel. Breaches of the Code were ruled. One ruling was the subject of an appeal which had not yet been heard by the Appeal Board. By the time this complaint, AUTH/1492/7/03, was considered by the Panel the Appeal Board had overturned the Panel's ruling in Case AUTH/1417/2/03 and ruled no breach of the Code.

Wyeth was aware that two leavepieces contained a comparison of amenorrhoea rates for Kliovance (73%) and Premique (57%). Wyeth was concerned that Novo Nordisk had used one leavepiece, at the recent British Menopause Society meeting, which contained a claim which Novo Nordisk had accepted was in breach in Case AUTH/1417/2/03, namely the comparison of 73% Kliovance and 57% Premique amenorrhoea rates at month 2. Moreover, that leavepiece was prepared in June 2003 which meant that Novo Nordisk had knowingly approved and used a claim already ruled in breach of the Code.

Wyeth further alleged a breach of Clause 2, as it considered that Novo Nordisk had disregarded the Panel's decision purely for commercial reasons – ie to encourage doctors to switch patients from Premique to Kliovance.

The Panel noted that in Case AUTH/1417/2/03 Novo Nordisk had been ruled in breach of the Code. It had appealed one of the Panel's rulings and had accepted the other rulings of a breach. One of the rulings of a breach of the Code which was accepted was with regard to the claim for Kliovance 'For amenorrhoea in HRT'. The requisite undertaking was given by Novo Nordisk in May 2003 stating that the material had been withdrawn. Novo Nordisk had withdrawn the material with the exception of one leavepiece. Thus the company had failed to comply with its undertaking and the Panel ruled a breach of the Code in relation to Case AUTH/1492/7/03. As material ruled in breach of the Code had not been withdrawn the Panel ruled a breach of Clause 2 of the Code.

The current complaint, Case AUTH/1492/7/03, had been submitted before consideration of the appeal which concerned whether 73% as the percentage of amenorrhoeic patients after 2 months of treatment with Kliovance was a fair reflection of the evidence. The Panel noted claims etc that were the subject of an appeal could continue in use until the Appeal Board ruled a breach of the Code and the claim etc had to be withdrawn as required by the Constitution and Procedure. As the appeal on this point had yet to be heard no undertaking had been given in this regard and thus there could be no breach of undertaking. The Panel ruled no breach of the Code and consequently no breach of Clause 2 of the Code.

The Panel noted that the second leavepiece included two claims regarding amenorrhoea. These being for Kliovance '73% of women amenorrhoeic after 2 months' referenced to Archer *et al* 1999 and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The claim for Premique followed the claim for Kliovance. The Panel noted that the material was not presented in a bar chart as in the material previously at issue. It therefore considered that it was not covered by its ruling in Case AUTH/1417/2/03 regarding the bar chart. No breach of the Code was ruled and consequently no breach of Clause 2 was ruled. These rulings were appealed by Wyeth.

The Appeal Board noted the two consecutive claims; these being for Kliovance '73% of women amenorrhoeic after 2 months' referenced to Archer *et al* (1999) and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'

referenced to Archer *et al* (1994). The Appeal Board disagreed with Wyeth's submission that the comparison *per se* was the issue. Wyeth had alleged a breach of undertaking and a breach of Clause 2 and so the only matter to be considered was whether the two claims constituted a breach of the undertaking given in Case AUTH/1417/2/03 which related to the depiction of the data within the same bar chart. The Appeal Board was not required to consider the validity of the comparison *per se*.

The Appeal Board considered that in the material now at issue the presentation of the data was sufficiently different to that in Case AUTH/1417/2/03 such that the leavepiece was not covered by the previous undertaking. The Appeal Board upheld the Panel's rulings of no breach of the Code.

Wyeth Pharmaceuticals alleged that two Kliovance (estradiol plus norethisterone acetate) leavepieces (refs KV/02/17 and KV/03/30), issued by Novo Nordisk Limited, contained claims previously ruled in breach in Case AUTH/1417/2/03. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with an undertaking. This accorded with advice previously given by the Code of Practice Appeal Board.

When this complaint, Case AUTH/1492/7/03, was received the previous case, Case AUTH/1417/2/03, had been considered by the Panel. Breaches of the Code were ruled. One ruling was the subject of an appeal which had not then been heard by the Appeal Board. When this complaint (Case AUTH/1492/7/03) was considered by the Panel the Appeal Board had overturned the Panel's ruling in Case AUTH/1417/2/03 and ruled no breach of the Code.

COMPLAINT

Wyeth sent two letters stating its position. In its first letter Wyeth requested that Novo Nordisk immediately withdrew all materials ruled in breach of the Code. It was aware that two leavepieces (KV/02/17 and KV/03/30) contained a comparison of amenorrhoea rates for Kliovance (73%) and Premique (57%). In its second letter Wyeth went into more detail and stated that it was extremely concerned that Novo Nordisk, at the recent British Menopause Society meeting (3-4 July 2003), had used a leavepiece (KV/03/30) which contained one of the claims ruled in breach and accepted by Novo Nordisk in Case AUTH/1417/2/03, namely the comparison of 73% Kliovance and 57% Premique amenorrhoea rates at month 2. Moreover, the leavepiece had a date of preparation of June 2003, which meant that Novo Nordisk had knowingly approved and used a claim already ruled in breach of the Code. Wyeth submitted that this was despite its repeated requests in earlier correspondence that Novo Nordisk reviewed all of its materials with respect to the Panel's rulings. Wyeth alleged that this represented a clear breach of undertaking in breach of Clause 22.

Wyeth further alleged a breach of Clause 2, as it considered that Novo Nordisk had shown a flagrant disregard for the Panel's decision, purely for commercial reasons – ie to be able to use the leavepiece as a displacement item to encourage doctors to switch patients from Premique to Kliovance. Commercially, this could have had major repercussions for Premique sales, so Wyeth considered it was an important issue. Such behaviour on the part of Novo Nordisk could only discredit and reduce confidence in the pharmaceutical industry.

Wyeth requested that Novo Nordisk urgently reviewed all of its Kliovance promotional materials, immediately withdrew all items containing the claims ruled in breach and confirmed in writing when this had been done and which items had been withdrawn (including the dates of withdrawal).

Wyeth stated that another leavepiece (ref KV/02/17) contained a comparison of amenorrhoea rates between Kliovance and Premique but it was sure that there were others – for example, the Kliovance detail aid was likely to contain the claims ruled in breach.

RESPONSE

Novo Nordisk noted that Wyeth had alleged a breach of a previous undertaking with regard to a new leavepiece (KV/03/30), a charge that Novo Nordisk took very seriously indeed. Novo Nordisk's understanding was that the alleged breach of undertaking was in regard to the unresolved issue of which percentage rate for amenorrhoea with Kliovance was a fair reflection of the available evidence (Case AUTH/1417/2/03).

Novo Nordisk submitted that it had signed an undertaking in May 2003 to withdraw all the materials found in breach in Case AUTH/1417/2/03 and confirmed this to be so. Novo Nordisk also confirmed that it had undertaken a review of all Kliovance promotional materials to check for any breaches as per Wyeth's complaint and further confirmed that similar materials not specified in the complaint had also been withdrawn.

Novo Nordisk submitted that the issue of the claim of an amenorrhoea rate at 2 months of 73% for Kliovance was the only matter subject to appeal from the original ruling and, as such, until the matter was resolved by the Appeal Board, its understanding of Paragraph 7.3 of the Constitution and Procedure was that it did not have to stop using this claim. Therefore it could not understand why Wyeth had objected to this. Clearly if the Appeal Board ruled against Novo Nordisk it would withdraw this new piece immediately but the data overwhelmingly supported this figure and so it denied breaches of Clauses 22 or 2.

Novo Nordisk submitted that high standards had been maintained since the two breaches contained in the previous leavepiece for Kliovance (KV/02/10) ie the bar graph and the statement 'For amenorrhoea in HRT' were not repeated and only the 73% figure was used again. Novo Nordisk had avoided potentially misleading artwork by making simple factual statements in KV/03/30. The third bullet point in this leavepiece stated that 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The reader could be left in absolutely no doubt that the amenorrhoea rate for Premique was

57% at 2 months and that this was derived from a separate study. The tag line had been replaced with a non-controversial statement 'Hormone replacement therapy from Novo Nordisk'.

Novo Nordisk summarised that Wyeth had included in its new complaint two separate pieces of promotional material; the sales aid KV/02/17 which had already been withdrawn and was not present at the recent British Menopause Society Meeting (3-4 July 2003) and also the new leavepiece KV/03/30 which used the claim under dispute as it considered it was entitled to do until there had been an Appeal Board ruling. Novo Nordisk submitted that it had undertaken not to use any of the previously complained about materials but it disputed the ruling on the 73% figure which it considered had resulted from a misunderstanding of the data presented in one clinical paper. Novo Nordisk submitted that it had been careful not to repeat any of the undisputed breaches and was fully justified in continuing to use its claim of 73% amenorrhoea at 2 months until it had a ruling from the Appeal Board.

In response to a request for further information Novo Nordisk stated that the leavepiece (KV/02/17) contained the strapline: 'Amenorrhoea in HRT'. [This had been ruled in breach of Clause 7.2 of the Code in Case AUTH/1417/2/03. Novo Nordisk had not appealed this ruling and had provided the requisite undertaking and assurance.] Novo Nordisk stated that the piece of material which was subject to the original complaint (KV/02/10) was part of an old campaign which was superseded by a new campaign on 10 January 2003.

Since the outcome of the complaint was not known until May 2003, these materials were presumed to be already out of use and returned by the representatives. Thus no active recall was put into place as representatives were expected to return old campaign materials to the warehouse for destruction.

Following the request for further information, Novo Nordisk noticed that KV/02/17 had unfortunately been overlooked by colleagues and that this item also contained the offending strapline 'Amenorrhoea in HRT'. For that reason, the representatives were notified on 17 July 2003 that the leavepiece must be returned with immediate effect.

In the past, withdrawal of materials found to be in breach of the Code which were in current use had been actively documented. For those materials which had merely been superseded by a new campaign, there had been a passive withdrawal process whereby the representatives returned old materials for destruction. This had never been a problem in the past since representatives did not have the space or any need to keep old materials. However, this situation had highlighted the potential for confusion, so a system was now being put in place for the active documented recall of all old materials in the event of a new campaign, whether they had been found to be in breach or not, to avoid this being an issue in the future.

Novo Nordisk sincerely apologised for the situation and assured the Authority that measures were being taken to avoid any future recurrence.

PANEL RULING

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 future. It was very important for the reputation of the industry that companies complied with undertakings. The Panel noted that in the previous case, Case AUTH/1417/2/03, Novo Nordisk had been ruled in breach of the Code. It had appealed one of the Panel's rulings and had accepted the other rulings of a breach.

In Case AUTH/1417/2/03, the Panel's ruling of a breach of Clause 7.2 relating to a claim for Kliovance 'For amenorrhoea in HRT' was not appealed, neither were the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.8 in relation to depiction of data for Kliovance, Premique and Femoston-conti in one bar chart when the data came from 3 different studies. The requisite undertaking was given by Novo Nordisk stating that the material had been withdrawn. The undertaking was received on 14 May 2003.

Novo Nordisk had accepted the Panel's ruling in Case AUTH/1417/2/03 that the claim 'Amenorrhoea in HRT' was in breach of Clause 7.2 of the Code. Novo Nordisk had provided the requisite undertaking and assurance and had withdrawn the material with the exception of the leavepiece KV/02/17. Thus the company had failed to comply with its undertaking and the Panel ruled a breach of Clause 22 of the Code in relation to Case AUTH/1492/7/03. This ruling was accepted by Novo Nordisk. The Panel noted that the company procedure had been changed as a result of this matter. Nevertheless material ruled in breach of the Code had not been withdrawn. The Panel thus ruled a breach of Clause 2 of the Code. This ruling was not appealed.

The current complaint, Case AUTH/1492/7/03, had been submitted before consideration of the appeal which concerned whether 73% as the percentage of amenorrhoeic patients after 2 months of treatment with Kliovance was a fair reflection of the evidence. The appeal was heard in July.

With regard to the issue of whether 73% was a fair reflection of the evidence, the Panel noted the requirements of Paragraph 7.3 of the Constitution and Procedure (2001) that if the respondent company accepted one or more of the Panel's rulings of breaches of the Code, but appealed one or more other such rulings, then within ten working days of notification of the Panel's rulings it must provide the undertaking required by Paragraph 7.1 in respect of the ruling or rulings which it was not appealing. It thus followed that claims etc that were the subject of an appeal could continue in use until the Appeal Board ruled a breach of the Code and the claim etc had to be withdrawn as required by the Constitution and Procedure.

In relation to the use of the figure of 73% for Kliovance patients, the appeal had not been heard. Novo Nordisk was therefore not prohibited from using this figure in its promotional material. No undertaking had been given in this regard and thus there could be no breach of undertaking.

Wyeth had complained that two leavepieces, KV/02/17 and KV/03/30, included claims that had been ruled in breach. With regard to KV/03/30 Wyeth referred to comparisons of amenorrhoea rates between Kliovance – given as 73% and Premique given as 57%. Wyeth stated that KV/02/17 included a similar comparison.

The Panel noted that KV/03/30 included two claims regarding amenorrhoea. These being for Kliovance '73% of women amenorrhoeic after 2 months' referenced to Archer *et al* 1999 and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The claim for Premique followed the claim for Kliovance.

The Panel noted that the material was not presented in a bar chart as in the material previously at issue. It therefore considered that it was not covered by its ruling in Case AUTH/1417/2/03 regarding the bar chart. The Panel ruled no breach of Clause 22 and consequently no breach of Clause 2 of the Code. These rulings were appealed by Wyeth.

APPEAL BY WYETH

Wyeth noted that the leavepiece KV/03/30 contained two consecutive bullet points: '73% of women amenorrhoeic after 2 months [on Kliovance]' and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. Wyeth accepted the figure of 73%, as per the recent appeal hearing (Case AUTH/1417/2/03), but was concerned about the implicit comparison between Kliovance and Premique amenorrhoea rates. Wyeth noted that the Panel's ruling stated that 'the material [comparison] was not presented in a bar chart as in the material previously at issue. It therefore considered that it was not covered by its ruling in Case AUTH/1417/2/03 regarding the bar chart'.

Wyeth submitted that the comparison *per se* was the issue regardless of the format in which it was made (bar chart, bullet points, pie chart etc). The Panel's ruling about leavepiece KV/02/10 in Case AUTH/1417/2/03 had stated that 'The Panel considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous-combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote ['Data from 3 different trials'] did not negate the overall impression given. The bar chart was misleading in this regard. A breach of Clauses 7.2, 7.3 and 7.8 was ruled'. Wyeth submitted that the Panel's ruling on the bar chart would equally apply to any other form of comparison, including the two consecutive bullet points in KV/03/30 particularly when one considered how Novo Nordisk sales representatives were likely to verbalise the data.

Wyeth considered that the two consecutive bullet points similarly and clearly invited the reader to make a comparison, and that the statement 'in a separate study' was an inadequate caveat, just as 'Data from 3 different trials' was inadequate in the original complaint. Consequently, the rulings of breaches of Clauses 7.2 and 7.3 with regard to the bar chart should equally apply to the leavepiece in question.

Wyeth did not consider it was acceptable for Novo Nordisk to continue making the 73% vs 57% comparison simply by changing the manner in which the comparison was made. By so doing, Novo Nordisk was not adhering to the spirit of the Code, or to its undertaking to abide by the Panel's ruling.

Wyeth referred to Case AUTH/1417/2/03 and the arguments contained therein regarding the comparison of amenorrhoea rates. Wyeth restated its key arguments:

- a comparison was made between Kliovance and Premique for percentage amenorrhoea at 2 months, despite the fact that the results were derived from two different studies. This was inappropriate for obvious reasons, including differences in patient population, inclusion criteria, the definition of amenorrhoea (eg how many episodes of spotting were allowed) and other methodological differences.
- Archer and Pickar (2002) had recently reviewed the assessment of bleeding patterns in postmenopausal women during continuous combined HRT, and stated that 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. Wyeth stated that expert opinion had thus supported its contention that a comparison of amenorrhoea rates from different studies, based on current non-standardized methodologies, was not valid. Notably, Archer, who made these comments in the review, was the lead investigator in the Kliovance trial reporting 73% amenorrhoea (Archer *et al*, 1999) so his comments were highly pertinent to the current complaint. Wyeth alleged that in the light of Archer's comments and reported results, it believed that any head-to-head comparison of amenorrhoea results from different trials with different methodologies, however presented, was untenable.

Wyeth was extremely concerned that Novo Nordisk had used leavepiece KV/03/30, which had a date of preparation of June 2003, at the British Menopause Society meeting held 3-4 July 2003. Thus, Novo Nordisk knowingly approved an item containing the 73% vs 57% comparison, which had already been ruled in breach by the Panel. Wyeth alleged that this represented a breach of the undertaking in breach of Clause 22.

Wyeth was concerned that following the Panel's ruling, Novo Nordisk had failed to apply due diligence and to act within the spirit of the Code by reviewing any similar items to assess whether or not the ruling applied to them. Instead, it knowingly approved a leavepiece containing identical points to those ruled in breach (albeit in a different format), and proceeded to use it as a displacement item at the UK's largest annual menopause meeting (British Menopause Society) to encourage doctors to switch patients from Premique to Kliovance. Wyeth alleged that this could have major implications for sales of Premique, and commercially was potentially very damaging, which was why it took it so seriously.

Wyeth further alleged a breach of Clause 2 as it considered that Novo Nordisk's actions discredited and reduced confidence in the pharmaceutical industry.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted that the Panel's ruling in Case AUTH/1417/2/03 referred to the comparison of amenorrhoea rates between Kliovance and Premique in a bar chart. The ruling stated that 'The Panel considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous-combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote ['Data from 3 different trials'] did not negate the overall impression given'. Breaches of the Code were ruled since the bar chart was deemed misleading in this regard. Novo Nordisk noted that this was reflected in the supplementary information to Clause 7 in the 2003 edition of the Code which stated 'In general claims should not be qualified by the use of footnotes and the like'. Novo Nordisk respected the Panel's decision and made it clear that the comparison referred to two separate studies by inserting 'in a separate study', into the second bullet point. However, Novo Nordisk noted that it was the way the data was presented, not the comparison *per se* that was found to be in breach, which was why the Panel did not consider leavepiece KV/03/30 to be in breach. Novo Nordisk strongly objected to Wyeth's appeal since this was an issue that was not found to be in breach in the first place. Novo Nordisk submitted that Wyeth must also acknowledge this or it would not be lodging this same issue repeatedly as a separate complaint (Case AUTH/1521/10/03). Novo Nordisk submitted that Wyeth's statement 'Novo Nordisk was not adhering to the spirit of the Code or to its undertaking to abide by the Panel's ruling', was unjustified and that the company did not breach Clause 22 or Clause 2 with leavepiece KV/03/30.

Novo Nordisk submitted that the comparison between Kliovance and Premique amenorrhoea rates in KV/03/30 was valid. It was clearly indicated that the data was taken from separate trials since it stated 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The comparison was sensible and appropriate since the definition of amenorrhoea was standardised between the two trials as illustrated below.

Archer *et al* (1999) was a prospective, double blind, randomised trial on 1176 healthy postmenopausal women aged 45 years and older (mean 56 years), assigned to assess the bleeding profile of Kliovance (n=295). At baseline the Kliovance patients had been period free for a mean of 7 years. Bleeding data for each day was recorded as either no bleeding or spotting, bleeding or spotting. In Case AUTH/1417/2/03 the Panel had considered it was clear from the definitions given by Archer *et al*, that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The results showed that 72.7% of patients on Kliovance had no bleeding at cycle 2.

Archer *et al* (1994) had assessed the bleeding patterns in 1724 postmenopausal women taking two continuous combined and two sequential regimens of conjugated oestrogens and medroxyprogesterone acetate and conjugated oestrogens alone. 338 patients were randomised to the Premique group, their mean age was 54 years and the mean time since last menses was 5.3 years. Bleeding and spotting were defined as vaginal bleeding that did or did not, respectively, required sanitary protection. For the analysis of data amenorrhea was defined as the absence of any bleeding or spotting during the entire 28 day medication cycle.

Novo Nordisk submitted that whilst the exact methodology, patient populations etc in the two studies were not identical (although the main author was the same and the methodology was similar) Wyeth's objection, taken to its logical conclusion, meant that no studies could ever be compared unless they were conducted in the exact same population of patients at the exact same time – an impossible scenario. Indeed if this were the case one would never be able to conduct a meta-analysis which accumulated the results of many separate studies together and large databases of trials such as the Cochrane Database would be somewhat useless! Novo Nordisk submitted that these studies, clearly depicted as being separate, were similar enough to bear comparison and it took particular care on this point, especially with regard to the definition of amenorrhoea (no bleeding or spotting at all) which was similar in both trials. Therefore Novo Nordisk did not consider that the comparison was unfair or misleading.

Novo Nordisk noted that Wyeth had used a quotation from Archer and Pickar to support its argument: 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. Novo Nordisk however challenged Wyeth's use of this quotation since in this case the bleeding pattern being compared, ie amenorrhoea, had a similar definition in both studies. This quotation presumably referred to the comparison of studies which defined amenorrhoea differently and therefore was irrelevant to this particular case. Wyeth had incorrectly extrapolated from this quotation, it certainly had not stated that data from different trials should not be compared when comparisons were sensible as in this case.

Novo Nordisk submitted that in order for physicians to practise evidence-based medicine and for bodies such as the National Institute for Clinical Excellence to operate effectively, it was essential that the pharmaceutical industry was upfront with its data. Sensible comparisons between data of different trials must be allowed in order to advance medical science and justify to an ethical standard the purpose of these very trials in the first place. This should not be actively prohibited by one company because its product had not come out favourably and there was no commercial advantage. Novo Nordisk submitted that in this instance it was Wyeth's behaviour which discredited and reduced confidence in the pharmaceutical industry and not its own.

FURTHER COMMENTS FROM WYETH

Wyeth made no further comments.

APPEAL BOARD RULING

The Appeal Board noted that the leavepiece KV/03/30 featured two consecutive claims regarding amenorrhoea. These being for Kliovance '73% of women amenorrhoeic after 2 months' referenced to Archer *et al* (1999) and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique' referenced to Archer *et al* (1994). In Case AUTH/1417/2/03 the Panel had considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote did not negate the overall impression given. The Panel had decided that the bar chart was misleading in this regard in breach of Clauses 7.2, 7.3 and 7.8.

The Appeal Board disagreed with Wyeth's submission that the comparison *per se* was the issue. Wyeth had alleged breaches of Clauses 2 and 22 and so the only matter to be considered was whether the two claims in the leavepiece constituted a breach of the undertaking given in Case AUTH/1417/2/03 which related to the depiction of the data within the same bar chart. The Appeal Board was not required to consider the validity of the comparison *per se*.

The Appeal Board considered that in the material now at issue the presentation of the data was sufficiently different to that in Case AUTH/1417/2/03 such that the leavepiece (KV/03/30) was not covered by the previous undertaking.

The Appeal Board upheld the Panel's rulings of no breach of Clauses 2 and 22. The appeal was unsuccessful.

Complaint received **15 July 2003**

Case completed **4 December 2003**

CASE AUTH/1496/7/03

CONSULTANT PSYCHIATRIST v LUNDBECK

Cipralex mailing

A consultant psychiatrist complained that a four page mailing for Cipralex (escitalopram) produced by Lundbeck was misleading on three counts. Firstly the front cover read 'Cipralex NOW RECOMMENDED FOR NHS SCOTLAND. Cipralex has recently been reviewed by the SMC [Scottish Medicines Consortium]. The SMC's final decision is that Cipralex is recommended for use within NHS Scotland'. The complainant noted that 'Recommended for use within NHS Scotland' was a quotation from the SMC Document No. 17/02 March 2003. Information in that document which was omitted in the mailing was that '… no clear benefits are demonstrated over the parent product – citalopram or other effective and cheaper agents'.

Page 3 of the mailing was headed 'Cipralex Recommended for use within NHS Scotland'. Beneath three headline claims 'Effective and well-tolerated', 'Early action' and 'Greater response rate', bullet points made claims in favour of Cipralex compared with Cipramil (citalopram) and venlafaxine XL: 'Cipralex offers earlier symptom relief than Cipramil', 'Cipralex delivers faster sustained remission than venlafaxine XL' and 'Significantly more patients achieve a ≥50%* improvement than Cipramil'. The complainant alleged that the juxtaposition of the quotation from the SMC and the claims of superiority of Cipralex were an attempt to mislead by implication. Further, claims for the superiority of Cipralex without providing the counter-interpretation of the SMC portrayed an unbalanced evaluation of the evidence. Finally, the claims of superiority for Cipralex were based on papers sponsored by Lundbeck that selectively interpreted the evidence and misrepresented its significance. None of the papers demonstrated a clinically relevant advantage for Cipralex over the comparators.

The Panel noted that the SMC Summary of Recommendation for Cipralex read 'Advice Recommended for use within NHS Scotland. REASONS FOR ADVICE Escitalopram has been shown to be as effective as citalopram in short-term use and the health economic model submitted suggests that it is also cost-effective. However, the resource usage assumptions and clinical evidence underpinning the model are not robust and no clear benefits are demonstrated over the parent product – citalopram or other effective and cheaper agents'.

The Panel noted that although the front page statements 'NOW RECOMMENDED FOR NHS SCOTLAND', '…recommended for use within NHS Scotland' and the heading on page 3 accurately reflected the SMC advice they would be read within the overall context of the mailing and so be seen to be linked to the clinical claims for Cipralex. In the Panel's view a reader would assume that the headline claims and comparative bullet points were a fair reflection of the reasons why Cipralex was recommended by the SMC. That was not so. The Panel noted the summary of the SMC's reasons for advice set out above. The Panel considered that the material was misleading. A breach of the Code was ruled.

The Panel did not consider that, as a general principle, claims for Cipralex which did not reflect the SMC recommendation were an unbalanced evaluation of the evidence *per se* as alleged by the complainant. No breach of the Code was ruled on this narrow point.

The Panel noted that the claim 'Cipralex offers earlier symptom relief than Cipramil' was referenced to Gorman *et al*, a meta-analysis of three studies which determined whether Cipralex represented an improved treatment for depression relative to Cipramil. The efficacy analysis was based on the pooled intent to treat population using both last observation carried forward (LOCF) and observed cases (OC) data.

The Panel noted that the efficacy parameters were assessed at weeks one and two and fortnightly thereafter; the Panel considered that such time intervals were too long to support a claim for early onset of action. In that regard the Panel noted that although there was a benefit for Cipralex compared with Cipramil at week 1 with regard to a reduction in Montgomery Asberg Depression Rating Scale (MADRS) score, this difference was lost by week 2 and did not reappear until week 6. The Panel further noted the study authors' caveats '… 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 Panel considered the claim overstated the data and was misleading. A breach of the Code was ruled.

Upon appeal by Lundbeck, the Appeal Board noted that although Gorman *et al* showed that Cipralex was statistically superior to Cipramil in improving the MADRS scores at week 1 (LOCF and OC) this early sign of benefit was not maintained; there was no statistically significant advantage for Cipralex compared to Cipramil again until weeks 6 (LOCF) and 8 (OC). In the Appeal Board's view the early sign of benefit at week 1 might be a rogue result given that the difference disappeared at weeks 2 and 4. The Appeal Board further noted that the between group difference at week 1 (LOCF) was only one point and it queried whether this difference was clinically meaningful particularly as there was no statistically significant difference in the Clinical Global Impressions of Improvement (CGI-I) scores at that time. (CGI-I scores were a subjective measurement dependent upon the patient's or doctor's consideration of how the patient felt. MADRS assessed ten core features of depression objectively).

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. In the Appeal Board's view the multiple comparisons weakened the statistical power.

The Appeal Board further noted that Section 4.2 of the Cipralex summary of product characteristics (SPC) stated that 'Usually 2-4 weeks are necessary to obtain antidepressant response …'. The SMC concluded that escitalopram had been shown to be as effective as citalopram in short-term use and that no clear benefits had been demonstrated over citalopram.

The Appeal Board considered that the claim 'Cipralex offers earlier symptom relief than Cipramil' had overstated the data and was misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Panel noted that the claim 'Cipramil delivers faster sustained remission than venlafaxine XL' was referenced to Montgomery *et al*, an eight week comparison of the efficacy and tolerability of Cipralex and venlafaxine XL. Patients were assessed weekly until week 4 and then fortnightly thereafter. The results showed that in terms of sustained remission statistically significantly more patients treated with Cipralex than with venlafaxine XL were in sustained remission at weeks 2, 3, 4 and 6. The study concluded that Cipralex was at least as efficacious as venlafaxine XL in the treatment of major depressive disorder and that Cipralex-treated patients reached sustained response and remission significantly faster than venlafaxine XL-treated patients. The Panel considered that the claim 'Cipralex delivers faster sustained remission than venlafaxine XL' fairly reflected Montgomery *et al*; no breach of the Code was ruled.

The Panel noted that the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' was referenced to Colonna *et al* which assessed the efficacy and tolerability of 24 weeks' treatment in primary care of Cipralex (10mg, n=85) and Cipramil (20mg, n=85) in patients suffering from moderate to severe depression. In the Panel's view the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' suggested an overall benefit for Cipralex compared with Cipramil. Although the claim reflected the results of Colonna *et al*, in the Panel's view it did not reflect the balance of the data. Gorman *et al* had included a similar patient population in a much larger study and shown no real difference between Cipralex and Cipramil. The Panel considered that the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' overstated the data, was not a fair reflection of the evidence and was misleading on this point. A breach of the Code was ruled.

Upon appeal by Lundbeck the Appeal Board agreed with the Panel and upheld the ruling of a breach of the Code.

A consultant psychiatrist complained about a four page mailing (ref 0403/ESC/511/026) for Cipralex (escitalopram) produced by Lundbeck Ltd.

The front cover read 'Cipralex NOW RECOMMENDED FOR NHS SCOTLAND. Cipralex has recently been reviewed by the SMC [Scottish Medicines Consortium]. The SMC's final decision is that Cipralex is recommended for use within NHS Scotland.' Advice within a highlighted band advised readers to visit the SMC website for the advice and to ask the Lundbeck representative for more information on Cipralex. Page 3 was headed 'Cipralex Recommended for use within NHS Scotland'. Beneath three headline claims 'Effective and well-tolerated', 'Early action' and 'Greater response rate' bullet points made comparative claims in favour of Cipralex.

The mailing was issued prior to 1 July 2003 and sent to primary and secondary care health professionals in Scotland.

COMPLAINT

The complainant noted that the statement 'Recommended for use within NHS Scotland' on both the outside and inside of the item was a quotation from the SMC Document No. 17/02 of 7 March 2003. Information in that document which was omitted in the mailing was that '… no clear benefits are demonstrated over the parent product – citalopram or other effective and cheaper agents'.

However, underneath the heading quoted from the SMC on page 3 the mailing claimed benefits over Cipramil and venlafaxine XL: 'Cipralex offers earlier symptom relief than Cipramil', 'Cipralex delivers faster sustained remission than venlafaxine XL' and 'Significantly more patients achieve a ≥50%* improvement than Cipramil'.

The complainant considered that these statements below the heading implied that the SMC recommendation was an endorsement of these claims though the opposite was the case. The claims were referenced to papers which described studies sponsored by Lundbeck. The conclusions from all of these papers were overstated in a manner that magnified possible advantages of Cipralex over the comparators. None of the papers demonstrated a clinically relevant advantage for Cipralex over the comparators.

The complainant alleged that the juxtaposing of the quotation from the SMC and the claims of superiority of Cipralex was an attempt to mislead by implication. Further, claims for the superiority of Cipralex without providing the counter-interpretation of the SMC portrayed an unbalanced evaluation of the evidence. Finally, the claims of superiority for Cipralex were based on papers sponsored by Lundbeck that selectively interpreted the evidence and misrepresented its significance. On all three grounds the complainant alleged a breach of Clause 7.2.

RESPONSE

Lundbeck had discussed and obtained agreement from the SMC to use the Cipralex advice statement of recommendation on its promotional material. The statement was taken from the SMC website and Lundbeck was careful not to imply any endorsement

by the SMC. The front cover of the mailer stated 'Cipralex NOW RECOMMENDED FOR NHS SCOTLAND'. On the cover it also explained that Cipralex had recently been reviewed by the SMC and that the above 'advice' had been given. Furthermore a statement on the cover urged readers to 'visit www.scottishmedicines.org.uk for the SMC advice and ask your Lundbeck representative for more information on Cipralex'. The statements about the recommendation and advice were factual. If readers visited the website the SMC 'advice' and 'reasons for advice' were available. The advice of the SMC following review of Cipralex was clearly stated – 'Recommended for use within NHS Scotland'. Lundbeck submitted that the advice was a stand-alone statement and that it was acceptable to reproduce this advice without necessarily reproducing the reasons for it. Details on how to access the website were given and, once in the website, details of how to access the Cipralex advice were provided. The statements used on the cover of the mailer were therefore clear, accurate, not unbalanced and therefore not in breach of Clause 7.2 of the Code.

The statements on page 3 of the mailer were obviously of a layout and design to be read as promotional claims, factually based and referenced, rather than a part of the SMC recommendations. The heading 'Cipralex Recommended for use within NHS Scotland' was solely there as a reminder of the SMC advice and not to suggest any endorsement by the SMC. Lundbeck refuted the allegation of a breach of Clause 7.2 in respect to that aspect of the complaint.

Lundbeck noted the complainant's view that certain information had been omitted from the mailing that would appear to counterbalance the company claims. The complainant had been selective in quoting from the section headed 'Reasons for advice' (ie quoting '… no clear benefits are demonstrated over the parent product – citalopram or other effective and cheaper agents'). Lundbeck presumed this was in order to suggest that 'benefits' alluded to by the SMC referred to the clinical claims made. The actual statement made by the SMC in the section 'Reasons for advice' referred to assumptions that were contained in a health economic report and model that was prepared specifically for the SMC with data pertinent to Scotland. This was clear if one read the complete second sentence of the 'Reasons for advice'. None of the above conclusions were related to any of the data referenced against the claims made subsequently in the mailer. The individual claims were fully substantiated and accurate.

The claim 'Cipralex offers earlier symptom relief than Cipramil' was referenced to a pooled analysis by Gorman *et al* (2002), published in a peer-reviewed journal and carried out in line with recommendations that such analyses constituted the top category, Level 1a, of evidence as required by bodies such as the National Institute for Clinical Excellence (NICE) and guideline development groups (Shekelle *et al* 1999). In Gorman *et al* earlier improvement in Cipralex-treated patients was observed at week 1 over both citalopram and placebo-treated patients. The results for Cipralex were statistically significant compared to citalopram and placebo when analysed by both the Observed Cases (OC) and the Last Observation Carried Forward (LOCF) intention to treat analyses. The rating measure, the Montgomery Asberg Depression Rating Scale (MADRS) looked at improvements in a variety of symptom clusters typically seen in depressive disorders. An improvement in MADRS score was therefore a measure of symptom improvement. Lundbeck submitted that the claim 'Cipralex offers earlier symptom relief than Cipramil' was thus derived from a published peer-reviewed paper, was clearly stated, unambiguous and not in breach of Clause 7.2 of the Code.

The claim 'Cipralex delivers faster sustained remission than venlafaxine XL' was referenced to a poster presented by Montgomery *et al* (2002) at the European College of Neuropharmacology Annual Meeting (ECNP), which was a peer-reviewed meeting for submitted material. The study compared the efficacy and tolerability of Cipralex versus venlafaxine XL, both flexibly dosed, over an eight-week study period. The overall result was of similar efficacy in the primary measure with various differences in secondary parameters. 'Cipralex … as effective as venlafaxine XL' appeared clearly prior to mention of the subsequent claim 'Cipralex delivers faster sustained remission than venlafaxine XL'. Lundbeck noted that patients treated with Cipralex achieved sustained remission significantly earlier than venlafaxine XL-treated patients (6.6 days earlier, $p<0.001$). Sustained remission was where patients achieved a reduction of their MADRS score to below 12 and maintained the achievement from that time point to the end of the study. Additionally patients treated with Cipralex had significantly better sustained response than venlafaxine-treated patients and also better tolerability. The claim 'Cipralex delivers faster sustained remission than venlafaxine XL' was therefore accurate, not unbalanced and consistent with the results of the comparator study and Lundbeck refuted any breach of Clause 7.2 of the Code.

In relation to the claim 'Significantly more patients achieve a ≥50% improvement than Cipramil', Lundbeck noted that the management of depression could be assessed in different phases of treatment. The initial phase, usually 6-8 weeks, looked at the acute response to treatment. The assessment of response at 8 weeks was used to decide on further management for the continuation phase (such as need to titrate, change, augment or continue medication). The continuation phase was often for a period of 4-6 months to prevent relapse of the depressive episode (WHO consensus statement, Pharmacotherapy of depressive disorders, 1989). Colonna *et al* (2002) was presented as a poster by at the International Federation of Mood and Anxiety Disorders (IFMAD) meeting, at which poster presentations were peer-reviewed. The study used the most commonly prescribed dose of citalopram (20mg) versus Cipralex (10mg) in fixed doses over a 6-month period in line with current treatment guidelines, and was the only study with this dosing regimen. The poster, used as a reference for this claim, described data from the subset of patients who were moderately depressed (MADRS score < 30). This was the patient type most

frequently seen in primary care and consequently of greatest interest to GPs, who were the majority audience of this mailing. The assessment at the eight-week time point was made to look for comparative efficacy after the acute treatment phase and prior to the continuation of longer-term treatment.

Colonna *et al* confirmed that Cipralex-treated patients were consistently better over Cipramil-treated patients in terms of improvement in MADRS scores, with significant benefit at weeks 6, 8, 16 and 24 (LOCF analysis) and significantly better response (≥50% reduction from baseline MADRS score) at weeks 6, 8, 10, 12 and 16 and numerically superior at all other time points. The claim, therefore, was accurately represented and explained in the adjacent footnote [from MADRS baseline, in moderately depressed patients at week 8]. Lundbeck denied that this claim was in breach of Clause 7.2 of the Code.

The complainant cast doubt on Lundbeck-sponsored studies and Lundbeck's interpretation of results from these studies. All the studies were randomised, double-blind, comparator studies done to the highest standards of Good Clinical Practice (GCP). The publications were either in peer-reviewed journals or presented at peer-reviewed meetings. Lundbeck utterly repudiated the insinuation that its sponsorship of these studies compromised their quality and invalidated the conclusions that could be drawn from them.

In conclusion Lundbeck denied any breaches of the Code as it had agreement from the SMC to quote its advice and it had made clear, accurate and robust claims from properly conducted studies.

PANEL RULING

The Panel noted that the SMC Summary of Recommendation for Cipralex read 'Advice Recommended for use within NHS Scotland. REASONS FOR ADVICE Escitalopram has been shown to be as effective as citalopram in short-term use and the health economic model submitted suggests that it is also cost-effective. However, the resource usage assumptions and clinical evidence underpinning the model are not robust and no clear benefits are demonstrated over the parent product – citalopram or other effective and cheaper agents.'

The Panel noted that the front page statements 'NOW RECOMMENDED FOR NHS SCOTLAND', '…recommended for use within NHS Scotland' and the heading on page 3 were an accurate reflection of the SMC advice. The Panel considered that the statements would not be read in isolation but within the overall context of the mailing and were thus inextricably linked to the clinical claims about Cipralex. In the Panel's view a reader would assume that the headline claims and comparative bullet points were a fair reflection of the reasons why the medicine was recommended by the SMC. That was not so. The Panel noted the summary of the SMC's reasons for advice set out above. The Panel considered that the material was misleading. A breach of Clause 7.2 was ruled. This ruling was not appealed.

The Panel did not consider that, as a general principle, claims for Cipralex which did not reflect the SMC recommendation were an unbalanced evaluation of the evidence *per se* as alleged by the complainant. The reasons for the SMC advice were based on a health economic model and not on the generality of the literature. No breach of Clause 7.2 was ruled on this narrow point. This ruling was not appealed. The Panel noted, however, that such claims could not be considered in isolation but within the overall context of the promotional item. The Panel noted its comments and ruling above on this point.

The Panel noted that the claim 'Cipralex offers earlier symptom relief than Cipramil' was referenced to Gorman *et al*, a meta-analysis of three studies which determined whether Cipralex (10-20mg / day, n=520) represented an improved treatment for depression relative to Cipramil (20-40mg / day, n=403). The efficacy analysis was based on the pooled intent to treat population using both LOCF and OC data. Cipralex was statistically significantly superior to Cipramil in improving MADRS scores at week 1 in both LOCF and OC analysis and week 6 in LOCF analysis, and week 8 in OC analysis. With regard to mean changes in MADRS, Cipralex produced statistically significant improvement relative to placebo after 1 week of treatment and that was maintained at every study visit. Cipramil was not statistically superior to placebo until week 4. In relation to the clinical global impression of improvement (CGI-I) Cipralex produced statistically significant improvements compared to Cipramil at weeks 4 and 6 using OC analysis. Cipralex produced significant improvement in CGI-I scores compared with placebo treatment from week 1 onward. Cipramil improved CGI-I scores compared to placebo reaching statistical significance at week 4 and this was maintained to endpoint. The Panel noted Gorman *et al* stated that 'This pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset of action and magnitude of antidepressant effect'. The study authors also noted '… 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 …' (emphasis added). The Panel considered that these were cautious statements.

The Panel noted that the efficacy parameters were assessed at weeks 1 and 2 and fortnightly thereafter; the Panel considered that such time intervals were too long to support a claim for early onset of action. In that regard the Panel noted that although there was a benefit for Cipralex compared with Cipramil at week 1 with regard to a reduction in MADRS score this difference was lost by week 2 and did not reappear until week 6. The Panel further noted the study authors' caveats regarding onset of action. The Panel considered the claim overstated the data and was misleading. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that the claim 'Cipramil delivers faster sustained remission than venlafaxine XL' was referenced to Montgomery *et al*, an eight week, randomised, double-blind study (n=288) designed to

compare the efficacy and tolerability of Cipralex (10-20mg) and venlafaxine XL (75-150mg). Patients were assessed weekly until week 4 and then fortnightly thereafter. The results showed that in terms of sustained remission statistically significantly more patients treated with Cipralex than with venlafaxine XL were in sustained remission at weeks 2, 3, 4 and 6. The study concluded that Cipralex was at least as efficacious as venlafaxine XL in the treatment of major depressive disorder and that Cipralex-treated patients reached sustained response and remission significantly faster than venlafaxine XL-treated patients. The Panel considered that the claim 'Cipralex delivers faster sustained remission than venlafaxine XL' was a fair reflection of Montgomery *et al*; no breach of Clause 7.2 was ruled. This ruling was not appealed.

The Panel noted that the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' was referenced to Colonna *et al* which assessed the efficacy and tolerability of 24 weeks' treatment in primary care of Cipralex (10mg, n=85) and Cipramil (20mg, n=85) in patients suffering from moderate to severe depression. The study was a non-inferiority study designed to show similarity between the two medicines. Analyses presented as LOCF, were undertaken on the intention to treat population and a subset of moderately ill patients. The medicines were similarly effective for severely ill patients. In moderately depressed patients Cipralex achieved a statistically significant reduction in the mean MADRS total score compared to Cipramil at weeks 6, 8, 16 and 24. The between group difference in the number of moderately depressed patients with a = 50% reduction in MADRS total score was statistically significant at weeks 6 and 8 ($p<0.01$) and weeks 10, 12 and 16 ($p<0.05$). The Panel noted that there was no statistically significant difference between the treatment groups at weeks 1, 2, 4, 20 and 24 (endpoint).

In the Panel's view the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' suggested an overall benefit for Cipralex compared with Cipramil in the treatment of depression. Although the claim reflected the results of the study to which it was referenced (Colonna *et al*) in the Panel's view it did not reflect the balance of the data. Gorman *et al* included a similar patient population to that studied by Colonna *et al* (the entry criteria for both included a minimum MADRS score of 22) and was a much larger study. Gorman *et al* had shown no real difference between Cipralex and Cipramil. The Panel considered that the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' overstated the data, was not a fair reflection of the evidence and was misleading on this point. A breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY LUNDBECK

In relation to the claim 'Cipralex offers earlier symptom relief than Cipramil' Lundbeck submitted that the mechanistic understanding of depression suggested that it was caused by a deficiency of neurotransmitters in the brain coupled with a change in functioning of the receptors of these neurotransmitters. Serotonin, the levels of which Cipralex increased, was one such neurotransmitter. In the treatment of depression, due to various adaptive effects, antidepressants might show gradual onset of action before optimal effect was obtained. This could be up to 3 weeks (Leonard, 2000; Nutt *et al*, 1999), and so the disparity between commencement of treatment and therapeutic effect was widely recognised. Lundbeck submitted that Cipralex consistently demonstrated a significantly earlier benefit in terms of symptom relief MADRS change compared to Cipramil and placebo. In Gorman *et al* this benefit could be seen as early as week 1 in both OC and LOCF analyses. This was shown in both the general population and the subset of patients with severe depression (MADRS score ≥30).

Lundbeck submitted that the MADRS was a well recognised rating instrument for clinical trials in depression. The scale rated the change/improvement in symptoms in patients being treated for depression and allocated a score. An improvement in a patient's MADRS score indicated an improvement in symptoms of depression. Furthermore, preclinical studies (Sanchez *et al*, Papp *et al* and Montgomery *et al*) had consistently demonstrated the earlier onset of action of Cipralex vs Cipramil and other antidepressants, and these models were highly predictive of clinical effects. The basis for the treatment of depression with serotonergic compounds such as Cipralex was the elevation in levels of serotonin in the brain. Lundbeck submitted that Cipralex also produced significantly more extracellular levels of serotonin than racemic citalopram (Mørk *et al*). There was clear emerging evidence that escitalopram, when given alone, produced higher levels of serotonin than escitalopram given in combination with the R-enantiomer as racemic citalopram (Cipramil). The R-enantiomer negatively influenced the effects of escitalopram.

Lundbeck submitted that in a disease area where traditional treatments might take weeks to show benefit, the early symptom relief (reduction in score from baseline MADRS) seen after one week was a positive benefit to patients and the data confirmed these findings and the claim.

The statement by Gorman *et al*, which the Panel had considered cautious, was due to the fact that the authors were discussing both onset and the magnitude of effect rather than just speed of onset alone. The speed of onset or improvement in symptoms was apparent from both LOCF and OC analyses. Lundbeck submitted that the conclusion, therefore, that 'Cipralex offers earlier symptom relief than Cipramil' was an accurate reflection of the data and was not in breach of Clause 7.2 of the Code.

Lundbeck submitted that the claim 'Significantly more patients achieved a ≥50% improvement than Cipramil' reflected data from a fixed dose study of Cipralex 10mg compared with Cipramil 20mg. Gorman *et al* compared pooled doses of Cipralex (10-20mg) with pooled doses of Cipramil (20-40mg). Because of this one might think the conclusions could differ. Lundbeck submitted that the results from Gorman *et al* showed that the response rate (defined as ≥50% improvement from baseline MADRS score)

for Cipralex was 59.3% and Cipramil 53.4%. Although only the significance values compared to placebo were included in the publication, Cipralex was also statistically significant as compared to Cipramil for the parameter of response ($p < 0.05$, data on file). In Lepola *et al* (2003), a flexibly dosed study, Cipralex treated patients had a significantly better response than those treated with Cipramil – 63.7% vs 52.6% respectively, $p < 0.05$.

Lundbeck submitted that in conclusion the Panel had in its ruling verified the accuracy of the referenced claim noted above, but contrary to its assumptions from the data in Gorman *et al* the data showed that at pooled doses as well as flexible doses (Lepola *et al*) Cipralex had been shown to be statistically significantly better than Cipramil in the clinically meaningful measure of 'response' (defined as ≥50% reduction from baseline MADRS score). Lundbeck therefore submitted that it was not overstating the data, the claim was a fair reflection of the data and had been accurately represented (as verified by the Panel) and was therefore not in breach of Clause 7.2 of the Code.

Lundbeck noted that in respect of the first claim the Panel had alluded to the 'cautious' wording of Gorman *et al* in its ruling of a breach of Clause 7.2. Lundbeck further noted that Gorman *et al* concluded that 'this pooled analysis consistently showed escitalopram to be superior to citalopram in terms of onset and magnitude of antidepressant effect'. With regard to the second claim however the Panel considered the findings of Gorman *et al* sufficiently robust to find against the improvement claim based on Colonna *et al*. Lundbeck had difficulty in reconciling this apparent inconsistent use of Gorman *et al*.

Lundbeck submitted that with regard to both claims, results from a very recent meta-analysis including data from all trials, in which both escitalopram and citalopram were included as treatment arms, had been accepted for publication. It analysed the three studies contributing to Gorman *et al* plus the short-term data from Colonna *et al* and concluded that in terms of treatment response rates (≥50% reduction from baseline MADRS score) for escitalopram versus citalopram the odds ratio was 1.35 ($CI_{95\%}$ of 1.09-1.70) which was statistically significant ($p=0.01$) in favour of escitalopram. Furthermore the mean change from baseline in MADRS total score was significantly greater for escitalopram-treated patients than for citalopram-treated patients as early as week 1 of treatment (estimated difference of 0.63; $CI_{95\%}$ of 0.08-1.17; $p=0.02$). Lundbeck noted that for this analysis a difference greater than 0 favoured escitalopram; a confidence interval not including 0 indicated a statistically significant difference with $p < 0.05$).

In conclusion Lundbeck submitted that all of these findings confirmed the benefits of treatment with escitalopram versus citalopram in terms of earlier symptom relief and response rate and in the light of the information provided it requested that the Appeal Board reverse the Panel's rulings.

COMMENTS FROM THE COMPLAINANT

The complainant agreed with the Panel's ruling that the claim 'Cipralex offers earlier symptom relief than Cipramil' had overstated the data and was misleading. The complainant alleged that although Gorman *et al* had used the methodology of a meta-analysis it was not a true meta-analysis. It was based on the observation that a result that had not reached statistical significance in three studies but when the data was pooled to provide a sample of larger size and hence greater statistical power, statistical significance was achieved. This did not justify Lundbeck's claim that Cipralex offered earlier symptom relief than Cipramil. This was not a statement based on clinical significance but relied on statistical artefact as was the claim 'Significantly more patients achieved ≥50% improvement than Cipramil'.

APPEAL BOARD RULING

The Appeal Board noted that the efficacy assessments in Gorman *et al* included the MADRS score and the CGI-I scale. Lundbeck's representatives explained that the MADRS score was an objective measure which assessed ten core features of depression. A patient's CGI-I score was more subjective and was dependent upon the patient's or doctor's consideration of how the patient felt. The Appeal Board noted that although Gorman showed that Cipralex was statistically superior to Cipramil in improving MADRS scores at week 1 (LOCF and OC) this early sign of benefit was not maintained; there was no statistically significant advantage for Cipralex compared to Cipramil again until weeks 6 (LOCF) and 8 (OC). In the Appeal Board's view the early sign of benefit at week 1 might be a rogue result given that the difference disappeared at weeks 2 and 4. The Appeal Board further noted that the between group difference at week 1 (LOCF) was only 1 point and it queried whether this difference was clinically meaningful particularly as there was no statistically significant difference in CGI-I scores at that time.

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. In the Appeal Board's view the multiple comparisons weakened the statistical power.

The Appeal Board further noted that Section 4.2 of the Cipralex summary of product characteristics (SPC) stated that 'Usually 2-4 weeks are necessary to obtain antidepressant response …'. The SMC concluded that escitalopram had been shown to be as effective as citalopram in short-term use and that no clear benefits had been demonstrated over citalopram.

The Appeal Board considered that the claim 'Cipralex offers earlier symptom relief than Cipramil' had overstated the data and was misleading. 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.

In the Appeal Board's view the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' suggested an overall benefit for Cipralex compared with Cipramil in the treatment of depression. Although the claim reflected the results of the study to which it was referenced (Colonna *et al*) in the Appeal Board's view it did not reflect the balance of the data. Gorman *et al*, a much larger study, had included a similar patient population to that studied by Colonna *et al* and had shown no real difference between Cipralex and Cipramil. The Appeal Board considered that the claim 'Significantly more patients achieve a ≥50%* improvement than Cipramil' overstated the data, was not a fair reflection of the evidence and was misleading on this point. 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.

Complaint received **17 July 2003**

Case completed **12 November 2003**

CASE AUTH/1497/7/03

HOSPITAL PHARMACIST v AMGEN

Neulasta leavepiece

A hospital pharmacist alleged that claims in a Neulasta (pegfilgrastim) leavepiece issued by Amgen were misleading.

The claim 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia' was referenced to Green *et al* (2003) and appeared above a graph showing that the incidence of febrile neutropenia in Neulasta-treated patients was 11% whilst in filgrastim-treated patients it was 19%. The complainant noted, however, that Green *et al* showed that the difference between filgrastim and Neulasta was not significant and concluded that they were comparable.

The Panel noted that Green *et al* had shown that over the study period of four cycles of chemotherapy, 13% of Neulasta-treated patients experienced febrile neutropenia compared with 20% of filgrastim-treated patients; there was no statistically significant difference between the two groups. The Panel considered that it was thus misleading to reference the claim to Green *et al*. Breaches of the Code were ruled. The Panel noted Amgen's submission that the correct reference should have been Siena *et al*.

The claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' appeared on the same page as the claim considered above, and was referenced to Siena *et al* which was a combined analysis of two trials where there was a significant benefit. The majority of patients in the study received a variable dose of Neulasta rather than the fixed dose which was licensed in the UK.

The Panel noted that Siena *et al* was a meta-analysis of two studies comparing Neulasta and filgrastim: Green *et al* (n=157), which used Neulasta as licensed in the UK ie a fixed 6mg dose, and Holmes *et al* (n=310) in which Neulasta was administered in a dose of 100mcg/kg bodyweight. Green *et al* showed no difference in the incidence of febrile neutropenia between the two products whereas Holmes *et al* demonstrated that across four cycles of chemotherapy febrile neutropenia occurred less often in Neulasta-treated patients than in those treated with filgrastim (9% vs 18% respectively; p=0.029). The meta-analysis of the two studies in which, as submitted by Amgen, just over half (114/226) of the patients were given the UK licensed dose of Neulasta 6mg, showed that the risk of febrile neutropenia was statistically significantly lower (11% vs 19% respectively; p<0.05) in patients receiving Neulasta than in those receiving filgrastim.

The Panel noted that the Neulasta summary of product characteristics (SPC) included a brief description and the results of Green *et al* and Holmes *et al*. No reference was made to Siena *et al*.

In the Panel's view readers would assume that the injection of Neulasta referred to in the claim was a fixed 6mg dose as licensed in the UK. This was not so. The results referred to were taken from Siena *et al* in which almost half of the patients had received a dose other than 6mg. The Panel accepted that although the results of Holmes *et al* were referred to in the Neulasta SPC so too was information regarding the dose (100mcg/kg bodyweight), thus allowing readers to put the results into a clinical context. The Panel noted Amgen's submission regarding the equivalence of a 6mg dose and a 100mcg/kg dose but nonetheless considered that promotional claims for Neulasta must relate to its use as licensed in the UK. In that regard the Panel considered that the claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' was misleading. Breaches of the Code were ruled.

Upon appeal by Amgen, the Appeal Board noted that Siena *et al* was a combined analysis of the data from two pivotal trials, Holmes *et al* and Green *et al*, to evaluate the efficacy and safety of a single once-per-cycle injection of Neulasta compared with daily injections of filgrastim during multi-cycle chemotherapy. Both studies were of a size to

support the conclusion of non-inferiority of Neulasta to filgrastim; they were not designed to prove the superiority of Neulasta. In the discussion section of Siena *et al* the authors noted that although the clinical results for febrile neutropenia were impressive and appeared consistent across both studies, they should be considered hypothesis generating and that the scientific rationale for the apparent superior efficacy observed required further investigation. Some members of the Appeal Board expressed concern as to the validity of the Siena *et al* analysis.

The Appeal Board noted that the Neulasta SPC referred to Holmes *et al* and Green *et al* as pivotal studies. The dose of pegfilgrastim used in each study was clearly stated as either a 6mg fixed dose or 100mcg/kg weight-adjusted dose, along with the outcome of each. The results were presented separately and there was no reference to Siena *et al*.

The Appeal Board did not consider that an unequivocal claim about superiority could be supported by pooled data from two non-inferiority studies. Siena *et al* was cautious about the significance of the febrile neutropenia results. Conversely Amgen had presented the superiority of Neulasta vs filgrastim as an absolute. The Appeal Board considered that the claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily GCSF (filgrastim) injections' was thus misleading and upheld the Panel's rulings of breaches of the Code.

A hospital pharmacist complained about a Neulasta (pegfilgrastim) leavepiece (ref 2231/320/UK/0203) issued by Amgen Limited.

1 Claim 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia'

This claim was referenced to Green *et al* (2003) and appeared above a graph showing that the incidence of febrile neutropenia in Neulasta-treated patients was 11% whilst in filgrastim-treated patients it was 19%.

COMPLAINT

The complainant noted that the claim was referenced to Green *et al*. However the difference between filgrastim and Neulasta was not significant and the paper concluded that they were comparable. It was alleged that the claim was misleading.

The Authority asked Amgen to respond in relation to the requirements of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Amgen stated that a typographical error had occurred with respect to the reference quoted. The reference used to support the claim should have been Siena *et al* from which the data illustrated in the graph was taken. A review of all other promotional materials had shown that this was the only such occurrence of misreferencing; the error had been corrected.

Amgen considered that the claim 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia' was supported by Siena *et al* and would therefore comply with Clauses 7.2 and 7.3 of the Code when correctly referenced.

PANEL RULING

The Panel noted that the claim 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia' was referenced to Green *et al* which had concluded that the two products were comparable. Over the study period of four cycles of chemotherapy, 13% of Neulasta-treated patients experienced febrile neutropenia compared with 20% of filgrastim-treated patients. The incidence of febrile neutropenia was not statistically significantly different between the two groups. The Panel considered that it was thus misleading to reference the claim to Green *et al*. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted Amgen's submission that the correct reference should have been Siena *et al*. The Panel considered the Siena *et al* study in point 2 below.

2 Claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections'

This claim was referenced to Siena *et al* (in press). Amgen provided a copy of the published paper which had appeared in Oncology Reports (2003).

COMPLAINT

The complainant noted that Siena *et al* was a combined analysis of two trials where there was a significant benefit. The majority of patients in the study received a variable dose of Neulasta rather than the fixed dose which was licensed in the UK. The complainant alleged that the claim was misleading.

The Authority asked Amgen to respond in relation to the requirements of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Amgen explained that Siena *et al* was a meta-analysis of two phase III pivotal trials, Holmes *et al* (2002) which used Neulasta at 100mcg/kg bodyweight and Green *et al* (2003) in which a fixed dose, 6mg, of Neulasta was administered. Amgen divided its response into three sections.

Is a dose of 100mcg/kg of Neulasta clinically equivalent to a 6mg fixed dose?

Amgen stated that in consideration of this question, it was necessary to understand a few principles that underpinned the calculation of appropriate doses and why these principles were not applicable to Neulasta. Generally, with small molecule medicines, it was considered that a 100mcg/kg dose was equivalent to a 6mg fixed dose only when the subject weighed 60kg. This conclusion rested on a number of important assumptions about the relationship between dose administered, biological effect and removal of the medicine from the body ie the pharmacokinetics of the medicine.

For the vast majority of medicines, the biological effect and rate of clearance were dependent primarily on the concentration of the medicine in the body. This mathematical relationship between concentration, biological effect and clearance allowed an appropriate dose and administration interval to be calculated (allowing for an appropriate degree of variation in response and clearance in different individuals).

These assumptions did not hold true with regard to the pharmacokinetics of Neulasta, which had a unique 'self-regulating' mechanism of clearance. In order to explain this further Amgen reviewed the biological effect of filgrastim (G-CSF, a protein growth factor) and its mechanism of clearance.

Filgrastim (and also Neulasta) stimulated the production of neutrophils and neutrophil precursors from stem cells located mainly in the bone marrow. Clearance of filgrastim from the body was understood to occur via two main mechanisms; renal clearance and removal by neutrophils and neutrophil precursors (cell types to which G-CSF bound via a specific receptor to exert its biological action).

Neulasta was manufactured by attaching a polyethylene glycol (PEG) molecule to filgrastim. By adding PEG the overall size of the molecule was increased and renal clearance eliminated. This left removal by neutrophils and neutrophil precursors as the primary route of clearance for Neulasta. Therefore during periods of low neutrophil count (neutropenia), Neulasta serum levels remained high. When the neutrophil count returned to normal, Neulasta was rapidly cleared.

A common side effect of chemotherapy was that neutrophils were damaged and neutrophil production reduced. Neulasta was given after chemotherapy to stimulate more rapid replacement of neutrophils. The initial dose of Neulasta saturated the neutrophil mediated clearance mechanism, reducing clearance to a minimal rate. This meant that serum levels of Neulasta then remained high until a new generation of neutrophils was produced (having been stimulated by high levels of Neulasta). This prolonged elevated serum level of Neulasta meant that it only needed to be dosed once per chemotherapy cycle.

Because the clearance mechanism became saturated, clearance of Neulasta was not related to either dose or time in the same manner as the majority of pharmaceuticals. In fact the serum clearance of Neulasta decreased as dose increased, the reverse of the expected relationship. Amgen referred to Section 5.2 of the Neulasta summary of product characteristics (SPC).

Thus the clearance of Neulasta did not conform to the principles outlined above and conventional rules regarding dose comparisons were also inappropriate. Doses of either 100mcg/kg or fixed 6mg were both in excess of that required to saturate the clearance mechanism and thus produced equivalent biological effects, regardless of the bodyweight of the patient.

Based on knowledge of this unique mechanism of clearance, the Neulasta clinical development programme contained two pivotal phase III studies. One with a fixed 6mg dose (Green *et al*) and one with a weight based 100mcg/kg dosage regimen (Holmes *et al*) of Neulasta. Both were randomised, double-blind, multi-centre studies. This approach was adopted to demonstrate to the regulatory authorities that both of these regimens were clinically equivalent to daily filgrastim at a weight based dose, in terms of the efficacy of reducing the duration of severe neutropenia (DSN) in the first cycle of chemotherapy. The DSN in cycle 1 was the primary end point for both pivotal studies.

The results from these two pivotal studies had been published in well respected peer reviewed journals. In both the 100mcg/kg dose regimen and the 6mg fixed dose studies Neulasta was shown to be clinically equivalent to daily filgrastim in reducing DSN in cycle 1, the primary endpoint. The US and European regulatory authorities were satisfied that the two dosage regimens were clinically equivalent in terms of reducing DSN to a daily weight based filgrastim regimen. Both dosage regimens were mentioned in Section 5.1 of the Neulasta SPC, as were the results of the primary endpoint for both trials.

It was clearly noted in the Neulasta EPAR (European Public Assessment Report) that no significant association was seen between patient weight and efficacy. This again supported the clinical equivalence of the 6mg fixed dose and 100mcg/kg weight based dose regimen.

The consistent clinical efficacy, regardless of patient weight, seen with both of the dose regimens of Neulasta was entirely predictable when the clearance mechanism explained above was taken into account.

In summary, the clinical equivalence of the two dose regimens of Neulasta was based on a unique mechanism of clearance, that;

a) appeared to be dependent on the neutrophil count – the serum concentration of Neulasta remained high during periods of neutropenia, but declined rapidly at the onset of neutrophil recovery.

b) was non-linear with respect to dose administered, becoming lower at higher doses of Neulasta as clearance was saturated. Doses of either 100mcg/kg or 6mg both appeared to saturate the clearance mechanism.

The clinical equivalence of the two dose regimens was further supported by data from two high quality pivotal trials. Data on both dose regimens were submitted to and assessed by the European and American regulatory authorities to support the licence application. This was reflected in the fact that the efficacy data from both trials and the dosage regimens used were explicitly stated within the Neulasta SPC.

Does the clinical data support the fact that 'A single dose of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' and that 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia'?

Whilst both dose regimens of Neulasta demonstrated clinical equivalence to daily filgrastim in terms of reducing DSN in cycle 1, there was a reduction in the incidence of febrile neutropenia when Neulasta, given as either dose regimen, was compared to daily

filgrastim. The incidence of febrile neutropenia was a pre-specified secondary end-point in both pivotal studies. Given that the primary statistical objective of both pivotal studies was met and the prospective intent to evaluate the incidence of febrile neutropenia, this analysis was a valid undertaking.

An absolute reduction in the incidence of febrile neutropenia of similar magnitude was observed in both pivotal studies. The reductions in febrile neutropenia achieved by both doses of Neulasta (100mcg/kg or 6mg) compared to daily filgrastim were also recorded in Section 5.1 of the Neulasta SPC.

In the 100mcg/kg weight based study (Holmes *et al*) there was a statistically significant reduction in the incidence of febrile neutropenia with Neulasta compared to daily filgrastim (p=0.029). A similar reduction in the incidence of febrile neutropenia was also noted with the 6mg fixed dose study (Green *et al*), but this did not reach statistical significance largely due to the considerably smaller sample size.

It was therefore not surprising that the meta-analysis based on these two trials confirmed a clinically and statistically significant reduction in the incidence of febrile neutropenia with Neulasta compared with filgrastim. This finding was not in any way at odds with the results of the two individual trials. The quality of both trials and the meta-analysis were supported by the fact that they had all been published in well respected, peer reviewed journals.

Amgen submitted that, in summary, Neulasta used in either a fixed dose or weight based regimen had demonstrated a consistent reduction in the incidence of febrile neutropenia compared to filgrastim in both pivotal trials and in the meta-analysis based on these two trials.

Is a meta-analysis of the two phase III trials a scientifically valid method of supporting the claims that 'A single dose of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' and that 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia'?

Amgen stated that a meta-analysis was a method of statistically analysing the combined treatment effect of a number of similar clinical trials. This was generally undertaken to establish with greater precision and certainty the benefit of a given intervention in a given population. Whilst the construction of a meta-analysis involved a certain degree of judgement on the part of the investigator, there were well agreed principles in the identification and selection of studies for inclusion in the analysis. These principles were explained in detail in the training materials available from the Cochrane Collaboration.

The Cochrane Collaboration was an internationally respected organisation which aimed to carry out high quality systematic reviews and meta-analyses of clinical data. Module 13 of the Cochrane training course dealt with understanding the potential problems of combining trials in a meta-analysis. This module clearly highlighted that the diversity and heterogeneity of studies included in the analysis should be taken into account to ensure that the meta-analysis was valid. It proceeded to identify that sources of diversity and heterogeneity could be divided into three broad categories – clinical, methodological and statistical. Each of these factors should be critically assessed to ensure that studies included in the meta-analysis were appropriately similar. Below was a critical analysis of these factors for the two pivotal phase III Neulasta studies included in Siena *et al*.

Clinical diversity

Same population – stage II-IV breast cancer.

Same chemotherapy regimen – docetaxel and doxorubicin.

Once per cycle Neulasta administered in both trials.

Methodological diversity

Both randomised, double-blind, multi-centre trials.

Both pre-specified DSN at cycle 1 as the primary endpoint.

Both pre-specified febrile neutropenia as a secondary endpoint.

Both analysed the data as intention to treat.

Statistical diversity

No unexpected statistical diversity or treatment effect interactions were noted between the results of the 2 trials included in the meta-analysis.

Amgen submitted that from this evaluation it was clear that the studies were closely matched apart from the differences in dose regimens the objection raised by the complainant. As referred to above, Amgen considered that the unique mode of clearance, the results of two pivotal trials and the Neulasta SPC supported the clinical equivalence of a 6mg fixed dose and a 100mcg/kg weight based dose.

Amgen stated that it had established that in the 100mcg/kg weight based study (Holmes *et al*) 37 patients, that is those who weighed between 55 and 65kg, would have received a dose of 6mg, rounded to the nearest whole milligram (ie 6mg ± 0.5mg). This meant that in the meta-analysis by Siena *et al*, 114 patients (77 from Green *et al* and 37 from Holmes *et al*) out of the total of 226 received a dose of 6mg of Neulasta ie just over 50% of patients evaluated.

From the information above it was clear that in all respects the Siena *et al* meta-analysis was scientifically valid. Careful comparison of the two trials revealed that they explored the effect of the same medicine, given at a clinically equivalent dose, in well matched populations, with identical methodological design. This conclusion was supported by the fact that the analysis was published in a well respected, peer reviewed journal.

This meta-analysis showed that there was a clinically and statistically significant 8% absolute risk reduction in the incidence of febrile neutropenia when Neulasta was used instead of daily filgrastim. To quote from Siena *et al* 'In this analysis, a single dose of pegfilgrastim was observed to be more effective at

reducing the incidence of febrile neutropenia than daily injections of filgrastim in patients receiving myelosuppressive chemotherapy'.

This combined result was entirely consistent with the results of the two individual studies, described in the pivotal trials and included in the Neulasta SPC. Thus Amgen considered that Siena *et al* supported the statements that 'Neulasta is more effective than daily G-CSF (filgrastim) for reducing the incidence of febrile neutropenia' and that 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections.'

PANEL RULING

The Panel noted that the claim at issue 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' was referenced to Siena *et al*. Siena *et al* was a meta-analysis of two studies comparing Neulasta and filgrastim; Green *et al* (n=157) which used Neulasta as licensed in the UK ie a fixed 6mg dose, and Holmes *et al* (n=310) in which Neulasta was administered in a dose of 100mcg/kg bodyweight. Green *et al* showed no difference in the incidence of febrile neutropenia between the two products whereas Holmes *et al* demonstrated that across four cycles of chemotherapy febrile neutropenia occurred less often in Neulasta-treated patients than in those treated with filgrastim (9% vs 18% respectively; p=0.029). The meta-analysis of the two studies in which, as submitted by Amgen, just over half (114/226) of the patients were given the UK licensed dose of Neulasta 6mg, showed that the risk of febrile neutropenia was statistically significantly lower (11% vs 19% respectively; p<0.05) in patients receiving Neulasta than in those receiving filgrastim.

The Panel noted that Section 5.1, Pharmacodynamic properties, of the Neulasta SPC included a brief description and the results of Green *et al* and Holmes *et al*. No reference was made to Siena *et al*.

In the Panel's view readers would assume that the injection of Neulasta referred to in the claim was a fixed 6mg dose as licensed in the UK. This was not so. The results referred to were taken from Siena *et al* in which almost half of the patients had received a dose other than 6mg. The Panel accepted that although the results of Holmes *et al* were referred to in the Neulasta SPC so too was information regarding the dose (100mcg/kg bodyweight) thus allowing readers to put the results into a clinical context. The Panel noted Amgen's submission regarding the equivalence of a 6mg dose and a 100mcg/kg dose but nonetheless considered that promotional claims for Neulasta must relate to its use as licensed in the UK ie a 6mg fixed dose. In that regard the Panel considered that the claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF (filgrastim) injections' was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

APPEAL BY AMGEN

Amgen recognised that it was an established principle that data supporting claims should be taken from studies using the licensed dose but restated its case that the 6mg and 100mcg/kg doses of Neulasta were therapeutically equivalent, that they were considered as such during the licence application and, therefore, that the use of Siena *et al* to support the claims was valid and relevant.

The licence for Neulasta was granted by both European and US regulators based on two pivotal phase III trials. One trial utilised a 100mcg/kg dose of Neulasta and the other a fixed 6mg dose. The combination of data from both of these trials was considered prior to the granting of a licence for Neulasta.

Green *et al* used a 6mg fixed dose and showed a trend in favour of Neulasta in reducing the incidence of febrile neutropenia when compared to daily filgrastim (13% v 20% (observed difference filgrastim v Neulasta –7%; 95% CI –19%, 5%)). This was a relatively small study with 157 subjects.

Holmes *et al* evaluated 100mcg/kg in a larger study (n=310) and confirmed the findings of Green *et al* with regard to the incidence of febrile neutropenia, with a rate of 18% in the daily filgrastim group compared with 9% with Neulasta. This difference was statistically significant (observed difference –9%; 95% CI –16.8%, –1.1%).

Clearly, in Holmes *et al*, the absolute doses of Neulasta that were given varied by weight, with 80% weighing 60kg or above and thus receiving 6mg or higher of Neulasta. The possibility of the statistically significant reduction in febrile neutropenia in this study being due to higher absolute doses being administered was considered by Siena *et al*. However, the analysis of the data demonstrated that at different body weights (<60kg, 60 to 90kg and >90kg) the incidence of febrile neutropenia was similar regardless of whether the subjects had been dosed by a 6mg fixed dose or at 100mcg/kg. This demonstrated a therapeutic equivalence of effect of the different dosing schedules.

Amgen noted that Neulasta was not unique in this regard. The lenograstim SPC also referred to a therapeutic equivalence of the product dosed by either bodyweight or body surface area. Calculating the dose by the two methods generally produced two different absolute doses for the same patient.

Amgen stated that it had selected a 6mg fixed dose as the licensed dose based on equivalent efficacy and more convenient administration than 100mcg/kg. That decision did not render data obtained using a 100mcg/kg dose regimen as irrelevant to clinicians seeking to understand the clinical data supporting the efficacy of Neulasta.

Indeed, the 100mcg/kg and 6mg fixed dose regime of Neulasta used in the pivotal trials were both explicitly mentioned in the Neulasta SPC, as were the results of the primary and febrile neutropenia endpoints for both trials. For promotional materials to contain data on both the 6mg fixed and the 100mcg/kg dose regimens was thus in accordance with the terms of the Neulasta marketing authorization and consistent with the particulars listed in its SPC.

COMMENTS FROM THE COMPLAINANT

The complainant noted that although Siena *et al* showed that 'a single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily G-CSF injections' it did not show that this was true for the fixed dose regime. As the majority of patients did not receive the fixed dose the claim could not be upheld for the dose licensed in the UK. Readers expected the data to refer to the UK dose. The complainant alleged that the unqualified claim was misleading.

The Cochrane Collaboration stated 'a meta-analysis that is not a systematic review is likely to be highly biased and should be used with extreme caution or not used at all'. Siena *et al* was not a meta-analysis but a combined analysis of two sets of data. A meta-analysis would include unpublished studies to exclude publication bias. The company could not claim that Siena *et al* was a meta-analysis. It was neither referred to as a meta-analysis nor did it use the statistical techniques associated with a meta-analysis. On this basis Amgen's appeal could not be upheld. Whilst the complainant agreed that the fixed dose regime was equivalent to a variable dose regime, they were not identical. Amgen had yet to prove that Neulasta was superior to filgrastim without qualification. Siena *et al* stated that 'lighter patients (<60kg) exhibited a better response to the fixed dose, compared with a body-weight-adjusted dose (presumably due to the total dose received per body weight)'. Variations in efficacy in patients of different weights meant that the doses were not equivalent. In addition the equivalence data was based solely on these trials.

The trials were based in a small subset of the population, namely women with breast cancer receiving a particular regime. Even if the equivalence existed for these patients (of which the complainant was not convinced) they could not be applied to men. Making claims without appropriate qualification was misleading.

The complainant noted Amgen's claim that the article was published in a well-respected, peer reviewed journal. Oncology Reports was published by the University of Crete. It had an Institute of Scientific Information Impact Factor of 1.17 which placed it 89 out of 114 in oncology journals. It required authors to pay $40 for each page beyond 4 pages. It did not appear in the list of 2,212 peer reviewed journals on the Cumulative Index to Nursing and Allied Health Literature (CINAHL) or on the American Medical Association's list of peer reviewed journals. The complainant noted that Amgen did not make any claims for superiority over filgrastim on its US website. Nor did the claim appear on the US package insert. The complainant did not consider that these claims could be made on the basis of this data.

APPEAL BOARD RULING

The Appeal Board noted that Siena *et al* was a combined analysis of the data from Holmes *et al* and Green *et al* both of which were pivotal trials to evaluate the efficacy and safety of a single once-per-cycle injection of Neulasta compared with daily injections of filgrastim during multi-cycle chemotherapy. Both studies were of a size to yield 95% power supporting the conclusion of non-inferiority of Neulasta to filgrastim. The studies were not designed to prove the superiority of Neulasta. In the discussion section of Siena *et al* the authors noted that although the clinical results for febrile neutropenia were impressive and appeared consistent across both studies, they should be considered hypothesis generating and that the scientific rationale for the apparent superior efficacy observed required further investigation. Some members of the Appeal Board expressed concern as to the validity of the Siena *et al* analysis.

The Appeal Board noted that Section 5.1 of the Neulasta SPC referred to Holmes *et al* and Green *et al* as pivotal studies. The dose of pegfilgrastim used in each study was clearly stated as either a 6mg fixed dose or 100mcg/kg weight-adjusted dose, along with the outcome of each. The results were presented separately and there was no reference to the Siena *et al* data.

The Appeal Board did not consider that an unequivocal claim about superiority could be supported by pooled data from two non-inferiority studies. Siena *et al* was cautious about the significance of the febrile neutropenia results. Conversely Amgen had presented the superiority of Neulasta vs filgrastim as an absolute. The Appeal Board considered that the claim 'A single injection of Neulasta led to a lower incidence of febrile neutropenia compared to daily GCSF (filgrastim) injections' was thus misleading and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3 of the Code. The appeal was unsuccessful.

Complaint received **21 July 2003**

Case completed **11 November 2003**

CASE AUTH/1508/8/03

CLEMENT CLARKE v ASTRAZENECA

Promotion of the Turbohaler

Clement Clarke complained about a 'Dear Doctor/Asthma Nurse' letter sent by AstraZeneca in support of its Turbohaler device. A laminated card headed 'Clinically Effective Inspiratory Flow' and a sticker, similarly labelled, accompanied the letter. The letter stated that although the ln-Check Dial marketed by Clement Clarke showed that the optimum inspiratory flow rate for the Turbohaler was 60-90L/min the device was nonetheless clinically effective at inspiratory flow rates from 30L/min. The letter also discussed a previous complaint made under the Code which concerned the promotional use of the In-Check Dial.

The laminated card was for the recipient to keep with the other information on the ln-Check Dial and the sticker was to stick on the device itself. The card depicted a graduated scale from 15L/min to 120L/min. A solid band ran from 30L/min to 90L/min representing the range over which the Turbohaler was clinically effective. The sticker had a similar scale with a solid band running from approximately 25L/min up to 90L/min.

Clement Clarke noted that the letter stated 'AstraZeneca believes it is important that information provided to healthcare providers is relevant. To assist you in your use of the 'In-Check' Inspiratory Flow Meter, we attach a card and sticker for you to place beside the existing 'In-Check' information on Turbohaler. The attached stickers contain accurate information concerning the clinical effectiveness of Turbohaler'. This implied that the information supplied with the In-Check Dial was not relevant; that without the card and the stickers supplied by AstraZeneca the information provided by Clement Clarke on the Turbohaler was inaccurate and insufficient for correct clinical use of the In-Check Dial. The modification proposed by AstraZeneca was entirely inappropriate since it converted the In-Check Dial from a device that described optimum inspiratory flow for a series of products to one that referred in addition to effective inspiratory flow for the Turbohaler only.

In all of its previous dealings with AstraZeneca, Clement Clarke had emphasised the differences between effective and optimum inspiratory flow for all inhalers. The In-Check Dial was designed only to identify optimum inspiratory flow and this was the use for which it was approved. Clement Clarke could not authorise the modification proposed by AstraZeneca.

Clement Clarke alleged that the letter disparaged Clement Clarke and the In-Check Dial by suggesting that the product required modification before it could be used effectively. AstraZeneca's suggestions carried the risk of personal liability for recipients of the letter; AstraZeneca failed to warn them of such risk. Consequently, Clement Clarke alleged that the letter was likely to bring discredit upon or reduce confidence in the pharmaceutical industry, in breach of Clause 2 of the Code.

Clement Clarke noted that the letter stated 'AstraZeneca wishes to draw your attention to the fact that the chart entitled 'Optimum Inspiratory Flow', which is distributed along with Clement Clarke's 'In-Check' Inspiratory Flow Meter, does not include data which AstraZeneca considers to be relevant for clinical decision making'. The chart which was supplied with the In-Check Dial was fully referenced and supported the conclusion that inspiratory flows of 60-90L/min were optimum for the Turbohaler. AstraZeneca could not dispute that, to achieve the level of medicine deposition stated in the Turbohaler summary of product characteristics (SPC), 25-30%, the patient needed to achieve an inspiratory flow of ≥60L/min. Consequently, for AstraZeneca to state that the chart did not include data 'relevant for clinical decision making' implied that an inspiratory flow rate of 60-90L/min was not clinically relevant. Clearly, however, by reference to the Turbohaler SPC, an inspiratory flow rate of 60-90L/min was clinically relevant. Clement Clarke alleged that the statement in the letter was thus inconsistent with the SPC. A similar breach of the Code was alleged because at the flow rates stated in the letter, only half of the medicine delivery dose listed in the SPC could be expected.

It was also alleged that as the letter was a promotional mailing it was in breach because it did not include any prescribing information. The letter was also alleged to be in breach because it was not balanced or fair and, as it drew attention to the ruling in an earlier case, Case AUTH/1096/11/00, and failed to give adequate recognition for amendments made to the In-Check Dial for promotional use by pharmaceutical companies, the letter left recipients questioning whether any In-Check Dial supplied since the previous complaint was suitable for the purpose intended.

Clement Clarke also alleged that the letter was a thinly disguised attack on it and the In-Check Dial masquerading as a response to a request for further information on the Turbohaler and inspiratory flow rates. This knocking copy was particularly unjustified since it referred to the version of the In-Check Dial which was introduced in response to the rulings made in Case AUTH/1096/11/00 and the letter implied that the product had not changed since that first complaint.

The Panel noted AstraZeneca's submission that the letter was to be used by its representatives in response to questions about inspiratory flow rate and the Turbohaler. A laminated card and a sticker accompanied the letter. The Panel considered that whether the materials were provided by representatives in response to an individual enquiry or were provided unsolicited they were being used as support for the promotion of AstraZeneca's medicines. In the Panel's view, the exemption in the Code for replies made in response to individual enquiries did not apply in this case; the replies were pre-printed and distributed by AstraZeneca

representatives to support the promotion of AstraZeneca's medicines. The Panel thus considered that the materials were promotional and it made its rulings in that context.

The Panel noted that supplementary information to the Code stated that where an advertisement related to the merits of a device used for administering medicines, such as an inhaler, which was supplied containing a variety of medicines, the prescribing information for one only needed to be given if the advertisement made no reference to any particular medicine. The Panel noted that the letter related to the merits of the Turbohaler thus prescribing information was required. No prescribing information was given for any product and a breach of the Code was ruled.

The Panel noted that Clement Clarke had produced two versions of the In-Check Dial. Both showed the flow rates for a number of devices. On neither version 1 nor version 2 did the main label on the device itself refer to optimum inspiratory flow although that was what the label depicted. Both were accompanied by a laminated card headed 'Optimum Inspiratory Flow'. Version 2 had an additional sticker on the device which stated, *inter alia*, 'Flow rates outside the optimum range can still produce effective (rather than optimum) drug delivery, but pulmonary deposition of the drug may be reduced'. In the Panel's view, even with the additional sticker on version 2, it was possible for a user to assume that devices were effective only in the ranges shown ie 60-90L/min for the Turbohaler. This was not so. The Panel noted Clement Clarke's submission that the In-Check Dial was designed only to identify optimum inspiratory flow and this was the use for which it was approved. The labelling, however, showed that it could be used to demonstrate inspiratory flow rates as low as 20L/min; in the Panel's view how any of the flow rates were described with regard to the inhalers shown was a function of the labelling on the device and not of the device itself.

In relation to references in the letter to the clinical effects seen with respiratory flow rates of 30-60L/min, the Panel considered that it was important for physicians to know that the Turbohaler was optimally effective at inhalation flow rates of 60-90L/min and also that it was clinically effective from rates of 30L/min. Only knowing the optimal values did not give the complete picture with regard to inspiratory flow rates and the clinical performance of the Turbohaler. The Panel noted that none of the SPCs for AstraZeneca's Turbohalers referred to inhalation flow rates. The Pulmicort Turbohaler 100 SPC stated that about 25-30% of the metered dose was deposited in the lungs. There was no statement however to indicate that this was the minimum effective dose. Similarly the Oxis Turbohaler 12 SPC stated the mean lung deposition of formoterol (21-37%) after inhalation via the Turbohaler but did not state that such values were the minimum required for a clinical effect. The Panel did not consider that the reference to flow rates which might result in a less than optimal lung deposition of medicine was inconsistent with the Turbohaler SPCs. No breaches of the Code were ruled in that regard.

The Panel did not consider that references in the letter to previous cases were misleading and no breach of the Code was ruled in that respect. The letter was not a review of the In-Check Dial *per se*. Given the subject of the letter the Panel did not consider that failure to refer to the use of the In-Check Dial by researchers and clinicians was misleading. The Panel also did not consider that failure to acknowledge that the In-Check Dial was an independently validated and widely researched medical instrument was misleading. The letter stated that since the ruling (in previous cases) the In-Check Dial had been amended. There was thus an acknowledgement that amendments had been made and so the Panel did not consider that the letter was misleading in that regard. Further, the Panel did not consider that the letter disparaged Clement Clarke or the In-Check Dial. No breaches were ruled in these regards.

The Panel did not consider that adding information to that already supplied with the In-Check Dial, such that a health professional was made aware of the whole picture with regard to inspiratory flow rate and clinical effect, would bring discredit upon or reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

In relation to the laminated card Clement Clarke noted that the Pulmicort Turbohaler SPC stated 'About 25-30% of the metered dose is deposited in the lungs. Of the fraction which is swallowed, approximately 90% is inactivated at first passage through the liver. The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5nmol/l and is reached after about 20 minutes'. According to the Turbohaler SPC the level of drug deposition reported, 25-30%, was only achieved when the inspiratory flow through the Turbohaler was ≥60L/min. AstraZeneca acknowledged this fact on the laminated card; the third bullet read 'Doubling the PIF ['Peak Inspiratory Flow'] to 60L/min increases the lung deposition to about 30%'. However, the title of the laminated card 'Clinically Effective Inspiratory Flow' clearly referred to the prominent blue bar that was seen between flow rates of 30-90L/min and the text immediately below that 'Turbohaler is clinically effective at an inhalation flow of 30L/min and above'. The blue bar was continuous between flow rate markings of 30-90L/min and, therefore, gave the impression that the Turbohaler was effective in that range. Only after further claims (about efficacy, drug delivery and the percentage of patients who could achieve 30L/min) was it noted on the card that the 30% lung deposition referenced in the Turbohaler SPC was only achieved when the peak inspiratory flow was 60L/min. At flow rates < 60L/min, (ie the section of the blue bar between 30L/min and 60L/min), the text on the card confirmed that pulmonary deposition of the medicine would not be 25-30%. Consequently, the card was inconsistent with the particulars listed in the Turbohaler SPC.

Clement Clarke further noted that the laminated card copied the style, general layout and size of the

original design which it had created for the 'Optimum Inspiratory Flow' card supplied with the In-Check Dial. The laminated card was entitled 'Clinically Effective Inspiratory Flow' and when compared to the original 'Optimum Inspiratory Flow' card that accompanied the In-Check Dial, confused doctors, nurses and pharmacists. The In-Check Dial was designed and approved to highlight optimum inspiratory flow for each inhaler depicted. There was a clear and recognisable difference between optimum and effective and in producing and distributing the laminated card similar to the original supplied with the device AstraZeneca was likely to mislead and confuse recipients.

The Panel noted its comments above with regard to a clinically effective inhalational rate, the optimal inhalational rate and the percentage lung deposition stated in the SPCs. The Panel considered that its ruling then also applied here and no breach of the Code was ruled.

The Panel did not consider that the layout of the laminated card would confuse users of the In-Check Dial. The card had been presented in a similar style to that provided with the In-Check Dial and so users would be familiar with its format. The card clearly set out the information relating to the Turbohaler, inhalation flow rate and percentage lung deposition. The card added to the information supplied with the In-Check Dial. The Panel thus did not consider that the style of the In-Check information had been copied in a way which was likely to confuse and no breach of the Code was ruled.

In relation to the sticker, Clement Clarke noted that it featured a blue bar that was continuous between flow rate markings of 25-90L/min and, therefore suggested that the Turbohaler was consistently effective in that range. However, at flow rates < 60L/min, (ie the section of the blue bar on the sticker between 25-60L/min, the Turbohaler SPC stated that pulmonary deposition of the medicine would not be 25-30%. Clement Clarke submitted that the sticker was promotional and alleged that it was not consistent with the particulars listed in the Turbohaler SPC.

Clement Clarke stated that the sticker was neither an abbreviated advertisement nor a promotional aid. The sticker did not include prescribing information and a breach of the Code was alleged. It was clear from the sticker that the scale adopted by AstraZeneca to distance the lines identifying flow rates of 20-120L/min corresponded exactly to the scale adopted by Clement Clarke in the original labelling on the In-Check Dial. This could easily be demonstrated by placing the sticker alongside the existing In-Check Dial's scale. AstraZeneca intended to encourage recipients to stick the sticker directly onto the In-Check Dial, thereby modifying the device. AstraZeneca's presentation of the sticker closely mimicked the layout originated and currently used by Clement Clarke on the In-Check Dial. There was a consequent risk of health practitioners being confused and misled.

The Panel noted that the sticker was labelled 'Clinically Effective Inspiratory Flow' and showed a solid blue band from approximately 26L/min up to 90L/min. The Panel noted its comments above with regard to the clinically effective inhalational flow rate, the optimum inhalational flow rate and the percentage lung deposition stated in the Turbohaler SPCs. The Panel did not consider that depicting flow rates of < 60L/min was inconsistent with the SPCs as alleged and no breach of the Code was ruled.

The sticker did not bear any product name although it did have on it a stylised diagram of a Turbohaler. The Panel noted AstraZeneca's submission that the sticker was not a promotional item and its own comments above regarding the promotional nature of the material. The Panel considered that the sticker was a promotional aid. It was inexpensive and, given its intended use, relevant to the practice of medicine. The sticker was thus exempt from the requirement to carry prescribing information and no breach of the Code was ruled.

The sticker presented information in a similar style to that on the label of the In-Check Dial and so users would be familiar with its format. The sticker was clearly labelled 'Clinically Effective Inspiratory Flow'. The Panel did not consider that users would be misled into thinking that the information supplied by Clement Clarke was incorrect and that the sticker was an update to rectify the error. The application of the sticker meant that the In-Check Dial would carry additional clinically relevant information about the Turbohaler to that which had been supplied by Clement Clarke. The Panel did not consider that users would be confused or misled and no breach of the Code was ruled.

Clement Clarke International Ltd complained about a 'Dear Doctor / Asthma Nurse' letter (ref Turb 02 11689) sent by AstraZeneca UK Limited in support of its Turbohaler device. A laminated card (ref Turb 02 11471a) headed 'Clinically Effective Inspiratory Flow' and a sticker (ref Turb 02 11471b), similarly labelled, accompanied the letter. The letter stated that although the ln-Check Dial marketed by Clement Clarke showed that the optimum inspiratory flow rate for the Turbohaler was 60-90L / min the device was nonetheless clinically effective at inspiratory flow rates from 30L / min. The letter also discussed a previous complaint made under the Code which concerned the promotional use of the In-Check Dial.

The laminated card was for the recipient to keep with the other information on the ln-Check Dial and the sticker was to stick on the device itself. The card depicted a graduated scale from 15L / min to 120L / min. A solid band ran from 30L / min to 90L / min representing the range over which the Turbohaler was clinically effective. The sticker had a similar scale with a solid band running from approximately 25L / min up to 90L / min.

Clement Clarke submitted that the letter, card and sticker were sent to primary and secondary health professionals between March and June 2003.

BACKGROUND FROM CLEMENT CLARKE

Clement Clarke stated that in September 1997 it introduced the In-Check device, a small, hand-held

mechanical flow meter that accurately measured the speed at which a patient inhaled.

During 1996/97 published literature and scientific comment revealed that the performance of the majority of pulmonary inhaler delivery devices was affected by the inspiratory flow rate through them. Dry powder inhalers such as the Turbohaler (AstraZeneca's delivery system for Pulmicort, Bricanyl and Oxis) had demonstrated reduced performance at lower flow rates as assessed by total lung deposition (the amount of medicine that would reach the lungs); fine particle fraction (the size distribution of the particles inhaled) and consistency of dose at different flows (the variation in dose in repeated use).

Patients using inhalers to deliver medicines to the lungs breathed in through them and the air passed through the inhaler before carrying the medicine into the mouth and respiratory system. Because the air must follow the internal structure of the inhaler, any diversion or partial physical barrier would impede the free passage of air – hence the 'resistance' a patient felt when inhaling through each device. Several designs of inhaler were available within the UK. The range of designs was reflected in a different resistance for each device – eg AstraZeneca's Turbohaler had a high resistance compared to the low resistance of GlaxoSmithKline's Accuhaler.

Richards and Saunders (1993) documented a method of determining the resistance of several different inhalers. This method formed the basis for assessments of resistance for various inhalers marketed in the UK; the available data was then used to design a 'resistance adaptor' for each delivery device. By placing the resistance adaptor between the patient and the In-Check device, it was possible to simulate the resistance of inhaling through the actual device, whilst measuring the inspiratory flows achieved. To ensure that the In-Check device was capable of simulating the resistance of each different inhaler, and measuring the flow accurately, it was subject to testing internally, and by external testing authorities. The result of this testing was the ability to demonstrate that the In-Check Inhaler Assessment Kit could measure the speed at which a patient with respiratory disease could inhale through their inhaler.

The importance of good inhaler technique had been well documented; the performance of various dry powder inhalers had been shown to be flow dependent, and the effect of inspiratory flow on medicine deposition had also received much attention.

Enquiries regarding inspiratory flow were made to medical information departments at pharmaceutical companies, both directly by Clement Clarke and independently by a third party. Information provided was added to data from published clinical research, with a resulting body of evidence that identified the minimum and optimum flow rates for these inhalers. This body of evidence was discussed with knowledgeable health professionals to ensure that Clement Clarke had taken a responsible position and had not drawn incorrect conclusions from the data.

In September 1998 the In-Check Inhaler Assessment Kit was introduced – a small pack that combined an inspiratory flow meter with up to six 'resistance adaptors' that allowed the inspiratory flow to be assessed for patients using several inhalers. Accompanying the pack was an instruction booklet that detailed the flow rates for each device – specifically stating the minimum and optimum thresholds and whether there was a variation in the amount of medicine between the two stated figures. For example, Turbohaler: minimum 30L/min; optimum 60L/min; high variation in dose over range. The product was sold successfully both in the UK and internationally and had stimulated interest amongst academics involved in respiratory medicine. Several abstracts had been published where the In-Check device had been used in research and there were clinical papers awaiting publication in relevant journals.

A development of this product, the In-Check Dial, made available in October 1999, further simplified the equipment needed to measure inspiratory flow through inhalers by incorporating a rotating dial that allowed the health professional to select one of several inhalers (without the need to fit 'resistance adaptors' that were used in the first product).

Feedback from users of the In-Check Inhaler Assessment Kit recommended simplifying the data for each inhaler. As the device was frequently used to train patients how to modify their inhaler technique (to suit the flows recommended for each device), the optimum inspiratory flow threshold for each device was identified from the research data, and used to represent the target flow range for patient training. The change of information supplied with the products (from minimum and optimum, to just optimum) coincided with the activity by AstraZeneca to disparage the In-Check range of products.

Clement Clarke stated that it had taken pharmaceutical and legal advice on the ability to represent the information as stated in literature accompanying the In-Check Dial.

AstraZeneca threatened Clement Clarke with a court injunction and legal proceedings in a letter dated 27 April 2000. Its legal representatives required withdrawal of the In-Check Dial internationally and a public retraction of the statements Clement Clarke had made that documented the optimum flow range for AstraZeneca's device being 60-90L/min. Clement Clarke had replied fully to AstraZeneca's questions and referenced much *in vitro* and *in vivo* work to support its position – it took advice from experts in this area and had maintained the product information without a change. Clement Clarke's solicitors continued to advise that it had a strong defence against any action brought by AstraZeneca due to the detailed information available on the Turbohaler. Clement Clarke noted that no legal proceedings had been brought. Clement Clarke had not withdrawn the In-Check Dial as requested, nor modified the way it had presented the information. The company's most recent reply to AstraZeneca, dated 18 July 2000, remained unanswered and unacknowledged.

Clement Clarke invited the Authority to review the exchange of correspondence, which would be made available on request, if it would be beneficial to the complaint.

Importantly, many of the scientific references Clement Clarke had cited were the same as those used by AstraZeneca itself to support its product.

Clement Clarke noted that the data available on inspiratory flow and the impact on inhaler performance and medicine deposition had supported a complaint it had made (Case AUTH/1101/11/00) concerning the activities of AstraZeneca and claims about the Turbohaler. This case was significant because AstraZeneca's claim 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI' was ruled to be misleading, and both the Panel and the Appeal Board accepted that at an inspiratory flow rate of 30L/min the Turbohaler delivered 15% of the nominal dose to the lungs and increasing the inspiratory flow rate to 60L/min doubled the lung deposition to 30%.

With recognition that the ideal inhaler should deliver a predetermined dose of medicine to the lungs, in an easy-to-use, reproducible and cost-effective manner, clinicians were now becoming aware that the Turbohaler might deliver varying amounts of medicine, even to the same patient, because inspiratory flow fluctuated, and medicine delivery from it was flow dependent.

The In-Check system had enabled general practitioners and asthma nurses, who were responsible for the majority of asthma care in the UK, to both teach the correct technique for maximum benefit from each inhaler and also ensure that patients who were to be prescribed a new inhaler had sufficient inspiratory flow to operate it optimally.

The most recent clinical guideline for asthma, the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Guideline on the Management of Asthma also emphasised the importance of correct inhaler technique and stated 'It is important that patients using dry powder devices can generate sufficient inspiratory flow for optimal use – devices to measure inspiratory flow are now available to assist in device selection'.

It was therefore appropriate and desirable for Clement Clarke to continue to market the In-Check Dial which identified the range of inspiratory flows associated with optimum performance of an inhaler, without further disparagement and confusing information conveyed by AstraZeneca's promotional activities.

Clement Clarke provided two In-Check Dials, version 1 and version 2. Both versions were marketed to health professionals in the UK; however, when sold to pharmaceutical companies for promotional use, only version 2 was supplied. The key difference between the two versions was the addition, in version 2, of a label stating: 'In-Check Dial can help educate and assess patients in optimal inspiratory technique for different devices. The green bars show the optimum inspiratory flow range for each device, and do not imply any comparison between devices. Flow rates outside the optimum range can still produce effective (rather than optimum) drug delivery, but pulmonary deposition of the drug may be reduced. Details are in the instruction booklet or at www.inspiratory.com'.

In summary Clement Clarke stated that it had developed the In-Check Dial to enable clinicians to measure the speed of inhalation for different delivery devices. A substantial body of data existed that documented the performance of inhalers such as the Turbohaler. AstraZeneca acknowledged, within its own promotional material, that medicine delivery from the Turbohaler at 30L/min was half that delivered at 60L/min, and that only at the higher flow rate did the dose delivered approach the figures stated in the Turbohaler summary of product characteristics (SPC).

The Turbohaler SPC stated that the percentage of metered dose delivered to the lungs was 25-30%. However, the evidence showed that AstraZeneca was prepared to promote the use of the Turbohaler at flow rates likely to achieve only half of that dose.

The In-Check Dial had only ever highlighted the optimum inhaler technique and was marketed as a device that could measure and help encourage patients to achieve the optimum inspiratory flow for the inhalers depicted. The In-Check Inhaler Assessment Kit was available to detail both effective and optimum inspiratory flow for those who wished to use it. To date, AstraZeneca had declined the offer to utilise this training and assessment device.

Clement Clarke alleged that the 'Dear Doctor/Asthma Nurse' letter, a laminated card and sticker together disparaged Clement Clarke and the In-Check Dial by implying that the device was only used in promotional activity. The letter incited the addressee to modify the device in a way that contravened the regulations governing Class 1 medical devices. This left the addressee unwittingly open to potential personal liability, confused the understanding of the purpose of the device and sought to promote the use of the Turbohaler in a way that was inconsistent with the level of medicine delivery listed in the Turbohaler SPC.

The choice of the materials used by AstraZeneca in its promotion was significant in that the laminated card was durable and designed to remain in the possession of recipients and the sticker was designed to be permanently fixed to the In-Check Dial.

Clement Clarke submitted that to repair the damage done AstraZeneca should be required, at its own expense, to recover from all recipients all material found to be in breach of the Code, replace the In-Check Dials which had been modified by addition of the sticker with new unadulterated In-Check Dials and publish in the UK's leading asthma/respiratory journals a prominent, full-page, unreserved statement that it regretted the confusion created by its activities and give details of the restorative actions ordered by the ruling and confirm that the In-Check Dial accurately reported the optimum inspiratory flow for the Turbohaler as being 60-90L/min.

BACKGROUND FROM ASTRAZENECA

AstraZeneca noted that it was disappointing that Clement Clarke, although not a pharmaceutical company or a member of the ABPI, did not enter discussions at the inter-company level to resolve the

issues. AstraZeneca was firmly committed to maintain high standards throughout all of its activities. It therefore strongly denied Clement Clarke's allegations that the activities under question ignored the Code, clinical evidence and the Turbohaler SPC.

The In-Check Dial had previously come under scrutiny in Cases AUTH/1096/11/00 and AUTH/1101/00. Case AUTH/1096/11/00 concluded that the inadequate labelling on the device itself was such that its use for promotional purposes was misleading. Even though Clement Clarke had subsequently modified the labelling on the In-Check Dial AstraZeneca still received queries related to inspiratory flow and the Turbohaler which led to the development of the letter, laminated card and sticker. These items were therefore an information source to address this specific need; they were not distributed as part of a mailing to any customers. The two previous cases were relevant in some areas to this current case.

AstraZeneca noted that the In-Check Inhaler Assessment Kit included an In-Check Dial and written materials. The latter had a table, which acknowledged the optimum inspiratory flow rate as different from the minimum inspiratory flow rate. AstraZeneca had chosen not to use this kit as part of any activity although it appreciated that it was available to health professionals. However it maintained that there was still a need to give clarity and information on the In-Check Dial.

AstraZeneca did not consider that applying the sticker to the In-Check Dial changed or affected its intended function or altered the information provided on the device. It did not disparage the device or any of the inhalers it depicted. AstraZeneca questioned whether comments which related to tampering with the device and the possible change in liability from such action fell within the remit of the Authority. AstraZeneca submitted that Clement Clarke's view regarding remedial action etc was inappropriate and the outcome of the complaints procedure must be awaited.

As outlined by Clement Clarke, not all In-Check Dials used in clinical practice were derived from the promotional activities of other companies. However the utilisation as a clinical tool remained the same whatever the source. AstraZeneca therefore found it peculiar that there should be two versions of the device available for use in clinical practice, with different information on each.

AstraZeneca stated that prescribing an inhaler for a patient involved a partnership between patient/carer and health professional taking factors such as age, lifestyle, manual dexterity, patient preference, medicines available in a particular device and ability to learn to use a device into account. This was an ongoing process when a patient was maintained on a particular device or changed to another. Inspiratory flow measurement was therefore only a small part of the assessment in the everyday clinical situation. The recent emergence of inspiratory flow rate as a significant clinical issue was important as a part of the discussion on the performance of inhaler devices. However for the purposes of clinical practice it was almost impossible to detach the performance of the device from that of the delivered medicine. The technical, scientific and clinical data might be confusing and needed to be clarified in a format that provided valuable practical help for health professionals delivering asthma care.

The clinical effectiveness of an inhaler depended on the molecular activity of the medicine which depended on the amount of medicine reaching the lung (lung deposition). Lung deposition data was most reliable from patient (*in vivo*) studies. *In vitro* studies had limited value especially when trying to extrapolate data into clinical effectiveness.

The *in vivo* lung deposition from a Turbohaler was less at an inspiratory flow rate of 30L/min than at 60L/min. However this must be put into perspective especially when comparing it to other devices. There was very limited comparable data for other devices that documented *in vivo* deposition at more than one flow rate in the same way as the Turbohaler. Comparisons with other devices were mainly derived from *in vitro* studies that showed that inspiratory flow rate affected delivery of medicine from the Turbohaler. Such comparisons did not evaluate the percentage of medicine that reached the lung from the devices at various inspiratory flow rates, ie there was no data (*in vivo* or extrapolated from *in vitro*) showing that the Accuhaler delivered a greater percentage of medicine to the lung than the Turbohaler at any particular inspiratory flow rates.

The optimum inspiratory flow rate for the Turbohaler was that at which it had been shown to deliver high percentages of medicine to the lungs. The Turbohaler by design delivered high percentages of medicines to the lung driven by inspiratory flow. The relevant clinical questions for any inspiratory flow rate were (i) how much medicine was actually delivered to the lung? and (ii) was the amount delivered sufficient to be clinically effective? At an inspiratory flow rate of 30L/min the Turbohaler delivered 15% medicine to the lung. This had been shown to be clinically effective even at this relatively low inspiratory flow rate. Almost all patients could achieve an inspiratory flow rate of 30L/min through a Turbohaler.

The optimum flow rate was therefore not the minimum flow rate at which the Turbohaler was clinically effective. The flow rate at which the Turbohaler was clinically effective was the clinically effective inspiratory flow rate. The Turbohaler by design was driven by inspiratory flow and therefore unlike other devices it had a range of inspiratory flow rates against which clinical effectiveness was assessed.

The In-Check Dial measured the inspiratory flow rate. It was therefore clinically important to clarify the difference between optimum inspiratory flow rate and the clinically effective inspiratory flow rate with respect to the Turbohaler.

AstraZeneca stated that it had identified a need to add further clarity and provide information to health professionals with a view to putting the Turbohaler and inspiratory flow rate into a relevant clinical perspective.

AstraZeneca had taken into account the effective *in vivo* deposition from the Turbohaler at low inspiratory flow rates and the lack of *in vivo* derived data supporting optimum flow rates for other devices. For the reasons detailed above AstraZeneca submitted that it was reasonable and helpful to provide information on clinically effective inspiratory flow rates in the case of the Turbohaler. This was in addition to the optimum inspiratory flow rates depicted on the In-Check Dial.

AstraZeneca had briefed its sales teams that the letter, laminated card and sticker were not for proactive use but only to be provided where the issue of optimum inspiratory flow rate and the Turbohaler were raised. The representatives were briefed that in addition to the letter customers could obtain the publications and further information through AstraZeneca's medical information department. This was an integral part of the information service on this issue. The reactive provision of this information by the representatives was appropriate as they were at the main interface where these particular issues arose. AstraZeneca considered that the provision of these items in response to a specific request for information did not constitute promotion. This became relevant when discussing the specific allegations below.

In summary AstraZeneca took a serious view of Clement Clarke's allegations. As a responsible pharmaceutical company it recognised its obligations and strongly considered that it had maintained high standards. As such it sought to strongly defend all allegations made. Inspiratory flow rate was one of a number of parameters considered in the clinical decision of selecting, and maintaining a patient on, an inhaler. Clinically effective inspiratory flow rate was an important consideration in the case of the Turbohaler. The items in question were part of a package (along with medical information) designed to give information and add clarity in the case of the In-Check Dial with respect to the Turbohaler. This package was informative and not misleading. As an offering to customers engaged in the care of asthmatic patients, this package did not bring discredit upon, or reduce confidence in the pharmaceutical industry.

A 'Dear Doctor/Asthma Nurse' letter

COMPLAINT

Clement Clarke stated that the 'Dear Doctor / Asthma Nurse' letter was the latest chapter in a lengthy dispute between the parties concerning AstraZeneca's perception of the effect that Clement Clarke's marketing of the In-Check Dial had on the market for AstraZeneca's Turbohaler. Fundamentally, AstraZeneca considered that the In-Check Dial misrepresented the performance of the Turbohaler. Clement Clarke alleged that the 'Dear Doctor / Asthma Nurse' letter not only ignored the Code but also the clinical evidence and the Turbohaler SPC.

Clement Clarke noted that Case AUTH / 1101 / 11 / 00 concerned similar claims by AstraZeneca to those now at issue. AstraZeneca was found in breach of three clauses of the Code in Case AUTH / 1101 / 11 / 00; evidence submitted by Clement Clarke which clearly identified the varying performance of the Turbohaler at different inspiratory flow rate was accepted.

Clement Clarke noted that the 'Dear Doctor / Asthma Nurse' letter stated 'AstraZeneca believes it is important that information provided to healthcare providers is relevant. To assist you in your use of the 'In-Check' Inspiratory Flow Meter, we attach a card and sticker for you to place beside the existing 'In-Check' information on Turbohaler. The attached stickers contain accurate information concerning the clinical effectiveness of Turbohaler'. This implied that the information supplied with the In-Check Dial was not relevant; that without the card and the stickers supplied by AstraZeneca the information provided by Clement Clarke on the Turbohaler was inaccurate and insufficient for correct clinical use of the In-Check Dial. The modification proposed by AstraZeneca was entirely inappropriate since it converted the In-Check Dial from a device that described optimum inspiratory flow for a series of products to one that referred in addition to effective inspiratory flow for the Turbohaler only.

In all of its previous dealings with AstraZeneca, Clement Clarke had emphasised the differences between effective and optimum inspiratory flow for all inhalers. The In-Check Dial was designed only to identify optimum inspiratory flow and this was the use for which it was approved. Clement Clarke could not authorise the modification proposed by AstraZeneca.

Clement Clarke alleged that the letter failed to make it clear to the reader the risks involved in adding the sticker to the In-Check Dial as suggested. Such a modification was contrary to the regulations laid down by the Medicines and Healthcare products Regulatory Agency (MHRA). By encouraging practitioners to tamper with the labelling of a registered Class I medical device, AstraZeneca was unwittingly transferring all responsibility and liability for the modified device to the doctor or nurse personally under the Medical Device Directive 93 / 42 / EEC. Furthermore, addition of the sticker invalidated the product liability insurance provided by Clement Clarke for the In-Check Dial. There was a risk that the sticker could be incorrectly positioned causing the optimum information on the In-Check Dial's existing label to be obscured, potentially leading the user to assume, incorrectly, that all inhalers depicted behaved in a similar fashion. Clement Clarke was not aware that AstraZeneca had alerted recipients of the 'Dear Doctor / Asthma Nurse' letter to any of these risks. UK doctors and nurses were unlikely to voluntarily accept liability associated with the use of a device which had been modified as suggested by AstraZeneca. Clement Clarke had written separately to the MHRA alerting it to the potential serious consequences of AstraZeneca's activities and seeking its advice.

Clement Clarke alleged that the 'Dear Doctor / Asthma Nurse' letter disparaged Clement Clarke and the In-Check Dial by suggesting that the product required modification before it could be used effectively. AstraZeneca's suggestions carried the risk of personal liability for recipients of the letter; AstraZeneca failed to warn them of such risk. Consequently, Clement

Clarke alleged that the letter was likely to bring discredit upon or reduce confidence in the pharmaceutical industry, in breach of Clause 2 of the Code.

Clement Clarke noted that the Pulmicort Turbohaler 100 SPC included, under Section 5.2 Pharmacokinetic Properties, 'About 25-30% of the metered dose is deposited in the lungs. Of the fraction which is swallowed, approximately 90% is inactivated at first passage through the liver. The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5nmol/l and is reached after about 20 minutes'.

The level of medicine deposition reported in the SPC, 25-30%, was only achieved when the inspiratory flow through the Turbohaler device was ≥60L/min. AstraZeneca acknowledged this fact in the laminated card by stating 'Turbohaler is effective at a peak inspiratory flow (PIF) of 30L/min, delivering ~15% of nominal dose to the lung…Doubling the PIF to 60L/min increases the lung deposition to about 30%'.

Clement Clarke noted that the 'Dear Doctor/Asthma Nurse' letter stated 'AstraZeneca wishes to draw your attention to the fact that the chart entitled 'Optimum Inspiratory Flow', which is distributed along with Clement Clarke's 'In-Check' Inspiratory Flow Meter, does not include data which AstraZeneca considers to be relevant for clinical decision making'. Clement Clarke stated that the chart which was supplied with the In-Check Dial was fully referenced and supported the conclusion that inspiratory flows of 60-90L/min were optimum for the Turbohaler. AstraZeneca could not dispute that, to achieve the level of medicine deposition stated in the Turbohaler SPC, 25-30%, the patient needed to achieve an inspiratory flow of ≥60L/min. Consequently, for AstraZeneca to state that the chart did not include data 'relevant for clinical decision making' implied that an inspiratory flow rate of 60-90L/min was not clinically relevant. Clearly, however, by reference to the Turbohaler SPC, an inspiratory flow rate of 60-90L/min was clinically relevant. Clement Clarke alleged that the statement in the letter was thus in breach of Clause 3.2 of the Code.

Clement Clarke also noted that the 'Dear Doctor/Asthma Nurse' letter stated '[C]lear clinical benefit in adults and children can be achieved with an inspiratory flow of 30L/min. At an inspiratory flow rate of 36L/min, the Turbohaler can deliver approximately 15% of the metered dose to the lungs. This is as good as a pMDI device when used with good technique. Approximately 98% of asthma patients can achieve an IFR of 30L/min through a Turbohaler in an acute setting'.

The 'Dear Doctor/Asthma Nurse' letter made a significant number of references to the clinical effect of Turbohaler at different inspiratory flows. Much of the argument made by AstraZeneca was that the clinical effect of Turbohaler would be seen at flows of not only 60-90L/min, but also at ≥30L/min. Clearly, the letter promoted the use of the Turbohaler when inspiratory flows were in the range 30-90L/min. As stated in AstraZeneca's own information, however, the level of medicine deposition for the Turbohaler was approximately 15% of nominal dose at peak inspiratory flows of 30L/min, and only doubled to the 25-30% range listed in the SPC when the inspiratory flow reached 60L/min. Therefore, at the flow rates stated in the letter, only half of the medicine delivery dose listed in the SPC could be expected. This lower level of medicine deposition was inconsistent with the particulars listed within the SPC. A further breach of Clause 3.2 was alleged.

Clement Clark noted that the 'Dear Doctor/Asthma Nurse' letter was a promotional mailing but it did not include any prescribing information. A breach of Clause 4.1 of the Code was alleged.

Clement Clark noted that paragraph 3 of the 'Dear Doctor/Asthma Nurse' letter stated that with regard to the outcome of Case AUTH/1096/11/00 'The rulings have been in favour of AstraZeneca'. Clement Clark alleged that this statement was highly subjective and failed to reveal all relevant information about the complaint and the rulings. The statement suggested that all rulings were in AstraZeneca's favour. This was not so. Not all AstraZeneca's allegations of a breach of the Code were upheld and, on appeal, one of the rulings of breach was overturned. Thus, the statement was inaccurate and misleading.

The 'Dear Doctor/Asthma Nurse' letter implied that the In-Check Dial was only used as a promotional item. This was wholly inaccurate and could mislead. Nowhere was there any qualifying explanation that the In-Check Dial was a medical device employed by researchers and clinicians that had proved of value in education, research and clinical practice. A large number of In-Check Dials had been purchased by asthma educators and researchers for use in clinical and research environments and had therefore never been used in promotional activity.

The 'Dear Doctor/Asthma Nurse' letter mentioned only briefly that the design of the In-Check Dial had been amended to reflect the ruling referred to by AstraZeneca. The majority of the letter referred to the detail of one part of a previous ruling against the promotional use by one pharmaceutical company of a standard medical device used as a free offer in a promotional campaign.

Finally, the 'Dear Doctor/Asthma Nurse' letter failed to acknowledge that the In-Check Dial was an independently validated, widely-researched medical instrument with sufficient clinical evidence to support the claims made by Clement Clarke about the variable performance of the Turbohaler at different inspiratory flows – both directly to AstraZeneca's medical and legal representatives and in Clement Clarke's submissions in Case AUTH/1101/11/00.

Clement Clarke alleged that the information contained in the 'Dear Doctor/Asthma Nurse' letter was not balanced or fair and as it drew attention to the ruling in Case AUTH/1096/11/00 and failed to give adequate recognition for amendments made to the In-Check Dial for promotional use by pharmaceutical companies, the letter inevitably left recipients questioning whether any In-Check Dial supplied since the previous complaint was suitable for the purpose intended. A breach of Clause 7.2 of the Code was alleged.

Clement Clarke noted that the 'Dear Doctor / Asthma Nurse' letter opened with: 'I understand that you would like further information on the Turbohaler on the issue of inspiratory flow rates'. The majority of the information that followed did not discuss the Turbohaler, but instead referred to the complaint made by AstraZeneca about another, unnamed, pharmaceutical company whose promotional activities included use of the In-Check Dial, Case AUTH / 1096 / 11 / 00. The letter implied that the In-Check Dial and Clement Clarke had misled UK health professionals through the use of the green bars seen on the In-Check Dial. On the contrary, the green bars were designed to make it easy for health professionals to identify the optimum inspiratory flow rate for each inhaler device depicted on the In-Check Dial. The selective reference to Case AUTH / 1096 / 11 / 00 clearly disparaged Clement Clarke and the In-Check Dial as it implied that both were found to be at fault.

At no point in the 'Dear Doctor / Asthma Nurse' letter did AstraZeneca acknowledge that in Case AUTH / 1096 / 11 / 00 its complaints were, in the main, concerned with the activities and promotional messages of another pharmaceutical company and that the In-Check Dial's use as a promotional item was ruled in breach of the Code for the sole reason that there was a risk that the booklet explaining the significance of the green bars could become separated from the meter; and at no point had the Authority ever found that Clement Clarke's representation of the optimum inspiratory flow rate (60-90L / min) for the Turbohaler was incorrect.

Clement Clarke's complaint against AstraZeneca's promotion of the Turbohaler, Case AUTH / 1101 / 11 / 00, was upheld following the presentation of evidence that clearly differentiated between the performance of the Turbohaler at optimum inspiratory flow and at other inspiratory flows.

Although the 'Dear Doctor / Asthma Nurse' letter purported to be a response to an enquiry for further information on the Turbohaler and the issue of inspiratory flow rates, there was no information on how differing inspiratory flow rates affected the Turbohaler performance, these being total emitted dose, fine particle fraction, oropharyngeal deposition and dose consistency on repeated actuation.

Clement Clarke stated that although several references were made in the letter to inspiratory flows the majority of these were associated with medicine deposition information that was inconsistent with the particulars listed within the Turbohaler SPC. Clement Clarke alleged that the 'Dear Doctor / Asthma Nurse' letter was a thinly disguised attack on it and the In-Check Dial masquerading as a response to a request for further information on the Turbohaler and inspiratory flow rates.

Two recipients of the 'Dear Doctor / Asthma Nurse' letter had told Clement Clarke that they had categorically not requested further information from AstraZeneca or any of its representatives. They each received all three promotional items unsolicited, either by post or after an AstraZeneca representative had visited their offices and left them behind, marked for their attention.

Clement Clarke alleged that this knocking copy was particularly unjustified since it referred to the version of the In-Check Dial which was introduced in response to the rulings made in Case AUTH / 1096 / 11 / 00; the letter implied that the product had not changed since that first complaint. A breach of Clause 8.1 of the Code was alleged.

RESPONSE

Taking into account the relevant background presented above AstraZeneca strongly denied any breach of Clause 2:

- there was a clearly identified clinical need to provide clarification on the difference between optimum and clinically effective inspiratory flow rates for the Turbohaler;
- information was provided reactively with a medical information type letter in addition to the laminated card and sticker.

AstraZeneca considered that its activities were focussed entirely on providing information and adding clarity on a specific limited clinical issue. They did not discredit or reduce confidence in the pharmaceutical industry.

There were no statements in paragraph 5 of the letter which suggested that the information on the In-Check Dial was not relevant, was insufficient for correct clinical use or was inaccurate. Any interpretation of its implications was subjective and in this case those listed by Clement Clark were contrary to AstraZeneca's intention of providing information within the overall flow of the letter.

As outlined above there was an important difference between optimum and clinically effective inspiratory flow rates. It was wholly appropriate and clinically relevant to add information on clinically effective inspiratory flow rates in the case of the Turbohaler. This was important in the context of the clinical use of the device.

Similar clinically relevant *in vivo* deposition data at different inspiratory flow rates was very limited for other devices.

AstraZeneca submitted that the letter did not challenge the concept of inspiratory flow rates and the difference between those which were optimum and those which were clinically effective. Indeed, the letter set out the clinically relevant differences between the two.

AstraZeneca contested Clement Clarke's assertions that any of its activities had affected safety or medical liability in connection with the In-Check Dial. AstraZeneca questioned whether these matters fell within the scope of the Code and sought clarification on this point from the Authority.

The sales force briefing instructed that the sticker should be applied to correspond with the gridlines on the In-Check Dial. The gridlines placed at the bottom of the sticker meant that the sticker could only be aligned to the In-Check Dial above and adjacent to and not over the current markings.

AstraZeneca submitted that any representations to the MHRA by Clement Clarke did not fall within the scope of this complaint. Indeed, Clement Clarke, AstraZeneca or the Authority did not know the final outcome of such exchanges at this stage.

For reasons discussed above AstraZeneca contested all the issues raised with regard to the alleged breaches of Clause 2 of the Code. In addition to challenging the allegations individually AstraZeneca submitted that collectively they did not constitute a breach of Clause 2.

As outlined above AstraZeneca did not consider that the letter was promotional. The letter did not promote the unlicensed use of any of the Turbohaler products. AstraZeneca strongly contested any alleged breach of Clause 3.2.

AstraZeneca noted that Section 5.2 of the SPC provided useful information for the prescriber. The prescriber was made aware of the effective deposition of the medicine into the lungs through the Turbohaler. Although this occurred at an inspiratory flow rate of 60L/min (which was not stated in the SPC) there was no recommendation that patients should only inhale at inspiratory flow rates > 60L/min. Clement Clarke had misrepresented this section of the SPC. There was no mention of the inspiratory flow rate in the SPC. Any information relating to medicine deposition at 30L/min was not outside the current licence.

The discussion of clinically effective inspiratory flow rate was wholly appropriate and important in clinical decision-making. Deposition from a Turbohaler at 30L/min was at least as good as the pressurised metered dose inhaler. This information was not included on the In-Check Dial. AstraZeneca therefore stood by the statement from the letter that 'AstraZeneca wishes to draw your attention to the fact that the chart entitled 'Optimum Inspiratory Flow' which was distributed along with Clement Clarke's 'In-Check' Inspiratory Flow Meter, does not include data which AstraZeneca considers to be relevant for clinical decision making'.

As stated above the deposition from the Turbohaler at 30L/min was clinically relevant. The SPC did not recommend inspiratory flow rates of only ≥60L/min. Indeed the SPC did not even mention inspiratory flow rates.

For reasons discussed above AstraZeneca contested all the issues raised in Clement Clarke's allegations of breaches of Clause 3.2 with regard to the 'Dear Doctor/Asthma Nurse' letter. In addition to challenging the individual allegations AstraZeneca submitted that collectively they did not constitute a breach of Clause 3.2.

With regard to the alleged breach of Clause 4.1 AstraZeneca stated that it received a significant number of enquires around the In-Check Dial, inspiratory flow rates and the Turbohaler. The letter in question was developed as a medical information type resource to address an important clinical need and for immediate use by the sales team. The letter was not used proactively but was only provided where the issue of optimum inspiratory flow rate and the Turbohaler were raised. The representatives were briefed to offer the additional resource of AstraZeneca's Medical Information department as an integral part of the information service on this issue. The provision of this information was partly by sales teams as they were at the main interface where these particular issues arose. AstraZeneca submitted therefore that the letter did not constitute promotion.

The Turbohaler was not a product in its own right. It was only available with contained medicines. The letter made no claims about any of the medicines delivered by the Turbohaler. AstraZeneca therefore denied a breach of Clause 4.1 based on its reasoning that the items did not constitute promotion.

AstraZeneca stated that it had developed materials in response to a particular need. They reflected current evidence and were fair and balanced without misleading the audience. The contents of the letter were entirely appropriate in providing information in an important clinical area. Any inferred implications or suggestions were entirely subjective and beyond reasonable interpretation of the letter by the reader in the context of the intended scenario for which it was developed.

AstraZeneca submitted that Clement Clarke's reference to the sentence 'The rulings have been in favour of AstraZeneca' was in itself misleading. The whole paragraph in the context of the letter was accurate and not misleading. There was no statement in the letter that all rulings were in AstraZeneca's favour. The interpretation that this was suggested was very subjective. The promotional use of the In-Check Dial was only referred to in the letter when considering the specific rulings of Case AUTH/1096/11/00. The letter was not concerned with the routes to acquiring the In-Check Dial. It was specifically focussed on providing more clinically relevant information on the Turbohaler than was available on the In-Check Dial, however acquired. The change in labelling of the In-Check Dial from version 1 to 2 was irrelevant here. The additional clinically relevant information applied to both versions of the device whether promotional or otherwise.

AstraZeneca did not challenge the validity of the In-Check Dial to measure inspiratory flow rates. Optimal inspiratory flow rates were derived for various devices through different types of studies. The Turbohaler was unique in that it had *in vivo* deposition data at different flow rates. The other devices were supported by deposition data mainly from *in vitro* studies. It was the evidence from *in vivo* or *in vitro* studies that Clement Clarke used to support the markings on the In-Check Dial. It was not the In-Check Dial which supported inspiratory flow rates/deposition claims. The In-Check Dial did not measure medicine deposition. AstraZeneca did not consider Clement Clarke's statements made with regard to this point were relevant or able to support an alleged breach of Clause 7.2.

As discussed above AstraZeneca did not consider the allegation that the letter was not balanced or fair was relevant. AstraZeneca challenged the idea that readers of the letter would inevitably question the suitability of the In-Check Dial for its intended use.

The letter was very specific and focussed and did not suggest these conclusions when read in its entirety. AstraZeneca denied a breach of Clause 7.2 of the Code.

AstraZeneca noted that the letter was one of three items designed to provide more information in a particular situation. The tone of the letter was informative throughout and did not disparage Clement Clarke or the In-Check Dial.

AstraZeneca noted that the letter was part of a response to a particular query. The opening statement 'I understand you would like further information on the Turbohaler on the issue of inspiratory flow rates' was therefore entirely appropriate. The majority of the information which followed was not about the previous case. Only one and a half of the six paragraphs of the letter provide information on Case AUTH/1096/11/00. AstraZeneca did not and had never challenged the concept that the green bars represented the optimum inspiratory flow rates. This was reflected throughout the text of the letter. The letter aimed to add clinically relevant information on the Turbohaler.

AstraZeneca noted that the letter specifically referred to the promotional use of the In-Check Dial with reference to the previous complaint. The letter did not state that the device was at fault. To the contrary, the letter stated 'To assist you in your use of the In-Check Inspiratory Flow meter'.

AstraZeneca did not challenge Clement Clarke's points with regard to the presentation of the data from Case AUTH/1096/11/00. However, the letter in question had been developed to provide relevant information of which the previous case was a part. It was not designed to be a comprehensive summary of the case. AstraZeneca's position was that although Clement Clarke's points were factually correct they did not add to the relevant information delivered within the aims of the letter. The omission of these facts was therefore not misleading. Again, although factually correct, the point about the ruling in Case AUTH/1101/1/00 made very little contribution to the question of whether the letter was misleading. AstraZeneca accepted the differences but was clarifying the clinical relevance.

AstraZeneca noted that total emitted dose, fine particle fraction, oropharyngeal deposition and dose consistency on repeated actuation were all relevant factors with regard to the clinical use of inhalers. Indeed, another important parameter to include within this list was *in vivo* drug deposition. The In-Check Dial measured the inspiratory flow and none of these parameters. The letter was designed to add clarity and give information on inspiratory flow rate and the In-Check Dial. Although the other parameters might be affected by inspiratory flow, the sum of all these factors (and many others) was clinical effect. The letter was aimed at health professionals engaged in patient care. Therefore the focus on the principal measure of interest ie clinically effective inspiratory flow rates was wholly appropriate. Omission of the other factors was not misleading in the context of the letter.

The need for the letter and the intentions of the letter were set out clearly above. AstraZeneca considered that it had met that need. The letter was designed to clarify the clinical relevance of optimum and clinically effective inspiratory flow rates. There was no intention to disparage Clement Clarke.

AstraZeneca stated that it was committed to maintaining high standards. The information provided by Clement Clarke with regard to two recipients who had received the 'Dear Doctor/Asthma Nurse' letter was limited and did not enable AstraZeneca to respond. The company urgently requested further information to allow it to fully investigate the matter.

AstraZeneca noted that Clement Clarke had stated that not all the In-Check Dials were acquired through promotional means. Recipients might therefore have one of two devices.

The purpose of the letter was to give clarity around inspiratory flow rates and clinically effective inspiratory flow rates for the Turbohaler. The issues addressed applied equally to both versions of the device.

For reasons discussed above AstraZeneca contested all the issues raised in the points related to an alleged breach of Clause 8.1. AstraZeneca considered that collectively or individually, these points did not constitute a breach of Clause 8.1.

PANEL RULING

The Panel noted AstraZeneca's submission that the 'Dear Doctor/Asthma Nurse' letter was to be used by its representatives in response to questions about inspiratory flow rate and the Turbohaler. A laminated card and a sticker accompanied the letter. The Panel also noted Clement Clarke's submission that two recipients of the letter had not requested further information from AstraZeneca or its representatives. The Panel considered that whether the materials were provided by representatives in response to an individual enquiry or were provided unsolicited they were being used as support for the promotion of AstraZeneca's medicines. In the Panel's view, the exemption to promotion given in Clause 1.2 of the Code for replies made in response to individual enquiries did not apply in this case; the replies were pre-printed and distributed by AstraZeneca representatives to support the promotion of AstraZeneca's medicines. The Panel thus considered that the materials were promotional and it made its rulings in that context.

The Panel noted that the supplementary information to Clause 4.1, Advertisements for Devices, stated that where an advertisement related to the merits of a device used for administering medicines, such as an inhaler, which was supplied containing a variety of medicines, the prescribing information for one only needed to be given if the advertisement made no reference to any particular medicine. The Panel noted that the 'Dear Doctor/Asthma Nurse' letter related to the merits of the Turbohaler. The Turbohaler was supplied containing a variety of medicines (terbutaline (Bricanyl); eformoterol (Oxis); budesonide (Pulmicort) and eformoterol/budesonide (Symbicort)) although no medicine in particular was mentioned.

The letter thus required prescribing information for one of the medicines supplied in a Turbohaler. No prescribing information was given for any product. A breach of Clause 4.1 was ruled.

The Panel noted that the Turbohaler was a breath actuated inhaler, the amount of medicine inhaled being dependent upon inspiratory flow. The letter stated that the Turbohaler had been shown to be clinically effective at inhalation flow rates of 30-90L/min with optimum effect at 60-90L/min. The Panel considered that there was a difference between the clinically effective inspiratory flow rate, ≥30L/min and the optimum inspiratory flow rate 60-90L/min.

The Panel noted that Clement Clarke had produced two versions of the In-Check Dial. Both showed the flow rates for a number of devices. On neither version 1 nor version 2 did the main label on the device itself refer to optimum inspiratory flow although that was what the label depicted. Both devices were accompanied by a laminated card headed 'Optimum Inspiratory Flow'. Version 2 had an additional sticker on the device which stated, *inter alia*, 'Flow rates outside the optimum range can still produce effective (rather than optimum) drug delivery, but pulmonary deposition of the drug may be reduced'. In the Panel's view, even with the additional sticker on version 2, it was possible for a user to assume that devices were effective only in the ranges shown ie 60-90L/min for the Turbohaler. This was not so. The Panel noted Clement Clarke's submission that the In-Check Dial was designed only to identify optimum inspiratory flow and this was the use for which it was approved. The labelling on the device, however, showed that it could be used to demonstrate inspiratory flow rates as low as 20L/min; in the Panel's view how any of the flow rates were described with regard to the inhalers shown was a function of the labelling on the device and not of the device itself.

The Panel noted that Clement Clarke had alleged a breach of Clause 3.2 with regard to the statement 'AstraZeneca wishes to draw your attention to the fact that the chart entitled 'Optimum Inspiratory Flow', which is distributed along with Clement Clarke's 'In-Check Inspiratory Flow Meter, does not include data which AstraZeneca considers to be relevant for clinical decision making'. The letter continued 'The chart purports to compare the inspiratory flow of a number of different inhalers. It suggests that the range of flow for which AstraZeneca's dry powder inhaler Turbohaler is optimal is between 60-90L/min. However Turbohaler has been shown to be clinically effective at inhalation flows of 30-90L/min'. The Panel considered that it was important for physicians to know that the Turbohaler was optimally effective at inhalation flow rates of 60-90L/min and also that it was clinically effective from rates of 30L/min. Only knowing the optimal values did not give the clinician the complete picture with regard inspiratory flow rates and the clinical performance of the Turbohaler. The Panel noted that none of the SPCs for AstraZeneca's Turbohalers referred to inhalation flow rates. Section 5.2, Pharmacokinetic properties, of the Pulmicort Turbohaler 100 SPC stated that about 25-30% of the metered dose was deposited in the lungs. There was no statement however to indicate that this was the minimum effective dose. Similarly the Oxis Turbohaler 12 SPC stated the mean lung deposition of formoterol (21-37%) after inhalation via the Turbohaler but did not state that such values were the minimum required for a clinical effect. The Panel did not consider that the reference to flow rates which might result in a less than optimal lung deposition of medicine was inconsistent with the Turbohaler SPCs. No breach of Clause 3.2 was ruled in that regard.

The Panel was concerned that the letter stated that the chart distributed with the In-Check Dial did not include data which AstraZeneca considered to be relevant for clinical decision making. The Panel considered that this was misleading as it implied that the chart contained no information which was relevant which was not so. There was, however, no allegation in this regard and so the Panel made no ruling but it requested that AstraZeneca be advised of its concerns.

The Panel noted that Clement Clarke had also alleged a breach of Clause 3.2 with regard to the statement '[C]lear clinical benefit in adults and children can be achieved with an inspiratory flow rate of 30L/min. At an inspiratory flow rate of 36L/min the Turbohaler can deliver approximately 15% of the metered dose to the lungs. This is as good as a pMDI device when used with good technique. Approximately 98% of asthma patients can achieve an [inspiratory flow rate] of 30L/min through a Turbohaler in an acute setting'. The Panel noted its comments above with regard to inspiratory flow rates and lung deposition. There were no statements in the Turbohaler SPCs to the effect that the percentage deposition stated was the minimum required to exert a clinical effect. The Panel thus did not consider that the letter, in referring to an inspiratory flow rate which might result in a lower percentage lung deposition than that stated in the SPC, was inconsistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled.

The Panel noted that Clement Clarke had alleged that the letter was misleading for a number of reasons. The first was that the statement 'The rulings have been in favour of AstraZeneca', in respect of Cases AUTH/1078/9/00 and AUTH/1096/11/00 (to which the statement was referenced), failed to reveal all relevant information about the complaint and the rulings. The Panel considered that the statement at issue was not about the cases in their entirety in that it followed on from the sentence 'The case focused on the mis-interpretation of 'optimum' flow for Turbohaler'. The Panel noted that in Case AUTH/1078/9/00 breaches of the Code were ruled throughout and none were appealed. In Case AUTH/1096/11/00 the ruling with regard to the use of optimum respiratory flow rates and the labelling of the In-Check Dial was in favour of AstraZeneca. The Panel thus considered that in the context in which it appeared the statement 'The rulings have been in favour of AstraZeneca' was not misleading. No breach of Clause 7.2 was ruled.

The Panel noted that the main focus of the letter was with regard to the promotional use of the In-Check Dial and the rulings made in Case AUTH/1096/11/00 in relation to the clinically effective inspiratory flow

and the optimum inspiratory flow. The letter was not a review of the In-Check Dial *per se*. Given the subject of the letter the Panel did not consider that failure to refer to the use of the In-Check Dial by researchers and clinicians was misleading. No breach of Clause 7.2 was ruled. The Panel also did not consider that failure to acknowledge that the In-Check device was an independently validated and widely researched medical instrument was misleading. No breach of Clause 7.2 was ruled. The letter stated that since the ruling (in previous cases) the In-Check Dial had been amended so that accompanying text clearly explained what the green bars actually represented. There was thus an acknowledgement that amendments had been made and so the Panel did not consider that the letter was misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel noted that Clause 8.1 stated that the medicines, products and activities of other pharmaceutical companies must not be disparaged. The Panel noted that Clement Clarke was not a pharmaceutical company. The supplementary information to Clause 8.1 stated that critical references to another company's products were acceptable if such critical references were accurate, balanced, fair etc and could be substantiated. The Panel noted that the letter was about the labelling of the In-Check Dial and the clinical interpretation of the data supplied with it. The Panel noted that in Case AUTH/1096/11/00 the Appeal Board had considered that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. The range for the maximum effect was 60-90L/min. The Appeal Board had considered that the inadequate labelling on the device itself was such that its use for a promotional purpose was misleading. The Appeal Board had upheld the Panel's ruling of a breach of Clause 7.2. Turning to the case now before it, Case AUTH/1508/8/03, the Panel noted that, as stated in the letter, the In-Check Dial had been amended since the ruling. The Panel considered that some customers might still have the unamended device. Taking all the circumstances into account the Panel did not consider that the content of the letter was disparaging as alleged. No breach of Clause 8.1 was ruled.

The Panel noted that the letter drew the reader's attention to the fact that due to the labelling of the device, the promotional use of the In-Check Dial had been previously ruled in breach of the Code. The letter stated that since the ruling the In-Check Dial had been amended so that accompanying text clearly explained what the green bars actually represented. The letter discussed the difference between the optimum inspiratory flow rate and the clinically effective inspiratory flow rate and noted that although the optimal rate was 60-90L/min as shown on the In-Check Dial a clinical effect would be seen with flow rates = 30L/min. In the Panel's view both pieces of information were important to any health professional trying to decide which inhaler device would be suitable for any patient. The Panel noted its comments above regarding the labelling of the In-Check Dial. The Panel did not consider that adding information to that already supplied with the In-Check Dial, such that a health professional was made aware of the whole picture with regard to inspiratory flow rate and clinical effect, would bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

During its consideration of these allegations, the Panel noted Clement Clarke's comments regarding modifying the In-Check Dial in a way that contravened the regulations for Class 1 devices and the perceived personal liability consequences. These were not matters specifically covered by the Code although they might come under the general clauses of the Code. The Panel noted that there were no specific allegations and it was thus not required to make a ruling.

B The laminated card

COMPLAINT

Clement Clarke alleged that the laminated card was in breach of Clauses 3.2 and 9.4 of the Code.

Clement Clarke noted that the Pulmicort Turbohaler SPC included the following under Section 5.2 Pharmacokinetic Properties: 'About 25-30% of the metered dose is deposited in the lungs. Of the fraction which is swallowed, approximately 90% is inactivated at first passage through the liver. The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5nmol/l and is reached after about 20 minutes'. According to the Turbohaler SPC the level of drug deposition reported, 25-30%, was only achieved when the inspiratory flow through the Turbohaler was = 60L/min. AstraZeneca acknowledged this fact on the laminated card; the third bullet read 'Doubling the PIF ['Peak Inspiratory Flow'] to 60L/min increases the lung deposition to about 30%'. However, the title of the laminated card 'Clinically Effective Inspiratory Flow' clearly referred to the prominent blue bar that was seen between flow rates of 30-90L/min and the text immediately below that 'Turbohaler is clinically effective at an inhalation flow of 30L/min and above'. The blue bar was continuous between flow rate markings of 30-90L/min and, therefore, gave the impression that the Turbohaler was effective in that range. Only after further claims (about efficacy, drug delivery and the percentage of patients who could achieve 30L/min) was it noted on the card that the 30% lung deposition referenced in the Turbohaler SPC was only achieved when the peak inspiratory flow was 60L/min. At flow rates < 60L/min, (ie the section of the blue bar between 30L/min and 60L/min), the text on the card confirmed that pulmonary deposition of the medicine would not be 25-30%. Consequently, the card was inconsistent with the particulars listed in the Turbohaler SPC. A breach of Clause 3.2 of the Code was alleged.

Clement Clarke further noted that the laminated card copied the style, general layout and size of the original design which it had created for the 'Optimum Inspiratory Flow' card supplied with the In-Check Dial. The laminated card was entitled 'Clinically Effective Inspiratory Flow' and when compared to the

original 'Optimum Inspiratory Flow' card that accompanied the In-Check Dial, confused doctors, nurses and pharmacists.

The In-Check Dial was designed and approved to highlight optimum inspiratory flow for each inhaler depicted. There was a clear and recognisable difference between optimum and effective and in producing and distributing the laminated card similar to the original supplied with the device AstraZeneca was likely to mislead and confuse recipients. A breach of Clause 9.4 of the Code was alleged.

RESPONSE

AstraZeneca repeated that the three items in question were distributed as a package to be used reactively as described above. AstraZeneca had outlined its case in point A above to support its position that the reactive use of these items was not promotional.

For the reasons discussed above with regard to the alleged breach of 3.2 in respect of the 'Dear Doctor / Asthma Nurse' letter, AstraZeneca maintained the same argument in the case of the laminated card in that Section 5.2 of the SPC provided useful information to the prescriber; Section 5.2 of the SPC did not mention the inspiratory flow rate of 60L / min; the SPC did not recommend an inspiratory flow rate and the discussion of clinically effective inspiratory flow rate for the Turbohaler was entirely appropriate and useful. There was no promotion outside the licences for the Turbohaler products and therefore no breach of Clause 3.2.

As discussed above AstraZeneca noted that it had identified a need for greater clarity and more information when using the In-Check Dial with respect to the Turbohaler. The laminated card (along with the other items in question) specifically addressed that need. AstraZeneca had therefore provided health professionals with valuable, clinically relevant information when using the In-Check Dial and dealing with the Turbohaler. The company had not caused confusion or misled the intended users. The laminated card was clearly labelled with the Turbohaler and AstraZeneca logos. AstraZeneca therefore maintained that there had been no breach of Clause 9.4.

PANEL RULING

The Panel noted that Clement Clarke had alleged that the laminated card was in breach of Clause 3.2 because it showed that a Turbohaler was clinically effective at an inhalational flow of 30L / min and above. The Panel noted its comments in point A above with regard to a clinically effective inhalational rate, the optimal inhalational rate and the percentage lung deposition stated in the SPCs. The Panel considered that its ruling at point A also applied here. No breach of Clause 3.2 was ruled.

The Panel did not consider that the layout of the laminated card would confuse users of the In-Check Dial. The card had been presented in a similar style to that provided with the In-Check Dial and so users would be familiar with its format. The card clearly set out the information relating to the Turbohaler, inhalation flow rate and percentage lung deposition. The card added to the information supplied with the In-Check Dial. The Panel thus did not consider that the style of the In-Check information had been copied in a way which was likely to confuse. No breach of Clause 9.4 of the Code was ruled.

C The sticker

COMPLAINT

Clement Clarke alleged that the sticker labelled 'Clinically Effective Inspiratory Flow' was in breach of Clauses 3.2, 4.1 and 9.4 of the Code.

Clement Clarke noted that, as stated above, the level of medicine deposition reported in the Turbohaler SPC, 25-30%, was only achieved when the inspiratory flow through the Turbohaler was ≥60L / min.

The sticker featured a blue bar that was continuous between flow rate markings of 25-90L / min and therefore suggested that the Turbohaler was consistently effective in that range. However, at flow rates < 60L / min (ie the section of the blue bar on the sticker between 25-60L / min) the Turbohaler SPC stated that pulmonary deposition of the medicine would not be 25-30%. Clement Clarke submitted that the sticker was promotional and alleged that it was not consistent with the particulars listed in the Turbohaler SPC in breach of Clause 3.2 of the Code.

Clement Clarke stated that the sticker was neither an abbreviated advertisement nor a promotional aid. The sticker did not include prescribing information. A breach of Clause 4.1 of the Code was alleged.

Clement Clarke stated that it was clear from the sticker that the scale adopted by AstraZeneca to distance the lines identifying flow rates of 20-120L / min corresponded exactly to the scale adopted by Clement Clarke in the original labelling on the In-Check Dial. This could easily be demonstrated by placing the sticker alongside the existing In-Check Dial's scale. AstraZeneca intended to encourage recipients to stick the sticker directly on to the In-Check Dial, thereby modifying the device. AstraZeneca's presentation of the sticker closely mimicked the layout originated and currently used by Clement Clarke on the In-Check Dial. There was a consequent risk of health practitioners being confused and misled. A breach of Clause 9.4 of the Code was alleged.

The information presented on the sticker was AstraZeneca's representation of the clinically effective inspiratory flow for the Turbohaler. By placing this information alongside the data presented on the existing In-Check Dial, the health professional risked being confused as to the purpose of the instrument. There was a significant risk that the health professional would be misled into regarding the optimum for the Turbohaler, (60-90L / min), as having been incorrectly reported by Clement Clarke and that the sticker was an update to rectify this error. The Authority had previously accepted that the optimum inspiratory flow for the Turbohaler had been correctly reported at being 60-90L / min.

RESPONSE

AstraZeneca submitted that its comments above with regard to alleged breaches of Clause 3.2 with regard to the letter and laminated card similarly applied in the case of the sticker. AstraZeneca denied a breach of Clause 3.2 in the case of the sticker.

AstraZeneca noted that it had already commented on the alleged breach of Clause 4.1 with regard to the letter. The sticker was part of the package to provide information and clarity. AstraZeneca therefore presented the same comments for the sticker as for the letter.

The principle of using a green bar to depict clinically effective inspiratory flow rates for the Turbohaler was the same as the use of green bars to depict optimum inspiratory flow rates on the In-Check Dial. The In-Check Dial did not contain prescribing information for the various inhaler devices illustrated. AstraZeneca maintained that the sticker was not a promotional item and therefore there was no breach of Clause 4.1.

Within the remit of the sticker clearly set out above the sticker added clarity and provided clinically relevant information and did not confuse or mislead. AstraZeneca stated that its comments about the laminated card also applied to the sticker. AstraZeneca therefore denied any breach of Clause 9.4.

PANEL RULING

The Panel noted that the sticker was labelled 'Clinically Effective Inspiratory Flow' and showed a solid blue band from approximately 26L / min up to 90L / min. The Panel noted its comments in point A above with regard the clinically effective inhalational flow rate, the optimum inhalational flow rate and the percentage lung deposition stated in the Turbohaler SPCs. The Panel did not consider depicting flow rates of < 60L / min was inconsistent with the SPCs as alleged. No breach of Clause 3.2 was ruled.

The Panel noted that the sticker did not bear any product name although it did have on it a stylised diagram of a Turbohaler. The Panel noted AstraZeneca's submission that the sticker was not a promotional item and its own comments at point A regarding the promotional nature of the material. The Panel considered that the sticker was a promotional aid within the meaning of Clause 18 of the Code. The sticker was inexpensive and, given its intended use, relevant to the practice of medicine. The sticker was thus exempt from the requirement to carry prescribing information. No breach of Clause 4.1 was ruled.

The Panel noted that the sticker presented information in a similar style to that on the label of the In-Check Dial and so users would be familiar with its format. The sticker was clearly labelled 'Clinically Effective Inspiratory Flow'. The Panel did not consider that users would be misled into thinking that the information supplied by Clement Clarke was incorrect and that the sticker was an update to rectify the error. The Panel considered that the application of the sticker meant that the In-Check Dial would carry additional clinically relevant information about the Turbohaler than had been supplied by Clement Clarke. The Panel did not consider that users of the In-Check Dial would be confused or misled as alleged. No breach of Clause 9.4 was ruled.

During its consideration of this point the Panel noted that the sticker showed that the Turbohaler was clinically effective with inspiratory flow rates ≥26L / min. AstraZeneca had submitted that the minimum inspiratory flow required for clinical effectiveness was 30L / min. The Panel additionally noted that the sticker implied that the Turbohaler was consistently effective over the range of 26-90L / min. In the Panel's view it might have been helpful if the blue line which depicted the clinically effective inspiratory flow could have been marked or shaded in some way so as to clearly show the optimum flow rates without reference to the other labelling on the In-Check Dial. The Panel requested that AstraZeneca be advised of its comments.

Complaint received **15 August 2003**

Case completed **27 October 2003**

CASES AUTH/1510/8/03 and AUTH/1511/8/03

NOVARTIS v BRISTOL-MYERS SQUIBB and SANOFI-SYNTHELABO

Promotion of Aprovel

Novartis complained about a detail aid and a leavepiece promoting Aprovel (irbesartan) issued by Bristol-Myers Squibb and Sanofi-Synthelabo. Aprovel was an angiotensin-ll receptor antagonist (AIIRA) indicated for the treatment of essential hypertension and the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

Novartis alleged that the claim 'Control. Pure and simple' which appeared in the detail aid was exaggerated and all-embracing. It implied that all patients would be controlled and that achieving this was 'simple'. A significant body of evidence demonstrated that only a small proportion of patients would achieve blood pressure target with any antihypertensive given as monotherapy, including Aprovel. Controlling blood pressure was not 'pure and simple' as claimed. Furthermore, 'Pure and simple' implied that treatment with Aprovel was not associated with any side effects, which was not true.

The Panel considered that the claim 'Control. Pure and simple' implied that all patients on Aprovel would have their blood pressure controlled and this was easily achieved without complications. This was not necessarily so. The Panel considered that the claim was all-embracing and exaggerated as alleged and ruled a breach of the Code. The Appeal Board upheld the Panel's ruling of a breach.

Novartis stated that physicians would read the heading to page two which referred to the current poor management of hypertension, the first two bullet points about the National Service Framework (NSF) for coronary heart disease targets , and then wrongly assume from the third bullet point, 'Aprovel as monotherapy normalised* BP in 66% of patients after 12 weeks', that the use of Aprovel monotherapy would result in 66% of patients achieving NSF targets. This was clearly not so as the study cited in support of the claim did not assess the proportion of patients achieving the NSF target of <140/85mmHg. Novartis alleged that, despite a footnote explaining that 'normalised' in the claim meant seated DBP<90mmHg, the claim was misleading.

The Panel considered that it was true to state that Aprovel helped achieve the NSF target. The context gave the impression that 66% of patients would reach this target and this was not so. The referenced study (Mimran *et al* 1998) had looked at patients reaching DBP<90mmHg and not the target of below 140/85mmHg. The Panel considered that in the context in which it appeared the claim at issue was misleading and ruled a breach of the Code. The Appeal Board upheld the Panel's ruling of a breach.

Novartis alleged that the claim that Aprovel was 'The only AIIRA with superior efficacy to full-dose losartan' referenced to Kassler-Taub *et al* (1998) and Oparil *et al* (1998) was inaccurate. Novartis referred to a study by Hedner *et al* (1999) that compared Diovan and losartan and showed that treatment with Diovan 160mg resulted in a greater response rate than losartan 100mg (61.6% vs 54.5%) which reached statistical significance. It was not uncommon for studies of anti hypertensives to use responder rates as a measure of efficacy.

The Panel noted the submission from Bristol-Myers Squibb and Sanofi-Synthelabo that the claim in question had been carefully worded to refer to efficacy and not refer to responder rates. In the opinion of the Panel this subtlety would be lost on readers. The Panel considered that given the data in the Hedner study relating to responder rates, which showed a statistically significant difference in favour of valsartan, it was misleading to give the impression that Aprovel was the only AIIRA with superior efficacy to Iosartan. The Panel thus ruled a breach of the Code. Upon appeal, the Appeal Board considered that given the results from Hedner *et al* and the fact that not all of the AIIRAs had been compared to losartan, it was misleading to state that Aprovel was the only AIIRA with superior efficacy to losartan. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Novartis alleged that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' on page 7 of the detail suggested that Aprovel might be used for renoprotection in patients who were not hypertensive if this was indeed independent of blood pressure lowering. The licensed indications for Aprovel were for the treatment of essential hypertension and for renal disease in hypertensive type 2 diabetic patients as part of an antihypertensive drug regimen. Hence any claims relating to renal protection outside of blood pressure lowering represented promotion of Aprovel outside the terms of its marketing authorization. This claim was repeated on pages 8 and 9 of the detail aid.

The Panel noted that page 2 of the detail aid referred to the fact that Aprovel was licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. This was repeated on page 5. On page 7 the Panel noted that although the patient characteristics had been defined the reason for giving Aprovel ie to reduce blood pressure, had not.

The Panel considered that on balance the claim for Aprovel's renoprotective effect being above and beyond its blood pressure lowering on pages 7 and 8 was not clearly set within the licensed indication ie treatment of blood pressure. This was inconsistent with the summary of product characteristics (SPC) and breaches of the Code were ruled. These rulings were appealed.

With regard to page 9, the Panel noted that the claim at issue was immediately followed by a statement

that Aprovel was the first AIIRA to be licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. The Panel considered that this page was not unreasonable. It had been made clear that the reason for giving Aprovel was for the treatment of hypertension. No breach of the Code was ruled in this regard.

The Appeal Board considered the detail aid had two distinct sections; pages 1-5 discussed Aprovel in relation to hypertension and pages 6-9 discussed the renoprotective effects of Aprovel within the context of the treatment of hypertension.

The Appeal Board noted from the layout in the detail aid that pages 6 and 7 made up a double page spread. Page 6 of the detail aid was headed 'PRIME importance' and discussed two studies on hypertensive patients with type 2 diabetes. The studies were described as covering the disease spectrum of type 2 diabetic renal disease. These being IRMA2; Parving *et al*, early stage (microalbuminuria) and the Irbesartan Diabetic Nephropathy Trial (IDNT); Lewis *et al*, late stage nephropathy. The Appeal Board noted that Section 5.1 of the Aprovel SPC under the heading 'Hypertension and type 2 diabetes with renal disease' discussed the IRMA2 and IDNT studies. The Appeal Board noted that within the context of hypertension Aprovel was licensed for renoprotection and considered that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' on page 7 was put into this context by the preceding page. The Appeal Board thus considered that the claim on page 7 was not inconsistent with the SPC and ruled no breach of the Code.

The Appeal Board considered that the claim on page 8 was put into context by pages 6 and 7 and page 9 which it faced. The Appeal Board thus considered that the claim on page 8 was not inconsistent with the SPC and ruled no breach of the Code.

Novartis alleged that a claim 'Aprovel – In control, in every way' was all-embracing.

The Panel considered that this claim was exaggerated and all-embracing and ruled a breach of the Code.

Novartis alleged that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' on pages 4, 5 and 6 of the leavepiece was in breach of the Code for the reasons highlighted above.

The Panel noted its rulings above. It considered that pages 4 and 5 of the leavepiece did not make it sufficiently clear that Aprovel was given to treat hypertension. The Panel thus considered that both pages were inconsistent with the SPC and each was ruled in breach of the Code. These rulings were appealed.

The Panel considered that page 6 was not unreasonable. It had been made clear that the reason for giving Aprovel was for the treatment of hypertension. No breach of the Code was ruled in this regard.

The Appeal Board noted its rulings above. The leavepiece, unlike the detail aid, referred only to the use of Aprovel for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus. The first three pages of the leavepiece provided details of the two studies (IRMA2 and IDNT) which were said to cover the disease spectrum of hypertensive type 2 diabetic renal disease. The Appeal Board considered that, on balance, the claim on pages 4 and 5 of the leavepiece was put into context by the preceding pages and as such the claim was not inconsistent with the SPC. The Appeal Board thus ruled that each claim was not in breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Aprovel (irbesartan) by Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthelabo Limited. The items at issue were a detail aid (ref APR1017) and a leavepiece (ref APR 1006). Aprovel was an angiotensin-ll receptor antagonist (AIIRA) indicated for the treatment of essential hypertension and the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen. Novartis marketed Diovan (valsartan). Correspondence between the parties had failed to resolve the matter.

A joint response was received from Bristol-Myers Squibb and Sanofi-Synthelabo.

A Aprovel detail aid APR1017

Bristol-Myers Squibb and Sanofi-Synthelabo stated that this item had been used with general practitioners between July 2002 and February 2003.

1 Claim 'Control. Pure and simple'

This claim appeared on the front cover of the detail aid.

COMPLAINT

Novartis alleged that the claim was exaggerated and all-embracing in breach of Clause 7.10 of the Code. It implied that all patients would be controlled with Aprovel and that achieving this control was 'simple'. There was a significant body of evidence which demonstrated that only a small proportion of patients would achieve blood pressure target with any antihypertensive agent given as monotherapy, including Aprovel. This was clearly acknowledged on the following page, which stated that 'In the United Kingdom, a recent survey indicated that only 6% of hypertensive patients had their blood pressure lowered to below 140/90mmHg'. It was therefore clear that controlling blood pressure in hypertensive patients was not 'pure and simple' as claimed. Furthermore, 'pure and simple' implied that treatment with Aprovel was not associated with any side effects, which was clearly not true. Novartis noted that the claim was repeated on subsequent pages of the detail aid and alleged that it was in breach of the Code on each occasion for the reasons stated above.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo did not agree that the claim was all-embracing. The word control referred to the marketing authorization for Aprovel for the treatment of hypertension. The regulatory authorities had therefore considered Aprovel effective in controlling blood pressure in order to grant this authorization. In the context of hypertension management, 'control' was taken to be a meaningful reduction in blood pressure but did not imply treatment to a specific target with a single agent in every patient. The British Hypertension Society Guidelines made clear that 'control' required further quantification in order to imply that patients had reached a required target stating: 'The frequency of follow-up for treated patients after adequate blood pressure control is attained depends on factors such as the severity of the hypertension, variability of blood pressure, complexity of the treatment regimen, patient compliance, and the need for non-pharmacological advice'.

Bristol-Myers Squibb and Sanofi-Synthelabo noted that hypertension affected over 50% of people over the age of 65. GPs therefore had extensive experience in the management of hypertension and were familiar with the challenges which often involved the use of several agents to control blood pressure to target. GPs would therefore not be misled in the way proposed by Novartis. As noted by Novartis the detail aid clearly recognised the challenge doctors faced in managing hypertension in the statement 'In the United Kingdom, a recent survey indicated that only 6% of hypertensive patients had their blood pressure lowered to below 140/90mmHg'.

Bristol-Myers Squibb and Sanofi-Synthelabo submitted that 'Pure and simple' was a figure of speech, meaning uncomplicated or straightforward; it did not refer to the side effect profile of Aprovel, this link was neither explicit nor implicit in this claim or anywhere else in the detail aid. It therefore followed that 'Control. Pure and simple' implied that Aprovel would reduce blood pressure to some degree and was relatively straightforward to use. Both of these assertions were supported by the summary of product characteristics (SPC).

The dosing of Aprovel was straightforward, justifying the use of 'pure and simple'. There were only two dose strengths and dosing was once daily. Further to this, data demonstrated that more patients prescribed Aprovel monotherapy remained on this treatment after one year compared to other classes of antihypertensives. Unlike all the other AIIRAs, Aprovel could be used in the elderly, patients with all degrees of renal impairment and patients with mild to moderate hepatic impairment without the need for dose adjustment. These attributes made it straightforward to use thus substantiating the use of the figure of speech 'pure and simple'. Bristol-Myers Squibb and Sanofi-Synthelabo noted that there were other examples where a figure of speech had been used in promotion and stated that it would underestimate doctors to believe that they were not capable of taking these concepts in the spirit in which they were intended.

The companies thus submitted there had been no breach of Clause 7.10 of the Code.

PANEL RULING

The Panel considered that the claim 'Control. Pure and simple' implied that all patients on Aprovel would have their blood pressure controlled and this was easily achieved without complications. This was not necessarily so. The Panel considered that the claim was all-embracing and exaggerated as alleged and ruled a breach of Clause 7.10 of the Code.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The companies submitted that the word 'control' had referred to the licensed indication for Aprovel in the treatment of hypertension and the phrase 'Pure and simple' was simply used as a figure of speech. GPs were generally experienced in the treatment of hypertension and were aware that almost half of patients would require more than one medicine to control their blood pressure to target. It was therefore underestimating doctors to suggest that that they would be led to believe that all patients would be controlled on Aprovel.

The companies submitted that phrases such as 'Pure and simple' were common and occurred frequently in pharmaceutical advertising without misleading doctors. Examples were given. The companies did not assert that these claims were in breach of the Code as clearly they were phrases that were common in every day language, just like 'Pure and simple'. The companies appealed the ruling that the claim 'Control. Pure and simple' was in breach of Clause 7.10 of the Code.

COMMENTS FROM NOVARTIS

Novartis noted that the respondents had stated that 'control' referred to the licensed indication for Aprovel and that 'Pure and simple' was simply a figure of speech. However it was important to appreciate the context and the way in which these words were used. 'Control' followed by a full stop implied a definitive outcome, ie all patients would be controlled. 'Pure and simple' gave the impression that Aprovel was free from adverse effects and that controlling hypertension was 'simple'. There was a significant body of data including the Health Survey for England that demonstrated that controlling hypertension was far from simple and it was widely acknowledged that only a minority of patients would have their blood pressure controlled to target with monotherapy. Furthermore the Aprovel SPC highlighted the possible adverse effects associated with treatment, hence the claim 'Control. Pure and simple' was all-embracing and exaggerated and in breach of Clause 7.10 of the Code.

Novartis noted that the respondents had stated that 'it was underestimating doctors to suggest that they would be led to believe that all patients would be controlled on Aprovel'. It was clear that despite all current efforts to control hypertension the British Hypertension Society had recently published a paper

entitled 'Better BP control: How to combine drugs' which provided a simplified approach to hypertension management (termed ABCD) with an emphasis on combining agents rather than persisting with monotherapy. This was in response to the situation where physicians tended to use a single agent with a reluctance to combine agents to achieve the desired target blood pressure. Novartis alleged that claims such as 'Control. Pure and simple' further exacerbated this situation by suggesting to physicians that monotherapy with Aprovel would result in all patients achieving BP targets when this was clearly untrue.

Novartis alleged that the reference to the promotional claims for other products was irrelevant as each case should be judged on its own merits.

APPEAL BOARD RULING

The Appeal Board considered that blood pressure control was not easy or simple; it was a highly complex treatment that often required constant monitoring and management. A high proportion of the hypertensive population would often be on more than one medicine to control their blood pressure.

The Appeal Board considered that the claim 'Control. Pure and simple' implied that all patients on Aprovel would have their blood pressure controlled and this was easily achieved without complications. This was not necessarily so. The Appeal Board considered that the claim was all-embracing and exaggerated as alleged and upheld the Panel's ruling of a breach of Clause 7.10 of the Code. The appeal was unsuccessful.

2 Claim 'Aprovel as monotherapy normalised* BP in 66% of patients after 12 weeks'

Page two of the detail aid was headed 'In the United Kingdom, a recent survey indicated that only 6% of hypertensive patients had their blood pressure lowered to below 140/90mmHG' followed by three bullet points:

- 'The National Service Framework for Coronary Heart Disease recommends treatment to maintain blood pressure below 140/85mmHg.
- Aprovel offers powerful control that helps you achieve NSF target.
- Aprovel as monotherapy normalised* blood pressure in 66% of patients after 12 weeks'.

The explanation for the asterisk was stated in a footnote as 'Normalised defined as SeDBP< 90mmHg'.

COMPLAINT

Novartis submitted that physicians would read the page heading regarding the current poor management of hypertension, the first two bullet points about NSF targets, and then wrongly assume from the third bullet point, the claim at issue, that the use of Aprovel monotherapy would result in 66% of patients achieving these targets. This was clearly not the case as the study cited in support of the claim did not assess the proportion of patients achieving the NSF target of <140/85mmHg. 'Normalised' in the claim meant seated DBP<90mmHg which was not the same as the NSF target. Novartis alleged that despite a footnote explaining what normalised meant the claim was misleading, in breach of Clause 7.2, with regard to Aprovel monotherapy and the percentage of patients achieving the NSF target.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo noted that the second bullet point clearly stated that Aprovel provided help in the achievement of blood pressure targets. This claim was justifiable as the regulatory authorities had granted Aprovel a marketing authorization for the treatment of hypertension. It therefore followed that this blood pressure lowering effect would help a GP achieve the target. The claim did not state that Aprovel would guarantee achievement of blood pressure targets in the majority of patients as interpreted by Novartis.

The claim that 66% of patients had their blood pressure normalised in 12 weeks was capable of standing alone as regards accuracy, it did not claim that NSF targets would be attained. Rigorous internal review deemed the use of an asterisk and footnote was appropriate, as doctors would know to seek details of the target that had been used within the trial in order to measure normalisation. The companies therefore submitted that there had been no breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that it was true to state that Aprovel helped achieve the NSF target. The context of the claim at issue gave the impression that 66% of patients would reach this target and this was not so. The referenced study (Mimran *et al* 1998) had looked at patients reaching DBP<90mmHg and not the target of below 140/85mmHg. The Panel considered that in the context in which it appeared the claim at issue was misleading as alleged and a breach of Clause 7.2 of the Code was ruled.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The companies submitted that the claim 'Aprovel as monotherapy normalised* BP in 66% of patients after 12 weeks' was capable of standing alone as regards accuracy. Further, the heading to the page referred to a recent survey in which only 6% of hypertensive patients had achieved lowering of blood pressure to below 140/90mmHg. Reducing diastolic blood pressure to below 90mmHg clearly met this target and thus the word 'normalised' in this context was more likely to be read in the context of the large font headline than the small font bullet point. The claim was not made that 66% of patients would achieve NSF targets on Aprovel monotherapy as suggested in the Panel ruling. Given these points the companies appealed the ruling that this claim was in breach of Clause 7.2 of the Code.

COMMENTS FROM NOVARTIS

Novartis noted that the respondents had stated that the claim 'Aprovel as monotherapy normalized* BP in 66% of patients after 12 weeks' was capable of standing alone as regards accuracy. Novartis stated that the nature of the complaint had been misunderstood; it was not the accuracy of the statement that was being questioned, rather its context. The heading to the page stated that in a recent survey only 6% of hypertensive patients achieved a BP of <140/90mmHg. This was then followed by a bullet point highlighting the BP target specified within the NSF for Coronary Heart Disease. The third bullet point beneath the headline was the claim in question. There was no doubt that a physician would conclude, incorrectly, that 66% of patients treated with Aprovel achieved the BP targets alluded to in the previous statements (<140/90mmHg or <140/85mmHg). The word 'normalized' in this context clearly meant bringing the patient to target whilst in the context of the study which was used to substantiate this claim 'normalized' meant achieving a seated diastolic BP<90mmHg which was referred to in a footnote by an asterisk adjacent to the word 'normalized'. A patient achieving a seated DBP<90mmHg was clearly very different from achieving a BP of <140/90mmHg and Novartis maintained that use of this claim in this context was a deliberate attempt to mislead physicians into believing that treating hypertensive patients with Aprovel would result in 66% achieving target BP(<140/90mmHg) when this was clearly not true. Furthermore this type of claim was likely to exacerbate the problem of suboptimal management of hypertension highlighted in point A1 above. If physicians believed this claim then they were less likely to combine antihypertensive agents in order to control BP to target. It was therefore clear that this claim was misleading and in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that in the context in which it appeared the claim at issue gave the misleading impression that 66% of patients would reach the NSF blood pressure target of 140/85mmHg. However, this was not so as the referenced study (Mimran *et al* 1998), had looked at patients reaching DBP<90mmHg. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

3 Claim 'The only AIIRA with superior efficacy to full-dose losartan'

The claim appeared on page three of the detail aid. It was referenced to Kassler-Taub *et al* (1998) and Oparil *et al* (1998).

Beneath the claim there was a bar chart comparing the adjusted mean change in trough and SBP at 8 weeks for Aprovel 300mg, Aprovel 150mg and Iosartan 100mg.

COMPLAINT

Novartis stated that Hedner *et al* (1999) compared Diovan with losartan and showed that treatment with Diovan 160mg resulted in a greater response rate than losartan 100mg (61.6% vs 54.5%) which reached statistical significance. It was not uncommon for studies of antihypertensives to use responder rates as a measure of efficacy. Novartis alleged that the claim that Aprovel was 'The only AIIRA with superior efficacy to full-dose losartan' was inaccurate and in breach of Clause 7.2.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo stated that this claim was as a result of a literature search (including the Hedner reference cited by Novartis) and was carefully worded so as not to breach the Code. Hedner *et al* stated that 'When valsartan was directly compared to losartan there was no statistically significant difference between the treatments. Both drugs showed comparable efficacy'. This referred to efficacy as defined by mean blood pressure lowering rather than the percentage of patients responding to treatment (responder rate). A statement that valsartan had superior efficacy to full dose losartan based on the above paper would clearly misinterpret the author's intended meaning. The claim clearly related to efficacy in terms of blood pressure lowering and not responder rates as the bar chart demonstrated. In light of the paper quoted by Novartis and the context of the claim the companies submitted there was no breach of Clause 7.2.

PANEL RULING

The Panel noted that Hedner *et al* compared valsartan with losartan in an eight week study. The study concluded that both products produced similar significant reductions in mean blood pressure at 4 and 8 weeks compared with placebo. When valsartan was directly compared to losartan there was no statistically significant difference between the two with both showing comparable efficacy. With regard to response rates there was a statistically significant difference in favour of valsartan (p=0.021).

The Panel noted the submission from Bristol-Myers Squibb and Sanofi-Synthelabo that the claim in question had been carefully worded to refer to efficacy and the detail aid did not refer to responder rates. In the opinion of the Panel this subtlety would be lost on readers. The Panel considered that given the data in the Hedner study relating to responder rates, it was misleading to give the impression that Aprovel was the only AIIRA with superior efficacy to Iosartan. The Panel thus ruled a breach of Clause 7.2 of the Code.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The companies noted that the claim at issue appeared on a page on which a graph depicting the blood pressure lowering comparison was the only other item. The claim therefore clearly referred to blood pressure lowering efficacy.

The companies submitted that Hedner *et al* had clearly stated 'When losartan was directly compared to valsartan there was no statistically significant difference between the two treatments. Both drugs

show comparable efficacy'. This statement was unambiguous and clearly stated that valsartan was not more efficacious than losartan in terms of blood pressure lowering. Blood pressure lowering was clearly what the Aprovel claim referred to given the context of the page and the graph presented.

The companies submitted that any potential subtlety on the difference between responder rates and blood pressure lowering was dispelled by the very prominent position of the graph depicting the blood pressure lowering effect. It was difficult to believe that this would be lost on a doctor viewing the page.

COMMENTS FROM NOVARTIS

Novartis noted that the respondents had stated that this page referred to blood pressure lowering, however the title of the page made a general claim that Aprovel was the only AIIRA with superior efficacy to full dose losartan with no qualification as to the meaning of 'efficacy' in this context. With regards to Hedner *et al* it was true that the BP lowering achieved with valsartan and losartan was similar, however it was important to appreciate that this was not the only measure of efficacy of an antihypertensive and that other measures might be more relevant to clinical practice. It was common for studies of antihypertensives to investigate efficacy through the measurement of responder rates, a measure used by the respondents on the previous page of the detail aid and discussed in point 2 above. If anything, responder rate was a more representative measure of efficacy as it took into account potential differences in baseline BP between treatment groups. Responder rate therefore provided a more meaningful measure of the efficacy of an antihypertensive. Furthermore with the increased emphasis on achieving BP targets as demonstrated by the new GP contract, this type of information was far more relevant to the prescribing clinician than mean absolute BP reductions. Hence the statistically significant superiority of valsartan compared to losartan 100mg with respect to responder rates demonstrated in Hedner *et al* was highly relevant and showed that Aprovel was not 'the only AIIRA with superior efficacy to full dose losartan'. Novartis alleged that this therefore supported its position that this claim was inaccurate and therefore in breach of Clause 7.2 of the Code as ruled.

APPEAL BOARD RULING

The Appeal Board considered the claim 'The only AIIRA with superior efficacy to full-dose losartan' implied that all of the AIIRAs available had been compared with losartan and that only Aprovel had been shown to have superior efficacy which was not so; not all of the AIIRAs had been compared with losartan.

The Appeal Board noted that Hedner *et al* had shown a statistically significant difference in favour of valsartan (p=0.021) against losartan with regard to responder rates.

The Appeal Board considered that given the results from Hedner *et al* and the fact that not all of the AIIRAs had been compared to losartan it was misleading to state that Aprovel was the only AIIRA with superior efficacy to losartan. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

4 Claim 'Aprovel's renoprotective effect is above and beyond its BP lowering'

The claim appeared on page 7 of the detail aid headed 'Microalbuminuria' and was referenced to Parving *et al* (2001).

COMPLAINT

Novartis alleged that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' was in breach of Clause 3.2 as it suggested that Aprovel might be used for renoprotection in patients who were not hypertensive if this was indeed independent of blood pressure lowering. The licensed indications for Aprovel were for the treatment of essential hypertension and for renal disease in hypertensive type 2 diabetic patients as part of an antihypertensive drug regimen. Hence any claims relating to renal protection outside of blood pressure lowering represented promotion of Aprovel outside the terms of its marketing authorization. This claim was repeated on pages 8 and 9 and each was alleged to be in breach of Clause 3.2.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the first bullet point on page 7 of the detail aid defined the patient population to which the data presented referred ie hypertensive type 2 diabetics with early stage renal disease. This was in accordance with Aprovel's marketing authorization for treatment of renal disease in patients with type 2 diabetes mellitus as part of an antihypertensive drug regimen. Aprovel was the only AIIRA licensed for early stage renal disease (microalbuminuria). The context was therefore clearly framed and was not extrapolated to non-diabetic, non-hypertensive patients as implied by Novartis.

Below the graph which related to the time to overt nephropathy the key findings of the study were presented including the claim at issue. Section 5.1 of the Aprovel SPC stated 'While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p=0.0004)'. This sentence clearly implied that the renoprotective effect was independent of the blood pressure lowering effect. This was a benefit seen in addition to blood pressure lowering and was the subject of a specific licensed indication granted by the European Medicines Evaluation Agency (EMEA).

Similarly pages 8 and 9 of the detail aid clearly defined the patient population studied in the trials presented ie hypertensive type 2 diabetics with renal disease and presented the key findings of the trials. Again this was in accordance with the marketing

authorization granted by the EMEA for renal protection in this patient group. There was no extrapolation beyond the marketing authorization.

As a result of this none of the instances constituted a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that page 2 of the detail aid referred to the fact that Aprovel was licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. This was repeated on page 5 of the detail aid. On page 7 the Panel noted that although the patient characteristics had been defined the reason for giving Aprovel ie to reduce blood pressure, had not.

The Panel noted the indications for Aprovel included the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

The Panel considered that on balance the claim for Aprovel's renoprotective effect being above and beyond its blood pressure lowering on page 7 was not clearly set within the licensed indication ie treatment of blood pressure. This was inconsistent with the SPC and a breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel considered that this ruling also applied to page 8 of the detail aid. A breach of Clause 3.2 of the Code was ruled. This ruling was appealed.

With regard to page 9, the Panel noted that the claim at issue was immediately followed by a statement that Aprovel was the first AIIRA to be licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. The Panel considered that this page was not unreasonable. It had been made clear that the reason for giving Aprovel was for the treatment of hypertension. No breach of Clause 3.2 of the Code was ruled in this regard. This ruling was not appealed.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The companies submitted that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' referred to the licensed indication for Aprovel for the treatment of renal disease in hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen. This claim appeared on page 7 of the detail aid. The first bullet point on the page clearly stated that the study upon which the licence was based was a study in hypertensives. Further to this, Section 5.1 of the Aprovel SPC stated 'While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300mg group (5.2%) than in the placebo (14.9%) … reached the end point of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p=0.0004)…'. This statement clearly implied that the renoprotective effect was beyond BP lowering and was used to support the claim at issue. Parving *et al* stated that the objective was to 'evaluate the renoprotective effect of irbesartan in…hypertensive patients'. Parving *et al* (upon which the licence was based) therefore was not a blood pressure lowering study as suggested by the Panel. The claim in question was clearly consistent with the SPC. The companies appealed the Panel's ruling of a breach of Clause 3.2 of the Code.

The companies noted that page 8 of the detail aid referred to Lewis *et al*. This study formed part of the evidence on which the Aprovel renoprotection licence was based (Section 5.1, Aprovel SPC) and was not designed as a blood pressure reducing study. The objective was 'to determine whether the use of an angiotensin receptor blocker or a calcium-channel blocker would provide protection against the progression of nephropathy due to type 2 diabetes beyond that attributable to the lowering of blood pressure'. The study concluded 'The angiotensin II receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes'.

The companies submitted that given these conclusions of a study on which the Aprovel licence was based and the first bullet point on the page indicating that the patient population was hypertensive they appealed the Panel's ruling of a breach of Clause 7.2 of the Code.

COMMENTS FROM NOVARTIS

Novartis stated that with regard to pages 7 and 8 of the detail aid, it was clear that Aprovel was licensed for the treatment of essential hypertension and for renal disease in hypertensive type 2 diabetic patients as part of an antihypertensive regimen. This was based on Parving *et al* and Lewis *et al* (2001) which had both required patients to be hypertensive to be included in the trial. Consequently any claim relating to renal protection must be set sufficiently within the context of the licensed indication namely as part of an antihypertensive regimen. The use of the claim in question on pages 7 and 8 did not make it clear that this related to a hypertensive patient population and the inference was that Aprovel could provide renoprotective benefits in patients without hypertension since this effect was not BP dependent. Consequently the use of the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' on pages 7 and 8 of the detail aid was in breach of Clause 3.2 of the Code as it had suggested that Aprovel might be used for renoprotection in an unlicensed population, namely patients who were not hypertensive if this effect was indeed independent of BP lowering.

APPEAL BOARD RULING

The Appeal Board considered that the detail aid had two distinct sections; pages 1-5 discussed Aprovel in relation to hypertension and pages 6-9 discussed the renoprotective effects of Aprovel within the context of the treatment of hypertension.

The Appeal Board noted from the layout in the detail aid that pages 6 and 7 made up a double page spread.

Page 6 of the detail aid was headed 'PRIME importance' and discussed two studies on hypertensive patients with type 2 diabetes. The studies were described as covering the disease spectrum of type 2 diabetic renal disease. These being IRMA2; Parving *et al*, early stage (microalbuminuria) and the Irbesartan Diabetic Nephropathy Trial (IDNT); Lewis *et al*, late stage nephropathy. The Appeal Board noted that an arrow across the bottom of page 6 pointed to page 7 on which the claim at issue appeared. The Appeal Board noted that Section 5.1 of the Aprovel SPC under the heading 'Hypertension and type 2 diabetes with renal disease' discussed the IRMA2 and IDNT studies. The Appeal Board noted that within the context of hypertension Aprovel was licensed for renoprotection and considered that the claim 'Aprovel's renoprotective effect is above and beyond its BP lowering' on page 7 was put into this context by the preceding page. The Appeal Board thus considered that the claim on page 7 was not inconsistent with the SPC and ruled no breach of Clause 3.2 of the Code. The appeal was successful.

The Appeal Board noted the claim at issue was repeated on pages 8 and 9 which discussed the conclusions of the IRMA2 and IDNT studies. The Appeal Board noted that page 9 stated that Aprovel was the first AIIRA to be licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. The Appeal Board considered that the claim on page 8 was put into context by the previous pages (6 and 7) and page 9 which it faced. The Appeal Board thus considered that the claim on page 8 was not inconsistent with the SPC and ruled no breach of Clause 3.2 of the Code. The appeal was successful.

5 Claim 'Aprovel – In control, in every way'

This claim appeared on the final page of the detail aid.

COMPLAINT

Novartis alleged that the claim 'Aprovel – In control, in every way' was all-embracing and in breach of Clause 7.10. The claim was not supported by any reference; indeed it would be hard to imagine what substantiation could be found for such a claim and it gave the physician the impression that all patients would be controlled with Aprovel in terms of efficacy (ie all patients would achieve target) and safety. Clearly this could not be substantiated and was an exaggeration of what could be expected when using Aprovel for its licensed indications.

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo stated that there was data that showed that Aprovel monotherapy was capable of controlling 66% of patients. Further to this the data mentioned above showed that a greater proportion of patients initiated on Aprovel monotherapy remained on this treatment after one year than any other class of antihypertensive. This implied that patient compliance was high and doctors were satisfied with the blood pressure control achieved. These were the two elements that must be satisfied in effective hypertension management. Also Aprovel was available in two dose strengths with the additional option of using the CoAprovel (irbesartan plus diuretic) combination tablet to help to achieve the blood pressure control. In light of this the companies did not consider that there had been a breach of Clause 7.10 of the Code.

PANEL RULING

The Panel considered that this claim was similar to the claim at issue point A1 above. The Panel considered that the claim 'Aprovel – In control, in every way' was exaggerated and all-embracing. A breach of Clause 7.10 of the Code was ruled.

B Aprovel leavepiece (APR 1006)

1 Claim 'Aprovel's renoprotective effect is above and beyond its BP lowering'

The claim appeared on page 4, headed 'Nephropathy', page 5, headed 'Microalbuminuria', and page 6 headed 'Conclusions'.

COMPLAINT

Novartis alleged that the claim was in breach of Clause 3.2 for the reason highlighted above (point A4).

RESPONSE

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the first bullet point on page 4 of the leavepiece defined the patient population to which the data presented referred ie hypertensive type 2 diabetics with late stage renal disease. This was in accordance with Aprovel's marketing authorization for treatment of renal disease in patients with type 2 diabetes mellitus as part of an antihypertensive drug regimen. The context was therefore clearly framed and was not extrapolated to non-diabetic, non-hypertensive patients as implied by Novartis.

Section 5.1 of the SPC for Aprovel stated 'While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p=0.0004)'. This sentence clearly implied that the renoprotective effect was independent of the blood pressure lowering effect. This was a benefit seen in addition to blood pressure lowering and was the subject of a specific licensed indication granted by the EMEA.

Similarly pages 5 and 6 of the leavepiece clearly defined the patient population studied in the trials presented ie hypertensive type 2 diabetics with renal disease and presented the key findings of the trials. Again this was in accordance with the marketing authorization granted by the EMEA for renal

protection in this patient group. There was no extrapolation beyond the marketing authorization.

As a result of this none of the instances constituted a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the leavepiece referred to PRIME, which was described as 'irbesartan mortality/morbidity evaluation'. It was stated that the PRIME programme consisted of two trials (IRMA 2 and IDNT) covering the disease spectrum of hypertensive type 2 diabetic renal disease.

The Panel noted its rulings in point A4 above. It considered that pages 4 and 5 of the leavepiece did not make it sufficiently clear that Aprovel was given to treat hypertension. The Panel thus considered that both pages were inconsistent with the SPC and each was ruled in breach of Clause 3.2 of the Code.

With regard to page 6, the Panel noted that the claim at issue was immediately followed by a statement that Aprovel was licensed for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive regimen. The Panel considered that this page was not unreasonable. It had been made clear that the reason for giving Aprovel was for the treatment of hypertension. No breach of Clause 3.2 of the Code was ruled in this regard.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

The companies submitted that as discussed in point A4 above the renal protection licence for Aprovel was based upon two studies (Parving *et al* and Lewis *et al*). Which examined the effect of Aprovel on renal disease in type 2 diabetics. Whilst the patients had to be hypertensive to be included the studies had not examined the antihypertensive effect of Aprovel. Both studies concluded that the renal effect of Aprovel was independent of its blood pressure lowering effect. This was reflected in Section 5.1 of the Aprovel SPC.

The companies submitted that the first bullet point made it clear that the patient group studied was hypertensive type 2 diabetics. The subsequent bullet points reflected the conclusions of the studies upon which the licence was based. As a result the companies appealed the ruling of a breach of Clause 3.2 of the Code.

COMMENTS FROM NOVARTIS

Novartis alleged that the claim in question which appeared on pages 4 and 5 of the leavepiece continued to be in breach of Clause 3.2 for the reason highlighted in point A4 above.

APPEAL BOARD RULING

The Appeal Board noted its rulings in A4 above. The leavepiece, unlike the detail aid, referred only to the use of Aprovel for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus. The first three pages of the leavepiece provided details of the two studies (IRMA2 and IDNT) which were said to cover the disease spectrum of hypertensive type 2 diabetic renal disease. The Appeal Board considered that, on balance, the claim on pages 4 and 5 of the leavepiece was put into context by the preceding pages and as such the claim was not inconsistent with the SPC. The Appeal Board thus ruled that each claim was not in breach of Clause 3.2. The appeal was successful.

Complaint received	**20 August 2003**
Cases completed	**AUTH/1510/8/03 on 6 January 2004** **AUTH/1511/8/03 on 5 January 2004**

CASE AUTH/1512/8/03

CONSULTANT PHYSICIAN v AVENTIS PHARMA

Insulin for Life Programme

A consultant physician complained about the promotion of Lantus (insulin glargine) by a representative of Aventis Pharma (Case AUTH/1482/6/03). It was not clear from the initial correspondence whether a complaint was also being made about the Insulin for Life Programme *per se*. In further comments on the matter the complainant stated that 'Whether the programme itself constituted a breach of the Code in terms of disguised promotion of Lantus was a decision for the Panel'. The Director decided that the complainant's comments about the Insulin for Life Programme would be taken up as a separate complaint, Case AUTH/1512/8/03.

The complainant stated that Aventis would train general practitioners' practice nurses to put patients on to Lantus on the understanding that ten patients per practice would be recruited. For the complainant the important issues were firstly, the impression made upon health professionals during promotion of the programme, and secondly, the choice of insulin actually used for the practical teaching. Locally the impression had been that practices must put ten patients on to Lantus to be eligible. It was for this reason, amongst others, that three of the local healthcare co-operatives had rejected the programme.

The Panel noted that the Code did not prevent the provision of medical and educational goods and services which would enhance patient care and benefit the NHS. The provision of such goods or services must not be done in such a way as to amount to an inducement to prescribe, supply, administer or buy any medicine. If medical representatives provided, delivered or demonstrated medical and educational goods and services then this must not be linked in any way to the promotion of products.

According to the representatives' briefing document headed 'Insulin for Life (IFL) Programme Materials Briefing Document' the aim of the Insulin for Life Programme was to train health professionals in primary care to manage their patients with type 2 diabetes in line with the Insulin for Life evidence based type 2 diabetes guidelines written by UK consultants, GPs and diabetes specialist nurses. The Insulin for Life package featured an accredited University of Warwick course for primary care professionals to facilitate blood glucose management, including insulin initiation, in line with National Service Framework (NSF) and National Institute for Clinical Excellence (NICE) standards; local practical support; support in the development and implementation of local protocols and a computer based application to help audit diabetic patients.

A leaflet provided to health professionals headed 'Insulin for Life Programme' discussed the management of type 2 diabetes and described the Insulin for Life Programme. No mention was made of Lantus, reference was made to insulin. The Panel noted the company's submission that at no time was any link made between the programme and an agreement to prescribe Lantus.

The Insulin for Life Process document advised representatives to identify potential pilot sites which would be happy to use Lantus as their basal insulin of choice. Once such sites were 'on board with Lantus' they were to be offered the concept of the Insulin for Life Programme. Aventis supplied a number of Diabetes Business Unit checklists. Each listed mandatory and preferred items. The primary care organisation (PCO) checklist listed under mandatory, *inter alia*, secondary care support for Lantus, secondary care champion for Lantus, PCO support for insulin initiation in primary care, including Lantus, and access for Aventis to all appropriate customers. Under preferred was listed, *inter alia*, growing market share for Lantus. The practice checklist listed under mandatory that practices must either 'implement the [Insulin for Life] consensus guideline or use their own type 2 diabetes protocol with Lantus agreed either first line or in line with NICE/[Scottish Medicines Consortium]' and 'Access for Aventis DAM/DAE to all appropriate customers'. One of the listed mandatory requirements for the trainers was that they were 'insulin initiators, preferably Lantus initiators'. The briefing document instructed representatives 'to continue to return to each practice to sell in the benefits of Lantus – in line with key performance indicators' which Aventis explained referred to representatives promoting Lantus.

The Panel considered that the Insulin for Life Programme itself was not necessarily in breach of the Code. The Panel was, however, concerned about the implementation of the programme; the representatives' briefing material was inappropriate in that the Panel considered that it advocated a course of action which would lead to a breach of the Code. The briefing material linked the provision of the service to the use and promotion of Lantus. The programme was directed towards PCOs which were already favourably predisposed towards Lantus and potential pilot sites had to be happy to use Lantus as their basal insulin of choice before they were to be offered the Insulin for Life Programme. The Panel considered that the role of the representatives in relation to the provision of the service was contrary to the requirements of the Code. The Panel was concerned about the dual role of representatives as they were responsible for selling Lantus and also had a key role in the implementation of the Insulin for Life Programme within their territories. This could give rise to difficulties given the representatives' briefing material.

The Panel considered that overall the provision of the service was too closely linked to the promotion of Lantus which in effect meant that the service was unacceptable. The Panel ruled a breach of the Code. The Panel did not consider the Insulin for Life Programme itself was disguised promotion. Nor did the Panel consider that the arrangements amounted to a breach of Clause 2 which was reserved as a sign of particular censure. The representatives were

involved in the implementation of the service but not its day to day running.

A consultant physician complained about the promotion of Lantus (insulin glargine) by a representative of Aventis Pharma Ltd (Case AUTH/1482/6/03). It was not clear from the initial correspondence whether a complaint was also being made about the Insulin for Life Programme *per se*. In further comments on the matter the complainant stated 'Whether the programme itself constituted a breach of the Code in terms of disguised promotion of Lantus was a decision for the Panel'. The Director decided that information had been received from which it appeared that Aventis might have contravened the Code and that the complainant's comments about the Insulin for Life Programme would thus be taken up as a separate complaint: Case AUTH/1512/8/03.

The matter was considered in relation to the requirements of the 2003 edition of the Code.

COMPLAINT

The complainant stated that Aventis would train general practitioners' practice nurses to put patients on to Lantus on the understanding that 10 patients per practice would be recruited. There was doubtless no stipulation in the company documents that health professionals must use Lantus in order to apply for a 'statement of extended practice'. The complainant stated that for her the important issues were firstly, the impression made upon health professionals during promotion of the programme, and secondly, the choice of insulin actually used for the practical teaching. Locally the impression had been that practices must put 10 patients on to Lantus to be eligible. It was for this reason, amongst others, that three of the local healthcare co-operatives had rejected the programme.

When writing to Aventis, the Authority asked it to respond in relation to Clauses 2, 10.2 and 18.1 of the Code.

RESPONSE

Aventis noted that the recently published National Service Framework (NSF) for Diabetes and the National Institute for Clinical Excellence (NICE) Guidelines for the treatment of type 2 diabetes highlighted the need for improvements in diabetes care across the UK. Inherent in this was the necessity for the GP to manage the increasing workload that would be associated with improvements in care, indeed the recent general medical services contract reflected this.

Aventis decided, along with Warwick Diabetes Care, University of Warwick, and a panel of independent experts, to create a two part programme to educate small numbers of GPs, already skilled in managing diabetes, in the intensive management of type 2 diabetes and insulin initiation. This programme was entirely non-promotional, and did not constitute disguised promotion. It was centred around two Warwick Diabetes Care training courses:

1 *Trainers Accreditation Programme:* the training of experienced diabetes professionals, usually diabetes specialist nurses or physicians (GPs or consultants) in the skills of facilitation and teaching. This training was conducted by Warwick Diabetes Care and those completing the course became Warwick trainers accredited to deliver the 'Intensive management in type 2 diabetes – local programme'.

2 *Intensive management in type 2 diabetes – local programme* – these trainers trained those GPs and their practice nurses who had a special interest in type 2 diabetes and wished to develop additional skills in managing their patients' care. This was a full day training course covering a wide variety of subjects including the implementation of the NSF, management of oral and insulin therapies and hypoglycaemia. A complete list of the topics was stated in the programme overview provided. All strategies for diabetes treatment were discussed, including diet and exercise regimes, oral agents, insulin regimens and insulin delivery devices.

In addition the programme provided practical support in implementing the theoretical skills taught on the course. The professionals taking part could apply for a 'statement of extended practice' from Warwick Diabetes Care. To achieve this, they had to demonstrate that the skills taught had been adopted in a safe and clinically effective way. This involved the successful, supervised initiation of ten patients on to insulin. Warwick Diabetes Care considered this to be both a practical and ethical way to ensure that the doctors/nurses had reached the appropriate skill level to enable them to be considered for the award of their competence statement.

Participating practices were offered the services of a registered nurse, employed by a third party company, to support practice personnel in achieving the competence goal. Aventis noted that these nurses, all of whom were experienced insulin initiators, only supported health professionals in implementing the management decisions of the responsible clinician, usually the GP. The complainant mistakenly suggested that practices must agree to put ten patients on to Lantus in order to be included in the programme. This was not true. Moreover, there was no stipulation that health professionals must use Lantus in order to apply for the statement of extended practice. The practice and each individual practitioner would be supported and assisted by the nurse in the implementation of their decisions.

Aventis' representatives were fully briefed on the non-promotional, educational nature of this programme and this was regularly reinforced by its management team. There was never any link between the Insulin for Life programme and an agreement to prescribe Lantus.

The Insulin for Life programme was a detailed, comprehensive and valuable educational service offered only to health professionals already experienced in diabetes care, who wished to augment and enhance their skills further through the intensive management of their patients. Aventis reiterated that in no part of this programme, or its communication to its representatives, was the stipulation to prescribe

Lantus made or inferred. Aventis was confident that the programme maintained the expected high standards of the industry and neither constituted disguised promotion nor an inducement to prescribe Lantus or any other Aventis product. Aventis believed that the Insulin for Life Programme adhered to the Code and thus denied breaches of Clauses 2, 10.2 and 18.1.

A Diabetes Business Unit briefing document headed 'Insulin for Life Process' had been supplied by Aventis in relation to Case AUTH/1482/6/03 and featured the phrase 'DAM/DAE to continue to return to each practice to sell in the benefits of Lantus'. With particular reference to the words 'sell in', Aventis explained that the Diabetes Account Managers or Executives (DAMs/DAEs) were Aventis Diabetes Business Unit representatives who worked in primary care. In this role they undertook the promotion of Lantus to health professionals in the usual manner. In addition, they had a key role in providing the necessary logistical and administrative support to allow the Insulin for Life Programme to run within their territories.

The DAMs/DAEs' remit extended to discussing the programme content with a number of key health professionals in their area. At the outset, they approached relevant individuals working within primary care organisations (PCOs) and the corresponding hospitals to discuss whether it would be beneficial for the programme to run in general practices within that PCO and hospital catchment area. If both were supportive of the programme, they progressed to discuss the role of Warwick Diabetes Care accredited trainer with appropriately experienced local diabetes professionals (who would deliver the 'Intensive management in type 2 diabetes – local programme'). Finally they introduced the programme to individual GPs and their practice nurses, who might wish to participate.

Aventis stated that the appendices to the Diabetes Unit briefing document showed that at each of these stages, the DAMs/DAEs were responsible for collating much of the paperwork and logistics necessary for the programme to run smoothly. It was important to stress that they did not have a role in any clinical activities; the registered nurses employed by the third party company in conjunction with GPs or practice nurses were the only people who undertook these.

The term 'sell in' was used in this context to refer to the DAMs/DAEs promoting Lantus. Any such promotional activity was undertaken separately from their role as 'local co-ordinators' for the Insulin for Life Programme and occurred irrespective of whether a health professional was participating in the programme.

The choices of therapy that individual GPs or practice nurses made continued to be entirely their decision and responsibility. At no time was a stipulation made that Lantus must be used if a practice was participating in the programme. Aventis trusted that therefore it was now very clear that Aventis representatives were not promoting Lantus as part of the Insulin for Life Programme.

Aventis also confirmed that no briefing material for Lantus representatives cross-referred to the Insulin for Life Programme.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.1 of the Code stated that Clause 18.1 did not prevent the provision of medical and educational goods and services which would enhance patient care and benefit the NHS. The provision of such goods or services must not be done in such a way as to amount to an inducement to prescribe, supply, administer or buy any medicine. The supplementary information also stated that if medical representatives provided, delivered or demonstrated medical and educational goods and services then this must not be linked in any way to the promotion of products.

The Panel noted that according to the representatives' briefing document headed 'Insulin for Life (IFL) Programme Materials Briefing Document' dated 21 January 2003 the aim of the Insulin for Life Programme was to train health professionals in primary care to manage their patients with type 2 diabetes in line with the Insulin for Life evidence based type 2 diabetes guidelines written by UK consultants, GPs and diabetes specialist nurses. The Insulin for Life package featured an accredited University of Warwick course for primary care professionals to facilitate blood glucose management, including insulin initiation, in line with NSF and NICE standards; local practical support; support in the development and implementation of local protocols and a computer based application to help audit diabetic patients.

The Panel noted that the leaflet provided to health professionals headed 'Insulin for Life Programme' (ref LAN2021202) discussed the management of type 2 diabetes and described the Insulin for Life Programme. No mention was made of Lantus, reference was made to insulin. The Panel noted the company's submission that at no time was any link made between the programme and an agreement to prescribe Lantus.

The Panel further noted that the conduct of a representative in relation to the Insulin for Life programme was the subject of Case AUTH/1482/6/03 wherein Aventis provided part of a representatives' Diabetes Business Unit Briefing document headed 'Insulin for Life Process', dated 7 March 2003. Aventis was asked to comment on this document in the present case.

The Panel noted that the Insulin for Life Process document advised representatives to identify potential pilot sites which would be happy to use Lantus as their basal insulin of choice. Once such sites were 'on board with Lantus' they were to be offered the concept of the Insulin for Life Programme. Aventis supplied a number of Diabetes Business Unit Checklists. Each listed mandatory and preferred items. After each item was a column to indicate yes or no and another headed 'Name of key contacts/Action points'. The primary care organisation (PCO) checklist listed under mandatory,

inter alia, secondary care support for Lantus, secondary care champion for Lantus, PCO support for insulin initiation in primary care, including Lantus, and access for Aventis to all appropriate customers. Under preferred was listed, *inter alia*, growing market share for Lantus. The practice checklist listed under mandatory that practices must either 'implement the [Insulin for Life] consensus guideline or use their own type 2 diabetes protocol with Lantus agreed either first line or in line with NICE/[Scottish Medicines Consortium]' and 'Access for Aventis DAM/DAE to all appropriate customers'. One of the listed mandatory requirements for the trainers was that they were 'insulin initiators, preferably Lantus initiators'. The briefing document instructed representatives 'to continue to return to each practice to sell in the benefits of Lantus – in line with key performance indicators' which Aventis explained referred to representatives promoting Lantus.

The Panel considered that the Insulin for Life Programme itself was not necessarily in breach of the Code. The Panel was, however, concerned about the implementation of the programme; the representatives' briefing material was inappropriate in that the Panel considered that it advocated a course of action which would lead to a breach of the Code. The briefing material linked the provision of the service to the use and promotion of Lantus. The programme was directed towards PCOs which were already favourably predisposed towards Lantus and potential pilot sites had to be happy to use Lantus as their basal insulin of choice before they were to be offered the Insulin for Life Programme. The Panel considered that the role of the representatives in relation to the provision of the service was contrary to the requirements of the supplementary information to Clause 18.1. The Panel was concerned about the dual role of representatives as they were responsible for selling Lantus and also had a key role in the implementation of the Insulin for Life Programme within their territories. This could give rise to difficulties given the representatives' briefing material.

The Panel considered that overall the provision of the service was too closely linked to the promotion of Lantus and thus did not meet the requirements of the supplementary information to Clause 18.1. This in effect meant that the service was unacceptable. The Panel ruled a breach of Clause 18.1 of the Code. The Panel did not consider the Insulin for Life Programme itself was disguised promotion; no breach of Clause 10.1 was ruled. Nor did the Panel consider that the arrangements amounted to a breach of Clause 2 which was reserved as a sign of particular censure. The representatives were involved in the implementation of the service but not its day to day running.

Proceedings commenced **1 September 2003**

Case completed **25 November 2003**

CASE AUTH/1515/9/03

GENERAL PRACTITIONERS v GLAXOSMITHKLINE

Asthma audit

The partners of a general practice complained that an asthma audit nurse, sponsored by GlaxoSmithKline, had added Seretide to the repeat prescription database of all but two patients that she saw without discussing this with any clinician in the practice. She also issued a prescription for this on the same day that she saw the patients. As she added Seretide to the repeat database the complainants assumed that it was an established prescription and hence it was signed. The complainants had not agreed to this in the study. The complainants only found out otherwise by looking in the nurse's folder and finding the 'Therapy recommendation register'. It was alleged that this was highly inappropriate and unethical.

The Panel noted that GlaxoSmithKline's instructions for carrying out the audit had not been followed. Changes had been made to patients' therapy on the practice database by the audit nurse without such changes being authorized by a GP. GlaxoSmithKline had submitted that the audit nurses believed that they had been given permission to enter treatment recommendations on to the computer and the practice nurse, who was also the key audit contact for the practice, would check with an appropriate GP that the changes were acceptable and request their signature of approval. The agreed procedure, however, was that even if nurses were allowed to enter data onto the computer database themselves then the therapy change register had first to be signed by all the GPs. The Panel noted that GlaxoSmithKline had not provided any documentation from the practice in question to show unequivocally that the audit nurses had been given permission to input prescribing recommendations on the patient database before the therapy change register had been signed by the GPs. The Panel considered that high standards had not been maintained and noted that GlaxoSmithKline had accepted that this might have been the case. A breach of the Code was ruled.

The Panel considered that, as implemented in the practice in question, the asthma patient review was in effect linked to the prescription of Seretide. A breach of the Code was ruled. The Panel noted that the action of the audit nurse, sponsored by GlaxoSmithKline, who had changed patients' prescriptions without prior agreement with the doctor, brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The partners of a general practice complained about the conduct of an asthma audit nurse sponsored by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainants stated that the audit nurse added Seretide to the repeat prescription database of all but two patients that she saw without discussing this with any clinician in the practice. She also issued a prescription for this on the same day that she saw the patients. As she added this to the repeat database the complainants assumed that it was an established prescription and hence it was signed. This was not something the complainants had agreed to in the study. The complainants only found out otherwise by looking in the nurse's folder and finding the 'Therapy recommendation register'.

The complainants alleged that this was highly inappropriate and unethical. They had subsequently contacted GlaxoSmithKline to explain the situation and to advise that they were stopping the study with immediate effect. They had also contacted the GlaxoSmithKline representative concerned who organised the audit and informed her of the same. The complainants stated that they would be recalling all patients from the study for review with their own practice nurse.

RESPONSE

GlaxoSmithKline explained that the audit was a non-promotional asthma patient review which it had sponsored and delivered through an independent agency. GlaxoSmithKline commissioned the agency to provide qualified nurses to administer the patient review and required the agency to ensure that such nurses followed the protocol throughout the review. The agency was responsible for monitoring the reviews as they progressed.

GlaxoSmithKline explained that the aim of the asthma patient review was to provide assistance to a practice to review poorly controlled patients (defined by the practice) and improve their care in an evidence based rational way. The patients were reviewed by a nurse employed by the agency who, with the permission of the practice, checked various aspects of the patient's treatment and recommended changes to patient management as appropriate to their clinical condition.

GlaxoSmithKline had reviewed the contracts and protocols and considered them to be appropriate and consistent with the supplementary information detailed in Clause 18.1 of the 2001 Code, and their content enabled the company to comply with the provisions of Clause 15 and the spirit of the Code in relation to contract workers.

The audit was performed without any condition regarding treatment choice applying ie there was no product bias. The project did not bear the name of any medicine. The audit nurses were employed and trained by the agency in accordance with operating procedures agreed with GlaxoSmithKline. Neither GlaxoSmithKline's non-promotional respiratory care associate nor the agency nurse were involved with promotion or promotional materials. The audit nurses (the audit nurse who originally visited the practice had left the agency and was replaced by the nurse in question) were appropriately experienced, qualified and professionally registered; only they had access to patient records. Patient confidentially was maintained and appropriate consent sought from the

practice. The nurses' remuneration was not linked to sales figures or treatment changes. Detailed contracts, operating procedures and training manuals had been agreed which identified the role of the nurses and stated that GP consent to therapy changes must be obtained. Further these instructions did not advocate any course of action which would be likely to lead to a breach of the Code. There was no attempt to hide GlaxoSmithKline's sponsorship. Written protocols were given to the practice and signed consent obtained at every step. No promotional materials were used as part of the audit. All briefing materials, contracts and training materials and protocols had been approved by Code of Practice signatories in accordance with company standard operating procedures.

GlaxoSmithKline provided copies of the briefing materials and training documents and gave details of the training of the audit nurse in question.

GlaxoSmithKline noted that the review protocols stipulated that a GP's signature must be obtained before activating any changes on the therapy recommendation register. In two reviews performed in the practice in question this did not appear to be the case. GlaxoSmithKline noted that the complainant had stated that the nurse in question had added Seretide to the repeat prescription database of all but two patients she saw. The company did not have detailed records to confirm which version was accurate.

Two copies of therapy registers had neither initials nor signatures of GPs in the correct places. GlaxoSmithKline agreed that this was a serious breach of the protocol agreed to by the practice.

GlaxoSmithKline noted the complainants' suggestion that the decisions made to change to Seretide might have been biased. Although the company had only been able to review two cases it considered that the changes made were rational and typical of management decisions that many clinicians would make. In addition GlaxoSmithKline considered that the changes were consistent with British Thoracic Society / Scottish Intercollegiate Guidelines Network Guideline on Asthma Management. GlaxoSmithKline provided anonymised details of the patients who had been changed to Seretide therapy.

GlaxoSmithKline noted that inhaler and device choice would always be subjective to some extent. Whilst all clinicians might not agree with all the changes made, the rationale and evidence base to support the nurse decisions were as follows:

All eight of the patients reviewed had issues with their asthma management; six were poorly controlled as documented by increased rescue medication use; three were poorly compliant and four had poor inhaler technique; seven patients were on relatively high doses of inhaled corticosteroids (average 1000mcg / day beclomethasone) and one was concerned about the cost of three prescription charges.

The nurse in question tried to maintain device consistency except where deliberately changing device to benefit the patient (eg to Easibreathe) and to make as few molecule changes as possible but take advantage of combination therapy. All patients changed to Seretide were taking salmeterol (one of the components in Seretide) and seven out of eight were taking an inhaled steroid not available in combination therapy. To change to the only other combination therapy (Symbicort) would have resulted in a change of two molecules (to formoterol and budesonide) and a device change, as Symbicort was only available in the Turbohaler. Changes to Seretide were made at equivalent or reduced inhaled steroid dose (where Seretide dose given). Seretide had been shown to be steroid sparing whilst maintaining overall asthma control. Changing from fluticasone and salmeterol to Seretide would incur reduced prescription item charges and might result in reduced prescribing costs, depending on dose prescribed. Where control and compliance were management issues Seretide was a rational choice as it was a combination therapy which had been shown to have control and compliance benefits over its component parts given concurrently or separately.

From the limited information available it seemed that the prescription changes made could be justified on clinical and cost grounds and would be seen as reasonable by many practitioners. GlaxoSmithKline stated that it would be happy for these changes to be assessed by an independent physician for their applicability to the general clinical management of asthma.

GlaxoSmithKline submitted that the nurses strongly believed that the practice had given instructions to them to behave as they did. They believed that it had been agreed that they should enter treatment recommendations directly onto the computer and that on the occasions mentioned a member of the practice staff would check with an appropriate GP that the changes were acceptable and request their signature of approval. They believed that this instruction was reinforced by the partners in the practice logging them onto the computer allowing them access to the prescribing system, a practice nurse helping them to repair the practice prescription printer during a clinic and verbal reassurances from the practice that things were going well. The GPs did sign prescriptions before they were given to patients.

The nurse in question was appropriately qualified and trained. Her CV and references, including some from other practices where she had performed reviews, were provided.

GlaxoSmithKline noted that the complainants had a different perspective of what had happened and that the prescription changes that had occurred had not been the GPs' intention.

The nurses had an excellent track record and were of a high standard. However the GPs' signatures did not appear in the appropriate place on the therapy recommendation register, which was a breach of the protocol. From the limited clinical records inspected it could be assumed that the changes made to medication were not unreasonable, fell within current national guidelines, and could be justified on clinical and cost grounds. Nevertheless the action which the nurse in question took did not comply with the protocol required by GlaxoSmithKline and agreed with the agency.

GlaxoSmithKline stated that after thorough investigation it considered that this issue had arisen as a consequence of an inadvertent and isolated failure to comply with the audit protocol. This was made by a well-qualified experienced nurse, who had been appropriately trained in asthma management and the patient review protocol. The nurse's action appeared to have been well intentioned but due to some misunderstanding she made changes to the practice prescribing system without getting signed authorization from GPs on the appropriate form. GlaxoSmithKline considered that the audit might have inadvertently breached Clause 9.1 ie high standards were not maintained. However GlaxoSmithKline considered that this was an isolated incident which the audit protocols, monitoring and training had been designed to prevent. The protocols complied with the requirements of, and supplementary information to, Clause 18.1; the company denied a breach of this clause.

The incident appeared to have arisen over a misunderstanding based upon a communication issue. The practice believed it was clear in its express intentions around the audit, whilst the nurses seemed unaware of its intent and were led to believe that they were acting according to the wishes of the practice. It seemed from the nurses' reports that they tried to ensure approval for treatment changes, but omitted to obtain a GP's signature as per the protocol.

GlaxoSmithKline considered that it had taken appropriate action at every step in the design, documentation and delivery of the patient review. The company also considered that it took appropriate action on hearing of the discontent. GlaxoSmithKline considered that the error was one that had occurred as a consequence of a random act by an individual and therefore considered that it was not in breach of Clause 2 of the Code.

In conclusion GlaxoSmithKline stated that it was confident that the intention and arrangements surrounding the audit fell within the guidance given in the Code and that its protocols and the training and briefing for company and agency employees were rigorous and fulfilled the requirements of the Code. The company considered that the audit nurse was appropriately trained and qualified. In this particular case the nurse made an error in not securing a GP's signature to agree to recommended treatment changes. This was clearly in breach of the audit protocols and the nurse's training; this was, however, an isolated incident. GlaxoSmithKline therefore concluded that whilst the conduct of the audit performed in this practice might have breached Clause 9.1, it considered that this was not in breach of Clauses 2 or 18.1 of the Code. The nurse concerned had been suspended from all activity involving GlaxoSmithKline sponsored work and would not be employed on such in the future. All agency nurses had received re-training and GlaxoSmithKline was reviewing its monitoring processes.

PANEL RULING

The Panel noted from the nursing agency's operations manual that the audit nurses were instructed to create a therapy recommendation register after each clinic. The register would record a patient's personal details together with current therapy, suggested therapy change and reasons for the recommendation. When the register was complete the audit nurses were to arrange a meeting with the GP to discuss the recommendations to medicine changes and to obtain a signature from the GP where such changes were agreed. Once the above had been completed the information would be passed on by the GP to practice staff for changes to be made to the practice database.

The audit nurses were advised that in some surgeries they might be asked to input data onto the computer database. If so they must ensure that the therapy change register was signed by all GPs, that instructions for the nurses to make such changes were documented, either in the Audit Protocol Documents or on surgery headed notepaper and that either or both were signed by participating GPs. Additionally audit nurses were advised to create an audit trail by using an individual password. It was stressed that the audit nurses must not make any amendments to patient information on computer without the express and written consent of the practice.

The Panel noted that the practice had amended the Surgery Protocol Guidance to add that the nurse advisor should 'consider Oxis before Serevent'. This had been handwritten next to the printed recommendation 'Add-in long acting ß2 Agonist'. The Panel noted GlaxoSmithKline's comments that the changes to the management of the patients could be justified on clinical and cost grounds.

The Panel noted that the instructions for carrying out the audit, issued by GlaxoSmithKline, had not been followed. Changes had been made to patients' therapy on the practice database by the audit nurse without such changes being authorized by a GP. GlaxoSmithKline had submitted that the audit nurses believed that they had been given permission to enter treatment recommendations on to the computer and the practice nurse, who was also the key audit contact for the practice, would check with an appropriate GP that the changes were acceptable and request their signature of approval. This understanding was reflected in the unsigned statements of the audit nurses which emphasised the role of the lead practice nurse in relation to the audit. The agreed procedure, however, was that even if nurses were allowed to enter data onto the computer database themselves then the therapy change register had first to be signed by all GPs. The Panel noted that GlaxoSmithKline had not provided any documentation from the practice in question to show unequivocally that the audit nurses had been given permission to input prescribing recommendations on the patient database before the therapy change register had been signed by the GPs. The Panel considered that high standards had not been maintained and noted that GlaxoSmithKline had accepted that this might have been the case. A breach of Clause 9.1 was ruled.

The Panel considered that, as implemented in the practice in question, the asthma patient review was in effect linked to the prescription of Seretide. A breach of Clause 18.1 was ruled. With regard to Clause 2, the Panel noted that a ruling of a breach of that clause

was a sign of particular censure and reserved for such use. The matter in hand involved an audit nurse, sponsored by GlaxoSmithKline, who had changed patients' prescriptions without prior agreement with the doctor. The Panel considered that such action brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **16 September 2003**

Case completed **1 December 2003**

CASE AUTH/1518/9/03

MEDIA/DIRECTOR v ORGANON LABORATORIES

Promotion of Cerazette

An article in the Drug and Therapeutics Bulletin, September 2003, entitled 'Is Cerazette the minipill of choice?', criticised claims made by Organon about its progestogen-only pill (minipill) Cerazette (desogestrel). The article reviewed Cerazette and its associated clinical evidence and considered whether it offered advantages over established progestogen-only pills (POP). The article concluded that 'Given the absence of published trials directly comparing Cerazette with a combined oral contraceptive, we believe the company's claim that Cerazette has the 'efficacy of a combined pill' is unsubstantiated and should be withdrawn'. In accordance with established procedure, the matter was taken up by the Director and dealt with as a complaint under the Code.

Organon provided a journal advertisement and detail aid which bore the claims 'The efficacy of a combined pill with the reassurance of an oestrogen free pill', '… with the efficacy of a combined pill' and 'the efficacy of a COC' [combined oral contraceptive].

The Panel noted Organon's submission that the claim 'the efficacy of a combined pill' was based on pharmacodynamic studies on ovulation inhibition, Pearl Indices (PIs), the clinical efficacy of Cerazette and the summary of product characteristics (SPC).

Cerazette had been shown consistently to inhibit ovulation within the range 98.3%-100% (Rice *et al* (1996 and 1999), Van Heusden (2000) and Obruca (2001)). The Panel noted Organon's submission that Cerazette's inhibition of ovulation was thus comparable to COCs. Section 4.8 of the Cerazette SPC stated that ovulation inhibition was close to 100%, in contrast to other POPs.

The Panel noted that comparative efficacy for a new oral contraceptive was generally determined by studying a sufficient number of menstrual cycles in the pivotal studies to give an overall Pearl Index (PI); the number of pregnancies per 100 woman years with a 95% confidence interval. The CPMP Guidance on the Clinical Investigations of Steroid Contraceptives stated that studies including an active comparator were generally not requested for efficacy purposes.

The Panel noted that the Collaborative Study Group (1998) compared the efficacy, acceptability and safety of Cerazette (n=979), with another POP, levonorgestrel (n=327) in 1320 subjects. Overall this study resulted in a PI of 0.41 for Cerazette and 1.55 for levonorgestrel. Similar differences between the two products remained when the results were reanalysed to take account of either documented gross non-compliance or breast feeding. It was noted that, excluding gross non-compliance but not breast feeding, the PI of Cerazette at 0.14 was within the range reported for low dose COCs. The study authors explained that Cerazette's PI was better than levonorgestrel due to its consistent inhibition of ovulation and its more pronounced suppression of the hypothalamic-pituitary-ovarian axis.

The Panel noted that the PI for levonorgestrel at 1.41 was in line with the PIs seen with POPs and that Cerazette's PI was within the range reported for the currently available ovulation inhibitors in the UK: 0.1 (Marvelon); – 0.7 (Yasmin). Section 5.1 of the Cerazette SPC stated that its PI was comparable to the one historically found for COCs in the general oral contraceptive-using population.

The Panel noted its comments above about the standing of the PI and the regulatory requirements for contraceptives. The Panel noted that neither the journal advertisement nor detail aid provided by Organon explained the basis on which the claim 'with the efficacy of a combined pill' was made. In the Panel's view many practitioners would assume that Cerazette had been directly compared with COCs in clinical trials which was not so. The estimated pregnancy rate for Cerazette (PI) had been shown by the Collaborative Study Group to be comparable with the historical pregnancy rates of COCs in general. The Panel considered that in the absence of direct comparative data the basis of the comparison should have been made clear and that without additional explanation the claim 'with the efficacy of a combined pill' was misleading. A breach of Clause 7.2 was ruled.

An article in the Drug and Therapeutics Bulletin, September 2003, entitled 'Is Cerazette the minipill of choice?', criticised claims made by Organon Laboratories Limited about its progestogen-only pill (minipill) Cerazette (desogestrel). In accordance with established procedure the matter was taken up by the Director as a complaint under the Code.

Organon provided a journal advertisement (ref 03645E) and detail aid (ref 03642K) which bore the claims 'The efficacy of a combined pill with the reassurance of an oestrogen free pill' and '…with the

efficacy of a combined pill' and 'the efficacy of a COC' [combined oral contraceptive].

COMPLAINT

The article began by noting that Cerazette was being promoted as 'the first oestrogen free pill to consistently inhibit ovulation' as having 'the efficacy of a combined pill, with the reassurance of an oestrogen free pill' and offering 'reliable contraception for women of any reproductive age'. The article reviewed Cerazette and its associated clinical evidence and considered whether it offered advantages over established progestogen-only pills (POP). The article concluded that 'Given the absence of published trials directly comparing Cerazette with a combined oral contraceptive, we believe the company's claim that Cerazette has the 'efficacy of a combined pill' is unsubstantiated and should be withdrawn'.

When writing to Organon the Authority asked it to respond in relation to the requirements of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Organon stated that the claim that Cerazette had the efficacy of a combined pill was based on four considerations: pharmacodynamic studies on ovulation inhibition, Pearl Indices, clinical efficacy and the summary of product characteristics (SPC).

Pharmacodynamic studies on ovulation inhibition

Traditional POPs were generally considered to act principally by increasing the viscosity of cervical mucus. A partial additional contribution to their mechanism of action was ovulation inhibition.

Four studies (Rice *et al* 1996 and 1999, Van Heusden 2000 and Obruca 2001) investigated ovulation inhibition in 127 cycles exposed to 75mcg desogestrel . A single ovulation was detected in these four studies (0.8%). Organon's considered that these four studies indicated that Cerazette consistently inhibited ovulation. Rice *et al* (1999) was performed in line with the Committee for Proprietary Medicinal Products (CPMP) Guidance on the Clinical Investigation of Steroid Contraceptives, and the size of the study was compatible with those conducted with other recently introduced contraceptives.

COCs were generally accepted as ovulation inhibitors. However, there was a wealth of information suggesting that even when using COCs, breakthrough ovulations could occur (Westcombe *et al*, 1987, Van der Vange, 1998, and Grimes *et al*, 1994). The ability of Cerazette to inhibit ovulation was therefore considered by Organon to be comparable to COCs.

It was important to contrast these figures with those reported on traditional POPs. In Rice *et al*, (1999), a direct comparative trial, ovulation was observed in 28% of the cycles with a levonorgestrel POP, and in their landmark review, McCann and Potter (1994) referred to ovulation occurring in 50% of the cycles with traditional POPs.

In summary, the primary mechanism of action of Cerazette had been assessed in appropriately sized studies, and found similar to that of COCs and dissimilar to that of POPs. Organon considered that Cerazette was the first oral contraceptive without oestrogen that blocked ovulation like a COC.

Pearl Indices

Organon stated that in standard practice, clinical efficacy of a contraceptive was expressed by its Pearl Index (PI), which reflected the number of pregnancies in 100 women using the method for one year. The calculation was based on 28-day cycles, thus in 1 year 100 women completed 1300 cycles of contraceptive use and PI = number of pregnancies x [1300 / number of investigated cycles].

The PI was a measure specifically designed to allow external comparisons between studies of different methods of contraception. This enabled practitioners to conclude, for example, that the use of barrier methods was less reliable than taking an oral contraceptive. Studies to calculate a PI were generally non-comparative because it was not necessary to assess a new PI for an active comparator. As the CPMP Guidance indicated: 'Studies including an active comparator are not generally requested for efficacy purposes'.

As pregnancies were intentionally an infrequent occurrence in study populations exposed to a contraceptive, there were certain minimum requirements for the size of the study in order to calculate robust pregnancy rates. The CPMP Guidance stipulated that at least 400 women should have completed one year of treatment with the product. In addition, the accuracy of the resulting PI was also used as a measure to qualify appropriateness of study size; the difference between the point estimate for the PI, and the upper limit of the 95% confidence interval should be less than 1.

Organon stated that the PI of Cerazette (0.41) was similar to those of the available COCs, which ranged from 0.1 to 0.7 and referred to published data and the table below.

Pearl Indices of the major currently available ovulation inhibitors in the UK (based on at least 400 women using the product for one year)

Trade name	*Estrogen/Progestogen*	*Pearl Index*
Mercilon	20mcg EE** / 150mcg desogestrel	0.2
Marvelon	30mcg EE / 150mcg desogestrel	0.1
Cilest	35mcg EE / 250mcg norgestimate	0.3
Femodene	30mcg EE / 75mcg gestodene	0.1
Yasmin	30mcg EE / 3000mcg drospirenone	0.7
Microgynon	30mcg EE / 150mcg levonorgestrel	0.4
Cerazette	75mcg desogestrel	0.4

** Ethinylestradiol

Organon submitted that these findings reflected the similar mechanism of action between Cerazette and the COCs.

The PIs of the currently available POPs were outlined in the table below. It was important to recognise that both clinical studies, and clinical consensus, demonstrated the lower efficacy achieved by traditional POPs.

Pearl Indices of currently available traditional progestogen-only pills in the UK (based on at least 400 women using the product for one year)

Trade name	*Progestogen*	*Pearl Index*
Femulen	500mcg ethynodiol diacetate	2.1
Micronor Noriday	350mcg norethisterone	2.3
Neogest	75mcg norgestrel	2.4
Microval Norgeston	30mcg levonorgestrel	3.0

Organon submitted that the PI of Cerazette was substantially lower than the traditional POPs and this reflected the pertinent difference in mode of action: the traditional POPs did not consistently inhibit ovulation, whereas Cerazette did. Cerazette's primary mode of action was therefore similar to that of the combined pill, whilst its formulation was that of a POP.

Clinical efficacy of Cerazette

The efficacy of Cerazette was assessed in a large (n=989) one-year study; 3 pregnancies occurred which translated to a PI of 0.41. Of the three women who became pregnant, one had missed 12 tablets and another woman had discontinued the study medication several weeks before conception.

Wording in the approved SPC

The SPC included wording that Organon considered supported its claims for ovulation inhibition and comparative efficacy; namely Section 4.4 'Cerazette consistently inhibits ovulation, …', Section 5.1 'In contrast to traditional progestogen-only pills, the contraceptive effect of Cerazette is achieved primarily by inhibition of ovulation as has been concluded from ultrasound monitoring of the ovaries and from the absence of both the midcycle LH-peak and an increase of luteal progesterone'. Section 5.1 'The Pearl-Index of Cerazette is comparable to the one historically found for combined OCs in the general OC-using population'.

Summary of efficacy

COCs consistently inhibited ovulation and were associated with PIs ranging between 0.1 and 0.7. Traditional POPs did not inhibit ovulation consistently; in about half the number of cycles the contraceptive effect depended on increased viscosity of the cervical mucus. In clinical studies, the traditional POPs had been associated with PIs ranging between 2 and 3. Cerazette consistently inhibited ovulation and had a PI of 0.41. Organon thus considered that Cerazette had a similar mechanism of action and similar contraceptive efficacy, as expressed by its PI, as COCs. The evidence for Cerazette's efficacy was derived from studies that complied with the European regulatory requirements for steroid contraceptives. The (external) comparison of the PIs derived from non-comparative studies – the usual and accepted approach in contraception – clearly indicated the PI of Cerazette to be comparable to those of COCs. Organon's view was that the PI was still a reliable method of measuring efficacy, which indeed was **designed specially** to enable comparison between products.

Organon thus submitted that the scientific data, and the wording in the SPC fully supported the claim 'the efficacy of a combined pill'.

Organon referred in detail to a MHRA review of a number claims for Cerazette including the claim 'the efficacy of a combined pill' at issue in this case. As a result of the review, Organon had agreed to certain actions including issuing corrective material.

In relation to the present complaint Organon approved, according to standard procedures, a promotional campaign for Cerazette, containing four claims that it considered complied with the requirements of the Code and with the approved SPC. Organon's interpretation of the underlying scientific evidence for the claim 'the efficacy of a combined pill' had found support from key opinion leaders. However, this claim had now been considered to be misleading by the MHRA and had been speedily withdrawn.

Organon regretted that the publicity arising from the complaints against its promotional campaign might reflect negatively on both the company and the pharmaceutical industry.

PANEL RULING

The Panel noted that this complaint arose out of an article published in the Drug and Therapeutics Bulletin which alleged that the claim that Cerazette had 'the efficacy of a combined pill' was unsubstantiated and should be withdrawn. Organon's response referred to additional matters considered by the MHRA. These were not before the Panel for consideration.

The Panel noted Organon's submission that the claim 'the efficacy of a combined pill' was based on pharmacodynamic studies on ovulation inhibition, PIs, the clinical efficacy of Cerazette and the SPC.

Cerazette had been shown consistently to inhibit ovulation within the range 98.3%-100% in 4 separate studies, Rice *et al* (1996), Rice *et al* (1999), Van Heusden (2000) and Obruca (2001). The Panel noted Organon's submission that Cerazette's inhibition of ovulation was thus comparable to COCs. Section 4.8 of the Cerazette SPC stated that ovulation inhibition was close to 100%, in contrast to other POPs.

The Panel noted that comparative efficacy for a new oral contraceptive was generally determined by studying a sufficient number of menstrual cycles in the pivotal studies to give an overall PI; the number of pregnancies per 100 woman years with a 95% confidence interval. The CPMP Guidance on the Clinical Investigations of Steroid Contraceptives stated that studies including an active comparator were generally not requested for efficacy purposes.

The Panel noted that the Collaborative Study Group (1998) compared the efficacy, acceptability and safety of Cerazette (n=979), with another POP, levonorgestrel (n=327) in 1320 subjects. Overall this study resulted in a PI of 0.41 for Cerazette and 1.55 for levonorgestrel. When excluding documented gross non-compliance the PIs were 0.14 and 1.17 for Cerazette and levonorgestrel respectively. Since one third of patients were breast-feeding at the start of the study, which might affect contraceptive efficiency, the PI was also calculated excluding these subjects resulting in 0.17 and 1.41 for Cerazette and levonorgestrel respectively. The study authors noted that these differences were not statistically significant. It was noted that the PI of Cerazette at 0.14 was within the range reported for low dose COCs. The study authors explained that Cerazette's PI was better than levonorgestrel due to its consistent inhibition of ovulation and its more pronounced suppression of the hypothalamic-pituitary-ovarian axis.

The Panel noted that the PI for levonorgestrel at 1.41 was in line with the PIs seen with POPs. The Panel also noted Organon's submission that Cerazette's PI was within the range reported for the currently available ovulation inhibitors in the UK; 0.1 (Marvelon) – 0.7 (Yasmin).

The Panel noted that Section 5.1 of the Cerazette SPC stated that its PI was comparable to the one historically found for COCs in the general oral contraceptive-using population.

The Panel noted its comments above about the standing of the PI and the regulatory requirements for contraceptives. The Panel noted that neither the journal advertisement nor the detail aid provided by Organon explained the basis on which the claim 'with the efficacy of a combined pill' was made. In the Panel's view many practitioners would assume that Cerazette had been directly compared with COCs in clinical trials which was not so. The estimated pregnancy rate (PI) for Cerazette had been shown by the Collaborative Study Group to be comparable with the historical pregnancy rates of COCs in general. The Panel considered that in the absence of direct comparative data the basis of the comparison should have been made clear and that without additional explanation the claim 'with the efficacy of a combined pill' was misleading. A breach of Clause 7.2 was ruled.

Proceedings commenced **22 September 2003**

Case completed **22 December 2003**

CASE AUTH/1521/10/03

WYETH v NOVO NORDISK

Kliovance leavepieces

Wyeth complained about comparisons that Novo Nordisk had made in two leavepieces between its own product Kliovance (estradiol, norethisterone acetate) and Wyeth's product Premique (conjugated oestrogen, medroxyprogesterone acetate). Both products were continuous combined hormone replacement therapies (HRTs).

In a previous case, Case AUTH/1417/2/03, Wyeth had complained, *inter alia*, that in a leavepiece a bar chart which directly compared the percentage of patients who were amenorrhoeic after two months' therapy with either Kliovance (73%) or Premique (57%) was inappropriate as the results were from two different studies, (Archer *et al* 1999 and Archer *et al* 1994 respectively). The Panel had considered that the depiction of the data within the same bar chart invited the reader to directly compare the data and implied that it was valid to do so; the footnote indicating that the data were from different trials did not negate the overall impression given. Breaches of the Code were ruled and accepted by Novo Nordisk.

In Case AUTH/1492/7/03 Wyeth had alleged that Novo Nordisk had breached its undertaking given in Case AUTH/1417/2/03 by, *inter alia*, continuing to use material which compared the percentage of patients who were amenorrhoeic after two months' therapy with either Kliovance or Premique. One of the pieces of material at issue was a second leavepiece which included two consecutive bullet points these being '73% of women amenorrhoeic after 2 months' and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The comparison, however, was not in the form of a bar chart as it had been previously and so the Panel considered that it was not covered by its ruling in Case AUTH/1417/2/03. No breach of the Code was ruled. Wyeth appealed this ruling.

The Panel noted that the second leavepiece was again at issue in the present case, Case AUTH/1521/10/03; at the time that the Panel considered this case Wyeth's appeal in Case AUTH/1492/7/03, with regard to the breach of undertaking, had yet to be heard by the Code of Practice Appeal Board.

The complaint now at issue with regard to the leavepiece was that even if it did not breach the undertaking given in Case AUTH/1417/2/03, then the comparison of the amenorrhoea data for Kliovance and Premique was misleading in whatever form it was presented ie pie chart, histogram, bullet points etc.

Wyeth was concerned by the implicit comparison between Kliovance and Premique amenorrhoea rates; the two consecutive bullet points clearly invited the reader to make a comparison. Moreover, the statement 'in a separate study' was an inadequate caveat, just as 'data from 3 different trials' was inadequate in the original complaint about the bar chart. Wyeth stated that the comparison between Kliovance and Premique was inappropriate for several reasons, including differences in patient population, inclusion criteria, the definition of amenorrhoea and other methodological differences between the two studies.

Archer and Pickar (2002) reviewed the assessment of bleeding patterns in postmenopausal women during continuous combined HRT, and stated that 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. In the light of Archer's comments and reported results, Wyeth alleged that any head-to-head comparison of amenorrhoea results from different trials with different methodologies, however presented, was untenable.

The Panel noted that in both Archer *et al* (1994) and Archer *et al* (1999) the women enrolled were all aged over 45 years and at least 12 months into their menopause. The women who took Kliovance (Archer *et al* 1999) had a mean age of 56 years and at baseline had been period free for a mean of 7 years. Women assigned to Premique (Archer *et al* 1994) were a little younger (mean age 54 years) and the mean time since last menses was 5.3 years. The Panel considered that 'no bleeding' in the Kliovance study was similar to that of 'amenorrhoea' in the Premique study; neither allowed for any bleeding or spotting at all. There were however differences in patient population, inclusion criteria and methodology. At month two 72.7% of Kliovance patients reported no incidence of bleeding (amenorrhoea) and in the Premique study 52.1% of women were amenorrhoeic.

Overall the Panel considered that there were similarities between Archer *et al* (1994) and Archer *et al* (1999). The data from the two studies were presented in two separate sequential bullet points. The second bullet point began '– in a separate study …'; it was thus immediately clear that the data had not come from a head-to-head study. Readers would not expect the two studies to be identical. The Panel noted that the percentage of women in each study who were amenorrhoeic appeared in emboldened print inviting the reader to compare the two. Nonetheless the Panel did not consider that the presentation of the data was misleading or an unfair comparison. No breach of the Code was ruled. No artwork was presented thus the Panel ruled no breach of the Code in that regard.

Wyeth complained about a further leavepiece entitled 'How soon can your HRT patients expect to be bleed-free?' which featured a bar chart of time (months) against % women amenorrhoeic. An inserted card could be slid inside the item to insert pieces of study data into the 2 and 6 month bar chart spaces to compare amenorrhoea rates between studies. The following three set of data were shown: Kliovance data at 2 and 6 months; Premique data at 6 months next to Kliovance data at 2 months; Femoston data at 6 months, next to Kliovance data at

2 months. Wyeth stated that for reasons discussed above, the comparison of amenorrhoea data from different studies in the same bar chart was unacceptable.

The Panel noted that the leavepiece in question had not been used for at least a year. Although never subject to a complaint itself, had the leavepiece still been in use earlier this year it would have been covered by the undertaking given in May with regard to Case AUTH/1417/2/03 and thus withdrawn. In that case Novo Nordisk had accepted the Panel's ruling that depiction of data from separate trials within the same bar chart was inappropriate. Given the outcome the Panel was concerned that Wyeth was now making the same complaint about a piece of promotional material that pre-dated Case AUTH/1417/2/03. In the Panel's view such a complaint was futile; it was nonetheless obliged to deal with it. The Panel noted that the three sets of data shown on the leavepiece combined data from different studies on the same bar chart. The Panel had no option but to rule breaches of the Code.

Wyeth Pharmaceuticals complained about comparisons that Novo Nordisk had made between its own product Kliovance (estradiol, norethisterone acetate) and Wyeth's product Premique (conjugated oestrogen, medroxyprogesterone acetate). The materials at issue were two leavepieces (ref KV/03/30 and KV/00/29). Both Kliovance and Premique were continuous combined hormone replacement therapies (HRTs).

In a previous case, Case AUTH/1417/2/03, Wyeth had complained, *inter alia*, that in a leavepiece (ref KV/02/10) a bar chart which directly compared the percentage of patients who were amenorrhoeic after two months' therapy with either Kliovance (73%) or Premique (57%) was inappropriate as the results were from two different studies, (Archer *et al* 1999 and Archer *et al* 1994 respectively). The Panel had considered that the depiction of the data within the same bar chart invited the reader to directly compare the data and implied that it was valid to do so; the footnote indicating that the data were from different trials did not negate the overall impression given. Breaches of the Code were ruled and accepted by Novo Nordisk.

In Case AUTH/1492/7/03 Wyeth had alleged that Novo Nordisk had breached its undertaking given in Case AUTH/1417/2/03 by, *inter alia*, continuing to use material which compared the percentage of patients who were amenorrhoeic after two months' therapy with either Kliovance or Premique. One of the pieces of material at issue was a leavepiece (ref KV/03/30). The Panel had noted that KV/03/30 included two consecutive bullet points these being '73% of women amenorrhoeic after 2 months' and 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The comparison, however, was not in the form of a bar chart as it had been previously and so the Panel considered that it was not covered by its ruling in Case AUTH/1417/2/03. No breach of the Code was ruled. Wyeth had appealed this ruling.

The Panel noted that leavepiece KV/03/30 was again at issue in the present case, Case AUTH/1521/10/03; at the time the Panel considered this case Wyeth's appeal in Case AUTH/1492/7/03, with regard to the breach of undertaking, had yet to be heard by the Code of Practice Appeal Board.

The complaint now at issue with regard to the leavepiece (ref KV/03/30) was that even if it did not breach the undertaking given in Case AUTH/1417/2/03 then the comparison of the amenorrhoea data for Kliovance and Premique was misleading in whatever form it was presented ie pie chart, histogram, bullet points etc.

A Leavepiece (ref KV/03/30)]

The leavepiece included two consecutive bullet points these being '**73%** of women amenorrhoeic after 2 months' and 'in a separate study **57%** of women were amenorrhoeic after 2 months on Premique'.

The leavepiece was produced exclusively for the British Menopause Society meeting in July 2003.

COMPLAINT

Wyeth accepted the figure of 73% but was concerned by the implicit comparison between Kliovance and Premique amenorrhoea rates. The company considered that the two consecutive bullet points clearly invited the reader to make a comparison, particularly when one considered how Novo Nordisk sales representatives were likely to verbalise the data. Moreover, the statement 'in a separate study' was an inadequate caveat, just as 'data from 3 different trials' was inadequate in the original complaint about the bar chart. The key arguments were:

- A comparison was made between Kliovance and Premique for percentage amenorrhoea at 2 months, despite the fact that the results were derived from two different studies. This was inappropriate for several reasons; differences in patient population, inclusion criteria, the definition of amenorrhoea (eg how many episodes of spotting were allowed) and other methodological differences.
- Archer and Pickar (2002) recently reviewed the assessment of bleeding patterns in postmenopausal women during continuous combined HRT, and stated that 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. In other words, expert opinion supported, Wyeth's contention that a comparison of amenorrhoea rates from different studies, based on current non-standardized methodologies, was not valid. Notably, Archer, who made these comments in the review, was the lead investigator in the Kliovance trial reporting 73% amenorrhoea (Archer *et al*, 1999), so his comments were highly pertinent to the current complaint. In the light of Archer's comments and reported results, Wyeth alleged that any form of head-to-head comparison of amenorrhoea results from different trials with different methodologies, however presented, was completely untenable.

Breaches of Clauses 7.2, 7.3 and 7.8 were alleged.

RESPONSE

Novo Nordisk considered that the comparison between Kliovance and Premique amenorrhoea rates in the leavepiece at issue was totally valid. It was clearly stated that the data was taken from separate trials since the second bullet point, 'in a separate study 57% of women were amenorrhoeic after 2 months on Premique'. The company submitted that the comparison was appropriate since the definition of amenorrhoea was standardised between the two trials as illustrated below.

The Kliovance study (Archer *et al* 1999) was a prospective, double blind, randomised trial on 1176 healthy postmenopausal women aged 45 years and older (mean 56 years), designed to assess the bleeding profile of Kliovance. Bleeding data for each day was recorded as either no bleeding or spotting, bleeding or spotting. It was clear from the definitions given by Archer *et al* that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The results showed that 72.7% of patients on Kliovance had no bleeding at cycle 2. The Kliovance patients (n=295) had a mean age of 56 years and at baseline had been period free for a mean of 7 years.

The Premique study (Archer *et al* 1994) assessed the bleeding patterns in 1724 postmenopausal women taking two continuous combined and two sequential regimens of conjugated oestrogens and medroxyprogesterone acetate and conjugated oestrogens alone. 338 patients were randomised to the Premique group, their mean age was 54 years and the mean time since last menses was 5.3 years. Bleeding and spotting were defined as vaginal bleeding that did or did not, respectively, require sanitary protection. For the analysis of data amenorrhea was defined as the absence of any bleeding or spotting during the entire 28 day medication cycle.

Novo Nordisk stated that whilst the exact methodology, patient populations etc in these two trials were not identical (although the main author was the same and the methodology was similar), to take Wyeth's objection to its logical conclusion would mean that no studies could ever be compared unless they were conducted in the exact same population of patients, at the exact same time – an impossible scenario. Indeed if this were the case one would never be able to conduct a meta-analysis which accumulated the results of many separate studies together and large databases of trials such as the Cochrane Database would be somewhat useless! Novo Nordisk submitted that the studies, clearly depicted as being separate, were similar enough to bear comparison and it had taken particular care on this point, especially with regard to the definition of amenorrhoea (no bleeding or spotting at all) which was similar between trials. Novo Nordisk did not consider that the comparison was unfair or misleading.

Novo Nordisk noted that Wyeth used a quotation from Archer and Pickar to support its argument: 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. Novo Nordisk challenged Wyeth's use of this quote since in this case the bleeding pattern being compared, ie amenorrhoea, had a similar definition in both studies. The quotation presumably referred to the comparison of studies which defined amenorrhoea differently and therefore was totally irrelevant to this particular case. Novo Nordisk considered that Wyeth was incorrectly extrapolating from this quotation – the quotation did not state that data from different trials should not be compared when comparisons were appropriate as in this case.

PANEL RULING

The Panel noted that Clause 7.2 of the Code required, *inter alia*, comparisons to be accurate, balanced, fair, objective, unambiguous, based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. Comparisons must not mislead either directly or by implication. There was no requirement that comparisons could only be made using data from the same study.

The Panel noted that in both Archer *et al* (1994) and Archer *et al* (1999) the women enrolled were all aged over 45 years and at least 12 months into their menopause. The women who took Kliovance (Archer *et al* 1999) had a mean age of 56 years and at baseline had been period free for a mean of 7 years. Women assigned to Premique (Archer *et al* 1994) were a little younger (mean age 54 years) and the mean time since last menses was 5.3 years. In the Kliovance study all months were classified into one of the following categories: month with no bleeding, month with bleeding (with or without spotting), or month with spotting only (no bleeding). Months classified as no bleeding therefore related to months where there had been no flow at all of uterine blood which implied amenorrhoea. In the Premique study amenorrhoea was defined as the absence of any bleeding or spotting during the entire 28 day medication cycle. The Panel thus considered that 'no bleeding' as described in the Kliovance study was similar to that of amenorrhoea as defined in the Premique study; neither allowed for any bleeding or spotting at all. There were however differences in patient population, inclusion criteria and methodology. At month two 72.7% of patients in the Kliovance study reported no incidence of bleeding (amenorrhoea) and at month two of the Premique study 52.1% of women were amenorrhoeic.

Overall the Panel considered that there were similarities between Archer *et al* (1994) and Archer *et al* (1999). The data from Archer *et al* (1994) and Archer *et al* (1999) were presented in two separate sequential bullet points. The second bullet point began '– in a separate study …'; it was thus immediately clear to the reader that the data had not come from a head-to-head study. Readers would not expect the two studies to be identical. The Panel noted that the percentage of women in each study who were amenorrhoeic appeared in emboldened print inviting the reader to compare the two. Nonetheless the Panel did not consider that the

presentation of the data was misleading or an unfair comparison. No breach of Clauses 7.2 and 7.3 was ruled. No artwork was presented thus the Panel ruled no breach of Clause 7.8 of the Code.

B Leavepiece (ref KV/00/29)

This leavepiece was entitled 'How soon can your HRT patients expect to be bleed-free?' and featured a bar chart of time (months) against % women amenorrhoeic. An inserted card could be slid inside the item to insert study data into the 2 and 6 month bar chart spaces to compare amenorrhoea rates between studies. The following three sets of data were shown: Kliovance data (Archer *et al*, 1998; Archer *et al*, 1999): 73% amenorrhoea at 2 months, 83% at 6 months; Premique data at 6 months (73% amenorrhoea rate; Archer *et al* 1994), next to Kliovance data at 2 months (73% amenorrhoea; Archer *et al* 1999); and Femoston data (estradiol, dydrogesterone) at 6 months (72% amenorrhoea; Solvay promotional material FEM166), next to Kliovance data at 2 months (73% amenorrhoea; Archer *et al*, 1999).

COMPLAINT

Wyeth noted that this leavepiece had not previously been the subject of a complaint. Wyeth stated that for reasons discussed in point A above, the comparison of amenorrhoea data from different studies in the same bar chart was unacceptable. Breaches of Clauses 7.2, 7.3 and 7.8 were alleged.

RESPONSE

Novo Nordisk stated that this very old promotional item (date of preparation 2000) was used by sales representatives in their discussions with GPs and was no longer in use. Wyeth had stated that this item had not been the subject of a previous complaint. This was not the case. The Panel ruling Case AUTH/1417/2/03 referred to the comparison of amenorrhoea rates between Kliovance and Premique in a bar chart similar to this. The ruling stated that 'The Panel considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous-combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote ('Data from 3 different trials') did not negate the overall impression given'. Breaches of the Code were ruled since the bar chart was deemed misleading in this regard. Novo Nordisk accepted the Panel's ruling and made it implicitly clear in subsequent material that the comparison referred to two separate studies by inserting 'in a separate study' into the second bullet point. Therefore this way of comparing data from separate studies on the same bar graph had already been found in breach and Novo Nordisk had already signed an undertaking to discontinue the relevant leavepiece as well as any similar material such as this. Novo Nordisk stated that if Wyeth had approached it with this complaint initially before going straight to the Authority it could have assured Wyeth of this and hopefully resolved the issue. Novo Nordisk was sorry that Wyeth did not do this and that the Authority had possibly been unnecessarily bothered. In addition it was not clear how Wyeth had obtained the leavepiece since it was out of use.

Novo Nordisk stated that the whole question of raising a complaint against very old and out of circulation material was an alarming one and could set a dangerous precedent. The Code was not clear on this issue and in principle one would accept that it was not acceptable for a company to produce an item and withdraw it almost immediately in the knowledge that the piece was potentially in breach of the Code. This should not stop a complaint being generated. However old, out of use materials which contained something found to be in breach in subsequent materials should not themselves be in breach if an undertaking to remove all such and similar materials had been given and the piece in question was no longer in use.

Novo Nordisk therefore did not consider that Wyeth was justified in making this complaint. In order for physicians to practise evidence-based medicine and for bodies such as the National Institute of Clinical Excellence (NICE) to operate effectively, it was essential that the pharmaceutical industry was upfront with its data even when this did not show its product in the best light and there was no commercial advantage. Sensible comparisons between data of different trials must be allowed in order to advance medical science and justify to an ethical standard the purpose of these very trials in the first place.

In response to a request for further information, Novo Nordisk stated that the leavepiece had been prepared in March 2000 and had not been used for at least the last year. The company did not know the exact date on which it was withdrawn as it was never itself the subject of a complaint, although it was covered by a previous ruling. Novo Nordisk stated that it was thus compliant with the undertaking given in May 2003 and so did not consider that Wyeth's complaint was valid.

PANEL RULING

The Panel noted that the leavepiece in question had not been used for at least a year. Although never subject to a complaint itself, had the leavepiece still been in use earlier this year it would have been covered by the undertaking given in May with regard to Case AUTH/1417/2/03 and thus withdrawn. In that case Novo Nordisk had accepted the Panel's ruling that depiction of data from separate trials within the same bar chart was inappropriate. Given the outcome the Panel was concerned that Wyeth was now making the same complaint about a piece of promotional material that pre-dated Case AUTH/1417/2/03. In the Panel's view such a complaint was futile; it was nonetheless obliged to deal with it. Paragraph 5.1 of the Constitution and Procedure stated, *inter alia*, that where a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication then the Director should normally let it proceed if it covered matters similar to those in a decision of the Panel which was not the subject of appeal to the Code of

Practice Appeal Board. The relevant ruling at issue in Case AUTH/1417/2/03 was not subject to appeal.

The Panel noted that the three sets of data shown on the leavepiece combined data from different studies on the same bar chart. The Panel had no option but to rule breaches of Clauses 7.2, 7.3 and 7.8 as alleged.

Complaint received **2 October 2003**

Case completed **11 December 2003**

CASE AUTH/1522/10/03

NOVARTIS/DIRECTOR v FUJISAWA

Breach of undertaking

Novartis alleged that an advertisement for Prograf (tacrolimus) issued by Fujisawa which appeared in the June issue of the Journal of the World Transplant Games Federation (WTGF) was in breach of the undertaking given in Case AUTH/1419/2/03 wherein a similar advertisement had appeared in the same journal, which was distributed to both health professionals and members of the public. Novartis referred to Fujisawa's persistent breach of the Code regarding direct to consumer advertising.

The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

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 in the future. It was very important for the reputation of the industry that companies complied with undertakings.

Case AUTH/1419/2/03 concerned a Prograf advertisement which had appeared in the November 2002 edition of the journal of the WTGF 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. A breach of the Code had been ruled.

Turning to the present case the Panel noted that the advertisement now at issue was similar to that considered previously but it was larger and the company and product logos appeared at the bottom rather than along the right-hand side of the advertisement. Further to Case AUTH/1419/2/03, Fujisawa UK had reminded the European marketing group of the need to involve Fujisawa UK in the copy approval procedure for future advertisements it placed in journals published in the UK or intended mainly for a UK readership. A copy of email correspondence between Fujisawa's senior international product manager and the journal was provided. The Panel queried whether the written instructions to the journal regarding the advertisement's withdrawal were adequate. The emails from Fujisawa's European marketing group referred to 'the ad' and stopping 'this appearing in further copies' [emphasis added] which suggested that there was only one. It was not made clear that all sizes, formats and closely similar versions of the advertisement needed to be withdrawn. A different version of the same advertisement had subsequently been published. The Panel considered that Fujisawa had failed to comply with its undertaking and the Panel ruled a breach of the Code.

The Panel considered that Fujisawa UK had been let down by the journal and its European head office. Although some effort had been made to comply with the undertaking, nonetheless the instructions to the journal were inadequate. High standards had not been maintained. A breach of the Code was ruled. The failure to provide adequate instruction in relation to the withdrawal of an advertisement for a prescription only medicine from a journal with a mixed audience had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

Novartis Pharmaceuticals Ltd complained about an advertisement for Prograf (tacrolimus) issued by Fujisawa Limited which appeared in the June issue of the Journal of the World Transplant Games Federation (WTGF). Novartis alleged that the advertisement was in breach of the undertaking given in Case AUTH/1419/2/03 wherein Fujisawa had voluntarily advised the Authority that an oversight had led to an advertisement for Prograf, rather than a corporate advertisement, appearing in the journal of the WTGF, which was distributed to both health professionals and members of the public. The Panel had ruled a breach of the Code as acknowledged by Fujisawa.

The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

COMPLAINT

Novartis complained in the strongest possible terms about Fujisawa's persistent breach of the Code regarding direct to consumer advertising. The company alleged that Fujisawa's activities were such as to bring discredit to the pharmaceutical industry in breach of Clause 2 of the Code.

The advertisement in question first appeared in the November issue of the journal of the WTGF which was a UK based organisation. This publication was widely distributed to organ transplant recipients who

participated in the games as well as to health professionals.

The advertisement purported to depict a liver transplant recipient aged 12 to whom a number of quotes were attributed, including 'feel very good', 'just like all the other kids' could 'lead a normal life' and 'can really enjoy myself now' ending with the assurance that her 'medication is no problem at all'. As a footnote, her name and age were given together with the fact that she was taking 13mg Prograf.

Novartis noted that two other companies had previously contacted Fujisawa about this advertisement and one had received the following assurances from Fujisawa:

- That the placement of this advertisement in a patient rather than a purely professional journal was a simple administrative error on the part of Fujisawa Munich.
- That Fujisawa would voluntarily bring the matter to the attention of the Authority to guard against any misunderstanding of the company's intent.

In view of this history, Novartis was concerned to note that the June 2003 issue of the WTGF journal carried the same advertisement, once again prominently situated on the inside cover but this time doubled in size.

Novartis did not consider such an advertisement suitable promotion even if exclusively directed at health professionals, due to its exploitative use of a child to make over simplified claims in a complex therapy area. In view of the questionable style of the advertisement, it was reasonable to expect extra care to be taken in its placement. Instead, despite inter-company dialogue to avert possibly unintentional abuse of the regulations, Fujisawa had repeated the advertisement and even increased its size in a patient journal, suggesting that this was a concerted campaign on its part. This was either a calculated attempt to promote direct to patients in breach of Clause 20.1 of the Code and in contravention of EC law or a reflection of complacency and disregard of the need for adequate internal control regarding the placement of promotional materials.

When writing to Fujisawa, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22 of the Code in addition to Clause 20.1 cited by Novartis.

RESPONSE

Fujisawa stated that it was notified by its European head office on 25 September 2003 that an error had been made by the publishers of the WTGF journal. In an astonishing repeat of a previous mistake the wrong advertisement had appeared in the current version of the journal. Fujisawa had been in discussions with its European marketing group and was in the process of gathering all the relevant correspondence together before contacting the Authority directly to bring this most unfortunate incident to its attention. However, Novartis' complaint pre-empted this. Fujisawa was concerned that Novartis had written directly to the Authority without making any attempt to correspond with Fujisawa.

Although Fujisawa in the UK had no involvement in placing this and the previous advertisement in the journal it accepted its responsibility under the Code. Fujisawa's European central marketing group was responsible for the placing of advertisements in the WTGF journal. Following the error in the previous edition of the journal (Case AUTH/1419/2/03), Fujisawa had reminded the European marketing group of the need to involve the UK in the copy approval procedure for future advertisements it placed in journals published in the UK or intended for a mainly UK readership.

Fujisawa provided a copy of the intended corporate advertisement along with the signatures of Fujisawa's signatories confirming the non-promotional nature of this advertisement and dated 20 March 2003. Also provided was an email, also dated 20 March 2003, from its senior international product manager – immunology, indicating both his intention to send all planned advertisements for copy approval to the UK office of Fujisawa and enclosing the advertisement that should have appeared in the earlier edition of the WTGF journal.

A copy of a series of emails between Fujisawa and the WTGF was provided. In an email dated 17 February 2003 Fujisawa made it very clear that it wished to prevent any further copies of the advertisement appearing. In the email dated 18 February 2003 Fujisawa had asked the WTGF to delete the advertisement previously sent. A reply from the WTGF in response to this using the phrase 'consider it done' suggested that the advertisement had or would be deleted from its files.

Fujisawa referred to a letter from the WTGF, dated 22 September 2003, which apologised for the error and made it clear that Fujisawa had provided the appropriate advertisement some time previously.

Fujisawa's European central marketing group had taken all reasonable steps to ensure that the correct advertisement was placed in the most recent edition of the WTGF journal and by doing so complied with its undertaking with respect to Case AUTH/1419/2/03. The company therefore denied any breach of Clauses 22, 9.1, 20.1 or Clause 2.

Fujisawa took very seriously its responsibilities to the Authority and prided itself on the very high standards that it applied to its copy approval procedures. Therefore Fujisawa found this latest episode especially embarrassing and expressed its sincere apologies for this error.

PANEL RULING

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 in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Case AUTH/1419/2/03 concerned an advertisement for Prograf which had appeared in the November 2002 edition of the journal of The World Transplant Games Federation. The Panel had 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. A breach of the Code had been ruled.

In relation to the alleged breach of undertaking, the Panel noted that the advertisement at issue was closely similar to that considered in the previous case; it was larger and the company and product logos appeared at the bottom rather than along the right-hand side of the advertisement. The content of the advertisement was otherwise identical. The Panel noted that further to Case AUTH/1419/2/03 Fujisawa UK had reminded the European marketing group of the need to involve Fujisawa UK in the copy approval procedure for future advertisements it placed in journals published in the UK or intended mainly for a UK readership. A copy of email correspondence between the Fujisawa's senior international product manager and the journal was provided wherein the journal was advised that it had been provided with 'the wrong ad' and that the company would 'like to stop this appearing in further copies'. The correct advertisement would be forwarded. A subsequent email stated that the original advertisement at issue in Case AUTH/1419/2/03 should be deleted. The Panel noted Fujisawa's submission that the journal's response 'consider it done' suggested that the advertisement had been (or would be) deleted from its files. The Panel did not have before it a copy of the email or other correspondence providing the journal with the correct version of the advertisement. The Panel however noted a letter from the WTGF stating that the appropriate advertisement had been provided by the company 'some time ago'. The Panel queried, however, whether the written instructions to the journal regarding the advertisement's withdrawal were adequate. The emails from Fujisawa's European marketing group referred to 'the ad' and stopping 'this appearing in further copies' [emphasis added] which suggested that there was only one. It was not made clear that all sizes, formats and closely similar versions of the advertisement needed to be withdrawn. A different version of the same advertisement had subsequently been published. The Panel considered that Fujisawa had failed to comply with its undertaking and the Panel ruled a breach of Clause 22 of the Code. The Panel considered that its ruling of a breach of Clause 22 covered the allegation of a breach of Clause 20.1 of the Code.

The Panel considered that Fujisawa UK had been let down by the journal and its European Head Office. The Panel considered that although some effort had been made to comply with the undertaking, nonetheless the instructions to the journal were inadequate. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that the failure to provide adequate instruction in relation to the withdrawal of an advertisement for a prescription only medicine from a journal with a mixed audience had brought discredit upon, and reduced confidence in, the pharmaceutical industry; a breach of Clause 2 was ruled.

Complaint received **2 October 2003**

Case completed **14 November 2003**

CASE AUTH/1523/10/03

NOVARTIS v SANKYO PHARMA

Promotion of Olmetec

Novartis complained about a leavepiece and a mailing, issued by Sankyo Pharma, which promoted Olmetec (olmesartan). The claims 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8' and 'Up to 46% greater reduction in DBP than losartan, valsartan and irbesartan by week 8' appeared in the leavepiece and mailing respectively. Both claims were referenced to Oparil (2002) *et al* while the claim in the mailing was additionally referenced to Brunner and Sanita (2003).

Novartis alleged that Oparil *et al* was an unfair comparison of the antihypertensive effects of Olmetec 20mg with other angiotensin II antagonists (AIIAs) (losartan 50mg, valsartan 80mg and irbesartan 150mg). The summaries of product characteristics (SPCs) for losartan, valsartan and irbesartan identified these doses as the starting doses in the majority of hypertensive patients. However the Olmetec SPC stated that the starting dose was 10mg with 20mg, which was described as the 'optimal' dose, recommended only if blood pressure was not controlled on 10mg.

However, as the treatment of hypertension was determined by the blood pressure reduction, rather than a target dose, antihypertensive therapy was only titrated if blood pressure did not fall to recommended goals after initial treatment. Therefore the useful information for the clinician was how the effects of starting doses compared. Novartis alleged that comparing the titration dose of Olmetec with the starting doses of the other AIIAs was unfair.

Oparil *et al* randomised untreated hypertensive patients to receive Olmetec 20mg rather than titrating through the 10mg licensed starting dose; patients were thus not treated according to the marketing authorization. Novartis alleged that this was inconsistent with the SPC.

The Panel noted that the Olmetec SPC stated that the recommended starting dose was 10mg once daily. In patients whose blood pressure was not adequately controlled at this dose, the dose might be 'increased to 20mg once daily as the optimal dose'. If additional blood pressure reduction was required the dose might be increased to a maximum of 40mg daily.

The Panel noted that losartan 50mg was described in the Cozaar SPC as the starting and maintenance dose for most patients. Similarly irbesartan 150mg was described in the Aprovel SPC as the usual recommended initial and maintenance dose. Valsartan 80mg was described in the Diovan SPC as the recommended dose for most patients. The Panel noted the submission that Oparil *et al* was an American study and in the USA Olmetec 20mg was the licensed starting dose. Oparil *et al* thus stated that all medicines were given at their recommended initial doses. However, given the products' licensed doses within the UK the Panel did not consider that the claims at issue compared the titration dose of Olmetec with the starting doses of losartan, valsartan and irbesartan as alleged. No breach of the Code was ruled in respect of each promotional item.

The Panel noted that patients had not been titrated from 10mg once daily, the recommended starting dose in the UK. The Panel did not consider, however, that the claims at issue were inconsistent with the SPC on this point as alleged; they did not state or imply that 20mg was the starting dose. No breach of the Code was ruled in respect of each promotional item.

Novartis noted the claim 'the real low down' which appeared in a highlighted red box within and on the front page of each item. The company considered that as the focus was the effectiveness of Olmetec to reduce blood pressure down to low levels, the 'low down' related to 'anti-hypertensive effect' by inference. This claim was then supported by bulleted points. To claim that Olmetec, provided 'the real low down' or was the real antihypertensive effect was alleged to be exaggerated, all-embracing and unsubstantiated.

The Panel considered that the phrase 'the real low down', within the context of each promotional item implied that each was providing the essential, key information about various aspects of the product. The Panel did not consider that the phrase 'the real low down' exaggerated Olmetec's antihypertensive efficacy as alleged; no breach of the Code was ruled.

Novartis alleged that the claim 'Olmetec dosing simplicity and cost may help reduce the incentive for an unplanned switch in therapy when patients reach primary care' which appeared in the leavepiece was speculation for which there was no substantiation. When read quickly this was likely to be understood as fact rather than speculation and therefore had the potential to mislead. Novartis considered it inappropriate to base this claim, of a potential advantage of Olmetec, on dosing simplicity. Within the AIIA class the dosing regimen for Olmetec was relatively complex. Novartis alleged that the claim was unsubstantiated.

The Panel noted that the claim at issue appeared beneath a table setting out the cost of 28 days' Olmetec therapy at the 10, 20 and 40mg dose and the claim 'Olmetec costs less at starting and optimal doses than any other available AIIA'.

The Panel considered that Sankyo's submission that the claim 'Olmetec dosing simplicity and cost may help reduce the incentive for an unplanned switch in therapy when patients reach primary care' was a reasonable supposition was at odds with its submission regarding 'the real low down' ie the provision of facts. The Panel noted that Sankyo had not provided any substantiation for the claim in question. A breach of the Code was ruled.

Novartis noted the claim 'Up to 90% greater DBP reduction and 130% greater SBP reduction versus captopril by week 8' appeared in the mailing only and was referenced to Stumpe *et al* (2002) and Ball *et al* (2001). These trials randomised patients to captopril or olmesartan 5mg with subsequent

titration dependent on blood pressure response. Ball *et al* confirmed a considerable proportion of the patients (41.7%) remained on the lowest dose of olmesartan (5mg) and the results were quoted for the overall group treated with olmesartan (all dosages). Olmesartan was only licensed for use at 10mg, 20mg and 40mg doses. Therefore the results used in the claim included patients treated with an unlicensed dose of olmesartan (5mg). This was promoting outside the terms of the marketing authorization for olmesartan.

The Panel noted that the claim at issue referred to efficacy not tolerability or safety. No mention of the dose of Olmetec was made nor that the claim was based on a comparison in mild to moderate hypertension. The claim was based on data using a lower dose than the recommended starting dose. The Panel did not consider that the claim constituted promotion outside the marketing authorization as alleged and thus ruled no breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Olmetec (olmesartan) by Sankyo Pharma UK. Two promotional items were at issue; a leavepiece (ref OLM 16.1) and a mailing (ref OLM 23.2).

1 Claims 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8' and 'Up to 46% greater reduction in DBP than losartan, valsartan and irbesartan by week 8'

The claims appeared in the leavepiece and mailing respectively. Both claims were referenced to Oparil (2002) *et al* while the claim in the mailing was additionally referenced to Brunner and Sanita (2003).

COMPLAINT

Novartis alleged that Oparil *et al* was an unfair comparison of the antihypertensive effects of Olmetec with other angiotensin II antagonists (AIIAs). The study compared the effects of Olmetec 20mg with losartan 50mg, valsartan 80mg and irbesartan 150mg. The summary of product characteristics (SPCs) for losartan, valsartan and irbesartan identified these doses as the starting doses in the majority of hypertensive patients. However the SPC for Olmetec stated that the starting dose was 10mg in all patients and the 20mg dose was recommended only if blood pressure was not controlled on 10mg.

The 20mg dose of Olmetec was described as the 'optimal' dose. However, as the treatment of hypertension was determined by the blood pressure reduction, rather than a target dose, antihypertensive therapy was only titrated if blood pressure did not fall to recommended goals after initial treatment. Therefore the useful information for the clinician was how the effects of starting doses compared. Novartis alleged that comparing the titration dose of Olmetec with the starting doses of the other AIIAs was thus unfair and gave the impression that Olmetec was more efficacious than it was, in breach of Clause 7.2 of the Code.

Novartis noted that in Case AUTH/1019/4/00 comparisons between the titration dose of one medicine and the starting dose of another were ruled to be misleading in breach of Clause 7.2 of the Code. Novartis submitted that this current issue contravened the same principle.

Oparil *et al* randomised untreated hypertensive patients to receive Olmetec 20mg rather than titrating through the 10mg licensed starting dose for all patients. This constituted using data in promotion in which patients were not treated according to the marketing authorization. Novartis alleged that this promoted Olmetec in an unlicensed fashion which was inconsistent with the SPC, in breach of Clause 3.2 of the Code.

Novartis noted that Oparil *et al* was carried out in the United States, where the Food & Drugs Administration (FDA) had granted a higher starting dose of 20mg for Olmetec. In contrast, in the UK the Medicines and Healthcare products Regulatory Agency (MHRA) had assessed the data presented to it and judged that Olmetec 10mg was the most appropriate starting dose for both efficacy and safety reasons.

RESPONSE

Sankyo noted that the claim in the leavepiece had already been found to be in breach of the Code in Case AUTH/1501/8/03 and the leavepiece withdrawn.

Sankyo noted that the dosing schedule for Olmetec with indicated dose restrictions was clearly tabulated in the leavepiece. This schedule was consistent with the SPC and clearly stated 10mg as a 'recommended' starting dose and 20mg as the optimal (maintenance) dose. Sankyo noted that the 'optimal dose' wording was that which existed in the SPC throughout Europe as a result of the mutually recognised regulatory procedure. Although not a preferred term it must be considered as the maintenance dose ie the dose on which the majority of patients would be maintained.

Sankyo did not agree that Olmetec 20mg was being compared to the starting doses of losartan, valsartan and irbesartan alone. Novartis had not made it clear in its complaint that each of these medicines had the same starting and maintenance dose. With 10mg being the starting dose of Olmetec and 20mg the maintenance dose there was obviously a dose titration prior to reaching 'maintenance' with Olmetec. This was not unusual ie telmisartan and, until recently, candesartan had similar dosing schemes. The representations made using 20mg as the maintenance dose of Olmetec were therefore a fair comparison of maintenance doses.

Sankyo provided a table setting out the recommended starting, maintenance and maximum doses of losartan, valsartan, candesartan, ibesartan, telmisartan, eprosartan and Olmetec.

'Usual maintenance dose comparisons' had been used as the convention in recent reviews of angiotensin II antagonists as made by MeRec and had included telmisartan (40mg) and candesartan (8mg) at their second dose titration ie the 'maintenance dose'. These had been compared to losartan 50mg, valsartan 80mg and irbesartan 150mg. This further justified the comparison used with Olmetec 20mg as being fair in the way that it was presented.

Sankyo disagreed with Novartis' interpretation that it was important that clinicians were aware of the effects of starting doses alone. Sankyo contended that it was important that comparisons were made at those doses where patients were maintained effectively. This should be the maintenance dose.

Sankyo did not consider that Case AUTH/1019/4/00, referred to by Novartis, was similar to this complaint. In that case one of the medicines was used at its highest dose whilst the other was used at its maintenance dose. The comparisons were ruled dissimilar and in breach of Clause 7.2. Sankyo submitted that the comparison of Olmetec 20mg was a fair comparison of recognised maintenance doses.

Sankyo disagreed that reference to Oparil *et al*, where a 20mg dose was used as a starting dose as licensed in the United States, was 'promotion outside the licence'. Sankyo did not ask doctors to start dosing with 20mg in any of its materials. Where required Sankyo stated clearly throughout its promotional material that the starting dose was 10mg with titration when required to 20mg which had been shown to have the optimal effect on blood pressure.

Furthermore Sankyo's sales force had been clearly informed and were required to remind doctors whenever they were seen, that the starting dose in all cases, whether changing or starting afresh, was 10mg daily with upward titration if required. Sankyo also disagreed that it was 'promoting in an unlicensed fashion', as 20mg was a licensed dose. It was only that it was not the starting dose and this had been addressed previously. Oparil *et al* had been presented in all promotional pieces as a fair comparison of efficacy of maintenance doses.

Sankyo disagreed with Novartis' suggestion that the most appropriate starting dose in the UK was 10mg as a result of safety and efficacy reasons following MHRA assessment; such inferences as to the reasoning for a lower dose in the UK were inaccurate and speculative. Olmesartan had been approved through the mutual recognition procedure with Germany as the reference member state. As a consequence dosing decisions were made following representations from all countries across the EU involved in the process. Any decision would be as a consequence of a number of factors and would accommodate all concerns and differences and these related to interpretation of a large amount of data. This allowed for the regional differences observed for doses derived in Europe and the USA.

Sankyo noted that the starting dose of one AIIA had recently been doubled from that originally licensed. This demonstrated that dosing patterns might change during use. It should not be speculated therefore that existing doses were such as a consequence of safety and efficacy concerns by a regulatory authority without fact.

Sankyo did not know how or why Novartis had concluded that safety might have been an issue. Certainly the SPC, all the references used in Sankyo's promotional material, and others too, concluded that the side effect profile of Olmetec at all doses 10-40mg was similar to placebo. Sankyo concluded that Novartis was attempting to 'muddy the waters'.

PANEL RULING

The Panel noted that it had ruled the claim in the leavepiece 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg, irbesartan 150mg by week 8' in breach of the Code in Case AUTH/1501/8/03. Sankyo had accepted the Panel's ruling and the leavepiece had been withdrawn.

The Panel noted that the Olmetec SPC stated that the recommended starting dose was 10mg once daily. In patients whose blood pressure was not adequately controlled at this dose, the dose might be 'increased to 20mg once daily as the optimal dose'. If additional blood pressure reduction was required the dose might be increased to a maximum of 40mg daily.

The Panel noted that in relation to the treatment of hypertension losartan 50mg (as used by Oparil *et al*) was described in the Cozaar SPC as the starting and maintenance dose for most patients. Similarly irbesartan 150mg was described in the Aprovel SPC as the usual recommended initial and maintenance dose. Valsartan 80mg was described in the Diovan SPC as the recommended dose for most patients. The Panel noted the submission that Oparil *et al* was an American study and in the USA Olmetec 20mg was the licensed starting dose. Oparil *et al* thus stated that all medicines were given at their recommended initial doses. However, given the products' licensed doses within the UK the Panel did not consider that the claims at issue compared the titration dose of Olmetec with the starting doses of losartan, valsartan and irbesartan as alleged. No breach of Clause 7.2 was ruled in respect of each promotional item.

The Panel noted that as Oparil *et al* was an American study patients had not been titrated from 10mg once daily, the recommended starting dose in the UK. The Panel did not consider, however, that the claims at issue were inconsistent with the SPC on this point as alleged; they did not state or imply that 20mg was the starting dose. No breach of Clause 3.2 was ruled in respect of each promotional item.

2 Claim 'the real low down'

This claim appeared in a highlighted red box within and on the front page of each item.

COMPLAINT

Novartis stated that in the context of a leavepiece which was about the benefits of treating hypertensive patients with Olmetec 'the real low down' took on a more specific meaning than in general usage and related to Olmetec and its therapeutic effect on hypertension and its effectiveness to reduce blood pressure down to low levels. It was clear that this was how it was intended that the claim should be understood as the first claim inside the leavepiece, 'New Olmetec gives you the low down beyond other AIIAs', conveyed this same meaning. This claim was then supported by bulleted points that emphasised the efficacy of Olmetec. This reinforced the meaning of 'low down' to be that of 'anti-hypertensive effect'.

To claim that Olmetec, provided 'the real low down' or was the real antihypertensive effect was alleged to

be an exaggerated all-embracing claim and in breach of Clause 7.10 of the Code as it could not be substantiated.

Novartis stated that its comments also applied to the mailing.

RESPONSE

Sankyo stated that customer research had revealed a need to create news and inform prescribers of hypertension relevant to their daily lives, to overcome common perceptions and misconceptions. Hence derivation of the commonly used phrase 'the real low down' as a term to inform. It was non-specific and did not make any product claims.

This phrase was designed to catch the eye and carry the message throughout that it intended to give the real low down in practice, on cost, on guidelines and regarding the product. Equally, it carried further messages that there was a need to treat hypertension properly and get the blood pressure down. The low down that was being given was 'real' and was a statement of fact. Sankyo submitted that as presented in this piece it had given the low down in several different areas.

Novartis had further challenged the use of the claim 'New Olmetec gives you the real low down beyond other AIIAs'. Sankyo believed this to be a truism. In head-to-head studies Olmetec reduced blood pressure by varying degrees more effectively than other AIIAs. Furthermore Sankyo was clearly giving information about Olmetec beyond other AIIAs. No other AIIA had direct head-to-head study data. The information given was real, not imagined and Sankyo disagreed therefore that this was exaggerated or all-embracing.

Sankyo recognised that the problem with any slogan was that it might be eye-catching and open to different interpretations. Sankyo questioned therefore the validity of using a derived inference regarding a slogan to further a claim that there was a real intention to mislead or exaggerate by using it. Surely it was the use of the slogan that dictated the interpretation and as Sankyo had clearly demonstrated in materials the intent was to inform by fact and give the '*real* low down' in a variety of different areas relating to Olmetec and hypertension.

Sankyo gave examples of other slogans used for different products which were clearly product specific. It was the purpose of such slogans to act as marketing 'hooks' as opposed to statements which were deliberately designed to mislead or exaggerate. Since the Olmetec message was not product specific and was used in manner to inform Sankyo submitted that it was thus being used as a characteristic 'marketing hook' and not a statement that exaggerated or misled as to the nature of Olmetec. It was therefore in accordance with the Code.

PANEL RULING

The Panel noted that the phrase 'low-down' was defined as 'the relevant information or fundamental facts' (ref the New Shorter Oxford English Dictionary 1993).

The Panel noted that within each item variations of the phrase 'the *real* low down' were used to describe different aspects of Olmetec; 'the low down in practice', 'the low down on cost' and 'the low down beyond other AIIAs'.

The Panel considered that the phrase 'the *real* low down', within the context of each promotional item implied that each was providing the essential, key information about various aspects of the product. The Panel did not consider that the phrase 'the *real* low down' exaggerated Olmetec's antihypertensive efficacy as alleged; no breach of Clause 7.10 was ruled.

3 Claim 'Olmetec dosing simplicity and cost may help reduce the incentive for an unplanned switch in therapy when patients reach primary care'

The claim appeared in the leavepiece.

COMPLAINT

Novartis alleged that this claim was speculation for which there was no supporting evidence. When read quickly, by busy clinicians, this was likely to be understood as fact rather than speculation and therefore had the potential to mislead.

In addition Novartis considered it inappropriate to base this claim, of a potential advantage of Olmetec, on dosing simplicity. Within the AIIA class the dosing regimen for Olmetec was relatively complex. Five of the seven agents had only 2 doses for use in the general hypertensive population, whereas Olmetec had 3 doses, as did one of the others. This was clearly not a specific benefit of Olmetec compared to the alternative similar agents and therefore should not be portrayed as such.

Novartis alleged that the claim was unsubstantiated in breach of Clause 7.4 of the Code.

RESPONSE

Sankyo contended that the claim was not presented as fact. It was clearly offered as an opinion which could be justified. As Olmetec was competitively priced and cost was now such an important factor when a doctor decided to prescribe a medicine, it was a reasonable supposition. Sankyo denied that it had the potential to mislead.

The reference to simplicity of dosing was intended to stress the once daily nature and simplicity of dosing, not as had been suggested that there was 'one dose for all'. The dose as reflected in this piece for Olmetec was clearly simple, being once daily with a recommended starting, optimal and maximum dose with a relevant single tablet dose form.

PANEL RULING

The Panel noted that the claim at issue appeared beneath a table setting out the cost of 28 days' Olmetec therapy at the 10, 20 and 40mg dose and the claim 'Olmetec costs less at starting and optimal doses than any other available AIIA'.

The Panel considered that Sankyo's submission that the claim at issue 'Olmetec dosing simplicity and cost may help reduce the incentive for an unplanned switch in therapy when patients reach primary care' was a reasonable supposition, was at odds with its submission in point 2 above regarding 'the real low down' ie the provision of facts. The Panel noted that Clause 7.4 required claims to be capable of substantiation; supposition was not a reasonable basis for such claims. Sankyo had not provided any substantiation for the claim in question. A breach of Clause 7.4 was ruled.

4 Claim 'Up to 90% greater DBP reduction and 130% greater SBP reduction versus captopril by week 8'

This claim appeared in the mailing only and was referenced to Stumpe *et al* (2002) and Ball *et al* (2001).

COMPLAINT

Novartis noted that the trials to which this claim was referenced randomised patients to captopril or olmesartan 5mg with subsequent titration dependent on blood pressure response. Ball *et al* confirmed a considerable proportion of the patients (41.7%) remained on the lowest dose of olmesartan (5mg) and the results were quoted for the overall group treated with olmesartan (all dosages). Olmesartan was only licensed for use at 10mg, 20mg and 40mg doses. Therefore the results used in the claim included patients treated with an unlicensed dose of olmesartan (5mg). This was promoting outside the terms of the marketing authorization for olmesartan in breach of Clause 3.2 of the Code.

Both this allegation and that relating to the comparative AIIA data at point 1 above illustrated the same fundamental issue. It was inappropriate to use data in promotional materials where patients had been treated in a fashion that was inconsistent with the SPC. Novartis was concerned that this approach appeared to be used repeatedly within the Olmetec materials.

RESPONSE

Sankyo noted Novartis' complaint about Ball *et al* stating that the study used olmesartan 5mg as well as other licensed doses; this was true. However, Sankyo submitted that it had not promoted this dose. The 5mg dose was a sub-licence dose. It could not be administered by any combination of marketed dose forms (this differed from doses which might be supra-maximal and could be administered). Many clinical studies included a range of doses not all of which were necessarily licensed; Sankyo recognised the promotion of such non-licensed doses as being in breach of the Code. However, the purpose of using these data was to demonstrate the overall efficacy of Olmetec with a collective claim against an ACE-inhibitor across a dose range (5-20mg) not at a specific dose (ie 5mg). It should be noted that this comparison used the lowest doses, 5-20mg of Olmetec against the low to high doses of captopril (25-100mg) in mild to moderate hypertensives. If anything the comparison was perhaps unjust in relation to the low doses used of Olmetec.

The majority (58.3%) of the patients receiving Olmetec, were on licensed doses of 10 or 20mg at week 12 of the study with the others taking 5mg. This compared to 85.9% of patients being on the high dose of 100mg of captopril. Therefore it was valid for any efficacy comparison to be made which if anything was at the disadvantage of Olmetec with relation to the doses used. As the 5mg dose did not have a marketing authorization it was not in Sankyo's interests to promote it and no attempt had been made to do so. The collective claim made was to demonstrate the greater DBP and SBP reduction at the end of the study in consideration of all doses used.

Sankyo had presented the results of a dose-titration study which was a fair and just comparison. However, if the doses of Olmetec had included a higher than licensed maximal dose then there would have been no question that this data would not have been used. Sankyo recognised that a supra-maximal dose was more often than not attainable with a combination of available dose strengths and obviously presented a clear concern with regard to safety and could create an impression of exaggerated efficacy.

There was an important general point here and one that was frequently addressed in complaints, namely the fine line between the provision of honest and comprehensive information and what was referred to as 'unlicensed promotion'. The temptation was to select only those data that were specific and ignore the remaining data as 'irrelevant'. Sankyo contended that in this case it was simply providing all the data to professionals who were well versed at interpretation of such data, rather than being selective or using a meta-analysis that would be open to suspicion.

PANEL RULING

The Panel noted that Ball *et al* and Stumpe *et al* examined the relative efficacy of olmesartan compared with other antihypertensives. Both groups reviewed a number of studies including what appeared to be the same one comparing olmesartan and captopril in patients with mild to moderate hypertension. The starting dose of olmesartan was 5mg with dose doubling at weeks 4 and 8 if required. Ball *et al* reported that at week 12, 41.7% of patients were controlled on 5mg olmesartan. The comparable figure for week 8 was not given in either Ball *et al* or Stumpe *et al* but the Panel considered that given the study designs, it had to be at least as great a proportion.

The Panel noted that the claim at issue referred to efficacy not tolerability or safety. No mention of the dose of Olmetec was made. Nor that the claim was based on a comparison in mild to moderate hypertension. The claim was based on data using a lower dose than the recommended starting dose. The Panel did not consider that the claim constituted promotion outside the marketing authorization as alleged and thus ruled no breach of Clause 3.2 of the Code.

Complaint received **2 October 2003**

Case completed **16 December 2003**

CONSULTANT ONCOLOGIST v GLAXOSMITHKLINE

Lamictal journal advertisement

A consultant oncologist complained about a journal advertisement for Lamictal (lamotrigine) issued by GlaxoSmithKline which featured a photograph of a young woman's face beneath 'Female: 16 – Partial epilepsy with secondarily generalised tonic-clonic seizures'. A strapline read 'If she was your daughter how would you treat her?'. Lamictal appeared in logo format in the bottom right-hand corner above the phrase 'peace of mind'.

The complainant alleged that the strapline implied that choice of optimal medication was in part determined by the patient's family connections and not by clinical need, given that most doctors tried to do their best for individual patients irrespective of family connections. The complainant alleged that this was misleading and implied substandard treatment for those not fortunate enough to be related to a doctor.

The Panel did not consider that the advertisement implied that clinicians treated their patients differently on the basis of familial connection and that those not related to a doctor received substandard treatment as alleged. The advertisement was not misleading or disparaging on this point and nor did it fail to maintain high standards; no breach of the Code was ruled.

A consultant oncologist complained about an advertisement (ref LAM:/FPA/03/08920/1) for Lamictal (lamotrigine) issued by GlaxoSmithKline UK Ltd which appeared in the BMJ, 13 September.

The advertisement featured a photograph of a young woman's face beneath 'Female: 16 – Partial epilepsy with secondarily generalised tonic-clonic seizures'. A strapline read 'If she was your daughter how would you treat her?'. Lamictal appeared in logo format in the bottom right-hand corner above the phrase 'peace of mind'.

COMPLAINT

The complainant alleged that the slogan 'If she was your daughter how would you treat her?' implied that choice of optimal medication was in part determined by the patient's family connections and not by clinical need, given that most doctors tried to do their best for individual patients irrespective of family connections. The complainant alleged that this was misleading and implied substandard treatment for those not fortunate enough to be related to a doctor.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 7.2, 8.2 and 9.2 of the Code.

RESPONSE

GlaxoSmithKline considered that the complainant had misunderstood the text and misconstrued the message the advertisement delivered. The advertisement showed a picture of a teenage girl (epilepsy sufferer). In the top left-hand corner was some demographic and diagnostic information about the patient.

The advertisement posed the question: 'If she was your daughter how would you treat her?' This asked the reader what they personally would want for such a patient if she was a family member. This was a question designed to elicit an emotional response such as 'the very best treatment possible'. This was a natural response of any parent to such a question. In this respect it was to be hoped that doctors' responses were no different to those of other parents.

However, it was also the case that prescribers knew their family members as multi-faceted people whereas they did not, and could not know most patients to this extent. It was clearly the case that considering all the implications of a treatment choice was easier when the choice was applied to someone a prescriber knew well. Thus the advertisement was deliberately provocative to challenge the way that prescribers thought about treatment selection.

For this reason the secondary question posed, but not answered, by the advertisement was 'what is the very best treatment possible for a female patient, age 16, with partial epilepsy with secondary generalised tonic-clonic seizures?' One possible answer was Lamictal, but the actual choice of prescription would depend on individual factors. The overall effect of the advertisement was thus to challenge the prescriber to think hard and long about how to optimise treatment for female teenagers with epilepsy.

This advertisement was based on a valid epidemiological fact. Epilepsy was common and could affect people in all walks of life, although it was often a hidden condition on account of the high degree of social stigma associated with it. The stigma was due both to the condition itself and unwanted effects of treatment. Applying epidemiological data, approximately 1% of doctors' daughters would develop epilepsy. The advertisement sought to highlight a real-life dilemma faced by some doctors and their families. By reflecting this fact the advertisement attempted to destigmatise the condition by implying that epilepsy might be a real-life scenario for a family member of any health professional.

The problem of how to optimise treatment for female teenagers with epilepsy was a very topical and difficult issue. For example the Epilepsy Action web site had a section specifically dedicated to the problems faced by teenage girls with epilepsy. On this web page there were links to two separate pages on contraception (drug interactions with oral contraceptives and increased risks associated with pregnancy in women with epilepsy) and on the cosmetic problems experienced as side effects of some anticonvulsants (acne, gum hypertrophy, weight

gain). Prescribing anticonvulsants for teenage girls required careful thought.

The advertisement was designed to stimulate such thought but in doing so made no claims for Lamictal. Publishing such an advertisement was an appropriate and responsible activity for a pharmaceutical company.

The second part of the complainant's argument was that most doctors tried to do their best for all patients in an impartial manner regardless of family ties. GlaxoSmithKline agreed that was what doctors strove for and hoped to believe about themselves. There was however some published evidence to suggest that this view of medical altruism was not always played out in practice.

For example, a recent publication explored prescribing patterns in psychiatry and compared them to the personal preferences expressed by psychiatrists in response to questions about which antipsychotic medicine they would wish to receive themselves (if they needed one) and which they would prefer for family members (Steinert 2003). Whereas 70% of prescriptions were written for typical antipsychotic medicines (which had marked side effects) and only 30% for the newer atypical antipsychotics (which were associated with better tolerability) over 95% of the psychiatrists surveyed wished to receive atypical antipsychotic medicines themselves. Some of the psychiatrists advocated different agents for themselves compared to their partners and children, perhaps as a result of their more in depth knowledge of those individuals. Thus there was a marked difference between what was prescribed in routine practice and what would be wanted for family members.

This example showed that what some doctors wanted for themselves and their families differed from what was prescribed for the majority of their patients. It underlined the importance of the issues outlined above.

GlaxoSmithKline submitted that its comments above had shown that the advertisement was not misleading (no breach of Clause 7.2) and could hardly be thought to be because it made no direct claims for Lamictal. The advertisement reflected known facts about epilepsy and the real issues that confronted patients and prescribers and thus did not disparage them or fail to recognise the special nature of medicines or the professional nature of the audience to whom the advertisement was directed (no breach of Clauses 8.2 or 9.2).

Although GlaxoSmithKline regretted the alleged offence the advertisement had caused to the individual complainant, GlaxoSmithKline took the view that such offence was based on a misunderstanding of the message conveyed by the advertisement and was not representative of the response which the advertisement elicited in the vast majority of prescribers. Thus the advertisement was not likely to cause offence but rather to prompt mature reflection on what might constitute best practice (no breach of Clause 9.2).

Thus GlaxoSmithKline took the view that focussing prescribers minds on what they might want as a treatment for their family members was an appropriate way to approach the identification of best practice and was not misleading or in any way intended to be offensive as alleged.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that the advertisement was designed to elicit an emotional response. The Panel considered that most readers would want to ensure the best possible treatment for a member of their family. The Panel did not however consider that the advertisement implied that clinicians treated their patients differently on the basis of familial connection and that those not related to a doctor received substandard treatment as alleged. The advertisement was not misleading or disparaging on this point, nor did it fail to maintain high standards; no breach of Clauses 7.2, 8.2 and 9.2 was ruled.

During its consideration of this case the Panel considered that most readers' response to the question 'If she was your daughter how would you treat her?' was likely to be with the best possible treatment. The advertisement might be seen as implying that Lamictal was the best possible treatment; this was reinforced by the strapline 'peace of mind' and the response from GlaxoSmithKline. The Panel queried whether such an implication met the requirements of Clauses 7.2 or 7.10 of the Code. There was no allegation before the Panel on this point. The Panel asked that GlaxoSmithKline be advised of its views in this regard.

Complaint received **2 October 2003**

Case completed **25 November 2003**

CASE AUTH/1526/10/03

NOVARTIS v ROCHE

Promotion of Bondronat

Novartis complained about three promotional items for Bondronat (ibandronate) which had been displayed by Roche at a regional breast cancer meeting. Bondronat was indicated for the treatment of tumour-induced hypercalcaemia with or without metastases.

Novartis noted a four page item entitled 'Medicine Matters September 2002 – issue 61', sponsored by an educational grant from Roche, consisted almost entirely of an article written by a hospital doctor entitled 'New third generation bisphosphonates: what advantages do they offer the patient?'. The article dealt only with the clinical efficacy of ibandronate and did not mention any other third generation bisphosphonate. Most of the data discussed was for ibandronate, including a phase III study of its effect on tumour-induced skeletal morbidity, which was outside the terms of the licence. The article also reported on several studies of ibandronic acid given as an infusion over 30 minutes, 1 hour and as a bolus, whereas in the summary of product characteristics (SPC) the recommended time for infusion was 2 hours. Novartis further noted the article discussed a phase II study of oral ibandronate in the treatment of bone metastases. Oral ibandronate was not currently licensed in the UK.

Novartis noted that the item included prescribing information and alleged that it was a disguised piece of promotional literature.

The Panel noted that no information had been given about the role of Roche in relation to the production of Medicine Matters September 2002 – issue 61 which the Panel considered was in effect promotional material for Bondronat. Although Medicine Matters was dated and had an issue number, suggesting one in a series of publications, the Panel considered that most readers would view the material as promotional despite the fact that it bore the statement 'This edition is sponsored by an educational grant from Roche Products Limited'. The document did not look like a medical journal or any other official publication. The Panel did not consider that the promotional nature of the material had been disguised. No breach of the Code was ruled.

The Panel noted that Bondronat was only available in the UK as a concentrate which was to be diluted and infused intravenously over two hours. Bondronat was indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. The document at issue referred to a phase III study on the prevention of tumour-induced skeletal morbidity by intravenous Bondronat. The infusion time in the study was 1-2 hours. Another study referred to had used an infusion time of 30 minutes in patients with bony metastases. The document also referred to a phase II study which looked at oral ibandronic acid taken over four months for the treatment of bone metastases. It was also stated that the efficacy of bolus injections of ibandronic acid in the treatment of tumour-induced hypercalcaemia had not yet been fully evaluated. The document thus referred to uses and infusion times which were not consistent with the Bondronat SPC. Medicine Matters also referred to an unlicensed form of Bondronat (oral). Breaches of the Code were ruled.

Novartis noted a reprint of an Adis New Drug Profile (1999), a review of ibandronate by Dooley and Balfour, included sections on bone metastases in normocalcaemic women with breast cancer, osteoporosis, and Paget's disease, all of which were outside the terms of the marketing authorization for Bondronat. A study of oral ibandronate in the treatment of bone metastases was also reviewed. Oral ibandronate, as previously noted, did not have a licence in the UK.

The Panel considered that in the context in which it was distributed, the reprint constituted promotion of Bondronat. The reprint referred to the use of the product in normocalcaemic women, patients with osteoarthritis and patients with Paget's disease none of which were consistent with the SPC. In addition the reprint referred to oral Bondronat which did not have a UK marketing authorization. Breaches of the Code were ruled.

Novartis stated that a leavepiece, entitled 'Introducing a potent 3rd generation bisphosphonate', featured throughout an image of a vertebral column, yet the only licensed indication for ibandronate was for tumour-induced hypercalcaemia with or without metastases. This image could therefore mislead the reader as other bisphosphonates had licences for the treatment for bony metastases in addition to tumour-induced hypercalcaemia. Novartis noted that on page 2 of the leavepiece the headline was 'Bondronat – A new first line choice', but there was no statement as to what indication. Novartis alleged that a claim 'The high potency of Bondronat allows lower dosing' was a hanging comparison and the high potency *per se* was not linked to any particular practical clinical benefit.

The Panel did not consider that the images of the spinal column *per se* would mislead as to the licensed indication for Bondronat as alleged and no breach was ruled.

The Panel noted that page 1 of the leavepiece featured the headline 'Introducing a potent 3rd generation bisphosponate', and included the Roche company logo and the Bondronat product logo together with a statement as to where the prescribing information could be found. The second page was headed 'Bondronat – A new first line choice'. Below it stated that hypercalcaemia of malignancy was the most common life-threatening metabolic disorder in patients with malignant disease. The Panel thus considered that the licensed indication for Bondronat was not stated at the outset. The product was introduced to readers as a potent third generation bisphosphonate; a new first line choice. The Panel noted that other bisphosphonates were licensed to treat a wider range of conditions than Bondronate. The Panel

considered that in the context of the front page and the images of the spinal column, the claim 'Bondronat – A new first line choice' was misleading as to the licensed indication for the product. In the Panel's view, reference to third generation bisphosphonates implied by association that Bondronat was similarly licensed which was not so. A breach of the Code was ruled.

The Panel considered that the claim 'The high potency of Bondronat allows lower dosing' was a hanging comparison and a breach of the Code was ruled.

In the Panel's view, although not clear, there was an implication that the comparison in the claim 'The high potency of Bondronat allows lower dosing' was with other 3rd generation bisphosphonates. The claim which followed read, 'The risk of blood diphosphonate-calcium complexes increases with higher molar concentrations'. Roche had not, however, submitted any data to show that the high potency of Bondronat was of significant clinical advantage in comparison to the other third generation bisphosphonates which might have to be administered in higher molar concentrations. The Panel considered that the claim 'The high potency of Bondronat allows lower dosing' was thus misleading in breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about the promotion of Bondronat (ibandronate) by Roche Products Ltd. Bondronat was indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. There were three items at issue which had been displayed on Roche's stand at a regional breast cancer meeting.

A Medicine Matters September 2002 – issue 61

This four page item, sponsored by an educational grant from Roche, consisted almost entirely of an article entitled 'New third generation bisphosphonates: what advantages do they offer the patient?'. The article had been written by a hospital doctor. Page 4 included the prescribing information for Bondronat.

COMPLAINT

Novartis noted that the article dealt only with the clinical efficacy of ibandronate rather than being a general piece on third generation bisphosphonates, and did not mention any other third generation bisphosphonate, in particular Novartis' own product, Zometa (zoledronic acid). Most of the data discussed was for ibandronate, although one study in an unlicensed indication for clodronate was included, and covered a number of unlicensed areas: treatment of bone metastases, and quality of life and survival of these patients. It discussed a phase III study of the effect of ibandronate on tumour-induced skeletal morbidity, which was outside the terms of the licence and therefore in breach of Clause 3.2. The article also reported on several studies of ibandronic acid given as an infusion over 30 minutes, 1 hour and as a bolus, whereas in Section 4.2 of the summary of product characteristics (SPC) the recommended time for infusion was 2 hours. Novartis alleged a breach of Clause 3.2.

Novartis further noted the article discussed a phase II study of oral ibandronate in the treatment of bone metastases. Oral ibandronate was not currently licensed in the UK; a breach of Clause 3.1 was alleged.

Novartis noted that the item included prescribing information and alleged that it was disguised promotion, in breach of Clause 10.1. In this capacity it contained unsubstantiated claims, was unbalanced in its information and promoted Bondronat outside the terms of its licence.

RESPONSE

Roche submitted that the article was written by a doctor experienced in the use of Bondronat. The edition of Medicine Matters in question was formally approved for use within the Code in October 2002. The company chose to add prescribing information to correspond to the sponsorship displayed on the front cover. The licensed indication for Bondronat was clearly discussed on the front page and the author decided to discuss some of the new therapeutic advances of this third generation bisphosphonate. Roche noted that Clause 3.2 allowed for the provision of scientific developments, which the company considered was legitimate at a scientific meeting. In addition, there was no intent to disguise the nature of this item, hence the presence of prescribing information. Roche thus denied a breach of Clause 10.1.

Roche noted that Novartis had raised concern that the item did not cover all third generation bisphosphonates, especially Zometa, but failed to cite any clause it considered had been breached. In addition, the title of the piece made it clear that it was about the advantages of new third generation bisphosphonates. Clearly the author did not consider that Zometa warranted inclusion in this class, possibly because, like most of the previous generations of bisphosphonates, it was only available as a parenteral formulation and not oral as was Bondronat.

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 content, 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 Panel noted that Medicine Matters September 2002 – issue 61 had been sponsored by Roche and had been made available on the company's stand at a regional breast cancer meeting. No information had been given about the role of Roche in relation to the production of the document. The company had approved the piece for use within the Code and chosen to add prescribing information.

The Panel noted Roche's submission with regard to Clause 3.2 allowing the provision of information about scientific developments at scientific meetings. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under that or any other clause. The Panel considered that Medicine Matters, September 2002, was in effect promotional material for Bondronat and it was upon this basis that it made its rulings.

Although Medicine Matters was dated and had an issue number, suggesting one in a series of publications, the Panel considered that most readers would view the material as promotional despite the fact that it bore the statement 'This edition is sponsored by an educational grant from Roche Products Limited'. The document did not look like a medical journal or any other official publication. The Panel did not consider that the promotional nature of the material had been disguised. No breach of Clause 10.1 was ruled.

The Panel noted that Bondronat was only available in the UK as a concentrate for solution for intravenous infusion. The concentrate was to be added to normal saline and infused over two hours. Bondronat was indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. The document at issue referred to a phase III study on the prevention of tumour-induced skeletal morbidity by intravenous Bondronat. The infusion time in the study was 1-2 hours. Another study referred to had used an infusion time of 30 minutes in patients with bony metastases. The document also referred to a phase II study which looked at oral ibandronic acid taken over four months for the treatment of bone metastases. It was also stated that the efficacy of bolus injections of ibandronic acid in the treatment of tumour-induced hypercalcaemia had not yet been fully evaluated. The document thus referred to uses and infusion times which were not consistent with the particulars listed in the Bondronat SPC. Breaches of Clause 3.2 were ruled in both regards. Medicine Matters also referred to an unlicensed form of Bondronat (oral) and so the Panel ruled a breach of Clause 3.1 of the Code.

B Reprint of an Adis New Drug Profile (1999)

This was a reprint of a review of ibandronate by Dooley and Balfour published in the Adis publication 'Drugs'.

COMPLAINT

Novartis stated that the article included sections on bone metastases in normocalcaemic women with breast cancer, osteoporosis, and Paget's disease, all of which were outside the terms of the marketing authorization for Bondronat and therefore in breach of Clause 3.2. In addition, the article reviewed a study of oral ibandronate in the treatment of bone metastases. Oral ibandronate, as noted in point A above, did not currently have a licence at all in the UK. Novartis alleged a breach of Clause 3.1.

RESPONSE

Roche noted that Adis was an internationally respected independent journal that exhaustively reviewed all aspects of medicines. Its availability to a responsible delegate audience at a scientific meeting was a service to the medical profession (Clause 3.2) and was not inconsistent with the licence for Bondronat and therefore was not a breach of Clauses 3.1 and 3.2.

PANEL RULING

The Panel noted that the Drugs reprint had been made available on the Roche stand at a regional breast cancer meeting. The Panel noted that the supplementary information to Clause 11.1 of the Code, provision of reprints, stated 'The provision of an unsolicited reprint of an article about a medicine constitutes promotion of that medicine and all relevant requirements of the Code must therefore be observed. Particular attention must be paid to the requirements of Clause 3'.

The Panel further noted Roche's reference to Clause 3.2 and its submission that the availability of the reprint to a responsible delegate audience at a scientific meeting was a service to the medical profession. The Panel did not consider, however, that Roche could claim the benefit of the supplementary information to Clause 3 whereby the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under that or any other clause. Bondronat was not being developed. A concentrate for infusion was available but its only licensed indication was for the treatment of tumour-induced hypercalcaemia with or without metastases.

The Panel thus considered, that in the context in which it was distributed, the Drugs reprint constituted promotion of Bondronat. The reprint referred to the use of the product in normocalcaemic women, patients with osteoarthritis and patients with Paget's disease none of which were consistent with the SPC. Breaches of Clause 3.2 were ruled. In addition the reprint referred to oral Bondronat which did not have a UK marketing authorization. The Panel ruled a breach of Clause 3.1 as alleged.

C Leavepiece (ref P116020/0103)

COMPLAINT

Novartis stated that the leavepiece, entitled 'Introducing a potent 3rd generation bisphosphonate' featured throughout an image of a vertebral column, yet the only licensed indication for ibandronate was for tumour-induced hypercalcaemia with or without metastases. This image could therefore mislead the reader, as other bisphosphonates such as pamidronate and zoledronic acid had licences for the treatment for bony metastases in addition to tumour-induced hypercalcaemia, and as such was in breach of Clause 7.8. Novartis noted that on page 2 of the leavepiece, the headline was 'Bondronat – A new first line

choice', but there was no statement as to what indication. This was alleged to be misleading in breach of Clause 7.2. Novartis alleged that the claim on page 3, 'The high potency of Bondronat allows lower dosing' was in breach of Clause 7.2 on two counts; namely as a hanging comparison (lower dosing than what?) and the high potency *per se* was not linked to any particular practical clinical benefit.

RESPONSE

Roche stated that it had used images of bone to reflect the licensed indication of hypercalcaemia of malignancy. The vertebral column was a major site of calcium loss in this condition. Roche noted that pictures of the vertebral column were stylised images. They were not medical scanned images and showed no discernable pathology (fractures, compression, etc). The use of this image was merely an artistic device and was not a breach of Clause 7.8.

With respect to 'Bondronat – A new first line choice', the indication was stated immediately below and in bold text, 'Hypercalcaemia of malignancy …'. That this title might mislead was, therefore, implausible. Roche denied a breach of Clause 7.2 of the Code.

Roche submitted that the claim 'The high potency of Bondronat allows lower dosing' was not a hanging comparative in that the meaning was self evident; it would be redundant to state further '… than a lower potency Bondronat formulation'. This was not a breach of Clause 7.2. Roche noted that this logic was also applied in one of the Panel's rulings in Case AUTH/1392/11/02. The claim was qualified in the next statement, which appeared immediately below in bold text, it stated that 'the risk of blood bisphosphonate-calcium complexes increases with higher molar concentrations'. The expert audience, for whom this item was intended, would appreciate the significance of this in binding to bone and, indeed, the clinical benefit followed immediately below, vis '76% of patients achieved serum calcium values > 2.7mM after treatment with a 4mg dose'. Potency was clearly linked, therefore, by a series of factually correct statements into a logical argument. This was not a breach of Clause 7.2.

PANEL RULING

The Panel noted Roche's submission that the stylised images of the spinal column, featured on each page of the leavepiece, did not show any discernable pathology. The Panel also noted Roche's submission that in tumour-induced hypercalcaemia the vertebral column was a major site of calcium loss. The Panel thus did not consider that the images of the spinal column *per se* would mislead as to the licensed indication for Bondronat as alleged. On that narrow point the Panel ruled no breach of Clause 7.8 of the Code.

The Panel noted that page 1 of the leavepiece featured the headline 'Introducing a potent 3rd generation bisphosponate'. The only other text on the first page was the Roche company logo and the Bondronat product logo together with a statement as to where the prescribing information could be found. The second page was headed 'Bondronat – A new first line choice'. Below this headline it was stated that hypercalcaemia of malignancy was the most common life-threatening metabolic disorder in patients with malignant disease. The Panel thus considered that the licensed indication for Bondronat was not stated at the outset. The product was introduced to readers as a potent third generation bisphosphonate; a new first line choice. The Panel noted that other bisphosphonates were licensed to treat a wider range of conditions than Bondronate. The Panel considered that in the context of the front page and the images of the spinal column, the claim 'Bondronat – A new first line choice' was misleading as to the licensed indication for the product. In the Panel's view, reference to third generation bisphosphonates implied by association that Bondronat was similarly licensed which was not so. A breach of Clause 7.2 was ruled.

The Panel considered that the claim 'The high potency of Bondronat allows lower dosing' was a hanging comparison. It was not clear with what Bondronat was being compared. In that regard the Panel disagreed with Roche's submission that the comparison was with a lower potency Bondronat formulation. A breach of Clause 7.2 was ruled.

The Panel noted that the supplementary information to Clause 7.2, Misleading Information, Claims and Comparisons, stated, *inter alia*, that claims for superior potency in relation to weight were generally meaningless and best avoided unless they could be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage. In the Panel's view, although not clear, there was an implication that the comparison in the claim 'The high potency of Bondronat allows lower dosing' was with other 3rd generation bisphosphonates. The claim which followed read, 'The risk of blood diphosphonate-calcium complexes increases with higher molar concentrations'. Roche had not, however, submitted any data to show that the high potency of Bondronat was of significant clinical advantage in comparison to the other third generation bisphosphonates which might have to be administered in higher molar concentrations. The Panel considered that the claim 'The high potency of Bondronat allows lower dosing' was thus misleading. A breach of Clause 7.2 was ruled.

Complaint received **8 October 2003**

Case completed **16 December 2003**

CASE AUTH/1528/10/03

MEDIA/DIRECTOR v LUNDBECK

Ebixa mailing

The Drug and Therapeutics Bulletin published an article headed 'Memantine for dementia?' which was critical of the promotion of Ebixa (memantine) by Lundbeck.

The article stated that memantine was the first medicine in its class to be licensed for the treatment of patients with moderately severe to severe Alzheimer's disease. On published evidence, it produced, at best, only a small reduction in the rate of deterioration in global, functional and cognitive scales in such patients. Whether this translated into important changes in quality of life or how long the effects lasted was unclear. The evidence for benefits in other types of dementia was unconvincing, as was the evidence that treatment with memantine reduced caregiver time and helped prevent institutionalisation. The authors believed the company's claim that 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' was not scientifically robust and that a public correction should be issued. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

Lundbeck stated that the only item which included the claim in question was a mailing. Page three, headed 'Ebixa benefits the activities of daily living' referenced to 'Data on file' and Reisberg *et al* (2002), featured a bar chart showing the frequency of improvement in six items of daily living. For every item there was a greater percentage of improvement with Ebixa than with placebo. Although no p values were given, a footnote on the bar chart stated 'significant improvements seen in 6/16 items on the D-Scale, (ITT, n=79)'. The claim at issue was below the bar chart.

The Panel noted the claim in question was referenced to Wimo *et al* which concluded that memantine treatment was associated with, *inter alia*, a trend toward later transition of patients to an institutional setting (p=0.052). The study took place over 28 weeks and in that time 5 placebo-treated patients entered an institution compared with 1 in the memantine group. The published paper of the same study (Wimo *et al* 2003) reported that at week 28 there was a statistically significant between group difference with regard to institutionalisation (p=0.04).

The Panel noted the chronic nature of Alzheimer's disease. Although Wimo *et al* had shown a trend towards memantine-treated patients avoiding becoming institutionalised for a longer time period than placebo-treated patients, there was no data to show that they avoided institutionalization altogether. In that regard the Panel considered that the claim at issue was misleading and unsubstantiated. Breaches of the Code were ruled.

The Panel noted that the bar chart depicted only 6 items out of 16 items on the D-Scale; for each item depicted there was a statistically significant difference in favour of memantine compared with placebo. Lundbeck had submitted that the 'Data on file', on which the bar chart was based, was a sub-group of patients taken from Winblad *et al*, a 12 week study in 167 patients with moderately severe or severe primary dementia. In Winblad *et al* the same six items showed a statistically significantly greater frequency of improvement in memantine-treated patients than in those receiving placebo. The other eight items showed advantages for memantine although these did not reach statistical significance. The Panel noted, however, that the evaluation of the D-Scale was a secondary efficacy variable. The authors stated that 'the response profile [shown in the 16 items of the D-Scale] is pertinent for day-to-day care of severely demented patients. These promising results remain to be confirmed in larger clinical trials with longer duration…'.

The Panel noted Reisberg *et al*, a poster and a published report, showed that caregivers spent significantly less time with patients receiving memantine than with placebo-treated patients (p=0.01). Data from the same study had also been presented as a poster by Galasko *et al*. All three publications reported a reduction in functional decline and a slowing of the loss of daily living skills in patients with moderate to severe Alzheimer's disease treated with memantine. This was in contrast to the promotional claims made for Ebixa which implied that the medicine would positively improve aspects of daily living.

Overall the Panel did not consider that the claim 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' adequately reflected the data. The claim implied that patients would improve and maintain a degree of independence whereas Reisberg *et al* and Galasko *et al* showed that the functional decline of patients was only slowed. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

The Drug and Therapeutics Bulletin, October 2003, included an article headed 'Memantine for dementia?' which was critical of the promotion of Ebixa (memantine) by Lundbeck Ltd. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

Lundbeck stated that the only item which included the claim in question was a mailing (ref 0902/EBI/511/003M). Page three was headed 'Ebixa benefits the activities of daily living' referenced to 'Data on file' and Reisberg *et al* (2002). The page featured a bar chart showing the frequency of improvement in six items of daily living. For every item there was a greater percentage of improvement with Ebixa than with placebo. Although no p values were given, a footnote on the bar chart stated 'significant improvements seen in 6/16 items on the D-Scale, (ITT, n=79)'. The data had been taken from 'Data on file'. Below the bar chart was the claim

'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' which was referenced to Wimo *et al* (2002).

COMPLAINT

The article in the Drug and Therapeutics Bulletin stated that memantine was the first N-methyl-D-aspartate receptor antagonist to be licensed for the treatment of patients with moderately severe to severe Alzheimer's disease. On published evidence, memantine produced, at best, only a small reduction in the rate of deterioration in global, functional and cognitive scales in such patients.

Whether this translated into important changes in quality of life or how long the effects lasted was unclear. The evidence for benefits in other types of dementia was unconvincing, as was the evidence that treatment with memantine reduced caregiver time and helped prevent institutionalisation. The authors believed the company's claim that 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' was not scientifically robust and that a public correction should be issued.

When writing to Lundbeck the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Lundbeck stated that the claim in question had only appeared in a launch mailing some 12 months ago that was sent out to relevant health professionals.

The 'Data on file' described a sub-group of patients in a study of memantine in Alzheimer's disease and vascular dementia (Winblad *et al* 1999). The D-Scale evaluated behaviour and functioning in demented patients and was described in Winblad *et al*. The data on file (reference 1 of the mailing) described how patients with Alzheimer's disease showed a significant improvement when treated with memantine in comparison with placebo in various key activities. The Reisberg poster (reference 2 of the mailing) was now published as Reisberg *et al* (2003). Reisberg *et al* showed clear benefits in the ADCS-ADLsev scale (Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory-severe) for memantine-treated patients, compared with placebo-treated patients. The positive benefits were in both last observation carried forward (LOCF) and observed case (OC) analyses, as recommended by UK regulatory guidance regarding medicines for Alzheimer's disease. The data from the same study was presented as a poster by Galasko *et al* (2003) to show the benefit in ADL (Activities of Daily Living) single items that memantine showed over placebo. This too demonstrated the clear benefits that memantine provided in terms of activities of daily living.

The claim highlighted by the Drug and Therapeutics Bulletin was referenced to an abstract by Wimo *et al*, which had now been superseded by a published paper (Wimo *et al* 2003). The data from the study clearly showed benefits in both caregiver time requirements and institutionalisation. Patients receiving memantine required significantly less caregiver time than placebo-treated patients (51.5 hours less per month, p=0.02). This benefit was seen in both the ITT and TPP (treatment per protocol) analyses. Analysis of residential status also favoured memantine in terms of institutionalisation at week 28 (p=0.04) and time to institutionalisation (p=0.052).

The Drug and Therapeutics Bulletin article in its attempt to criticise the Wimo *et al* data stated that 'a subsequent analysis using unadjusted results from the study suggested that memantine did not significantly reduce the amount of caregiver time a patient needed during the trial', wrongly referencing it to Wimo *et al* to suggest that this analysis was done by the authors. Lundbeck could only assume that the 'subsequent analysis', was done by the Drug and Therapeutics Bulletin and as it was not privy to any actual study data it was difficult to know the basis for the analysis.

Wimo *et al* also mentioned the reduction in caregiver time as 42 hours, but the pre-specified statistical analysis plan for the study dictated that adjusted results were used, controlled for baseline imbalances in caregiver times, patient gender, caregiver gender, caregiver relationship to patient and baseline residential status. This analysis provided the adjusted caregiver time mentioned in the previous paragraph.

The scientifically correct way of presenting the data was according to the statistical analysis plan, as Lundbeck had done but sadly the statement by the Drug and Therapeutics Bulletin not only presented a misleading impression of Wimo *et al*, but was scientifically flawed.

A decline in ADL was associated with an increase in institutionalisation as shown by Scott *et al* (1997), Wolinsky *et al* (1993) and Hutton *et al* (1985). Scott *et al* stated that 'clients with a decline in the ability to perform ADLs were 3.5 times as likely to be institutionalised as clients with no decline or improvement'.

Wolinsky *et al* concluded 'the risk of nursing home placement was associated with deterioration in advanced (i.e. cognitive) ADLs and lower body function'. Hutton *et al* concluded, 'Items most closely associated with placement *[in a nursing home]* were incontinence of bladder and bowel, inability to speak coherently and inability to bathe and groom oneself'. Memantine had benefits in all of these areas (Galasko *et al*, Winblad *et al*).

Data from Galasko *et al* and Reisberg *et al*, and that in the 'Data on file' summary from Winblad *et al* showed a number of clear benefits for memantine-treated patients versus placebo in ADLs. There were benefits shown in activities of daily living, caregiver time and institutionalisation. All this data was scientifically robust and supported the claim 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care'. Lundbeck noted that the claim was qualified by the phrase 'potentially avoiding'.

Lundbeck denied that the Ebixa data was scientifically unsound, and considered that it supported the claim in question.

PANEL RULING

The Panel noted Lundbeck's submission that it had qualified the claim 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' by use of the word potentially. In the Panel's view such qualification rarely negated the impression that a product would produce the outcome stated. In this case one of the key messages from the page in question was that Ebixa-treated patients would avoid the need for nursing home care.

The claim in question was referenced to a poster presentation by Wimo *et al*. The authors concluded that memantine treatment was associated with, *inter alia*, a trend toward later transition of patients to an institutional setting (p=0.052). The study took place over 28 weeks and in that time 5 placebo-treated patients entered an institution compared with 1 in the memantine group. The published paper of the same study (Wimo *et al* 2003) reported that at week 28 there was a statistically significant between group difference with regard to institutionalisation (p=0.04).

The Panel noted the chronic nature of Alzheimer's disease. Although Wimo *et al* had shown a trend towards memantine-treated patients avoiding becoming institutionalised for a longer time period than placebo-treated patients, there was no data to show that they avoided institutionalisation altogether. In that regard the Panel considered that the claim at issue was misleading and unsubstantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the bar chart depicted only 6 items out of 16 items on the D-Scale; for each item depicted there was a statistically significant difference in favour of memantine compared with placebo. Lundbeck had submitted that the 'Data on file', on which the bar chart was based, was a sub-group of patients taken from Winblad *et al*, a 12 week study in 167 patients with moderately severe or severe primary dementia. In Winblad *et al* the same six items of daily living, plus two others, showed a statistically significantly greater frequency of improvement in memantine-treated patients than in those receiving placebo. The other eight items showed advantages for memantine although these did not reach statistical significance. The Panel noted, however, that the evaluation of the D-Scale was a secondary efficacy variable. The authors stated that 'the response profile [shown in the 16 items of the D-Scale] is pertinent for day-to-day care of severely demented patients. These promising results remain to be confirmed in larger clinical trials with longer duration…'.

The Panel noted Lundbeck's reference to Reisberg *et al* which had been presented as a poster and published as a paper. Reisberg *et al* showed that caregivers spent significantly less time with patients receiving memantine than with placebo-treated patients (p=0.01). Data from the same study had also been presented as a poster by Galasko *et al*. All three publications reported a reduction in functional decline and a slowing of the loss of daily living skills in patients with moderate to severe Alzheimer's disease treated with memantine. This was in contrast to the promotional claims made for Ebixa which implied that the medicine would positively improve aspects of daily living.

Overall the Panel did not consider that the claim 'Improvements in activities of daily living help patients to maintain a degree of independence and be easier to care for, potentially avoiding the need for nursing home care' adequately reflected the data. The claim implied that patients would improve and maintain a degree of independence whereas Reisberg *et al* and Galasko *et al* showed that the functional decline of patients was only slowed. The Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Proceedings commenced 15 October 2003

Case completed 19 December 2003

CASE AUTH/1530/10/03

GENERAL PRACTITIONER v SANKYO PHARMA

Newspaper article on Olmetec

A general practitioner complained that Sankyo Pharma appeared to be advertising its antihypertensive, Olmetec (olmesartan), directly to the public via an article in the Daily Mail. The article stated that Olmetec, *inter alia*, was 'being hailed by experts as a major breakthrough in the battle against one of Britain's biggest health problems'.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The Olmetec press briefing had consisted of presentations detailing the significance of hypertension and the need to control it. Attendees had been given a corporate press release in addition to one of three others depending upon their affiliation. The corporate press release referred to Olmetec as a 'potent orally active angiotension II receptor antagonist …' and that 'This combination of greater efficacy together with excellent tolerability and minimal effects on a patient's lifestyle makes Olmetec a cutting-edge antihypertensive therapy and a very exciting development indeed'. The press release which had, in addition, been given to the journalist who had written the article in question referred to Olmetec as 'a powerful new option …'. In a discussion of Olmetec, angiotension II receptor antagonists (AIIAs) and the new GP contract it was stated that 'it is important for GPs, as well as patients, that hypertension is managed effectively'.

Attendees were told that the safety profile of Olmetec was similar to that of placebo. The company's slide presentation included the product logo and claims which had been used in Olmetec promotional material ie 'the real low down' and 'Down Right. Effective BP Control'.

The Panel noted that Olmetec was the latest AIIA to be launched, there were already six available, and in that regard questioned its description as 'a cutting-edge antihypertensive therapy, and a very exciting development indeed'. The Panel considered that, within the context of the press release, the description of Olmetec as a 'potent' or 'powerful' antihypertensive created the impression of a general claim for superiority compared with all other antihypertensives. In addition the statement that 'it is important for GPs, as well as patients, that hypertension is managed effectively' implied that this could only be achieved with Olmetec. The press releases and the presentation on Olmetec referred to the safety profile of Olmetec being similar to that of placebo. The Olmetec SPC, however, noted some differences between the two, in particular dizziness which occurred more often in olmesartan-treated patients than in those treated with placebo.

The Panel considered that although the materials used at the press launch did not constitute an advertisement to the general public for Olmetec, and so no breach of the Code was ruled, they were not presented in a balanced way and so a breach of the Code was ruled in that regard. High standards had not been maintained and a further breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such use. The Panel did not consider that the case before it merited such a ruling.

A general practitioner complained about an article in the Daily Mail of 30 September which related to Olmetec (olmesartan), an antihypertensive marketed by Sankyo Pharma UK Ltd. The article stated that Olmetec, *inter alia*, was 'being hailed by experts as a major breakthrough in the battle against one of Britain's biggest health problems'. Olmetec was an angiotensin II receptor antagonist (AIIA) or sartan.

COMPLAINT

The complainant stated that the company appeared to be advertising directly to the public against the agreed standards of the UK pharmaceutical industry. The article was a clear advertisement dressed up as information and also made claims which the general public was in no position to assess.

When writing to Sankyo Pharma, the Authority asked it to respond in relation to Clauses 2, 9.1, 20.1 and 20.2 of the Code.

RESPONSE

Sankyo stated that the author, a freelance medical journalist who attended a press launch, wrote the article completely independently. Sankyo had no involvement in the editorial content of the article and it was not informed by the Daily Mail of it being published. Sankyo's public relations company first made the company aware of the article at 9.30am on the day it was published.

Sankyo provided copies of all of the materials used at the Olmetec Primary Care Press Launch on 11 September 2003 and explained that there was one standard corporate press release available to all and three further press releases provided to individuals dependent on their affiliation. The freelance medical journalist who had written the article at issue was issued with item 3 below.

1 GP publications received 'Olmetec launch gives GPs powerful, well tolerated new option for effective management of hypertension'.

2 Health professional publications received 'Olmetec launch gives healthcare professionals a powerful, well tolerated new option for effective management of hypertension.

3 General health media publications received 'New treatment offers fast, powerful blood pressure control and is well tolerated'.

No further materials were provided to the journalist or any contact made with Sankyo further to this initial provision.

The press conference involved four short presentations from two professors, one of clinical pharmacology and the other of cardiovascular

medicine, Sankyo's medical director and a GP. Copies of the slides were provided. The two professors covered the importance and impact of hypertension in the UK and the need for efficient and proper reduction using multiple medicines in combination. Further details on the current British Hypertension recommendations and attributes of the sartan class of medicines was also provided as background prior to introducing Olmetec. Sankyo's medical director then presented the data for Olmetec in the management of essential hypertension and the comparative data from clinical trials. Finally, the GP outlined his experience as a prescriber of Olmetec, presenting data on several patients he was currently treating. After the presentations, time for questions was provided. Sankyo was not aware that the author of the article raised any questions or discussed further any issues with the speakers.

Sankyo submitted the information provided at the press launch was balanced, fair and accurate, in line with the summary of product characteristics (SPC).

Sankyo stated that the article in the Daily Mail was written at the discretion of the journalist and was not instigated by Sankyo. Sankyo had no knowledge of the article and no opportunity to view it prior to publication; the company had no influence or control over the article. There was no intention on behalf of Sankyo in the factual information provided to 'induce' patients to demand the product from their doctors or to raise unfounded hopes of successful treatment. The interpretation of this information and the way it was presented in the Daily Mail was entirely the decision of the journalist and the newspaper. As a consequence Sankyo did not agree that its actions constituted advertising to the public either directly or indirectly and therefore did not consider that it was in breach of Clause 20.1.

Sankyo considered that it had acted in accordance with the Code in providing balanced and accurate information, consistent with the SPC, whilst maintaining the highest standards at all times in its actions. These actions, it believed, were not in breach of Clause 9.1 or Clause 20.2 and did not bring discredit upon, or reduce confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The Olmetec press briefing had consisted of presentations detailing the significance of high blood pressure and the need to control it. Sankyo's medical director had reviewed the clinical data for Olmetec and a GP had given the primary care perspective of treating hypertension as well as an account of his personal experience of using Olmetec. Attendees had been given a corporate press release entitled 'Sankyo Pharma (UK) Limited gains Market Authorisation for new antihypertensive OLMETEC (olmesartan medoxomil)'. In addition attendees had been given one of three other press releases depending upon their affiliation. The author of the article in question had been given the press release entitled 'New treatment offers fast, powerful blood pressure control and is well tolerated'.

The Panel noted that the corporate press release referred to Olmetec as a 'potent orally active angiotensin II receptor antagonist …' and that 'This combination of greater efficacy together with excellent tolerability and minimal effects on a patient's lifestyle makes Olmetec a cutting-edge antihypertensive therapy, and a very exciting development indeed'. The press release that had, in addition, been given to the journalist in question referred to Olmetec as 'a powerful new option in the battle against high blood pressure …'. In a discussion of Olmetec, AIIAs, treatment guidelines and the new GP contract it was stated that 'it is important for GPs, as well as patients, that hypertension is managed effectively'. Both press releases and the presentation on the clinical data for Olmetec referred to the safety profile of Olmetec being similar to that of placebo. The presentation by Sankyo's medical director included a number of slides that had similarities to the promotional material used to advertise Olmetec to health professionals. These being the claims 'the real low down' and 'Down Right. Effective BP Control' and use of the product logo. The press releases and presentation slides were submitted as one document. The introductory page to the Olmetec Press Briefing included similar claims and layout to that used in the medical director's presentation referred to above.

The Panel noted the requirement of Clause 20.2 that information about a medicine which was made available to the general public either directly or indirectly must 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. The Panel noted that Olmetec was the latest AIIA to be launched, there were already six available, and in that regard questioned its description as 'a cutting-edge antihypertensive therapy, and a very exciting development indeed'. The Panel considered that, within the context of the press release the description of Olmetec as a 'potent' or 'powerful' antihypertensive created the impression of a general claim for superiority compared with all other antihypertensives. In addition the statement that 'it is important for GPs, as well as patients, that hypertension is managed effectively' implied that this could only be achieved with Olmetec. The press releases and the presentation on Olmetec referred to the safety profile of Olmetec being similar to that of placebo. The Olmetec SPC, however, noted some differences between the medicine and placebo, in particular dizziness which occurred in 2.5% of olmesartan-treated patients and 0.9% of those treated with placebo.

The Panel did not consider that the material used at the press launch for Olmetec constituted an advertisement to the general public for the product. No breach of Clause 20.1 was ruled. The Panel considered, however, that the press materials at issue were not presented in a balanced way and therefore ruled a breach of Clause 20.2 of the Code. High standards had not been maintained and the Panel ruled a breach of Clause 9.1.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such use. The Panel did not consider that the case before it merited such a ruling.

Complaint received **21 October 2003**

Case completed **8 January 2004**

CASE AUTH/1534/10/03

ANONYMOUS v LILLY

Arrangements for meeting

An anonymous complainant stated that Lilly was to hold a meeting at St Andrews on 7-9 November during which there was to be a maximum of two hours of medical content; 'the rest was a freebie'.

The Panel noted Lilly's submission that the meeting had been organised by a sales manager acting in isolation and outside of the company's policies and procedures. When notified of the complaint Lilly had cancelled the meeting.

The Panel was extremely concerned that at the time of the complaint neither formal written invitations nor agendas had been distributed to invitees. The provisional agenda showed that the meeting was to be held over two days on 8 and 9 November at the St Andrews Hotel. There was to be virtually 4 hours of educational content between 10am and 3pm on day one; drinks were to be served at 7.30pm before dinner which was followed by a 45 minute talk about GP mind mapping. The programme for day two consisted of a one hour question and answer session.

The Panel noted that the forty invitees were from the Eastern and Western Scottish regions; eighteen came from Glasgow and in all 31 came from west of Edinburgh. The Panel queried the rationale of holding the meeting in St Andrews.

The Panel did not consider that the arrangements justified a two day meeting with overnight stay. Given the educational content and the geographical spread of the audience, the meeting could have been held at a more central venue on one day with no overnight accommodation. The hospitality offered was not in proportion to the occasion. A breach of the Code was ruled.

The Panel further considered that the sales manager had failed to maintain a high standard of ethical conduct; he had not followed the company's standard operating procedure nor had he complied with all the relevant requirements of the Code. A further breach of the Code was ruled. Given the circumstances the Panel did not consider that the company itself had failed to maintain a high standard; no breach the Code was ruled in that regard.

The Panel did not consider that the arrangements warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

An anonymous complainant left a voicemail message about a meeting held by Eli Lilly & Company Ltd. In accordance with established practice the matter was treated as a complaint under the Code and taken up with Lilly.

COMPLAINT

The complainant stated that a meeting was to be held by Lilly at St Andrews Hotel, St Andrews on 7, 8 and 9 November. The complainant stated that there was a maximum of two hours of medical content and 'the rest was a freebie'.

When writing to Lilly the Authority asked it to respond in relation to Clauses 9.1, 15.2, 19.1 and 2.

RESPONSE

Lilly stated that it took such matters seriously; upon receipt of the complaint an investigation was initiated and as a result the meeting was cancelled.

The intended audience for the meeting, which was to take place over two days, 8 and 9 November, and not three days as stated by the complainant, was a group of 30 GPs. Accommodation was offered to delegates and the speaker for the night of 8 November. The speaker, who would be travelling from Northern Ireland, was also offered accommodation for the night of 7 November. In addition to the two hours of medical content alluded to by the complainant, a further two hours were included in the afternoon and 45 minutes in the evening, no recreational activities were included, hospitality provided included lunch and dinner on day one together with breakfast on the following day. The day delegate cost for the meeting was £230 per person.

Lilly had a strict standard operating procedure (SOP) with regard to meetings and hospitality. A revised SOP was implemented on 2 July 2003 to supplement the company's policy document on good promotional practice on which sales managers and representatives received electronic training on 1 July 2003 with subsequent follow-up training by sales managers in regional meetings during the week commencing 14 July 2003. A copy of the SOP was provided.

Upon investigation it became apparent that the meeting was organised by a sales manager acting in isolation; no formal written invitations to the meeting were issued and no formal agenda had been distributed to the intended audience prior to the meeting. Sales representatives reporting in to the manager concerned had spoken to their customers to gauge interest in the meeting and no further details had been given. The meeting had therefore been

organised outside of Lilly's policy and procedures. As no written invitations had been prepared or issued at the time of receipt of this complaint, Lilly was unable to provide copies. The agenda for the meeting was being drafted internally at the time of the complaint; a copy of the agenda as it stood was provided.

As a result of the investigation into the complaint, the sales manager concerned was being investigated under Lilly's disciplinary procedures. Until this procedure was completed it was not possible to predict the outcome. However, the company took breaches of the Code of this magnitude very seriously and dismissal was one of the options considered in circumstances. If the individual was not dismissed as a result of the disciplinary review, re-training on the SOP for meetings and hospitality and the Code in general would be given.

It was with sincere regret and deep disappointment that Lilly received this complaint. During the last year Lilly had gone to great lengths to further raise the awareness of its employees regarding the Code and compliance therewith. Lilly itself instigated an external audit of its activities under the Code by an independent consultant and had undertaken a substantial review of its procedures in relation to the Code. Significant training of the relevant people involved with the Code had been implemented (including direct training by external experts on the Code).

The situation in which Lilly found itself appeared to be the action of a maverick sales manager, who having passed the ABPI examination and received recent further training in the Code and the meetings and hospitality SOP, had no excuse for his actions. Lilly had procedures in place that would have picked up this issue and had trained its representative appropriately. Upon being made aware of this meeting, Lilly cancelled it and instigated an investigation under its disciplinary procedures against the individual concerned.

Lilly considered that it had not brought the industry into disrepute. It also believed that the company had maintained high standards in the steps that it had taken to endeavour to ensure that activities of this type did not occur. Lilly therefore suggested that the circumstances of this particular case lent themselves more towards Clauses 15.2 and 15.10 than they did to Clauses 9.1 and 2 of the Code. The company acknowledged that notwithstanding that it was not aware of anything else that could have been done to prevent this activity taking place, it had an obligation under Clause 15.10 to accept responsibility for the activities of its representatives if they were within the scope of their employment even if they were acting contrary to the instructions they had been given.

In response to a request for further information Lilly stated that the meeting was a collaboration between two Scottish regions, East and West. The organising sales manager was from the Western region and the venue was in the Eastern region. A list of invitees and their geographical spread was provided.

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 costs involved should not exceed those which participants might normally pay when paying for themselves. The supplementary information to Clause 19.1 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 Lilly's submission that the meeting was organised by a sales manager acting in isolation and outside of the company's policies and procedures. The Panel noted that nonetheless Clause 15.10 provided that companies were responsible for the activities of their representatives if these were within the scope of their employment even if contrary to instructions given. This was acknowledged by Lilly.

The Panel noted that when notified of the complaint, on 31 October, Lilly undertook an investigation and cancelled the meeting.

The Panel was extremely concerned that at the time of the complaint neither formal written invitations nor an agenda had been distributed to invitees. A copy of a provisional agenda which was being drafted at the time of the complaint was provided. The meeting was to be held over two days on 8 and 9 November at the St Andrews Hotel. The draft agenda provided for virtually 4 hours of educational content between 10am and 3pm on day one. Thereafter pre-dinner drinks were to be served at 7.30pm for dinner at 8pm followed at 9.45pm by a 45 minute talk about GP mind mapping. The programme for day two consisted of a question and answer session from 9am to 10am.

The Panel noted that the geographical spread of the invitees comprised the Eastern and Western Scottish regions. Eighteen of the forty invitees, however, came from Glasgow and in all 31 of the invitees came from west of Edinburgh. The Panel queried the rationale of holding the meeting in St Andrews, some 45 miles north of Edinburgh.

The Panel did not consider that the arrangements justified a two day meeting with overnight stay. Given the educational content and the geographical spread of the audience, the meeting could have been held at a more central venue on one day with no need to provide overnight accommodation. The hospitality offered was not in proportion to the occasion. The Panel ruled a breach of Clause 19.1.

The Panel further considered that the sales manager had failed to maintain a high standard of ethical conduct; he had not followed the company's SOP nor had he complied with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled.

The Panel noted that the meeting at issue was organised by a sales manager outside of the

company's policies and procedures. The Panel did not consider that the company itself had failed to maintain a high standard; no breach of Clause 9.1 was ruled.

The Panel did not consider that the arrangements 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 **31 October 2003**

Case completed **12 January 2004**

CASE AUTH/1535/11/03 ***NO BREACH OF THE CODE***

HEALTH PROFESSIONAL VIA THE MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY v GLAXOSMITHKLINE

Seroxat mailing

The Medicines and Healthcare products Regulatory Agency (MHRA) stated that a health professional had complained about a Seroxat (paroxetine) mailing sent by GlaxoSmithKline. The mailing comprised a square, reflective silver envelope which bore the phrase 'Mirror mirror on the wall…' on the front and a statement on the back that should the envelope be undelivered it should be returned to GlaxoSmithKline. Inside the envelope was a six page, gate-folded leaflet, the front page of which was also reflective silver. The only text on the front page was 'love you loads xxx'. The complainant strongly objected to the presentation of the material as a greeting card and indicated that secretarial staff had been misled as to the nature of the material when opening the post.

The MHRA stated that upon opening the card it became clear that this was a promotional item for Seroxat. The MHRA queried whether the mailing was in breach of the Code regarding high standards, format and suitability causing offence and disguised promotional material.

The Panel noted that the Code required high standards to be maintained at all times and all materials and activities to recognise the special nature of medicines and the professional nature of the audience and not be likely to cause offence. The Panel considered that although the complainant had objected to the presentation of the mailing it was unlikely that the majority of those who saw it would do so. The Panel therefore ruled no breach in this regard.

The Panel noted the presentation and style of the envelope and that it had GlaxoSmithKline's name and address printed on the back. The Panel considered that recipients would expect such an envelope to contain promotional material. The Panel did not consider that the leaflet in the envelope had the appearance of a greetings card. The Panel thus did not consider that the promotion of Seroxat had been disguised and ruled no breach of the Code.

The Medicines and Healthcare products Regulatory Agency (MHRA) stated that a health professional had complained about a Seroxat (paroxetine) promotional mailing sent by GlaxoSmithKline UK Limited. The mailing comprised a square, reflective silver envelope (ref SRX/MLP/03/09053/1 July 2003), which bore the phrase 'Mirror mirror on the wall…' on the front and a statement on the back that should the envelope be undelivered it should be returned to GlaxoSmithKline. Inside the envelope was a six page, gate-folded leaflet (ref SRX/MLP/03/09052/1 July 2003) the front page of which was also reflective silver. The only text on the front page was 'love you loads xxx'.

COMPLAINT

The MHRA stated that the complainant strongly objected to the presentation of the material as a greeting card and indicated that secretarial staff had been misled as to the nature of the material when opening the post.

The advertisement was presented in a silver mirror envelope bearing the phrase 'Mirror, mirror on the wall…' inside which appeared to be a tri-fold greeting card with the phrase 'love you loads xxx' on the upper most face of the card.

The MHRA stated that upon opening the card it became clear that this was a promotional item for Seroxat. The MHRA queried whether the mailing was in breach of Clauses 9 and 10 regarding high standards, format and suitability causing offence and disguised promotional material.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clauses 9.1, 9.2 and 10.1 of the Code. The Authority had not seen a copy of the mailing when it wrote to GlaxoSmithKline.

RESPONSE

GlaxoSmithKline explained that the 'Mirror mirror' concept was part of a long-running campaign in which the positive outcomes of treating depression and related psychological/psychiatric disorders were presented in terms of how a patient might feel about him/herself after successful treatment with Seroxat. The visual image chosen derived from the concept that mirrors provided reflections of ourselves and having recovered from their illness a patient could

look in the mirror see that they were well again. Seeing this recovery might also boost a patient's self esteem, which was the basis of the 'love you loads xxx' slogan.

GlaxoSmithKline submitted that high standards, the professional nature of the audience and the special nature of medicines had been fully respected. Furthermore it was appropriate to draw health professionals' attention to the beneficial impact that Seroxat might have in relation to how a patient felt about him/herself once their depression had been successfully treated. This aspect of managing depression and related disorders was often overlooked, despite its importance to patients. In this case GlaxoSmithKline had chosen to convey this message with artwork, which complied with the Code. Similarly GlaxoSmithKline denied that the mailing was likely to cause offence. The company denied breaches of Clauses 9.1 or 9.2.

GlaxoSmithKline also denied the allegation that the mailing was disguised promotion. The mailing was sent to doctors in a franked, pre-paid envelope bearing a typewritten address sticker and GlaxoSmithKline's name and address appeared on the flap of the envelope. No attempt had been made to disguise the mailing as a safety communication or other non-promotional information and GlaxoSmithKline submitted that the format of the envelope and the way in which it had been addressed was consistent with Clause 10.1 of the Code and its supplementary information. The shiny envelope was an extension of the mirror concept and was favoured for direct advertising as such envelopes were more likely to be opened. GlaxoSmithKline was therefore surprised to learn that, given the envelope displayed the GlaxoSmithKline name and address, persons opening this mailing thought that the contents were anything other than promotional material. Similarly the mailing itself was clearly a promotional item and was fully compliant with the Code in this respect.

GlaxoSmithKline stated that with regard to the point that a health professional misconstrued this mailing as a greeting card, it was clear that in this case secretarial staff had opened the mailing not the health professional to whom it was addressed. As discussed above, the envelope indicated to the recipient that it contained an item from GlaxoSmithKline. The company noted that it appeared that only the contents of the envelope were presented to the health professional by secretarial staff, thereby modifying the item. However, even without the envelope the mailing was clearly promotional and consequently GlaxoSmithKline denied a breach of Clause 10.1.

PANEL RULING

The Panel noted the company's submission that the 'Mirror mirror' concept was part of a long-running campaign for Seroxat.

The Panel noted that Clause 9.1 of the Code required high standards to be maintained at all times. Clause 9.2 stated that all materials and activities must recognise the special nature of medicines and the professional nature of the audience to which they were directed and must not be likely to cause offence. The Panel considered that although the complainant had objected to the presentation of the mailing it was unlikely that the majority of those who saw it would find it objectionable. The Panel considered that the mailing was not unreasonable in relation to the requirements of Clauses 9.1 and 9.2. The Panel therefore ruled no breach of those clauses.

The Panel noted the presentation and style of the envelope and that it had GlaxoSmithKline's name and address printed on the back. The Panel considered that recipients would expect such an envelope to contain promotional material. The Panel did not consider that the leaflet in the envelope had the appearance of a greetings card. The Panel thus did not consider that the promotion of Seroxat had been disguised and ruled no breach of Clause 10.1 of the Code.

Complaint received **4 November 2003**

Case completed **6 January 2004**

CASE AUTH/1536/11/03

WYETH v ABBOTT LABORATORIES

Humira leavepiece

Wyeth complained about an Humira (adalimumab) leavepiece issued by Abbott. Humira was indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic medicines had been inadequate. To ensure maximum efficacy, Humira was given in combination with methotrexate (MTX) but could also be given as monotherapy in cases of intolerance to methotrexate or when continued treatment with methotrexate was inappropriate.

Wyeth noted that below a sub-heading of 'Effect on structural joint damage' was a graph showing the effect of Humira plus methotrexate vs methotrexate alone on disease progression. The differences between the two treatment groups at six months and one year were statistically significant ($p \leq 0.001$) in favour of Humira. Beneath the graph was the statement 'Humira is not licensed for inhibition of disease progression'. Wyeth alleged that this was outside the marketing authorization.

The Panel considered that the graph gave the visual impression that combination therapy inhibited disease progression while methotrexate on its own did not. The statement below the graph was not sufficient to negate the impression that Humira could be used to inhibit disease progression. The product was only indicated for the treatment of RA. The Panel considered that the section of the leavepiece at issue promoted Humira in a way that was not in accordance with the terms of its marketing authorization. A breach of the Code was ruled.

Wyeth alleged that the claim 'Humira is licensed for use both in combination with MTX and as monotherapy' which appeared as the last of five bullet points below a heading of 'RA control made convenient' was misleading because it implied that the decision between monotherapy and concomitant methotrexate with Humira was both straightforward and unconditional. This conflicted with the marketing authorization for Humira.

The Panel noted that the summary of product characteristics (SPC) stated 'To ensure maximum efficacy, Humira is given in combination with methotrexate Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate'. The Panel considered that it was implicit that Humira should only be given as monotherapy when combination therapy was not an option. In the Panel's view the claim 'Humira is licensed for use both in combination with MTX and as monotherapy' implied that there was a simple choice between the two regimens which was not so. The Panel considered that the claim was inconsistent with the particulars listed in the SPC and was misleading in that regard. Breaches of the Code were ruled.

Wyeth considered that the statement in the SPC that 'Patients treated with Humira should be given a special alert card' was critical to patient safety. The company alleged that omission of this information from the prescribing information was in breach of the Code.

The Panel noted that the Humira SPC stated that treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Humira should be given the special alert card. There was no reference to the special alert card in the prescribing information. The Panel considered that by not referring to the need to give patients a special alert card the prescribing information did not include some important, relevant information about the use of Humira. A breach of the Code was ruled.

Wyeth Pharmaceuticals complained about an Humira (adalimumab) leavepiece (ref SXHUM2003050) issued by Abbott Laboratories Ltd. Humira was indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic medicines had been inadequate. To ensure maximum efficacy, Humira was given in combination with methotrexate (MTX) but could also be given as monotherapy in cases of intolerance to methotrexate or when continued treatment with methotrexate was inappropriate.

1 Effect on structural joint damage

On page 3 of the leavepiece, below a sub-heading of 'Effect on structural joint damage' a graph showed the effect of Humira plus methotrexate vs methotrexate alone on disease progression; over the course of a year modified total Sharp score rose in patients treated with methotrexate alone but not in those treated with Humira and methotrexate. The differences between the two treatment groups at six months and one year were statistically significant ($p \leq 0.001$). Beneath the graph was the statement 'Humira is not licensed for inhibition of disease progression'.

COMPLAINT

Wyeth alleged that as Humira was not licensed for the inhibition of disease progression this promotion directly conflicted with Clause 3.2 of the Code and represented promotion outside the marketing authorization.

RESPONSE

Abbott submitted that in the lead up to the launch of Humira the question 'Does Humira impact the progression of bone disease in rheumatoid arthritis?' was frequently posed to the medical information department by health professionals. Humira was not specifically licensed for the inhibition of disease progression, although a regulatory variation to seek approval for this indication was planned imminently.

In light of this, and as part of the pre-licence preparation of the leavepiece, Abbott contacted the Authority for general verbal guidance on this matter. Abbott noted that the Authority did not review the item in question, and the company accepted that the

advice given did not represent the formal opinion of the Authority.

Further to this advice, Abbott decided that the question: 'Does Humira impact the progression of bone disease in rheumatoid arthritis?' was a frequently asked question, and a subject of genuine scientific interest. As such, a section was included with a graph of relevant data, with no associated product claims. Further, the statement that 'Humira is not licensed for inhibition of disease progression' was included within the graph, so that the health professional would be absolutely clear as to the current licensing status for Humira in this regard.

The efficacy of medicines used to treat rheumatoid arthritis could be assessed using a variety of outcome measures, including the total Sharp score. As stated above, the effect of Humira on the total Sharp score was an area of particular interest for clinicians, and requests for such information were received frequently by the medical information department. The graph on page 3 provided clear, factual scientific information on one of the many treatment effects of Humira, ie the effect on total Sharp score, when prescribed in accordance with the summary of product characteristics (SPC). Data were presented in a balanced and non-promotional way and no product claims were made.

Abbott understood that the inclusion of data not specifically detailed in the SPC was not prohibited in cases where the information was of genuine scientific interest and frequently asked by customers, and where no claims were made. Abbott did not, therefore, accept that the inclusion of these data constituted a breach of Clause 3.2.

PANEL RULING

The Panel noted that the Authority could only give informal advice; if a complaint were subsequently received it would have to be dealt with in the usual way.

The Panel considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel considered that the graph of itself made a claim for inhibition of disease progression with Humira/methotrexate combination therapy. The visual impression was that combination therapy inhibited disease progression while methotrexate on its own did not. The statement below the graph that 'Humira is not licensed for inhibition of disease progression' was not sufficient to negate the impression that Humira could be used to inhibit disease progression. The product was only indicated for the treatment of RA. The Panel considered that the section of the leavepiece at issue promoted Humira in a way that was not in accordance with the terms of its marketing authorization. A breach of Clause 3.2 was ruled.

2 Claim 'Humira is licensed for use both in combination with MTX and as monotherapy'

This claim appeared as the last of five bullet points on page 5 of the leavepiece below a heading of 'RA control made convenient'.

COMPLAINT

Wyeth alleged the claim was misleading because it implied that the decision between monotherapy and concomitant methotrexate with Humira was both straightforward and unconditional. This conflicted with the marketing authorization for Humira and consequently Clauses 3.2 and 7.2 of the Code. The SPC stated 'To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can only be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate'.

RESPONSE

Abbott submitted that the claim was factual. It was in accordance with the marketing authorization and was not inconsistent with the SPC. The SPC contained comprehensive information for prescribers, including details of the conditions under which Humira could be used as a monotherapy.

The leavepiece was intended to provide a summary of key data, and not a definite prescribing guide. Abbott expected clinicians to consult the prescribing information (which was integral to the leavepiece) and the SPC before prescribing Humira. Abbott noted that the intended audience was health professionals experienced in the management of rheumatoid arthritis. Abbott did not therefore believe that the inclusion of this statement constituted a breach of either Clause 3.2 or 7.2.

PANEL RULING

The Panel noted that Wyeth had not quoted the licensed indication for Humira correctly. The SPC stated 'To ensure maximum efficacy, Humira is given in combination with methotrexate Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate'. There was no statement in the SPC that Humira could only (emphasis added) be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate was inappropriate. Nonetheless the Panel considered that it was implicit that Humira should only be given as monotherapy when combination therapy was not an option. In the Panel's view the claim 'Humira is licenced for use both in combination with MTX and as monotherapy' implied that there was a simple choice between the two regimens which was not so. The Panel considered that the claim was inconsistent with the particulars listed in the SPC and was misleading in that regard. Breaches of Clauses 3.2 and 7.2 were ruled.

3 Prescribing information

COMPLAINT

Wyeth noted that the prescribing information at the back of the leavepiece concerning dosage did not

include information in the SPC that 'Patients treated with Humira should be given the special alert card'.

Patients who were prescribed monoclonal antibodies such as Humira and Infliximab, as stated in the SPC, should be given an alert card. In view of the above and the safety of patients being paramount, Wyeth alleged that the omission of reference to the provision of the alert card on the prescribing information was critical to patient safety and in breach of Clause 4.2 of the Code.

RESPONSE

Abbott stated that the requirements for inclusion of information in the prescribing information were outlined in the Code. Prescribing information should be an accurate reflection of important information included in the SPC. Abbott submitted that the Humira prescribing information was representative of the SPC.

Abbott did not consider that it was a specific requirement to include information regarding the special alert card in the Humira prescribing information, as it had processes in place to assist customers in accessing the card. However, it appreciated that inclusion of this information in the prescribing information would provide more complete guidance for the customer. It therefore intended to change the prescribing information to reflect this and would amend all promotional material at the next print run. Abbott stated that this position had been previously agreed by both companies; it was unfortunate that, having reached a mutually acceptable plan of action in this regard, Wyeth had subsequently decided to formally complain on this matter.

Abbott's position on this issue was unchanged, it did not believe that the omission of the special alert card constituted a breach of Clause 4.2 of the Code but, nevertheless, would update the prescribing information at the next print run in order to provide more complete information for clinicians.

PANEL RULING

The Panel noted that Clause 4.2 of the Code required the prescribing information to include, *inter alia*, a succinct statement of the information in the SPC relating to the dosage and method of use relevant to the indication quoted in the advertisement and, where not otherwise obvious, the route of administration. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of this clause and not of Clause 4.2.

The Humira SPC stated that treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Humira should be given the special alert card. The Panel noted that the reference to the special alert card was not highlighted in the SPC as submitted by Wyeth. Nonetheless there was no reference to the special alert card in the prescribing information. The Panel considered that by not referring to the need to give patients a special alert card the prescribing information did not include some important, relevant information about the use of Humira. A breach of Clause 4.1 was ruled.

Complaint received **6 November 2003**

Case completed **8 January 2004**

CODE OF PRACTICE REVIEW – FEBRUARY 2004

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1465/5/03	**Roche v Ortho Biotech**	**Promotion of Eprex**	**Breaches Clauses 4.1 and 4.9 Four breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.4 Breaches Clauses 7.7 and 7.8 Two breaches Clause 7.10 Breach Clause 8.1 Two breaches Clause 9.1 Breach Clause 9.9**	**Appeal by respondent**	**Page 3**
1470/5/03 & 1488/6/03	**Norgine and Continence Nurse Specialist v Schwarz Pharma**	**Promotion of Idrolax**	**Breach Clause 7.2 Five breaches Clause 8.1 Breach Clause 9.1**	**Appeal by respondent**	**Page 20**
1477/6/03	**Bristol-Myers Squibb and Sanofi-Synthelabo v Novartis**	**Promotion of Diovan**	**Three breaches Clause 3.2**	**Appeal by respondent**	**Page 31**
1484/6/03	**Pfizer v Gilead Sciences**	**Promotion of AmBisome**	**Four breaches Clause 7.2 Five breaches Clause 7.3**	**Appeal by complainant**	**Page 39**
1486/6/03	**Former Representative v AstraZeneca**	**Failure to adequately train representative**	**Breaches Clauses 2, 9.1 and 15.1**	**Appeal by respondent**	**Page 51**
1490/7/03	**Primary Care Trust Medicines Management Programme Director v Aventis Pasteur MSD**	**Promotion of Viatim**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 68**
1491/7/03	**Novartis v Fujisawa**	**Promotion of Protopic**	**Breaches Clauses 3.2 and 15.2**	**Appeal by respondent**	**Page 72**
1492/7/03	**Wyeth/Director v Novo Nordisk**	**Breach of undertaking**	**Breaches Clauses 2 and 22**	**Appeal by complainant**	**Page 80**
1496/7/03	**Consultant Psychiatrist v Lundbeck**	**Cipralex mailing**	**Three breaches Clause 7.2**	**Appeal by respondent**	**Page 86**
1497/7/03	**Hospital Pharmacist v Amgen**	**Neulasta leavepiece**	**Two breaches Clause 7.2 Two breaches Clause 7.3**	**Appeal by respondent**	**Page 92**
1508/8/03	**Clement Clarke v AstraZeneca**	**Promotion of the Turbohaler**	**Breach Clause 4.1**	**No appeal**	**Page 98**
1510/8/03 & 1511/8/03	**Novartis v Bristol-Myers Squibb and Sanofi-Synthelabo**	**Promotion of Aprovel**	**Two breaches Clause 7.2 Two breaches Clause 7.10**	**Appeal by respondents**	**Page 113**
1512/8/03	**Consultant Physician v Aventis Pharma**	**Insulin for Life Programme**	**Breach Clause 18.1**	**No appeal**	**Page 122**
1515/9/03	**General Practitioners v GlaxoSmithKline**	**Asthma audit**	**Breaches Clauses 2, 9.1 and 18.1**	**No appeal**	**Page 126**

1518/9/03	**Media/Director v Organon Laboratories**	**Promotion of Cerazette**	**Breach Clause 7.2**	**No appeal**	**Page 129**
1521/10/03	**Wyeth v Novo Nordisk**	**Kliovance leavepieces**	**Breaches Clauses 7.2, 7.3 and 7.8**	**No appeal**	**Page 133**
1522/10/03	**Novartis/Director v Fujisawa**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 22**	**No appeal**	**Page 137**
1523/10/03	**Novartis v Sankyo Pharma**	**Promotion of Olmetec**	**Breach Clause 7.4**	**No appeal**	**Page 140**
1524/10/03	Consultant Oncologist v GlaxoSmithKline	Lamictal journal advertisement	No breach	No appeal	Page 145
1526/10/03	**Novartis v Roche**	**Promotion of Bondronat**	**Two breaches Clause 3.1 Three breaches Clause 3.2 Three breaches Clause 7.2**	**No appeal**	**Page 147**
1528/10/03	**Media/Director v Lundbeck**	**Ebixa mailing**	**Two breaches Clause 7.2 Breaches Clauses 7.3 and 7.4**	**No appeal**	**Page 151**
1530/10/03	**General Practitioner v Sankyo Pharma**	**Newspaper article on Olmetec**	**Breaches Clauses 9.1 and 20.2**	**No appeal**	**Page 154**
1534/10/03	**Anonymous v Lilly**	**Arrangements for meeting**	**Breaches Clauses 15.2 and 19.1**	**No appeal**	**Page 156**
1535/11/03	Health Professional via the Medicines and Healthcare products Regulatory Agency v GlaxoSmithKline	Seroxat mailing	No breach	No appeal	Page 158
1536/11/03	**Wyeth v Abbott Laboratories**	**Humira leavepiece**	**Breaches Clauses 3.2 and 4.1**	**No appeal**	**Page 160**

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).