PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 25 AUGUST 1999

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.

Statutory regulation or self-regulation?

As previously reported, The Medicines (Advertising and Monitoring of Advertising) Amendment Regulations 1999 (SI 1999 No 267) came into operation on 5 April. Both the Authority and the ABPI have reservations about the need for, and nature of, the further statutory enforcement provisions which have been introduced. Legal advice taken on behalf of the industry indicated that the lack of a proper appeal procedure might be in breach of the European Convention on Human Rights but the Medicines Control Agency (MCA) is now to establish an Independent Review Panel (IRP) which will consider appeals. The Health Ministers will not be bound by the IRP's views but reasons will be given if they are not accepted.

It remains to be seen how the new system will operate but the Authority was pleased to note that in MAIL 113 (May-June 1999), it was stated that 'The MCA fully supports the self-regulatory system which is permitted under the European Directive on advertising and has no intention of usurping its role'.

IFPMA Internet report

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has published 'The Internet and Pharmaceutical Products: The State of the Art and the Way Forward' which is the report of a symposium on the Internet held in October 1998.

Copies can be obtained from the IFPMA at 30 rue de St-Jean, P O Box 9, 1211 Geneva 18, Switzerland. Telephone 00 4122 340 1200. Facsimile 00 4122 340 1380. It will be available on the IFPMA Website at http://www.ifpma.org

Economic evaluation of medicines

The supplementary information to Clause 7.2 of the Code covers claims based on economic evaluations and refers to guidance jointly issued by the ABPI and the Department of Health.

Before making a claim based on such a study, companies are advised to satisfy themselves that the study remains up-to-date and is reflective of today's practices and prices and, in relation to a study carried out abroad, that it is relevant to current UK practices and prices.

Approved information on the Internet

As reported in a supplement to the May Code of Practice Review, the EU Pharmaceutical Committee has given interpretative guidance indicating that the unmodified and unabridged publication on the Internet of the public assessment report, the summary of product characteristics and the package leaflet will not be regarded as advertising and can thus be on open access.

This is consistent with UK practice but it will represent a significant change in those European countries which until now have considered such information to be advertising.

The references to summaries of product characteristics and package leaflets in the supplementary information to Clause 20.2 of the Code and in the Authority's Internet guidance should be regarded as applying also to public assessment reports. The Internet guidance, which was included in the May 1996 Review, can be obtained from the Authority.

The EU Committee is to set up a working group to review the issue of information on medicines and the possible need to amend the Directive on the advertising of medicinal products for human use.

Price reductions

As companies are aware, the revised Pharmaceutical Price Regulation Scheme requires prices of medicines to be reduced with effect from 1 October so as to achieve an overall reduction for a company of 4.5%.

It is in the interest of advertisers to indicate the new lower prices on promotional material as soon as possible. In the period 1 October to 31 December, however, promotional material will not be considered to be in breach of the Code if it still carries the previous higher price.

Care should be taken, however, to ensure that there is no discrepancy between what representatives say and what is said on written material left with the doctor etc by the representative as this could give rise to complaints.

It will not be acceptable at any time to give comparative prices in promotional material where these involve the new lower price of the advertiser's product and the superseded higher prices of competitor products.

Every effort should be made to ensure that journal advertisements are correct at the time of publication.

Material left with agencies and printers

From time to time a journal advertisement which has been ruled in breach of the Code is subsequently published again and the excuse put forward as the reason for this is that the agency or the printer erroneously used an old film which had remained in their possession.

When an advertisement is ruled in breach of the Code it is in the interest of the company concerned to ensure that the films of it are withdrawn and destroyed so that they cannot be used again in error.

1998 Annual Report

The Authority's Annual Report for 1998 has now been published and has been sent to all those who receive the Review.

Further copies are available on request.

New member of the Authority's staff

The Authority has welcomed Mrs Lisa Matthews to its staff. Lisa is the secretary to Etta Logan and Jane Landles. Her telephone number is 0171 930 9677 extension 1473.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, open to all comers, are run by the Code of Practice Authority on a regular basis at the Royal Society of Medicine in London.

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

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

Tuesday, 2 November

Friday, 26 November

Friday, 10 December

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 (0171-930 9677 extn 1443).

How to contact the Authority

Our address is:

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

Telephone: 0171-930 9677
Facsimile: 0171-930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Jean Rollingson (0171-930 9677 extn 1443).

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

Heather Simmonds: 0171-747 1438
Etta Logan: 0171-747 1405
Jane Landles: 0171-747 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/818/12/98

DIRECTOR/MEDIA v SANOFI WINTHROP

Epilepsy therapy cards

A letter in The Pharmaceutical Journal (PJ) headed 'Therapy cards a dangerous precedent', criticised a scheme of Sanofi Winthrop and the British Epilepsy Association to distribute cards to epilepsy patients to encourage them to ask for continuation of their branded anticonvulsant. The letter, from a clinical pharmacist, referred to an article which had appeared previously in the PJ headed '"Please ensure I receive this brand" says epilepsy patient card'. The article mentioned a fact sheet to be sent to patients with the cards which suggested that if a prescription which usually specified a brand name was now written in the generic name, or if tablets looked different, patients should ask their doctor or pharmacist to explain the change. In accordance with established procedure the criticisms were taken up by the Director and dealt with as a complaint under the Code.

The letter stated that those who worked in the field of epilepsy had over the past 12 months been bombarded with propaganda circulated by Sanofi Winthrop with regard to not changing brands of anticonvulsants. In the present climate, where one should rely on evidence based medicine to make clinical decisions, it seemed that the evidence for not changing brands was feeble at best. Research to date had proved nothing. The author stated that the issue he found most disturbing was that Sanofi Winthrop was cloaking its sole motivation of blatant commercial gain in a blanket of 'caring only for the patient's welfare'. In the process, it had not only brought into question the professionalism of doctors and pharmacists for prescribing and dispensing generally, but it was now using the patients themselves as vehicles for its message. Pharmaceutical companies directly influencing patients into choosing their prescription medications were surely pushing the legal boundaries and definitely overstepping ethical boundaries.

The Panel noted that there were important and valid concerns about the problems associated with switching anti-epileptic treatment, be it from a brand to a generic, from a generic to a brand or from a generic from one manufacturer to a generic from another manufacturer. It was not unreasonable to advise patients about such concerns so long as the provision of such information was factual, balanced, non-promotional and otherwise not in breach of the Code. The fact sheet advocated that patients stabilised on branded anticonvulsants should ensure that they always received the same version. The Panel noted the advice given in both MIMS and BNF regarding changing from one preparation to another and considered that a switch from any formulation of an anticonvulsant medicine to another version of the same medicine should be done cautiously as recommended, and this was not necessarily detrimental to the patient. The possibility that doctors might choose to change patients, with the right safeguards, from one medicine to another was not conveyed in the fact sheet. The Panel considered that the letter was not balanced in that respect and ruled a breach of the Code. The Panel considered that the provision of the patient fact sheet and therapy card was not unacceptable *per se* and they did not fail to recognise the special nature of medicines. No breach of Clause 9.1 was ruled. The Panel noted that the declaration of sponsorship appeared at the end of the fact sheet in normal typeface and considered that readers of the letter would not be aware of the sponsorship at the outset. A breach of the Code was ruled.

Upon appeal by the author of the letter against the ruling that there had been no breach of Clause 9.1, the Appeal Board considered that the provision of patient fact sheets and therapy cards was not unacceptable *per se* so long as their content was not otherwise in breach of the Code. The Appeal Board did not consider that the provision of the patient fact sheet and therapy card failed to either recognise the special nature of medicines or to maintain high standards. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1 of the Code.

A letter in The Pharmaceutical Journal (PJ) of 19/26 December 1998 headed 'Therapy cards a dangerous precedent', criticised a scheme of Sanofi Winthrop Limited and the British Epilepsy Association (BEA) to distribute cards to epilepsy patients to encourage them to ask for continuation of their branded anticonvulsant. The letter, from a clinical pharmacist, referred to an article which had appeared in the PJ of 21 November 1998 headed '"Please ensure I receive this brand" says epilepsy patient card'. The article mentioned a fact sheet to be sent to patients with the cards which suggested that if a prescription which usually specified a brand name was now written in the generic name, or if tablets looked different, patients should ask their doctor or pharmacist to explain the change. The article also stated that a spokeswoman for the Royal Pharmaceutical Society had said that the Society had some concerns about the initiative. An editorial in the same issue of the PJ, entitled 'Prescribing Anticonvulsants', stated that the journal had some unease about the cards.

In accordance with established procedure the criticisms were taken up by the Director and dealt with as a complaint under the Code.

COMPLAINT

The author of the letter stated that those who worked in the field of epilepsy, to whatever degree, had over the past 12 months been bombarded with propaganda circulated by Sanofi Winthrop with regard to not changing brands of anticonvulsants.

The author stated that in the present climate where one should rely on evidence based medicine to make clinical decisions, it seemed that the evidence for not changing brands was feeble at best. Research to date had proved nothing.

The author stated that the issue he found most disturbing was that Sanofi Winthrop was cloaking its sole motivation of blatant commercial gain in a blanket of 'caring only for the patient's welfare'. In

the process, it had not only brought into question the professionalism of doctors and pharmacists for prescribing and dispensing generally, but it was now using the patients themselves as vehicles for its message.

In the author's view this was a dangerous precedent that was being set by Sanofi Winthrop and one which was, to their credit, not being supported by any other manufacturers of brand name anticonvulsants. Pharmaceutical companies directly influencing patients into choosing their prescription medications were surely pushing the legal boundaries and definitely overstepping ethical boundaries.

The author stated that it was unfortunate that the British Epilepsy Association had associated itself with this initiative to distribute cards to epilepsy patients when the empirical evidence did not support its concerns.

If Sanofi Winthrop wished to regain its reputation as an ethical pharmaceutical company it should produce the evidence through legitimate research.

Finally, if The Pharmaceutical Journal had concerns about this initiative the author questioned why had it seen fit to publish full page advertisements which were heavily disguised as articles.

RESPONSE

Sanofi Winthrop noted that the article in the PJ, November 21, stated that a series of therapy cards was available, namely Epilim, Epilim Chrono, Tegretol, Tegretol Retard and Epanutin. It also clearly stated that the production of these cards was sponsored by Sanofi Winthrop. Copies of the therapy cards and the correspondence from the other companies whose products were involved, confirming their agreement to participate in the initiative, were provided.

Sanofi Winthrop believed that high standards had been maintained and that the declaration of sponsorship was clear on the documents which accompanied the therapy card, and that there had been no breach of Clauses 9.1 or 9.9 of the Code.

Sanofi Winthrop stated that from the letter it was not clear to what the author referred to when he mentioned 'propaganda'. However, there were several publications in the public domain which addressed the issue of brand or generic prescribing. Some of these publications had been referred to by Sanofi Winthrop in a pharmacist leavepiece which was provided.

Sanofi Winthrop considered the leavepiece to be 'balanced, fair, objective and unambiguous' and 'based on up-to-date evaluation of all the evidence'. The company also considered that clear reference to published data had been given on the item in question, and that it did not contravene Clauses 7.2 or 7.3 of the Code.

Sanofi Winthrop referred to a series of advertisements that had appeared over the course of 1998. In each case, the fact that they had been advertisement features or promotions had been clearly apparent at the top of the articles and there had never been any attempt or desire to mislead the reader, or to contravene the Code in any way.

The majority (over 90%) of BEA funding was from voluntary contributions. The remainder was from various sources: for example, the BEA Sapphire Nurses were epilepsy specialist nurses funded by another pharmaceutical company, the Roald Dahl Foundation and the Kings Fund.

Like other pharmaceutical companies, Sanofi Winthrop was happy to support BEA educational initiatives as part of the company's commitment to epilepsy patient care, and some of this work was conducted by third parties on the company's behalf. The issue of switching a patient from their usual medicine to a different version had been a concern of the BEA for a number of years. In 1992, 800 of its members known to have epilepsy were targeted with a postal questionnaire; a 56% response rate was subsequently reported. More frequent seizures and increased side effects were recorded where patients had been switched from a branded medicine to a generic and vice versa. It was concluded that there was a problem with the poor consistency of supply rather than a question of the quality of the medicines.

The BEA discussed the findings with Sanofi Winthrop and subsequently undertook a larger study to fully evaluate this issue. Sanofi Winthrop provided the BEA with funds to support this work. The results of this study were published (Crawford *et al* (1996)).

As a consequence to the findings of this study, the BEA Therapy Card was suggested as an additional means of helping patients ensure they received the brand on which they had been stabilised. Sanofi Winthrop provided a grant to the BEA for development and production of the cards. The project was started in 1996 but not launched until 1998. Patients, doctors and pharmacists could request the therapy cards, which were only available through the BEA. In 1998 a series of articles was published in the pharmacy media to support the central message of the need for consistent supply.

Sanofi Winthrop considered this initiative to be entirely consistent with both the company's and the BEA's commitment to patients with epilepsy.

PANEL RULING

The Panel noted that two other companies had agreed to have their products included in the initiative.

The fact sheet which was provided to patients together with the therapy card was headed 'Epilepsy and Branded Medicines' and the introductory paragraph stated that the purpose of the therapy cards was to help people who usually received a branded medicine ensure that they always received the same version. The fact sheet went on to mention that in epilepsy a proportion of people reported problems associated with a switch from one version of a medicine to another.

The subsequent paragraph introduced the concept of generic medicines and the fact sheet stated that pharmacists could buy generic medicines from any licensed manufacturer which meant that the supply

could vary. It was the variation in supply that was causing concern. The next section of the fact sheet was headed 'Medical evidence' beneath which the results of a survey undertaken by the BEA were discussed. The survey had revealed that almost half of the people who switched to a different manufacturer's version of the same epilepsy medicine said that their epilepsy worsened. Sixteen percent suffered a breakthrough seizure and a quarter reported more frequent seizures. The fact sheet also referred to a study (assumed to be Crawford et al (1996)) stating that of 251 people with epilepsy who reported switching between different manufacturers' versions of the same epilepsy medicine, about a third reported that seizure frequency or side effects increased following the switch. The section concluded by stating that most problems occurred when people changed from the branded medicines to a generic version, although some problems were associated with switches from one generic version to another or from a generic to the branded medicine.

The fact sheet went on to state that MIMS recommended that doctors should specify the brand name of epilepsy medicines on the prescription to ensure a continuous supply from the same manufacturer. Patients were told, however, that if their epilepsy was controlled using a generic medicine, and both they and their doctor were happy, then their medication should not be changed. (The Panel queried why a patient stabilised on a generic medicine would be in receipt of a branded therapy card). The fact sheet ended with the statement 'The BEA Therapy Card initiative is sponsored by an educational grant from Sanofi Winthrop'.

The Panel noted that neither the BEA survey nor the study (Crawford *et al* (1966)) cited as 'medical evidence' in the fact sheet included a control group of patients whose medication had not been switched.

The fact sheet stated that MIMS recommended that doctors should specify the brand name of epilepsy medicines on the prescription to ensure continuous supply from the same manufacturer. The Panel noted, however, that MIMS January 1999, in its prescribing notes on anticonvulsants and under a heading of 'NB: Bioavailability', stated 'Recent evidence indicates that there is a loss of seizure control when a patient's medication is switched between different manufacturers' versions of the same anticonvulsant because of differences in bioavailability. It is therefore recommended that all anticonvulsants are prescribed by brand name, and that patients are not transferred from one preparation or formulation to another without full clinical assessment and retitration'.

The Panel noted that the BNF (No. 36, September 1998) stated that 'The changeover from one antiepileptic drug regimen to another should be made cautiously, withdrawing the first drug only when the new regimen has been largely established.' The entry for non-proprietary carbamazepine contained the note 'Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing formulation'. The non-proprietary phenytoin entry included the note 'On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but some clinics prefer patients to remain on the same brand whenever possible.'

The Panel noted that there were important and valid concerns about the problems associated with switching anti-epileptic treatment be it from a brand to a generic, from a generic to a brand or from a generic from one manufacturer to a generic from another manufacturer. It was not unreasonable to advise patients about such concerns so long as the provision of such information was factual, balanced, non-promotional and otherwise not in breach of the Code.

The Panel noted that the fact sheet advocated that patients stabilised on branded anticonvulsants should ensure that they always received the same version. The Panel noted the advice given in both MIMS and the BNF regarding changing from one preparation to another and considered that a switch from any formulation of an anticonvulsant medicine to another version of the same medicine should be done cautiously as recommended, and this was not necessarily detrimental to the patient. The possibility that doctors might choose to change patients, with the right safeguards, from one medicine to another was not conveyed in the fact sheet. The Panel considered that the fact sheet was not balanced in that respect. The Panel noted that the fact sheet was supplied to patients and therefore it came within Clause 20 as well as Clause 7.2 as cited by the Director in her letter to Sanofi Winthrop asking for comment. The Panel considered that the requirement in Clause 7.2 about information, etc, being balanced was reflected in Clause 20.2 which required, *inter alia*, that information should be presented in a balanced way. The Panel decided that Clause 20.2 was the more relevant clause and a breach of that clause was ruled.

The Panel considered that the provision of the patient fact sheet and therapy card was not unacceptable *per se* and they did not fail to recognise the special nature of medicines. No breach of Clause 9.1 was ruled.

The Panel considered Clause 9.9 of the Code which stated that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The supplementary information stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The Panel noted that the declaration of sponsorship appeared at the end of the fact sheet in normal typeface and considered that readers of the fact sheet would not be aware of the sponsorship at the outset. The Panel ruled a breach of Clause 9.9 of the Code.

The Panel did not consider that the Code had been breached by the other two companies in relation to the cards bearing the names of their products.

The Panel considered that the pharmacist leavepiece did not meet the requirements of the Code. It referred to generic prescribing and possible problems and advocated prescribing by brand. It could be argued that it in effect promoted branded products in epilepsy and should have included prescribing information for Sanofi Winthrop's product. It

certainly needed to indicate its origin which was strikingly absent. The Panel requested that Sanofi Winthrop be advised of its concerns.

APPEAL BY COMPLAINANT

The complainant took issue with several of the points made.

Firstly, the research article (Crawford *et al* (1996)), as had been pointed out, was inherently flawed in that it was simply a questionnaire based study that had no control group comparison and as such it had no significant results. Therefore, it was not research that would stand up to serious professional criticism.

Secondly, with regard to the referencing of MIMS, January 1999, under the heading 'NB: Bioavailability. Recent evidence indicates that there is a loss of seizure control when a patient's medication is switched between different manufacturers' versions of the same anticonvulsant because of differences in bioavailability. It is therefore recommended that all anticonvulsants are prescribed by brand name, and that patients are not transferred from one preparation or formulation to another without full clinical assessment and retitration'. Sanofi Winthrop itself had laid bare this claim of bioavailability being a significant problem. In the technical brochure for Gabitril (tiagabine), another of its medicines, it said 'Tiagabine reduces the plasma concentration of valproate by about 10%. However, this is not considered to be clinically important and a dose increase is not necessary'. If it was not a clinically important problem there, why should it be a problem when changing brands of anticonvulsants? It was not possible to access comparative bioavailability and dissolution profiles of various products as this was confidential information known only to the respective pharmaceutical companies and the Medicines Control Agency.

Thirdly, the complainant considered that the references from the BNF might have been taken out of context. 'The changeover from one antiepileptic drug regimen to another should be made cautiously, withdrawing the first drug only when the new regimen has been largely established'. This was well recognised and was standard clinical practice, but this bore little relevance to the issue being discussed here. The patients being considered here had had neither their drug regimen nor their dosage adjusted. The entry for carbamazepine contained the note 'Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing formulation'. Although not specific, it seemed to be indicating that a change from normal tablets to SR tablets would lead to a change in bioavailability. It then confirmed this by asking the reader to 'See notes above on how side-effects may be reduced'. This then said 'Use of modified release tablets also significantly lessens the incidence of dose related side-effects'. Hence, it was referring to a change of formulation, rather than a change of brand, which would lead to a change in bioavailability. Indeed it was referring to carbamazepine, not sodium valproate.

In light of these points it would seem that there was little evidence to support the stance of Sanofi Winthrop advocating the discouragement of changing brands. As a result of this the complainant appealed against the ruling that there had been no breach of Clause 9.1 of the Code.

The information presented in the advertisements was of a dubious nature and hence was not respecting nor recognising the professional standing of the audience. Evidence based medicine was the gold standard that should be aspired to, and here the evidence was somewhat lacking. Added to this were the patient cards which were being presented by patients to GPs and pharmacists and placing them in a difficult position by compromising them professionally. That was by trying to coerce them into prescribing and dispensing branded products when they could be using generic products if they wished to do so. This was indeed offensive and was hardly representative of 'High standards which must be maintained at all times'. In view of this it would seem that Sanofi Winthrop had breached Clause 9.1 of the Code.

This marketing strategy, though, did seem to be having an impact. On several occasions the issue had been raised by various people within the epilepsy care framework. Hence, the complainant reiterated that Sanofi Winthrop should invest its time and energy into providing substantive evidence to prove its point, not into dubious marketing.

RESPONSE FROM SANOFI WINTHROP

Sanofi Winthrop said that it was at a loss to see how Clause 9.1 of the Code might be considered to have been breached.

Sanofi Winthrop's interpretation of Clause 9.1, and it believed that of the Panel, was that it referred to 'Format, Suitability and Causing Offence' purely in the context of advertising style.

Indeed the supplementary information to Clause 9.1 clearly stated that:

'It follows therefore that certain types, styles and methods of promotion, even where they might be acceptable for the promotion of products other than medicines, are unacceptable. These include:

- the display of naked or partially naked people for the purpose of attracting attention to the material…*etc*.
- 'teaser' advertising…*etc*'

Sanofi Winthrop believed that the provisions of the Code pertaining to factual content in terms of 'Information, Claims and Comparisons' gave clear guidance as set out in Clause 7 and Clause 20 of the Code. The complainant had based his appeal of the ruling of no breach of Clause 9.1 on the incorrect premise that it was this clause that referred to the issue of factual content.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that the points he had made had been misconstrued. Sanofi Winthrop said that Clause 9.1 referred only to 'Format, Suitability and Causing Offence' of the advertising style and not to the content. The complainant assumed that Sanofi

Winthrop was referring to the advertisements appearing in The Pharmaceutical Journal as well as other similar publications. Indeed, it was the format of these advertisements which took the form of a referenced article with a clear banner headline at the top such as 'Valproate – the clinical case for brand prescribing' which the complainant questioned. Even though it clearly stated at the very top 'Advertisement Feature', the style of the advertisement was one which mimicked a genuine article which would normally appear in the journal. This then gave the advertisement added credibility where it was not deserved.

Hence, the style of the advertisement was heavily orientated around the content of the message it was trying to get across. So the complainant did not think it was right to say that when interpreting Clause 9.1, in the context of the advertising style, that this bore no relation to the content of the message.

Indeed, it was this message that was the basis for the 'Epilepsy Therapy Cards' that had been distributed to epilepsy patients, which they in turn were expected to present to their GPs and pharmacists. Hence, it was the dubious nature of this whole marketing strategy that was offensive and was in no way consistent with the 'high standards' which the Panel expected to be maintained at all times. Offensive material used in advertising to the medical professions was not simply limited to the use of naked people or 'teaser' advertising.

In light of this the complainant trusted that the Appeal Board would view his appeal in the context in which it was intended.

APPEAL BOARD RULING

The Appeal Board considered that the provision of patient fact sheets and therapy cards was not unacceptable *per se* so long as their content was not otherwise in breach of the Code. In the case in question Sanofi Winthrop had accepted the Panel's rulings of breaches of the Code with regard to the content of the patient fact sheet. With regard to the provision of the patient fact sheet and therapy card the Appeal Board did not consider that such a service failed either to recognise the special nature of medicines or to maintain high standards. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1 of the Code.

The appeal was thus unsuccessful.

Proceedings commenced 23 December 1998

Case completed 19 May 1999

CASE AUTH/819/1/99 *NO BREACH OF THE CODE*

BRISTOL-MYERS SQUIBB v MERCK SHARP & DOHME

Promotion of Zocor

Bristol-Myers Squibb complained about two similar claims being made by Merck Sharp & Dohme for its product Zocor (simvastatin), these being that Zocor significantly reduced the incidence of angina, by 26% ($p < 0.0001$), and that Zocor reduced the risk of new or worsening angina by 26% in post-MI and angina patients. Zocor was indicated for patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater to reduce the risk of mortality, reduce the risk of coronary death and non-fatal myocardial infarction, reduce the risk for undergoing myocardial revascularisation procedures, and to slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions. Bristol-Myers Squibb alleged that the claim that Zocor reduced the risk of new or worsening angina was outside the licensed indications and in breach of the Code.

The Panel noted that the reference supplied by Bristol-Myers Squibb stated that coronary atherosclerosis was often asymptomatic and the development of symptoms related in part to stenosis of the coronary luminal diameter in excess of 70% which might restrict flow to the extent that myocardial oxygen delivery failed to meet demand. This produced myocardial ischaemia experienced by the patient as angina. The Panel considered that patients with angina would have coronary atherosclerosis but not all patients with coronary atherosclerosis would have angina. The reference also stated that myocardial infarction was usually produced as a result of total occlusion of a coronary artery. The Panel noted that both the leavepiece and the advertisement referred to the effects of Zocor in post-MI and angina patients. The Panel considered that a subgroup of the patient population for which Zocor was licensed would already have angina or, if coronary atherosclerosis progressed, would develop angina. Angina was one of the clinical manifestations of the underlying disease process for which Zocor was indicated. The Panel did not consider that the claims promoted Zocor outside the terms of its licence. No breach of the Code was ruled.

Upon appeal by Bristol-Myers Squibb, the Appeal Board considered that general practitioners would be familiar with statins and their uses and know that they were indicated to lower raised cholesterol levels and not to treat angina per se, ie they were licensed to treat the underlying pathology and not the presenting symptom. The Appeal Board noted that the claim in the advertisement referred to reducing the risk of new or worsening angina in post-MI and angina patients. The claim did not refer to treating angina. This was an important difference as the term risk implied prevention or attenuation of the rate of progression of new or worsening angina. The Appeal Board noted that the

text of the advertisement stated that the significant mortality benefits of Zocor 20 to 40mg daily for five years in post-MI and angina patients with raised cholesterol levels had been convincingly proven in the 4S study. The Appeal Board did not consider that the claims in question promoted Zocor outside the terms of its marketing authorization and upheld the Panel's ruling of no breach of the Code.

Bristol-Myers Squibb Pharmaceuticals Limited complained about two similar claims used by Merck Sharp & Dohme Limited for its product, Zocor (simvastatin). The claim that Zocor significantly reduced the incidence of angina, by 26% ($p<0.0001$), had appeared in a leavepiece (ref 03-99 ZRC.97.GB.70347.B.15m.HO.398). (The leavepiece provided by Merck Sharp & Dohme carried the reference 03-99 ZCR.97.GB.70347.B.10M.HO.598 1R, which the company explained was a later print run but identical to the leavepiece referred to by Bristol-Myers Squibb). The claim that Zocor reduced the risk of new or worsening angina by 26% in post-MI and angina patients had appeared in a journal advertisement (ref 08-99 ZCR.98.GB.70118.J) in Pulse, 12 December 1998.

Zocor was indicated for patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater to: reduce the risk of mortality; reduce the risk of coronary death and non-fatal myocardial infarction; reduce the risk for undergoing myocardial revascularisation procedures, and to slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

COMPLAINT

Bristol-Myers Squibb alleged that the claim that Zocor reduced the risk of new or worsening angina was outside the licensed indications for simvastatin and in breach of Clause 3.2 of the Code.

Bristol-Myers Squibb noted that it had written to Merck Sharp & Dohme expressing its concerns about the claim in the leavepiece that Zocor reduced the risk of angina by 26% ($p<0.0001$). In inter-company correspondence Bristol-Myers Squibb noted that Merck Sharp & Dohme referred to a section of the Zocor summary of product characteristics (SPC) which pertained to the indication that simvastatin slowed the progression of atherosclerosis. Bristol-Myers Squibb stated that this surrogate endpoint, however, was not equivalent to a clinical diagnosis of angina. It was well documented that coronary atherosclerosis was often asymptomatic and angina did not develop until a coronary artery was occluded by about 70% (Timmis (1998)).

Bristol-Myers Squibb noted that the claim that simvastatin was proven to reduce the risk of new or worsening angina had been repeated in an advertisement in Pulse, 12 December.

RESPONSE

Merck Sharp & Dohme submitted that the complaint contained a confusing statement; namely that progression of atherosclerosis was a 'surrogate endpoint'. The company failed to see how a term which described the underlying disease process in coronary artery disease could be a surrogate marker for anything. Indeed, it was angina which was a surrogate marker for coronary atherosclerosis because, as Bristol-Myers Squibb quite rightly pointed out, patients could have severe atherosclerosis with no clinical symptoms in the form of angina.

Merck Sharp & Dohme stated that in this way it fully endorsed and accepted the point being made by Timmis in the reference quoted by Bristol-Myers Squibb. Merck Sharp & Dohme stated that, contrary to the implication in the complaint, it had never claimed that progression of atherosclerosis was equivalent in everyone to progression of angina. Those with progression of the clinical symptom of angina represented a subgroup of those with progression of atherosclerosis.

Merck Sharp & Dohme submitted that since patients with new or worsening angina in general had new or worsening atherosclerosis (although the converse was not true), they fell under the terms of the Zocor licence which stated that the product was indicated to 'slow the progression of coronary atherosclerosis…'

Merck Sharp & Dohme rejected the assertion that this was promotion outside the terms of its licence for Zocor. The licence recognised that Zocor could slow the progression of coronary atherosclerosis and in this promotion the company had thereby chosen to highlight that subgroup in which this equated to preventing the progression of angina.

PANEL RULING

The Panel noted that in patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater, Zocor was licensed to '…slow the progression of coronary atherosclerosis, including the development of new lesions and new total occlusions'. The Panel noted that the reference supplied by Bristol-Myers Squibb stated that coronary atherosclerosis was often asymptomatic and the development of symptoms related in part to stenosis of the coronary luminal diameter in excess of 70% which might restrict flow to the extent that myocardial oxygen delivery failed to meet demand. This produced myocardial ischaemia experienced by the patient as angina. The Panel considered that patients with angina would have coronary atherosclerosis but not all patients with coronary atherosclerosis would have angina. The reference also stated that myocardial infarction was usually produced as a result of total occlusion of a coronary artery. The Panel noted that both the leavepiece and the advertisement referred to the effects of Zocor in post-MI and angina patients.

The Panel considered that a subgroup of the patient population for which Zocor was licensed would already have angina or, if coronary atherosclerosis progressed, would develop angina. Angina was one of the clinical manifestations of the underlying disease process for which Zocor was indicated. The Panel did not consider that the claims promoted Zocor outside the terms of its licence. No breach of Clause 3.2 was ruled.

APPEAL BY BRISTOL-MYERS SQUIBB

Bristol Myers Squibb agreed with the Panel that the underlying disease in angina was atherosclerosis. However, the consequences of atherosclerosis were numerous and diverse and included myocardial infarction, angina, congestive heart failure, stroke and peripheral vascular disease. Product licences were granted for specific clinical indications and for each indication benefit had to be demonstrated in clinical trials. For simvastatin, benefit had not been shown for the indication of 'reducing the risk of new or worsening angina', only for the angiographically demonstrated phenomenon of atherosclerosis. To Bristol-Myers Squibb's knowledge, no link had been established between the reduction of angiographically demonstrable atherosclerosis by simvastatin and the concomitant reduction of new or worsening symptoms of angina.

In the Scandinavian Simvastatin Survival Study (4S), the only study with simvastatin that had resulted in indications for the prevention of clinical events, angina was not a pre-specified endpoint (4S group (1994)). Since no objective measurements of angina were made in this study, data on the incidence of angina were only available from results derived from patients' records of symptoms and clinical examinations. As stated by the 4S investigators, 'the data are subjective and include interobserver variability' and 'a systematically applied objective measurement of atherosclerosis was not included' in the trial design (Pedersen *et al* (1998)). Therefore, no benefit had been shown with simvastatin for reduction of clinically diagnosed angina, which corresponded with the absence of this indication in the summary of product characteristics for simvastatin.

Bristol-Myers Squibb therefore maintained that a claim that simvastatin reduced new or worsening angina was outside the marketing authorization for simvastatin and was in breach of Clause 3.2 of the Code.

RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme noted that Bristol-Myers Squibb agreed with the Panel that the disease coronary atherosclerosis was responsible for angina. Merck Sharp & Dohme's advertising was simply promoting the benefits of Zocor treatment on progression of this symptom given that it was well accepted as one consequence of progression of coronary atherosclerosis.

1 The Zocor licence

Merck Sharp & Dohme noted that, as stated in previous correspondence, the product licence for Zocor stated that it was indicated to 'slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.' The licence did not specify only that Zocor slowed the progression of 'angiographically demonstrable atherosclerosis,' but was much broader indicating that there was sufficient evidence for it to be considered as slowing the whole disease process.

2 Angina pectoris

Merck Sharp & Dohme noted that The Oxford Textbook of Medicine stated: 'The word "angina" describes a classic symptom. In common usage, however, it implies also that the symptom is due to myocardial ischaemia.'

'Angina' was thus not a diagnosis but a symptom in the same way that 'shortness of breath' could be a symptom of lung pathology. However, because this particular symptom was quite specific (though not sensitive) for coronary atherosclerosis, doctors frequently made the diagnosis of 'angina' when in truth they meant 'angina resulting from significant coronary atherosclerosis.' There were non-atherosclerotic causes of this symptom but they were rare. As the symptom term 'angina' was often used interchangeably, but strictly speaking incorrectly, for the diagnosis 'significant coronary atherosclerosis', this occasionally led to confusion. Merck Sharp & Dohme considered it was the fallacy on which Bristol-Myers Squibb had based its complaint. This was amply demonstrated in the appeal in which Bristol-Myers Squibb listed a symptom (angina) amongst a variety of vascular and cardiovascular diagnoses.

Merck Sharp & Dohme stated that if, with an intervention, the progression of a disease was slowed, one would naturally expect to slow the progression of symptoms of that disease. The company's advertising was simply promoting the benefits on symptom progression (angina) of treating the underlying disease progression (coronary atherosclerosis). Merck Sharp & Dohme did not accept that a medicine could be licensed to treat a pathology but not licensed to treat well recognised symptoms of that pathology.

Merck Sharp & Dohme stated that the only way in which the complaint could be valid was if the progression of the symptom 'angina' was completely unrelated to the progression of coronary atherosclerosis. This was clearly not the case and Bristol-Myers Squibb accepted that angina resulted from atherosclerosis.

3 Quality of the evidence

In its appeal, Bristol-Myers Squibb attacked the quality of the data in support of Merck Sharp & Dohme's advertising on this issue. Since the case was based not on Clause 7.3 (substantiation of the claim) but on Clause 3.2 (whether the claim was within licence) Merck Sharp & Dohme found this unhelpful and in any case considered that the comments were invalid. The paper from which Bristol-Myers Squibb drew its quotes (Pedersen et al (1998)) did indeed look retrospectively at 4S data to produce an estimate of how effectively the symptom of angina was prevented in patients treated with simvastatin. The paper also looked at the frequency of non-coronary signs and symptoms in the simvastatin and placebo groups. Merck Sharp & Dohme believed the cautionary comments in the paper related principally to these non-coronary results which reflected disease in different vascular beds to coronary atherosclerosis.

Merck Sharp & Dohme also pointed out that in 4S the risk of undergoing a coronary revascularisation

procedure was 37% less in those treated with simvastatin compared to those treated with placebo. These procedures were usually performed to relieve angina and this was a pre-specified end-point.

Summary

Merck Sharp & Dohme stated that angina was a symptom of coronary atherosclerosis and not a 'clinical diagnosis' or disease process in its own right, as Bristol-Myers Squibb had attempted to suggest.

Where treatment of a pathological condition with a licensed product also led to relief of associated symptoms, Merck Sharp & Dohme considered it was acceptable for promotional claims about that relief to be made, whether or not they were included in the licensed indication for the product. Otherwise the licensed indication section for almost any product would be absurdly long, as it would set out not only the conditions treated but also all the symptoms, associated with those conditions, which were relieved.

FURTHER COMMENTS FROM BRISTOL-MYERS SQUIBB

1 The simvastatin licence

Bristol-Myers Squibb said that it was demonstrated in the Multicentre Anti-Atheroma Study (MAAS) that simvastatin slowed the progression of atherosclerosis including reducing the development of new lesions and new total occlusions. The wording of the corresponding indication in the simvastatin product licence was derived from this study. However, the MAAS investigators noted that in this study 'There was no difference in clinical outcome'. The study made no attempt to correlate angiographic regression of coronary atherosclerosis with a reduction in the incidence of new or worsening angina and, as Bristol-Myers Squibb had stated in previous correspondence, no such link had been established in any clinical trial with simvastatin.

It was worthy of note that many products had a specific indication for the prevention of angina eg nitrates and calcium channel blockers. These products had satisfied the regulatory agencies that they had clinical benefit for this indication and they had been granted a product licence accordingly. This had not been the case for simvastatin.

Bristol-Myers Squibb therefore maintained that the claim that simvastatin reduced the risk of new or worsening angina was outside the product licence and was in breach of Clause 3.2 of the Code.

2 Angina pectoris

Bristol-Myers Squibb was surprised that Merck Sharp & Dohme categorically stated that angina was not a diagnosis but a symptom. The second edition of the Oxford Textbook of Medicine contained several pages dealing with the clinical diagnosis of angina pectoris. The third edition, which was the same reference quoted by Merck Sharp & Dohme, also talked about the diagnosis of angina. The 'Textbook of Internal Medicine' and 'Clinical Medicine A Textbook for Medical Students and Doctors' also included a section on the diagnosis of angina and a similar section would be found in most modern medical textbooks. On balance, it was clear that angina was a recognised diagnosis, a typical symptom of which was chest pain. Bristol-Myers Squibb did not accept the argument of Merck Sharp & Dohme that atherosclerosis was synonymous with angina: indeed, angina was well known to occur in the absence of significant atherosclerosis.

3 Quality of evidence to support the indication 'to reduce the risk of angina'

Bristol-Myers Squibb agreed with Merck Sharp & Dohme that the case under review was based on Clause 3.2 and not on Clause 7.3 of the Code. However, it considered that an understanding of the poor quality of evidence of benefit with simvastatin in reducing the risk of new or worsening angina was relevant to this case. This point was made to illustrate the fact that while Merck Sharp & Dohme did not hold a product licence for this indication, neither did it have sufficient evidence to support an application for the stated indication. Bristol-Myers Squibb was unable to accept the suggestion made by Merck Sharp & Dohme that the cautionary comments made in the paper related principally to the non-coronary results reported. There was nothing in the paper to this effect and such an interpretation would appear to be speculation on the part of Merck Sharp & Dohme.

APPEAL BOARD RULING

The Appeal Board noted that Zocor was only indicated for those patients with coronary heart disease and a plasma cholesterol level of 5.5mmol/l or greater. The Appeal Board considered that general practitioners would be familiar with statins and their uses and know that they were indicated to lower raised cholesterol levels and not to treat angina per se ie they were licensed to treat the underlying pathology and not the presenting symptom.

The Appeal Board noted that the claim in the journal advertisement referred to reducing the risk of new or worsening angina in post-MI and angina patients. The claim did not refer to treating angina. The Appeal Board considered that this was an important difference as the term risk implied prevention or attenuation of the rate of progression of new or worsening angina.

The Appeal Board noted that the text of the advertisement stated that the significant mortality benefits of Zocor 20 to 40mg daily for five years in post-MI and angina patients with raised cholesterol levels had been convincingly proven in the 4S study.

The Appeal Board did not consider that the claims in question promoted Zocor outside the terms of its marketing authorization. The Appeal Board upheld the Panel's ruling of no breach of Clause 3.2.

The appeal was unsuccessful.

Complaint received **4 January 1999**

Case completed **19 May 1999**

CASE AUTH/822/1/99

WYETH v NOVO NORDISK

Promotion of Kliovance

Wyeth complained about a Kliovance outsert and a leavepiece issued by Novo Nordisk. Kliovance was a continuous combined hormone replacement therapy (HRT) containing a 1mg 17ß-estradiol/0.5mg norethisterone acetate (NETA) combination.

In relation to the claim 'The Optimal Balance, low dose, period-free HRT', Wyeth alleged that the phrase 'The Optimal…' was a superlative. The claim also suggested that Kliovance had properties not found in any other bleed-free HRT preparation. There was a lack of comparative studies and Wyeth alleged it was misleading and difficult to substantiate. The Panel noted that Novo Nordisk had provided data from its clinical development programme which aimed to establish the lowest dose of hormones which would effectively control symptoms whilst minimising side effects. The Panel considered, however, that 'The Optimal Balance…' was not a superlative but the claim was all embracing and misleading. The Panel ruled breaches of the Code. Upon appeal by Novo Nordisk, the Appeal Board considered that the claim was one for superiority, underlined by the use of the word 'The'. The Appeal Board considered that such a claim for superiority was misleading and upheld the Panel's rulings of breaches of the Code.

Wyeth alleged that the use of the phrase 'First choice…' in the claim 'First choice period-free HRT for post-menopausal women' was a superlative. The implication was that Kliovance was either a recognised gold standard or had some added benefit and this was misleading. The Panel noted that Kliovance was indicated as HRT for oestrogen deficiency symptoms in women who were more than one year past the menopause. There was no indication that Kliovance could only be used where other therapy had failed or could not be tolerated. Kliovance could thus be used as a first choice therapy but the Panel considered that the claim in question implied that the product was the only first choice therapy. The Panel considered that the claim was all embracing and misleading and ruled breaches of the Code.

Wyeth alleged that the claim 'Achieves therapeutic benefit with lowest effective dose was misleading'. It implied that the full range of accepted HRT benefits were provided by Kliovance, this implication was particularly worrying when used in conjunction with a statement about the beneficial effects of NETA on bone formation. Kliovance did not appear to have a licence for the prevention of osteoporosis. The Panel considered that some readers might assume that the term 'therapeutic benefit' encompassed all of the therapeutic reasons for administering HRT, including postmenopausal osteoporosis, which was not the case. In this regard the Panel noted that the leavepiece included references to NETA being shown to increase bone formation. The Panel did not consider that the claim promoted the use of Kliovance for postmenopausal osteoporosis *per se* and so no breach was ruled in that regard. The Panel did, however, consider that the claim was not sufficiently clear as to the therapeutic benefit of Kliovance and ruled a breach of the Code. Upon appeal by Novo Nordisk, the Appeal Board considered that in association with a claim referring to NETA increasing bone formation, 'therapeutic benefit' could be taken to include positive effects in postmenopausal osteoporosis. The Appeal Board considered that given the context in which the claim 'Achieves therapeutic benefit' appeared, it was misleading and the Panel's ruling of a breach of the Code was upheld.

Wyeth alleged that the use of the word highly in the claim 'A highly acceptable bleed profile' was a hanging comparison. The Panel did not consider that the claim was a hanging comparison. It was a statement about Kliovance and no comparison with any other treatment was implied. No breach of the Code was ruled.

Wyeth considered that the substantiation offered in support of the claim 'A side effect profile to aid compliance' was insufficient. That 40% of women discontinued HRT in the first few months of therapy was an accepted fact, but to claim that comparison of this fact with a '…95% completion rate at 12 months in placebo controlled trials…' was sufficient to claim that compliance would improve if women used Kliovance was misleading. The statement also implied that Kliovance had a better safety profile that other bleed-free HRT preparations. Given the lack of comparative data this was misleading and also disparaging. The Panel noted that a study by Baerug *et al* showed that all patients in the Kliovance arm of a clinical study completed 12 weeks of treatment. The Panel noted Novo Nordisk's submission that Kliovance was associated with a high degree of adherence to treatment. The Panel considered that the claim was not unreasonable. There was no implied comparison with other products. No breach of the Code was ruled.

In relation to the claim 'Contains NETA, the only progestogen shown to increase bone formation', Wyeth said that, as it had already commented, Kliovance did not appear to have a licence for protection against, or treatment of, osteoporosis. The use of this statement clearly indicated that this product had a proven benefit in this area and implied that Kliovance was therefore of benefit in treating osteoporosis. This constituted a claim outside the limits of the product licence. The Panel noted that Kliovance was not licensed for postmenopausal osteoporosis. The Panel considered that the claim constituted promotion of Kliovance for osteoporosis, an indication not covered by its marketing authorization. A breach of the Code was ruled.

Wyeth complained about a Kliovance outsert (ref KV/95/27) and a leavepiece (ref KV/98/05) issued by Novo Nordisk Pharmaceuticals Ltd. Kliovance was a continuous combined, hormone replacement therapy (HRT) containing a 1mg 17ß-estradiol/0.5mg

norethisterone acetate combination. Wyeth stated that the claims to which it referred were being used in all Kliovance promotional items and were not limited to the items it specified. Wyeth marketed a continuous combined, period free HRT, Premique (conjugated oestrogens 0.625mg/medroxyprogesterone 5mg).

COMPLAINT

Wyeth complained about claims which were presented as stab points.

- 'The Optimal Balance, low dose, period-free HRT'

Wyeth alleged that the use of the phrase 'The optimal…' was a superlative. This statement also suggested that Kliovance had properties not found in any other bleed free HRT preparations. Given that there was a lack of comparative studies, this statement was both misleading and difficult to substantiate. Wyeth alleged breaches of Clauses 7.2 and 7.8 of the Code.

- 'First choice period-free HRT for post-menopausal women'

Wyeth stated that the use of the phrase 'First choice…' was a superlative. The implication was made that Kliovance was either a recognised 'Gold Standard' or had some added benefit which would lead prescribers to consider it ahead of other bleed free HRT preparations; this was misleading. Wyeth alleged breaches of Clauses 7.2 and 7.8 of the Code.

- 'Achieves therapeutic benefit with lowest effective dose'

Wyeth alleged that this statement was misleading. It implied that the full range of accepted HRT benefits were provided by Kliovance, this implication was particularly worrying when used in conjunction with a statement about the beneficial effects of norethisterone acetate (NETA) on bone formation. Kliovance did not appear to have a licence for the prevention of osteoporosis. Wyeth alleged breaches of Clauses 3.2 and 7.2 of the Code.

- 'A highly acceptable bleed profile'

The use of the word 'highly' in this context was a hanging comparison and Wyeth alleged that it was therefore in breach of Clause 7.2 of the Code.

- 'A side effect profile to aid compliance'

Wyeth considered that the substantiation offered in support of this claim was insufficient. That 40% of women discontinued HRT in the first few months of therapy was an accepted fact, but to claim that comparison of this fact with a '…95% completion rate at 12 months in placebo controlled trials…' was sufficient to claim that compliance would improve if women used Kliovance was misleading. The statement also implied that Kliovance had a better safety profile than other bleed free HRT preparations. Given the lack of comparative data this was again misleading and also disparaging. Wyeth alleged breaches of Clauses 7.2, 7.3 and 8.1 of the Code.

- 'Contains NETA, the only progestogen shown to increase bone formation'

As Wyeth had already commented, Kliovance did not appear to have a licence for protection against, or treatment of, osteoporosis. The use of this statement clearly indicated that this product had a proven benefit in this area and implied that Kliovance was therefore of benefit in treating osteoporosis. This constituted a claim outside the limits of the product licence and, in Wyeth's view, amounted to a breach of Clause 3 of the Code.

RESPONSE

Novo Nordisk stated that it led into the HRT area with the first continuous combined (or 'period-free') formulation Kliofem (2mg 17ß-estradiol and 1mg norethisterone acetate). For the first time, this gave postmenopausal women the option of controlling menopausal symptoms whilst avoiding the consequence of renewed monthly bleeding. Novo Nordisk considered that Kliovance (1mg 17ß-estradiol and 0.5mg norethisterone acetate) now followed as a genuine and much needed innovation in this field.

As evidence had emerged that some of the risks associated with HRT, eg breast cancer, might be partly due to total oestrogen exposure, Novo Nordisk responded to the wishes of clinicians to establish whether a lower dose preparation would still provide effective symptom control. Clinicians had also highlighted the significant proportion of women who discontinued HRT due to side effects such as unwanted bleeding and breast tenderness. There was a desire to raise awareness of the potential longer term benefits of HRT in terms of osteoporosis and cardiovascular disease prevention. However, in order to achieve long term compliance, tolerability must also be optimal.

Novo Nordisk submitted that there was still a significant proportion of postmenopausal women who had not experienced bleeding for more than 12 months, and who were initiated on sequential HRT with the consequence of renewed monthly bleeds. There was also a large proportion of women who were clearly postmenopausal who had been taking sequential HRT for several years longer than necessary. There remained a lack of awareness amongst clinicians and women of the period-free alternatives which were more acceptable to women, and in terms of the endometrium, evidence was emerging to suggest they might be safer as a long-term therapy. Doctors asked Novo Nordisk for clear guidelines on when to initiate each particular HRT treatment option and its promotional literature had therefore also set out to address this educational/ awareness need.

With these principles in mind, Novo Nordisk designed a clinical development plan to establish the lowest doses of hormones that would effectively control vasomotor symptoms and assure endometrial safety whilst minimising the side effects of bleeding and breast tenderness which were known to be the main reasons for stopping treatment early.

Women primarily sought medical help during the menopause because of vasomotor symptoms (hot flushes and night sweats). The oestrogen dose finding study demonstrated that 1mg 17ß-estradiol (E2) controlled hot flushes almost as well as 2mg 17ß-estradiol. It also revealed that fewer women had side

effects and therefore continued their treatment on the lower dose thus 'aiding compliance'. On the addition of 0.5mg norethisterone acetate to 1mg 17ß-estradiol the incidence of hot flushes was reduced further still. 97% of women in the Kliovance arm of the trial reported a 90% reduction in their hot flush symptoms. The Kliovance combination was therefore shown to be the 'lowest effective dose' of the combination of 17ß-estradiol and NETA, and one which 'aids compliance' due to less women experiencing adverse effects. Kliovance presented a therapeutic option which did not previously exist and would, therefore, result in a shift of the treatment algorithm. It seemed reasonable, therefore, to suggest that for women who were 12 months postmenopausal, the low dose Kliovance formulation should be 'first choice' treatment over Kliofem or other equivalent higher dose preparations, and also instead of sequential preparations such as Trisequens which would reintroduce regular bleeding unnecessarily. Novo Nordisk hoped that by indicating that Kliovance could be a 'first choice' clinicians would give due consideration to the most appropriate form of therapy for this often inappropriately treated group of women. Novo Nordisk recommended that clinicians titrated the dose required so that women needing a larger dose might graduate to a 2mg HRT such as Kliofem. This was in keeping with good medical practice.

For any HRT preparation for women with intact uterus, the dose of progestogen used must ensure endometrial protection. The dose finding study for NETA established that doses as low as 0.1mg would be adequate. However, at the lower doses of NETA tested women reported unwanted bleeding side effects. Achieving the balance between assured safety, the 'lowest effective dose' and 'optimal' bleeding profile was the paramount objective of this study. It was, therefore, established that 0.5mg of NETA was the 'lowest effective dose' with a 'side effect profile' likely to be tolerated by women and therefore 'aid compliance'. Novo Nordisk had been able to compare the Kliovance study looking at the incidence of amenorrhoea and unwanted bleeding with other combinations of a range of oestrogens and progestogens. From the published data, it would appear that the 'balance' of hormones in Kliovance was the most successful at maintaining amenorrhoea and avoiding unwanted bleeding which reduced compliance. Novo Nordisk was also able to compare the incidence of unwanted bleeding in perimenopausal (3-11 months without periods) to postmenopausal women (more than 12 months without periods). The combination of 1mg 17ß-estradiol and 0.5mg NETA was found to cause less unwanted bleeding than the 1mg 17ß-estradiol and 0.25mg NETA combination.

With regard to therapeutic effectiveness in addition to control of vasomotor symptoms and endometrial protection there were other benefits to consider. Menopausal women complained of symptoms such as tiredness, forgetfulness and depression. Quality of life scales were available and proved comparable for Kliovance (1mg 17ß-estradiol, 0.5mg NETA) and Kliofem (2mg 17ß-estradiol, 1mg NETA). Kliovance was also found to have a comparable effect on the vaginal dryness and urogenital problems reported by menopausal women.

With regard to compliance, Baerug *et al* (1998) reported that in a trial comparing 1mg estradiol/ 0.25mg NETA with Kliovance it was only in the Kliovance group that all women completed the trial. Throughout the clinical trials Kliovance was associated with a high degree of adherence to treatment as 95% of the woman remained on treatment in placebo controlled trials of 3-12 months' duration. In placebo controlled trials the rate of discontinuation due to adverse events was similar in the Kliovance group (2%) and the placebo group (4%), again substantiating the claim that Kliovance had a 'side effect profile to aid compliance'.

Data had also been collected to ensure that markers considered to confer long term benefits from HRT were conserved with this dosage combination. Kliovance was found to have the expected and beneficial effects on lipid profiles, carbohydrate metabolism and haemostatic parameters.

Although not yet licensed for osteoporosis prophylaxis, trials had been conducted to study the effects of Kliovance on bone mineral density, which was a marker for osteoporosis protection. Kliovance was found to have a positive effect on bone mineral density over two years with results showing that the addition of 0.5mg NETA increased bone formation compared to 1mg 17ß-estradiol alone. This was consistent with the published data showing norethisterone to 'independently promote bone formation'. Published abstracts of some of the Kliovance bone studies were already in the public domain.

Once an osteoporosis licence had been granted for Kliovance, Novo Nordisk would produce new promotional material clearly stating that. In the meantime the statement 'Contains NETA, the only progestogen shown to increase bone formation' was scientifically correct. Clinicians often wanted to know why a company had used a particular progestogen and increasingly the scientific community was becoming aware of the variation in the actions of different progestogens. Companies were responding to this by differentiating their products by the progesterone component of the HRT. This was the reason for the inclusion of the statement about the actions of NETA. Furthermore, it was well known that the use of HRT in osteoporosis was a separate indication from symptom relief, and the Kliovance entries in both MIMS and the BNF clearly stated that Kliovance was licensed only for the relief of menopausal symptoms.

Novo Nordisk hoped that this helped to clarify why it believed the claims made in the Kliovance promotional literature were scientifically robust. It could be seen from the clinical data described why it considered that it had developed an HRT with the 'optimal balance' of hormones.

Novo Nordisk provided the comments made by clinicians in response to Novo Nordisk promotional literature when it followed them up to make sure that the messages it wanted to convey were being accurately received.

PANEL RULING

The Panel considered each claim at issue in turn.

- 'The Optimal Balance, low dose, period-free HRT'.

The Panel noted that Novo Nordisk had provided data from its clinical development programme which aimed to establish the lowest dose of hormones which would effectively control symptoms whilst minimising side effects. The Panel considered, however, that 'The Optimal Balance…' was not a superlative but the claim was all embracing and misleading. The Panel ruled breaches of Clauses 7.8 and 7.2 of the Code.

- 'First choice period-free HRT for post-menopausal women'.

The Panel noted that Kliovance was indicated as HRT for oestrogen deficiency symptoms in women who were more than one year past the menopause. There was no indication that Kliovance could only be used where other therapy had failed or could not be tolerated. Kliovance could thus be used as a first choice therapy but the Panel considered that the claim in question implied that the product was the only first choice therapy. The Panel considered that the claim was all embracing and misleading and ruled breaches of Clauses 7.8 and 7.2 of the Code.

- 'Achieves therapeutic benefit with lowest effective dose'.

The Panel noted that Novo Nordisk had provided data regarding the benefit of Kliovance in terms of endometrial protection, bleed profile, vasomotor symptoms, etc. The Panel noted that, in addition to symptomatic relief of vasomotor symptoms, some period free HRT preparations, however, were also licensed for postmenopausal osteoporosis protection. The Panel considered that some readers might assume that the term 'therapeutic benefit', in relation to Kliovance, encompassed all of the therapeutic reasons for administering HRT, including postmenopausal osteoporosis, which was not the case. In this regard the Panel noted that the leavepiece included references to NETA being shown to increase bone formation. The Panel noted that, according to comments made in response to the promotional literature, some clinicians viewed Kliovance as half dose Kliofem (also marketed by Novo Nordisk) and as effective as Kliofem. The Panel noted that Kliofem was indicated for the prophylaxis of postmenopausal osteoporosis in women at risk of developing fractures. The Panel did not consider that the claim promoted the use of Kliovance for postmenopausal osteoporosis *per se* and so no breach of Clause 3.2 was ruled. The Panel did, however, consider that the claim was not sufficiently clear as to the therapeutic benefit of Kliovance. A breach of Clause 7.2 was ruled.

- 'A highly acceptable bleed profile'.

The Panel did not consider that the claim was a hanging comparison as alleged. It was a statement about Kliovance and no comparison with any other treatment was implied. No breach of Clause 7.2 was ruled.

- 'A side effect profile to aid compliance'.

The Panel noted that the study by Baerug *et al* showed that all patients in the Kliovance arm of a clinical study completed 12 weeks of treatment. The Panel noted Novo Nordisk's submission that Kliovance was associated with a high degree of adherence to treatment. The Panel considered that the claim was not unreasonable. There was no implied comparison with other products. No breach of Clauses 7.2, 7.3 or 8.1 was ruled.

- 'Contains NETA, the only progestogen shown to increase bone formation'

The Panel noted that Kliovance was not licensed for postmenopausal osteoporosis. In the Panel's view, however, the claim implied that Kliovance was so licensed. The Panel noted its comments above regarding clinicians perceiving Kliovance to be half dose Kliofem. The Panel considered that the claim constituted promotion of Kliovance for osteoporosis, an indication not covered by its marketing authorization, contrary to the requirements of Clause 3.2 of the Code. A breach of that clause was ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk stated that it was disappointing and concerning that some of its material had been found in breach. The promotional statements were developed in conjunction with general practitioners and gynaecologists to most fairly and clearly represent Kliovance and its usefulness in clinical practice. Novo Nordisk appealed the rulings in relation to two of the claims at issue.

- 'The Optimal Balance, low dose, period-free HRT'

Novo Nordisk stated that the phrase 'the optimal balance' referred to the ratio of oestrogen and progesterone contained in Kliovance. The doses were selected as a result of the largest clinical development programme of any HRT product to achieve an uncompromising high level of efficacy whilst balancing this with ensured safety and a higher degree of tolerability, ie the best possible, or most advantageous, balance of the two hormones (which was in fact the dictionary definition of the term optimal). From reviewing the results it would be seen why so many gynaecologists were endorsing this achievement. Taking the word optimal out of context might imply the 'optimal' HRT. This was very much not the claim or what doctors understood by the statement. It had to be seen in the context in which it was always presented, that was with reference to the carefully selected ratio of hormones and efficacy versus safety and tolerability substantiated by clinical results.

- 'Achieves therapeutic benefit with lowest effective dose'

Novo Nordisk believed that it was well recognised by doctors that for HRT products prophylaxis of osteoporosis was a distinct indication from relief of menopausal symptoms and that not all HRT products included this additional indication. Doctors would check the licence before prescribing. Novo Nordisk believed that 'therapeutic benefit' in relation to HRT would always be taken as meaning only treatment of menopausal symptoms and not prevention of bone loss unless this was specifically stated. The extensive dose-ranging studies in the clinical development

programme established the lowest dose of each hormone component which was effective in providing the required therapeutic effect. Therefore Novo Nordisk believed the claim was sufficiently clear and substantiated by the clinical trial results.

APPEAL BOARD RULING

The Appeal Board considered each claim in turn.

- 'The Optimal Balance, low dose, period-free HRT'.

The Appeal Board considered that the claim was one for superiority, underlined by the use of the word 'The'. The Appeal Board considered that such a claim for superiority was misleading. The Panel's rulings of breaches of Clauses 7.2 and 7.8 of the Code were upheld.

The appeal on this point was unsuccessful.

- 'Achieves therapeutic benefit at lowest effective dose'.

In consideration of this claim the Appeal Board noted that another claim 'Contains NETA, the only progestogen shown to increase bone formation' had been ruled, by the Panel, to be in breach of the Code because it implied that Kliovance was licensed for postmenopausal osteoporosis which was not so. Novo Nordisk had accepted the ruling and agreed to stop using the claim. The Appeal Board considered, however, that in association with a claim referring to NETA increasing bone formation, 'therapeutic benefit' could be taken to include positive effects in postmenopausal osteoporosis. The Appeal Board considered that given the context in which the claim 'Achieves therapeutic benefit' appeared it was misleading and the Panel's ruling of a breach of Clause 7.2 was upheld.

The appeal on this point was unsuccessful.

Complaint received **6 January 1999**

Case completed **18 June 1999**

CASE AUTH/831/1/99

ALLERGAN v MERCK SHARP & DOHME

Cosopt detail aid

Allergan complained about a detail aid for Cosopt issued by Merck Sharp & Dohme. Cosopt was a fixed combination eye drop containing dorzolamide (a carbonic anhydrase inhibitor) and timolol (a beta-blocker) indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when beta-blocker monotherapy was not sufficient. The detail aid was intended for use with ophthalmology specialists.

The statement 'IOP-lowering of dual therapy' was followed by the statement 'With the convenience of a single bottle'. Allergan alleged that this was misleading as it implied that Cosopt provided equivalent IOP lowering to any combination of glaucoma medications. The message was reinforced throughout the detail aid by the strapline 'Power of two, ease of one'. The Panel did not consider that the statement was in breach as alleged and no breach of the Code was ruled.

A page was headed 'Managing the progression of glaucoma' and referred to glaucoma being a progressive disease often requiring multiple therapy that might compromise compliance. A section headed 'For patients on multiple therapy' referred to beta-blockers in combination with topical carbonic anhydrase inhibitors (TCAIs), pilocarpine, prostaglandins and alpha agonists. Allergan stated that it implied that the efficacy of Cosopt was equivalent to any of these combinations. This implication was not capable of substantiation as Cosopt had only been compared to timolol plus dorzolamide. The Panel did not consider that the section so implied. In the Panel's view the section invited the ophthalmologist to consider simplifying dosing for patients on multiple therapy and ruled no breach of the Code. Upon appeal by Allergan, the Appeal Board noted that an arrow led from the list of combinations to the statement 'When patients need easier dosing Simplify Cosopt'. In the Appeal Board's view, despite the reference to easier dosing, specifying four combinations suggested that Cosopt had equal efficacy to them. The statement was not a general claim about convenience. There were no data to show that the efficacy of Cosopt was equivalent to all of the stated combinations and the Appeal Board ruled a breach of the Code.

Allergan referred to the claim that a single bottle might lead to 'Potential for better therapeutic effect'. Although greater convenience and compliance might be claimed for single bottle use, this could not be extrapolated to greater therapeutic efficacy. The claim was alleged to be misleading. The Panel noted that the page referred to enhancing compliance and less potential for confusion. It did not claim greater therapeutic efficacy. The Panel considered that the claim was sufficiently qualified by the preceding text. No breach of the Code was ruled.

Under a heading 'When using Cosopt', the question 'Which patients are suitable for Cosopt?' was followed by two answers, 'Patients on monotherapy who need further IOP lowering' and 'Patients on concomitant therapy who may benefit from a simplified dosage regimen'. Allergan stated that the reference to patients on monotherapy had not been sufficiently qualified. It should have been to patients on beta-blocker monotherapy and it was

alleged that this was promotion outside the licensed indication Allergan made a similar allegation in relation to patients on concomitant therapy as Cosopt was for use 'when beta-blocker therapy is not sufficient.' The Panel noted that glaucoma was commonly first treated with a topical beta-blocker and considered that ophthalmologists would understand the reference to monotherapy to be to beta-blockers. The Panel did not consider that the claim promoted Cosopt outside its licence and ruled no breach of the Code. With regard to the reference to patients receiving concomitant therapy who would benefit from a simplified dosage regimen, the Panel considered that the majority would be patients in whom beta-blocker therapy had not been sufficient. In view of the audience to which the detail aid was targeted, the Panel ruled no breach of the Code.

Allergan Limited complained about a Cosopt detail aid (ref 09-99 CST.98.GB (W6009) 55008.DA3.5c.HO.998) issued by Merck Sharp & Dohme Limited. Cosopt was a fixed combination eye drop containing dorzolamide (a carbonic anhydrase inhibitor) and timolol (a beta-blocker) indicated in the treatment of elevated intracular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when beta-blocker monotherapy was not sufficient. The detail aid was used by representatives when discussing Cosopt with ophthalmology specialists.

1 Statement 'IOP-lowering of dual therapy'

This statement appeared on page one (front cover) of the detail aid and was followed by the statement 'With the convenience of a single bottle'.

COMPLAINT

Allergan alleged that the statement was misleading as it implied that Cosopt provided equivalent IOP lowering to any combination of glaucoma medications. As far as Allergan was aware data did not exist to support this. This message was reinforced throughout the detail aid by the strapline 'Power of two, ease of one' which appeared under the Cosopt logo on almost every page, especially when this was linked to the information on page 3 (see point 2 below). Allergan alleged breaches of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Merck Sharp & Dohme pointed out that at present no other dual therapy was available in the UK as a single bottle. Therefore the statement, taken in the context in which it appeared in the detail aid, 'IOP-lowering of dual therapy With the convenience of a single bottle' clearly related only to Cosopt. No suggestion had been made that Cosopt was equivalent or superior to other combinations of glaucoma medication in the treatment of elevated IOP.

Merck Sharp & Dohme submitted that it was inappropriate to extract, out of context, a single statement from the outer cover of a detail aid. A detail aid was used by representatives as an information flow tool. The statement reflected a small element in the flow of discussion between the representative and the ophthalmologist. It was therefore inappropriate to select a statement such as the above and use it as a stand alone statement when it was clear that this was not the context in which it would be used.

In addition, it was accepted by ophthalmologists that when treating glaucoma some patients needed to progress to a combination of therapies in order for IOP levels to be adequately controlled. It was also accepted that combination therapy (dual therapy) provided additional IOP lowering compared to that experienced with monotherapy. Therefore the statement reflected this currently accepted clinical principle ie there was an expected additional IOP lowering effect of dual therapy *per se* over monotherapy. No attempt had been made to compare the specific IOP lowering effect of Cosopt with other possible combinations of therapy and this was certainly not implied.

Merck Sharp & Dohme pointed out that timolol and dorzolamide were widely prescribed by ophthalmologists both as monotherapies and in combination using the individual components. Therefore many ophthalmologists already had experience of the IOP lowering effect of timolol and dorzolamide given in combination. In the context of the detail aid, Merck Sharp & Dohme believed that ophthalmologists would not misinterpret the statement to mean that Cosopt provided equivalent IOP lowering to all known combinations of glaucoma medication.

The statement was believed to be simple, easily understood and not misleading, either directly or by implication.

PANEL RULING

The Panel did not accept that the statement implied that Cosopt provided equivalent IOP lowering to any combination of glaucoma medications as alleged. The page introduced the concept of dual therapy in a single bottle. The Panel did not accept that the statement was misleading as alleged and ruled no breach of Clauses 7.2 and 7.3 of the Code.

2 Section headed 'For patients on multiple therapy'

Page 3 of the detail aid was headed 'Managing the progression of glaucoma' and referred to glaucoma being a progressive disease often requiring multiple therapy that might compromise compliance. The page stated that Cosopt was suitable for a wide range of patients. For patients on monotherapy (beta-blockers) Cosopt could be added when patients needed additional IOP lowering.

With regard to multiple therapy the relevant section referred to beta-blockers in combination with topical carbonic anhydrase inhibitors (TCAIs), pilocarpine, prostaglandins or alpha agonists.

COMPLAINT

Allergan noted that the detail aid stated that if patients on beta-blockers plus one of the following:

TCAIs, pilocarpine, prostaglandins or alpha agonists, needed easier dosing, then they should be changed to Cosopt. This implied that the efficacy of Cosopt was equivalent to any of the above combinations. As mentioned in point 1 above this message was further reinforced by the strapline 'Power of two, ease of one' at the bottom of the page and 'IOP lowering of dual therapy' on the front page.

The implication was not capable of substantiation as the efficacy of Cosopt had only been compared to timolol plus dorzolamide and not, as far as Allergan was aware, any of the other combinations listed. A breach of Clause 7.3 of the Code was alleged.

RESPONSE

Merck Sharp & Dohme did not agree with Allergan that 'easier dosing' would be misinterpreted as equivalent efficacy. Merck Sharp & Dohme submitted that ophthalmologists already had extensive experience using combination therapy and did not expect that all combinations would have the same efficacy for all patients. The relevant section of the detail aid clearly related to the convenience and simplified regimen of using one bottle compared with two. The flow boxes in the detail aid used the words 'When patients need easier dosing' and 'Simplify' and neither of these dealt with efficacy issues.

The wording 'Power of two, ease of one' was on every occasion juxtaposed to Cosopt and the non-proprietary names of the product's two components. It was therefore clear that the 'Power of two…' related solely to the IOP lowering of timolol and dorzolamide. The equivalent efficacy of Cosopt to that of any other combination therapy was not inferred by this statement. In addition pages four and five of the detail aid were totally dedicated to the statement 'Power of two' ie the power of dorzolamide and timolol, and page six dealt in the same way with the statement 'ease of one'. Merck Sharp & Dohme did not believe that the meaning of 'Power of two, ease of one' could be any clearer.

Merck Sharp & Dohme repeated that the statement 'IOP lowering of dual therapy' made no comparison of the efficacy of Cosopt versus other combination therapies.

It was clear that none of the above points could mislead the reader to make the assumption that the efficacy of Cosopt had been demonstrated to be equivalent to any other combination of therapies. There was no breach of Clause 7.3 of the Code.

PANEL RULING

The Panel did not consider that the section implied that the efficacy of Cosopt was equivalent to any of the combinations mentioned. In the Panel's view the section invited the ophthalmologist to consider simplifying dosing for patients on multiple therapy. The Panel noted that the page referred to glaucoma being a progressive disease often requiring multiple therapy that might compromise compliance. No mention was made of efficacy. Ophthalmologists would be aware of the effect of each of the constituent parts of Cosopt. The Panel did not accept the allegation and no breach of Clause 7.3 of the Code was ruled.

APPEAL BY ALLERGAN

Allergan stated that the page was headed 'Managing the progression of glaucoma'. Under the heading 'Cosopt – suitable for a wide range of patients' it detailed two groups of patients, namely patients on monotherapy and patients on multiple therapy. Allergan considered that the statements relating to the second group were misleading.

The piece identified patients on multiple therapy as those receiving beta-blockers plus TCAIs, pilocarpine, prostaglandins or alpha agonists and stated that 'when patients need easier dosing' this should be simplified to Cosopt. There was, to Allergan's knowledge, no data comparing the efficacy of Cosopt and any of the combinations listed, other than the beta-blocker, timolol, and the TCAI, dorzolamide – the constituents of Cosopt. As it was therefore not possible to substantiate that all these combinations could be effectively replaced by Cosopt, Allergan considered this statement misleading.

Merck Sharp and Dohme had argued that this statement related solely to the convenience and simplified regimen of using one bottle compared with two, that the statements 'When patients need easier dosing' and 'Simplify' did not deal with efficacy issues and that the statements could not mislead the reader to make the assumption that the efficacy of Cosopt had been demonstrated to be equivalent to any other combination of therapies.

While Allergan accepted that the statement itself dealt specifically only with convenience, it remained Allergan's opinion that it was likely, in the context, to carry implications of equivalent efficacy, for the following reasons:

- The headline of the page 'Managing the progression of glaucoma' suggested that the page dealt with efficacy issues.
- The statements relating to patients on monotherapy, in the section above the one in question, were efficacy related, not convenience related.
- The suggestion that multiple therapy could be simplified to a single therapy surely made the assumption of equivalent efficacy as otherwise no such substitution could be considered. No doctor was likely to consider substituting a drug which was less effective – no matter how convenient.
- The bottom line 'Power of two, ease of one' implied both efficacy and convenience. In the context of the page, this could be considered to refer to Cosopt in relation to patients on multiple therapy.

While accepting that any misinterpretation might be avoided by a detailed discussion between a representative and an experienced ophthalmologist, Allergan did not consider that this would necessarily occur on every occasion. Allergan therefore considered that the statement relating to patients on multiple therapy was misleading and in breach of Clause 7.3 of the Code.

RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme acknowledged Allergan had accepted that the statement, 'When patients need easier dosing… SIMPLIFY…COSOPT', dealt specifically with convenience but Merck Sharp & Dohme did not share Allergan's belief that 'easier dosing' could be misinterpreted as equivalent efficacy. Allergan had raised several points relating to this issue which formed the basis of its appeal and Merck Sharp & Dohme addressed these in turn.

- The headline of the page 'Managing the progression of glaucoma' suggested that the page dealt with efficacy issues.

It had been suggested that 'Managing the progression of glaucoma', the heading on page three, dealt with efficacy issues and therefore implied that 'easier dosing' related to an efficacy issue. Merck Sharp & Dohme believed that managing a disease involved many facets, including both pharmacological and non-pharmacological components, and was not intimately linked with efficacy alone. The statement immediately below the page heading, 'Glaucoma – a progressive disease often requiring multiple therapy that may compromise compliance', captured two components in the management of glaucoma, namely the need to upgrade from beta-blocker monotherapy and the compliance problem with multiple therapies. These were two quite separate concepts, upgrading treatment and improving compliance. To address these issues page three had been clearly divided under two distinct underlined headings in order to provide instances of how Cosopt might be suitable for a wide range of patients in particular circumstances. Firstly to deal with patients receiving beta-blocker monotherapy who required further assistance in lowering IOP and might upgrade to Cosopt, and secondly, to deal with patients on multiple therapy who might require a simplified dosing regimen that might improve compliance. Therefore Merck Sharp & Dohme believed that the statement 'When patients need easier dosing…SIMPLIFY' clearly related to the convenience and simplified regimen of using one bottle compared to two. No implication with regard to efficacy had been made in the section.

- The statements relating to patients on monotherapy, in the section above the one in question, were efficacy related, not convenience related.

As stated above Merck Sharp & Dohme believed that managing a disease involved many components including efficacy and compliance. These two components were identified within the statement immediately below the heading on page three and were clearly considered separately under two distinct underlined headings. Merck Sharp & Dohme did not believe the layout of this page could be any clearer and it felt that the meaning of 'easier dosing' and 'SIMPLIFY' was not in any way misleading.

- The suggestion that multiple therapy could be simplified to a single therapy surely made the assumption of equivalent efficacy as otherwise no such substitution could be considered. No doctor was likely to consider substituting a drug which was less effective – no matter how convenient.

Convenience was an important issue when it had an impact on compliance and no matter how effective a drug might be, it was of little use if the patient did not take it. This point was highlighted by Patel and Spaeth (1995) who confirmed 'the well known finding that a substantial proportion of patients fail to take their medication precisely as prescribed' and that 'it is reasonable to assume that in a substantial number of cases, non-compliance likely decreases the probability of successful treatment'.

In addition Merck Sharp & Dohme suggested that the management of glaucoma could be considered the 'bread and butter' of ophthalmology. Therefore it would not be unreasonable to assume that all ophthalmologists would have extensive personal experience using combination therapy for the treatment of glaucoma (including that of timolol and dorzolamide), and would not expect that all combinations had the same efficacy for all patients. Merck Sharp & Dohme believed that the section relating to easier dosing did not imply equivalent efficacy and certainly the audience to which the detail aid was directed would not be misled to believe that this was the case.

- The bottom line 'Power of two, ease of one' implied both efficacy and convenience. In the context of this page, this could be considered to refer to Cosopt in relation to patients on multiple therapy.

The 'Power of two, ease of one' was on every occasion juxtaposed to Cosopt and the individual component drug names (timolol and dorzolamide). It was therefore clear that the 'Power of two…' related solely to the IOP lowering of timolol and dorzolamide. The equivalent efficacy of Cosopt to that of any other combination therapy was clearly not inferred by this statement.

'Power of two, ease of one' positioned at the bottom of page three was clearly a strapline. Not only was it presented on page three, it was also presented on pages five, seven, eight and the back cover. Page five related to efficacy, page seven was completely dedicated to tolerability and page eight reflected prescribing information, while the back cover summarised efficacy, tolerability issues and compliance. Therefore presenting this strapline at the bottom of a page did not automatically dictate that the content of that page must be an efficacy issue, it could equally relate to a compliance issue '…ease of one'.

Finally, it had been suggested that misinterpretation of the data on page three relating to multiple therapy would only be avoided following detailed discussion by a representative with an experienced ophthalmologist. Merck Sharp & Dohme would reiterate the point that the treatment of glaucoma was a fundamental part of the workload of any general ophthalmologist. In addition, the issue of compliance was not a novel or complicated issue to comprehend, even though it might be a difficult problem to resolve, It certainly did not require a detailed discussion to reveal that patients who had difficulty with multiple therapy might benefit from a simplified dosing regimen.

In conclusion, Merck Sharp & Dohme believed that the claim had been presented in an accurate and easy

to understand manner, did not mislead and was in accordance with the Code.

FURTHER COMMENTS FROM ALLERGAN

Allergan had no further comments.

APPEAL BOARD RULING

The Appeal Board noted that beneath the sub-heading 'For patients on multiple therapy' four combinations were listed: beta-blocker plus TCAIs; beta-blocker plus pilocarpine; beta-blocker plus prostaglandins and beta-blocker plus alpha agonists. An arrow led from the list of combinations to the statement 'When patients need easier dosing Simplify Cosopt'. In the Appeal Board's view, despite the reference to easier dosing, specifying four combinations suggested that Cosopt had equal efficacy to those particular combinations stated. The statement was not a general claim about the convenience of Cosopt versus multiple therapy. The Appeal Board noted that there were no data to show that the efficacy of Cosopt was equivalent to all of the stated combinations. A breach of Clause 7.3 was ruled.

The appeal was thus successful.

3 Claim 'Potential for better therapeutic effect'

Page 6 of the detail aid was headed 'Cosopt – The ease of one'. It referred to a single bottle for greater convenience and listed the following advantages of Cosopt, 'easier to use', 'may enhance compliance', 'less potential for patient confusion' and 'no risk of washout'. The page stated that these might lead to 'Potential for better therapeutic effect'.

COMPLAINT

Allergan referred to the claim that a single bottle might lead to 'potential for better therapeutic effect'. Although greater convenience and compliance might be claimed for single bottle use, this could not be extrapolated to greater therapeutic efficacy.

Paradoxically, a study by Hutzelman referenced elsewhere in the detail aid, stated that IOP reduction was comparable (not better) to that seen with concomitant use of dorzolamide and timolol.

Allergan alleged that the claim was misleading and in breach of Clause 7.3 of the Code as once again there was no supporting data.

RESPONSE

Merck Sharp & Dohme pointed out that the statement 'may enhance compliance', referenced in the detail aid to Patel *et al* (1995), confirmed the well known finding that a substantial proportion of patients failed to take their medication precisely as prescribed and that 'it is reasonable to assume that in a substantial number of cases, noncompliance likely decreases the probability of successful treatment'. In addition the link between complicated eye drop medication regimens and noncompliance, with the resultant decrease in successful treatment, was confirmed.

It was accepted that any factor affecting compliance and/or the administration of a medicine had the potential to influence the desired therapeutic effect of that medicine. In light of this fundamental fact, Merck Sharp & Dohme believed that the use of the statements 'easier to use', 'less potential for patient confusion' and 'no risk of washout' were therefore self explanatory in terms of their impact on therapeutic effect and did not require further elaboration.

It was clear that the page was concerned with patient factors that might influence the therapeutic effect of a medicine and the statement 'Potential for better therapeutic effect' was not a between treatment comparison as suggested by Allergan. It was a straightforward concept that if Cosopt could eliminate factors that might cause noncompliance, the result might lead to the potential for better therapeutic effect.

The page of the detail aid was not misleading and data was available to support the claim.

PANEL RULING

The Panel noted that the page referred to enhancing compliance and less potential for confusion. The Panel noted Merck Sharp & Dohme's submission that any factor affecting compliance was likely to influence the desired therapeutic effect. The Panel did not accept that the page was claiming greater therapeutic efficacy. The page set out the features of Cosopt which might increase compliance and this was likely to benefit patients. The Panel considered that the claim 'Potential for better therapeutic effect' was sufficiently qualified by the preceding text and was not unacceptable. No breach of Clause 7.3 of the Code was ruled.

4 Section headed 'Which patients are suitable for Cosopt?'

The question, which appeared beneath the heading to Page 8 'When using Cosopt', was followed by two answers: 'Patients on monotherapy who need further IOP lowering' and 'Patients on concomitant therapy who may benefit from a simplified dosage regimen.' The two answers were followed by details of Cosopt's indications, precautionary information, contra-indications and dosage and administration.

COMPLAINT

Allergan alleged that the reference to patients on monotherapy had not been sufficiently qualified. Reference should have been made to patients on beta-blocker monotherapy as per the licensed indication for Cosopt. The absence of the word 'beta-blockers' promoted use of the product outside its licensed indication and even though this was mentioned in smaller type further down the page, it might not be noticed by doctors. A breach of Clause 3.2 of the Code was alleged.

Allergan also pointed out that the detail aid promoted the use of Cosopt for 'patients on concomitant therapy who may benefit from a simplified dosage regimen'. This was not consistent with the licensed indication which recommended the use of Cosopt in patients

'when beta-blocker monotherapy is not sufficient'. A further breach of Clause 3.2 of the Code was alleged.

RESPONSE

Merck Sharp & Dohme submitted that Allergan had taken the statement 'Patients on monotherapy who need further IOP lowering' out of context. The statement was a general bullet point that immediately led on to the detailed 'indications' information. The precise words to which Allergan referred, 'when beta-blocker monotherapy is not sufficient', were clearly highlighted in bold text within this indication section. In addition, the company did not believe that doctors would miss out such a critical issue as the indication for a new medicine. The product was therefore clearly not being promoted outside its licensed indication.

Merck Sharp & Dohme noted that the 'indications' section, which appeared immediately below the statement 'Patients on concomitant therapy who may benefit from a simplified dosage regimen', had the precise words to which Allergan referred, 'When beta-blocker monotherapy is not sufficient', printed in bold type.

In any event, the majority of patients with open angle glaucoma commenced on a beta-blocker as first line therapy. Due to the natural progression of the disease or insufficient efficacy, some patients required an additional agent to maintain IOP control. These patients, currently receiving combination therapy, still obviously fell into the category of patients in whom beta-blocker monotherapy was not sufficient. It would therefore be perfectly appropriate for a physician to choose to prescribe Cosopt to these patients.

Merck Sharp & Dohme did not believe that the present licence for Cosopt precluded physicians from prescribing Cosopt to patients already receiving a combination of therapies.

PANEL RULING

The Panel noted that glaucoma was commonly first treated with a topical beta-blocker unless such medicines were contra-indicated. The British National Formulary stated that other medicines were added as necessary to control the IOP. The Panel noted the reference to monotherapy but considered that ophthalmologists, to whom the detail aid was specifically aimed, would understand this to be topical beta-blockers. In the Panel's view, in those patients for whom monotherapy was not a beta-blocker, Cosopt was probably contra-indicated by virtue of its timolol content. The Panel did not accept that the section promoted Cosopt outside its licence as alleged. No breach of Clause 3.2 of the Code was ruled.

With regard to the reference to using Cosopt in patients receiving concomitant therapy who might benefit from a simplified dosage regimen, the Panel accepted that the majority of patients receiving combination therapy would still fall into the category of patients in whom beta-blocker monotherapy had not been sufficient. It was a question of simplifying the dosage schedule. Those patients not receiving background therapy with a beta-blocker in all probability were not suitable for Cosopt because it contained timolol. In view of the audience to whom the detail aid was targeted the Panel ruled no breach of Clause 3.2 of the Code.

Complaint received **25 January 1999**

Case completed **17 June 1999**

CASE AUTH/836/1/99

WYETH v LILLY

Promotion of Evista

Wyeth complained about a number of promotional items for Evista (raloxifene) issued by Lilly. Wyeth was concerned about the broad focus of the campaign, particularly the claim of 'non-hormonal protection'.

In a journal advertisement the claim 'Non-hormonal protection for post-menopausal women' appeared as part of the heading and as the final claim. Wyeth stated that it suggested that Evista could deliver the same range of therapeutic benefits as conventional hormone replacement therapy (HRT) and alleged that this was highly misleading. Its licensed indications were limited to the prevention of non-traumatic vertebral fractures in post-menopausal women at an increased risk of osteoporosis. Wyeth also alleged that the claim 'Evista prevents bone loss and reduces the risk of vertebral fractures' was misleading as it implied that Evista was clearly suitable for the management of osteoporosis in post-menopausal women, and that the claim 'Evista has reduced the incidence of newly diagnosed breast cancer' was misleading, the summary of product characteristics (SPC) clearly stating that 'The long term effect of Evista on the risk of breast cancer is unknown.'

The Panel noted that the claim relating to breast cancer had already been ruled in breach of the Code in Case AUTH/810/12/98. The Panel considered that the very broad claim 'Non-hormonal protection for post-menopausal women' was misleading. It was not consistent with the indications in the SPC, which limited the use of Evista to post-menopausal women at increased risk of osteoporosis, and a breach of the Code was ruled.

Wyeth had similar concerns about a leavepiece entitled 'A new way of protecting women after the menopause without using hormones'. The claim 'Non-hormonal protection for women at increased risk of osteoporosis' appeared as a heading to a section of the leavepiece and was followed by the claims 'Evista increases bone mass and reduces the risk of vertebral fracture', 'Evista improves the lipid profile' and 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials'. A claim '53% reduction in breast cancer incidence in clinical trials' also appeared in the leavepiece. Wyeth alleged that the use of such data was highly misleading and outside the terms of the marketing authorization.

The Panel considered that the use of the claim 'Non-hormonal protection' was sufficiently qualified in the leavepiece by the identification of the patient group. In this respect it was different to the journal advertisement and no breach of the Code was ruled. The claim relating to a reduction in breast cancer incidence reflected the SPC but the Panel considered that it was misleading given that the SPC also stated that the long term effect on the risk of breast cancer was unknown. This claim was not covered by the ruling in Case AUTH/810/12/98 and the Panel ruled it in breach of the Code.

A 'Dear Doctor' letter was headed 'Introducing a new way of protecting women after the menopause without using hormones'. Wyeth said that many of its concerns had already been detailed above but there were additional statements regarding safety and efficacy in comparison with HRT such as '…without some of the drawbacks of HRT' and '…concerns over the possible long term effects of HRT'. It would be logical to think that these referred to the occurrence of thromboembolic events and the link between long term HRT use and breast cancer. Evista seemed to have the same risks of thromboembolic events.

The Panel noted that a section headed 'No effect on breast or uterine tissues' stated that Evista had been shown to reduce the incidence of newly diagnosed breast cancer in post-menopausal women. The Panel considered that the ruling of a breach of the Code in Case AUTH/810/12/98 also applied to the 'Dear Doctor' letter. The Panel considered that the letter, by drawing parallels with HRT, implied that Evista had similar indications to HRT which was not so. The heading to the letter was broad and the letter did not make clear the specific indication for which Evista was licensed. The Panel considered that the letter was misleading with regard to the licensed indication for Evista and ruled breaches of the Code.

Wyeth complained about a number of promotional items for Evista (raloxifene) issued by Eli Lilly and Company Limited which Wyeth stated were examples of a wider range of material currently in circulation. Wyeth was concerned as to the broad focus of the campaign, particularly the claim of 'Non-hormonal protection' provided by Evista.

A Journal Advertisement (ref EV 100)

The claim 'Non-hormonal protection for post-menopausal women' appeared as the heading to the advertisement.

COMPLAINT

Wyeth stated that considerable emphasis was placed on the non-hormonal properties of the product and the use of such an all embracing headline invited direct comparison with hormonal products and suggested that Evista could deliver the same range of therapeutic benefits as conventional hormone replacement therapy (HRT).

To imply that Evista had the same benefits as HRT was highly misleading. For example, Wyeth's HRT products were licensed for the treatment of 'Menopausal and post-menopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis and prophylaxis of osteoporosis in women at risk of developing fractures'.

Evista's licensed indications, as given in its summary of product characteristics (SPC), were limited to the

'…prevention of non-traumatic vertebral fractures in post-menopausal women at increased risk of osteoporosis'.

Wyeth referred to two stab points beneath the heading. Firstly that 'Evista prevents bone loss and reduces the risk of vertebral fractures'. Wyeth alleged that this was again misleading. The implications were that Evista was clearly suitable for the management of osteoporosis in post-menopausal women. Secondly the claim 'Evista had reduced the incidence of newly diagnosed breast cancer'. Wyeth considered that this claim was highly misleading. It implied that Evista was 'breast safe' (the SPC clearly stated that 'The long-term effect of Evista on the risk of breast cancer is unknown') and suggested that Evista was suitable for use in the prevention of breast cancer. Once again the information provided was misleading and clearly fell outside the terms of Lilly's marketing authorization.

The final claim in the advertisement reiterated the fact that Evista provided: 'Non-hormonal protection'.

Wyeth stated that the use of the word 'protection' without further qualification implied that Evista could deliver the same range of protection in the case of osteoporosis as that delivered by HRT. Evista's indications were limited as described above, and did not include the 'prevention and management of osteoporosis' which this claim (in conjunction with the earlier claim of preventing bone loss) suggested.

On this basis it would seem that most of the claims were outside the terms of Lilly's marketing authorization and were highly misleading. Breaches of Clauses 3.2 and 7.2 of the Code were alleged.

RESPONSE

Lilly stated that Wyeth expressed concern about the emphasis on the non-hormonal properties of Evista and that the use of such an 'all embracing headline invited direct comparison with hormonal products'. This was a factual headline and Lilly was not making any direct comparison. In any event, Lilly did not consider that inviting comparison with other products was against the Code.

Lilly made no claims that Evista had the same benefits as HRT and it acknowledged that Evista had no place in treating menopausal symptoms, one of the main indications for HRT. The headline stated that Evista was 'for post-menopausal women'. They were clearly different medicines and Lilly had been careful not to make any direct comparison with HRT or any other medicines in this advertisement. Therefore, Lilly did not consider that this was misleading.

With regard to the claim 'Evista prevents bone loss and reduces the risk of vertebral fracture', Lilly submitted that the wording simply stated the facts that were inherent in the licensed indication that the product was for 'the prevention of non-traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis'. Lilly made no claim that Evista should be used for the management of established osteoporosis.

The headline reflected Evista's protection of post-menopausal women from osteoporotic vertebral fractures and its beneficial effect on lipids which Lilly did not consider was ambiguous, misleading, exaggerated or all-embracing; Lilly therefore did not accept that it was in breach of either Clause 3.2 or Clause 7.2 of the Code. The dictionary definition of protection was 'The action of protecting; the fact or condition of being protected; defence from harm, danger or evil'. This appeared to be in agreement with the indication for Evista which was 'for the prevention of non traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis'. Again Lilly made no claim that Evista was licensed for the management of osteoporosis and made no comparison in this advertisement with HRT or any other medicine.

PANEL RULING

The Panel noted that Evista was indicated for the prevention of non-traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis. The claim 'Non-hormonal protection' appeared both as part of the heading and as the final claim. The Panel noted that three bullet points of equal prominence appeared beneath the heading. The Panel noted that the advertisement in question, and in particular the third bullet point, 'Evista reduces the incidence of newly diagnosed breast cancer in clinical trials', had been the subject of Case AUTH/810/12/98 which had been ruled by the Panel, and upheld by the Code of Practice Appeal Board, to be misleading in breach of Clause 7.2 of the Code. The Appeal Board's view was that the context of the claim and its position within the advertisement meant that the advertisement was misleading with regard to the effect of Evista on the incidence of breast cancer.

The Panel considered that the very broad claim 'Non-hormonal protection for post-menopausal women' was misleading. The claim was not consistent with the indications in the SPC which limited the use of Evista to postmenopausal women at increased risk of osteoporosis. The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code.

B Leavepiece (ref EV 118)

Lilly advised that the leavepiece and 'Dear Doctor' letter (ref EV 102 – see C below) were mailed to all UK general practitioners, consultant rheumatologists, gynaecologists and endocrinologists and other senior hospital doctors in these specialities.

The leavepiece was entitled 'A new way of protecting women after the menopause without using hormones.' The claim 'Non-hormonal protection for women at increased risk of osteoporosis' appeared as a heading to a section of the leavepiece. The heading was followed by the claims 'Evista increases bone mass and reduces the risk of vertebral fracture', 'Evista improves the lipid profile' and 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials'.

COMPLAINT

Wyeth stated that its concerns were similar to the journal advertisement above. Whilst the heading had

been qualified in terms of protection against osteoporosis the other claims remained the same, and Wyeth alleged that the leavepiece was in breach of Clauses 3.2, 7.2 and 7.8 of the Code.

Wyeth referred to the claim '53% reduction in breast cancer incidence in clinical trials' which appeared in a section of the leavepiece detailing Evista's effects on oestrogenic pathways in reproductive tissues. Wyeth stated that this was another variation of the claim already discussed above. Wyeth acknowledged that the figures presented were accurate, but considered the use of such data was highly misleading and outside the terms of Lilly's marketing authorization in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Lilly referred to its submission for the journal advertisement above. Lilly did not consider that the heading was exaggerated or all-embracing. It confirmed information about the product that was contained in the SPC and package leaflet.

With regard to the claim '53% reduction in breast cancer incidence in clinical trials', Lilly stated that this information was presented well away from the indication for Evista and was one of several bullet points that provided further details about the product. Lilly submitted that the claim was clearly not intended to suggest that this was an indication but simply presented facts that were included in the SPC. The statement made no claims about long-term effect but informed physicians of some of the results of clinical trials. The issues relating to the claim 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials' had been covered in Case AUTH/810/12/98.

Lilly submitted that the information in the leavepiece was not misleading nor did it promote Evista for an indication which was outside its marketing authorization and was therefore not in breach of the Code.

PANEL RULING

The Panel noted that the claim 'Non-hormonal protection' appeared as a strapline on the front and back of the leavepiece. The layout and content of the leavepiece was different to the advertisement. The leavepiece referred to the oestrogenic pathways involved in bone and lipid metabolism. In prominent type on the front of the leavepiece it was stated that Evista was a new way of protecting women after the menopause without using hormones. A section of the leavepiece headed 'practical considerations' stated that 'Evista is for post-menopausal women at increased risk of osteoporosis. It is not suitable for pre-menopausal or menopausal patients'. The Panel considered that the use of the claim 'Non-hormonal protection' in the leavepiece was sufficiently qualified by the identification of the patient group. In this regard the leavepiece was different to the journal advertisement. The Panel ruled no breach of Clauses 3.2, 7.2 and 7.8 of the Code.

With regard to the claim '53% reduction in breast cancer incidence in clinical trials', the Panel noted that the Evista SPC stated that 'In clinical trials with Evista involving over 12,000 patients… the relative risk of newly diagnosed breast cancer was significantly lower (53% reduction, relative risk 0.47) in Evista-treated than in placebo-treated postmenopausal woman in a combined analysis of several studies.' The Panel considered that the claim was misleading given that the SPC also stated that 'The long-term effect of Evista on the risk of breast cancer is unknown.' The Panel considered that this claim was not covered by the Appeal Board's ruling in the previous case. The Panel ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the claim was in breach of Clause 3.2 as alleged and no breach of that clause was ruled.

C 'Dear Doctor' letter (ref EV 102)

The letter was headed 'Introducing a new way of protecting women after the menopause without using hormones'.

COMPLAINT

Wyeth stated that many of its concerns regarding the content of this letter had already been detailed above. There were however additional statements made regarding the safety and efficacy of Evista in comparison with HRT, statements such as '…without some of the potential drawbacks of HRT' and '…concerns over the possible long term effects of HRT'.

Wyeth pointed out that it would seem logical to assume that these referred to the occurrence of thromboembolic events and the link between long-term HRT use and breast cancer. Evista would seem to have the same risk of thromboembolic events occurring and given that the Evista SPC stated that 'The long-term effect of Evista on the risk of breast cancer is unknown', it would seem misleading and disparaging to suggest otherwise.

Wyeth alleged that the claims had been deliberately and carefully structured to give the impression that Evista had a much wider range of licensed uses than the actual product authorization allowed. Accordingly, Wyeth alleged that these claims, which underpinned the whole Lilly campaign, consistently breached Clauses 3.2, 7.2 and 7.8 of the Code.

RESPONSE

Lilly submitted that it had made no comparison with HRT regarding efficacy. Lilly accepted that Evista shared the occurrence of thromboembolic events with HRT which was one of the reasons that the letter referred only to 'some of' the potential drawbacks of HRT. Evista acted as an oestrogen antagonist in the breast and the uterus. It did not cause stimulation of the postmenopausal uterine endometrium and compared to placebo, Evista was not associated with spotting or bleeding or endometrial hyperplasia which were also known to be potential drawbacks to patients on HRT.

Lilly submitted that if women were concerned about a potential, albeit very small, increased risk of breast cancer associated with long-term HRT, Evista might

be useful. Lilly accepted that the long-term effect of Evista on the risk of breast cancer was unknown but the mailing made no such claims. However, Lilly considered that Evista might be useful for women (or physicians) who had concerns about the long-term effects of HRT on breast cancer risk because the medicine had shown a reduction of newly diagnosed breast cancers after 30 months of therapy in Lilly's trials. Lilly did not accept therefore that these statements were misleading or disparaging.

The letter from Wyeth concluded that the claims had been 'deliberately and carefully structured' to suggest that Evista had a wider range of licensed uses than the marketing authorization allowed. Lilly had been most careful not to make any such suggestion and had stuck very carefully to the licensed indication. Lilly therefore considered that none of its advertising campaign for Evista breached any part of the Code.

PANEL RULING

The Panel noted that the 'Dear Doctor' letter was headed with the broad claim 'Introducing a new way of protecting women after the menopause without using hormones' and contained statements which compared Evista with HRT. A section headed 'No effect on breast or uterine tissues' stated that Evista had been shown to reduce the incidence of newly diagnosed breast cancer in post-menopausal women. The Panel considered that the Appeal Board's ruling of a breach of Clause 7.2 of the Code in Case AUTH/810/12/98 also applied to the 'Dear Doctor' letter.

The Panel considered that the letter, by drawing parallels with HRT, implied that Evista had similar indications to HRT which was not so. The heading to the letter was broad and the letter did not make the specific indication for which Evista was licensed clear. The Panel considered that the letter was misleading with regard to the licensed indication for Evista and ruled breaches of Clauses 3.2 and 7.2 of the Code.

Complaint received **29 January 1999**

Case completed **13 May 1999**

CASE AUTH/838/2/99

DIRECTOR/MEDIA v PROCTER & GAMBLE

Letter in BMJ about Didronel PMO

In accordance with established practice, a letter in the BMJ from two university correspondents critical of the promotion of Didronel PMO by Procter & Gamble was taken up as a complaint.

The letter stated that the advertisement claimed that the combination of disodium etidronate 400mg and calcium carbonate 1250mg (Didronel PMO) 'is proven and licensed to protect bones from corticosteroid induced osteoporosis.' However, the data presented to support the claim that 'Initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% compared to control (p=0.19)' did not provide evidence of benefit. Although the authors of the letter recognised that a non-significant effect did not mean that there was no effect, the absence of confidence intervals did not allow clinical significance to be evaluated. The supporting references indicated that the study was not designed to show the effect of disodium etidronate on the incidence of fractures (a secondary endpoint), a treatment effect was seen only in postmenopausal women, and there seemed to be a greater frequency of vertebral fractures occurring among men in the group taking disodium etidronate (4 of 19 men in the etidronate group v 3 of 25 in the placebo group). Furthermore, in a post hoc logistic regression analysis which accounted for the disproportionately lower bone mineral density at baseline in the placebo group (making them more likely to have fractures) and the higher proportion of patients with rheumatoid arthritis (21 v 13 in the etidronate group), this finding of an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group (1 of 31 women v 7 of 32 women in the placebo group) failed to reach the conventional level of statistical significance.

The Panel noted that Didronel PMO was licensed for the treatment of osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis. It was particularly indicated in patients who were unable or unwilling to take oestrogen replacement therapy. Didronel PMO was also indicated for the prevention and treatment of corticosteroid induced osteoporosis. The Panel considered that the claim 'Only Didronel PMO is proven and licensed to protect bones from corticosteroid induced osteoporosis' was covered by the licensed indications. The Panel noted that the Code provided that substantiation did not need to be provided in relation to the validity of indications approved in the marketing authorization. The claim was in effect substantiated by the licensed indications. The Panel therefore ruled no breach of the Code in that regard.

The Panel noted the claim in the advertisement that 'Didronel PMO increases bone mass at the hip and spine significantly compared to control. Initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% compared to control (p=0.19)'. Although the p value was stated in the advertisement, the impression given was that there was a statistically significant difference in the incidence of new vertebral Fractures, which was not

so. The Panel noted that in a letter published in the same BMJ as the letter at issue, and headed 'Manufacturer's reply', Procter & Gamble accepted that the study did not provide definitive proof of a reduction in the incidence of fractures. The Panel considered that the advertisement was misleading regarding the significance of the 85% reduction in the incidence of vertebral fractures in postmenopausal women and therefore ruled a breach of the Code.

A letter from two university correspondents critical of the promotion of Didronel PMO by Procter & Gamble Pharmaceuticals UK, Limited appeared in the BMJ on 30 January. In accordance with established practice, the letter was taken up by the Director as a complaint under the Code of Practice.

COMPLAINT

The letter stated that the clinical research edition of the 13 June issue of the BMJ contained an advertisement for Didronel PMO. The advertisement claimed that the combination of disodium etidronate 400mg and calcium carbonate 1250mg (Didronel PMO) 'is proven and licensed to protect bones from corticosteroid induced osteoporosis.' However, the data presented to support the claim that 'Initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% compared to control (p=0.19)' – did not provide evidence of benefit. Although the authors of the letter recognised that a non-significant effect did not mean that there was no effect, the absence of confidence intervals did not allow clinical significance to be evaluated. The supporting references, Adachi *et al* (1997a) and subsequent correspondence and post-hoc analysis, Adachi *et al* (1997b), in the New England Journal of Medicine, added further confusion. These references indicated that: the study was not designed to show the effect of disodium etidronate on the incidence of fractures (a secondary endpoint); a treatment effect was seen only in postmenopausal women; and there seemed to be a greater frequency of vertebral fractures occurring among men in the group taking disodium etidronate (4 of 19 men in the etidronate group v 3 of 25 in the placebo group).

Furthermore, in a post hoc logistic regression analysis which accounted for the disproportionately lower bone mineral density at baseline in the placebo group (making them more likely to have fractures) and the higher proportion of patients with rheumatoid arthritis (21 v 13 in the etidronate group), this finding of an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group (1 of 31 women v 7 of 32 women in the placebo group) failed to reach the conventional level of statistical significance.

The authors of the letter added that surely advertisements in the BMJ should be expected to meet the same rigorous standards that were applied to primary research papers.

The letter was followed in the BMJ by a response from Procter & Gamble.

When writing to Procter & Gamble, the Authority drew attention to Clauses 3.2, 7.2 and 7.3 of the Code.

RESPONSE

Procter & Gamble submitted that the advertisement complied with the Code. The company provided detailed comments in relation to specific comments made in the letter.

1 However, the data presented to support the claim that 'Initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% (p=0.19)' – did not provide evidence of benefit.

Procter & Gamble stated that the letter in the BMJ suggested that the reduction in incidence of fractures was the only basis to justify the headline 'Only Didronel PMO is proven and licensed to protect bones from Corticosteroid Induced Osteoporosis' (CIO), and appeared to dismiss the protective effects of a therapy that increased or maintained bone mineral density (BMD). However, Procter & Gamble believed this to be a false suggestion and noted that in its published reply to the letter it stated:

'The assessment of bone protection is multidimensional, and its evaluation may include measures of mass, density, structure and quality. Of these, bone mineral density can readily be assessed in clinical practice and is one of the most important predictors of fracture at several sites.'

Further, Procter & Gamble believed that the overwhelming consensus of experts in this field would agree with it, and subscribe to the view that a therapy that maintained or increased BMD in the face of long-term high dose corticosteroids had a 'bone protective effect'. This was clearly evident from a review of relevant literature published by consensus groups, patient bodies, and randomised, controlled, clinical trials, where the continuing efficacy of a therapy in CIO was measured on the ability to prevent bone loss and maintain the BMD. Therefore Procter & Gamble agreed that a therapy that was shown to reduce fractures had a bone protective effect, but as shown above, this was not an exclusive requirement for 'bone protection'.

Given the evidence presented from the Adachi references in the advertisement, and the consistent evidence that Didronel PMO significantly increased bone mass at sites such as the hip and spine compared to control, in several clinical trials before and since this publication, Procter & Gamble believed that Didronel PMO had a 'bone protective effect'.

Procter & Gamble referred to the Didronel summary of product characteristics (SPC), which stated that 'Didronel PMO is also indicated for the prevention and treatment of osteoporosis'. Therefore, Procter & Gamble believed that the advertisement was in accordance with the terms of Didronel PMO's marketing authorization and was consistent with the particulars listed in the Didronel PMO SPC.

2 Although the authors of the letter recognised that a non-significant effect did not mean there was no effect, the absence of confidence intervals did not allow clinical significance to be evaluated. '…Surely advertisements in the BMJ should be expected to meet the same rigorous standards that were applied to primary research papers.'

Procter & Gamble agreed that confidence intervals/limits were of use in assessing the possible clinical relevance of a given significance test, and certainly they provided more information than significance tests. Procter & Gamble also agreed that advertisements in medical journals should be expected to meet rigorous standards (ie the Code of Practice). However, Procter & Gamble noted that the Adachi references it had used were accepted by the rigorous standards of the New England Journal of Medicine Editorial Board when applied to primary research papers. Further, the statistical plan that appeared in the original paper (Adachi *et al* (1997a)) did not include a confidence limit analysis, and therefore no confidence intervals were detailed in the publication. As such, Procter & Gamble was unable to place such data in its advertisement.

Therefore, in quoting the data from this publication and the subsequent re-analysis (Adachi *et al* (1997b)) Procter & Gamble believed it had conformed to Clauses 7.2, and 7.3 of the Code, and had taken extreme care to ensure that there was a sound statistical basis for the claims made, to the extent that the readjusted p-value following the post-hoc analysis was included in the advertisement. Further, the reduction in vertebral fractures was presented with the non-significant p-value in clear association with the claim, and therefore Procter & Gamble did not believe that this was misleading, and believed that all the claims made were capable of substantiation.

3 'These references indicated that: the study was not designed to show the effect of disodium etidronate on the incidence of fractures (a secondary endpoint); a treatment effect was seen only in postmenopausal women; and there seemed to be a greater frequency of vertebral fractures occurring among men in the group taking disodium etidronate (4 of 19 men in the etidronate group v 3 of 25 in the placebo group).'

Procter & Gamble agreed in that the rate of fracture reduction between the etidronate group and placebo was not a primary outcome measure. However, any results obtained remained valid even if these only represented a secondary endpoint of a clinical trial. Also, no therapy available at that time (1996-7) had been shown to have any effect on fractures in CIO, and so primary outcome measures were designed around changes in BMD. This fact was specifically commented on in the discussion section of Adachi *et al* (1997a) where it was further stated that with respect to etidronate therapy (given as Didronel PMO in this study):

'It is therefore reasonable to conclude that etidronate therapy had a protective effect with respect to the fracture rate in corticosteroid-treated postmenopausal women'.

With reference to the point in the letter regarding the fact that a treatment effect was only seen in postmenopausal women, Procter & Gamble referred to its comments in point 1 above regarding the validity of changes in BMD in the assessment of treatment effects, and pointed out that Adachi *et al* (1997a) showed statistically significant changes in lumbar spine BMD vs placebo, in premenopausal women (p=0.02) as well as in postmenopausal women (p=0.001).

With reference to the point that there seemed to be a greater frequency of vertebral fractures occurring among men in the group taking disodium etidronate, Procter & Gamble pointed out that this finding had no clinical or statistical significance and referred to the commentary by Adachi *et al* (1997b):

'The greater frequency of fractures in etidronate-treated men represents only one more fracture in the etidronate group than in the placebo group. The small numbers preclude any meaningful interpretation'.

Also, this comment was contradictory and inconsistent with the rest of the argument in the letter in which it was indicated that in-depth statistical analysis should be the basis for claims, and yet the letter picked at random a non-statistically significant difference with a small absolute difference in groups to justify the point.

4 'Furthermore, in a post hoc logistic regression analysis which accounted for the disproportionately lower bone mineral density at baseline in the placebo group (making them more likely to have fractures) and the higher proportion of patients with rheumatoid arthritis (21 v 13 in the etidronate group), this finding of an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group (1 of 31 women v 7 of 32 women in the placebo group) failed to reach the conventional level of statistical significance.'

Procter & Gamble considered that the numbers of rheumatoid patients in each group had no bearing on the outcome of the result, and referred to Adachi *et al* (1997b):

'We agree that patients with rheumatoid arthritis are predisposed to osteoporosis. Our control population, however was one that required corticosteroid therapy. To our knowledge there is no evidence that patients with other disorders requiring corticosteroids are any less prone to fractures than those with rheumatoid arthritis. In our study, only one patient with rheumatoid arthritis in the placebo group had a new vertebral fracture, whereas there were two in the etidronate group'.

With regard to the point concerning the 85% fracture reduction failing to reach the conventional level of statistical significance, Procter & Gamble concurred with the interpretation in the letter and had very clearly indicated the correct non-statistically significant level of probability (p=0.19) in the body text of the advertisement, immediately in conjunction with the claim, so as not to give any impression of being misleading. As indicated in point 3 above,

Procter & Gamble believed that this was a clinically significant result based on the fact that no other therapy had previously reduced fracture rate in CIO.

PANEL RULING

The Panel noted the therapeutic indications for Didronel PMO given in the SPC. It was licensed for the treatment of osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis. Didronel PMO was particularly indicated in patients who were unable or unwilling to take oestrogen replacement therapy. Didronel PMO was also indicated for the prevention and treatment of corticosteroid induced osteoporosis.

The Panel considered that the claim 'Only Didronel PMO is proven and licensed to protect bones from corticosteroid induced osteoporosis' was covered by the indication in the Didronel SPC. The Panel noted that Clause 7.3 of the Code required that information, claims, etc had to be capable of substantiation. Clause 7.4 of the Code provided that substantiation did not need to be provided in relation to the validity of indications approved in the marketing authorization. The claim was in effect substantiated by the licensed indications. The Panel therefore ruled no breach of Clause 7.3 of the Code.

The Panel noted that Adachi *et al* (1997a) was a 12 month randomised, double-blind placebo controlled study of 141 patients aged 19 to 87 years of age who had recently started high-dose corticosteroid therapy. Patients were stratified according to sex and menopausal status. The study was designed to measure the difference in the change in the bone density of the lumbar spine. Secondary outcome measurements included the rate of new vertebral fractures. The Panel noted that the study was not designed to demonstrate the effect of etidronate on the incidence of fracture. The study concluded, *inter alia*, that there was an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group compared to the placebo group (1 of 31 patients v 7 of 32 patients respectively (p=0.05)). Subsequent correspondence had questioned this finding and the Panel noted that a post-hoc logistic regression analysis of the incidence of fracture in postmenopausal women determined that the statistical significance of the treatment effect was reduced (p=0.19) when corrected to account for the lower bone mineral density at baseline in the placebo group of postmenopausal women.

The Panel noted the second paragraph in the body of the advertisement, that 'Didronel PMO increases bone mass at the hip and spine significantly compared to control. Initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% compared to control (p=0.19)'. The Panel noted that although the p value was stated in the advertisement the impression given was that there was a statistically significant difference in the incidence of new vertebral fractures which was not so. The Panel noted that in a letter published in the same BMJ immediately after the letter at issue, and headed 'Manufacturer's reply', Procter & Gamble accepted that the study did not provide definitive proof of a reduction in the incidence of fractures. The Panel considered that the advertisement was misleading regarding the significance of the 85% reduction in the incidence of vertebral fractures in postmenopausal women. The Panel therefore ruled a breach of Clause 7.2 of the Code.

Proceedings commenced 2 February 1999

Case completed 20 April 1999

CASE AUTH/839/2/99

RHÔNE-POULENC RORER v PIERRE FABRE

Promotion of Navelbine

Rhône-Poulenc Rorer complained about the promotion of Navelbine (vinorelbine) by Pierre Fabre. Navelbine was indicated *inter alia* in the treatment of advanced breast cancer stage 3 and 4 relapsing after, or refractory to, an anthracycline containing regimen.

A folder 'Metastatic Breast Cancer Navelbine As A Single Agent' referred to a study by Fumoleau *et al*. Rhône-Poulenc Rorer pointed out that the majority of the patients reported had not received an anthracycline. Rhône-Poulenc Rorer alleged that the folder clearly promoted the use of Navelbine in patients with breast cancer who had not previously received an anthracycline and was not in accordance with Navelbine's summary of product characteristics (SPC). The Panel noted that the folder gave details of prior treatment with adjuvant chemotherapy. It was stated that 29% of patients so treated had received an anthracycline and that 14% had not. The Panel assumed that the remaining 57% of patients had received no prior adjuvant chemotherapy. Thus a total of 71% of patients had not been pre-treated with an anthracycline. The data therefore included patients who had not been treated in accordance with the SPC. The folder in effect promoted Navelbine for patients who had not relapsed after, or were refractory to, an anthracycline containing regimen. The Panel therefore ruled a breach of the Code.

A folder 'Metastatic Breast Cancer Navelbine + Doxorubicin' referred to a study by Spielmann *et al*. Rhône-Poulenc Rorer pointed out that only 22% of the patients in the study had been exposed to anthracyclines and alleged that the folder promoted the use of Navelbine (with doxorubicin) for patients who had not previously received an anthracycline. The Panel noted that the folder stated that 22% of the patients in the study had previously received anthracycline treatment; 78% of patients presumably had not. An overall response rate for those patients who had not been previously exposed to anthracyclines was given. The Panel considered that this was similar to point 1 above. The folder in effect promoted Navelbine for patients who had not been treated in accordance with the SPC. The Panel therefore ruled a breach of the Code.

A folder 'Metastatic Breast Cancer Navelbine + 5FU' referred to a study by Dieras *et al*. Rhône-Poulenc Rorer pointed out that the folder clearly identified that patients in the study had received no prior chemotherapy for metastatic disease and that only 54% of the patients had received an anthracycline in the adjuvant setting. Therefore, nearly half of the patients in this study were treated outside the terms of the marketing authorization for Navelbine. Page 3 of the folder claimed that Navelbine was valuable in 'Patients unable to receive anthracyclines' and three sub-groups of such patients were identified, resistance, cardiac toxicity and patient refusal. The folder did not refer to patients unable to continue to receive anthracyclines. Rhône-Poulenc Rorer accepted that resistance to anthracyclines might imply that the patients had been previously treated with anthracyclines and had failed (though resistance could also be tested *in vitro*), cardiac toxicity might arise from a number of causes other than anthracycline therapy (for example radiotherapy to the heart area) and, most significantly, patient refusal to receive an anthracycline (for whatever reason) indicated that the patients had not received one. Rhône-Poulenc Rorer alleged that the folder clearly constituted promotion of Navelbine for patients who had not received a previous anthracycline. Furthermore, virtually all of the data presented on pages 2 and 3 were obtained from a mixture of patients, some of whom had been treated within the terms of the marketing authorization for Navelbine (because they had relapsed after or were refractory to an anthracycline containing regimen) and some of whom were outside those terms (because they had not). On page 4, the most prominent claim was that Navelbine +5FU was '…an effective alternative treatment for patients in whom anthracyclines are contra-indicated'. Rhône-Poulenc Rorer believed that the use of a medicine as an alternative to a contraindicated therapy was not the same as the use of that medicine after the therapy had been tried and had failed. Such patients had, by definition, not received a previous anthracycline, and therefore this constituted promotion of Navelbine outside the terms of its SPC and must therefore also be in breach of the Code.

The Panel noted that it was stated that 54% of patients had been treated with an anthracycline; 46% presumably had not. The Panel considered that this was similar to points 1 and 2 above. The folder in effect promoted Navelbine for patients who had not been treated in accordance with the SPC. The Panel therefore ruled a breach of the Code. The Panel considered that the claim 'Patients unable to receive anthracyclines – resistance – cardiac toxicity – patient refusal' could be interpreted as including patients who had never received anthracyclines. The Panel decided that the claim was not consistent with the SPC and ruled a breach of the Code. The Panel noted Pierre Fabre's submission that '…patients in whom anthracyclines are contra-indicated' were, with regard to doxorubicin, those patients in whom dosage should not be repeated, suggesting therefore some prior exposure to the medicine. The Panel noted, however, that the contraindications for epirubicin, another anthracycline, were patients with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy and those with a current or previous history of cardiac impairment. In the Panel's view, therefore, some patients could be excluded from therapy with epirubicin without ever having received a dose of it or any other anthracycline. The Panel thus considered that the claim 'It is an effective alternative treatment for patients in whom anthracyclines are contra-indicated' was not within the terms of the SPC and a breach of the Code was ruled.

A booklet 'Navelbine Regimens Non-small cell lung cancer Advanced breast cancer' referred to Navelbine in combination with other agents. The final part of this section referred to patient selection in advanced breast cancer stating 'Early relapse after adjuvant anthracycline therapy' and 'Problems related to anthracycline use – resistance – cardiac risk – patient refusal'. Rhône-Poulenc Rorer pointed out that the claim in the booklet was similar to the claim referred to in point 3 above. The company accepted that anthracycline resistance probably implied previous exposure to an anthracycline, cardiac risk was a broad term, which might occur as a result of many unrelated clinical issues and did not imply that the patient had received a previous anthracycline. Finally, patient refusal to receive an anthracycline at all, not refusal to continue with an anthracycline, was not consistent with a patient having received a anthracycline and either failed to respond to it or relapsed after it. Rhône-Poulenc Rorer alleged that the booklet was also in breach of the Code. The Panel considered that the booklet was less likely to be misinterpreted than the folder at issue in point 3 above. The folder in point 3 referred to 'patients unable to receive anthracyclines' whereas the booklet now at issue stated 'Problems related to anthracycline use'. The Panel considered that on balance this section was not unacceptable and no breach of the Code was ruled.

Rhône-Poulenc Rorer Limited complained about the promotion of Navelbine (vinorelbine) by Pierre Fabre Ltd. Navelbine was indicated *inter alia* in the treatment of advanced breast cancer stage 3 and 4 relapsing after, or refractory to, an anthracycline containing regimen. The items at issue were three A4 folders and a booklet. They had been distributed to specialist health care professionals by representatives and had been made available at a number of UK exhibitions.

1 Folder 'Metastatic Breast Cancer Navelbine As A Single Agent'

The folder (ref PFO 24) referred to a study by Fumoleau *et al* giving details of the inclusion criteria, patient characteristics, activity and tolerance.

COMPLAINT

Rhône-Poulenc Rorer pointed out that the folder identified that patients in the study had received no previous chemotherapy for metastatic disease, and that only 29% of patients had received adjuvant chemotherapy with an anthracycline. (A further 14% of patients were actually identified as having received adjuvant chemotherapy without an anthracycline). The remaining patients had clearly received no previous chemotherapy at all, and certainly had not received an anthracycline. Therefore the majority of patients reported had not received an anthracycline.

All of the activity and tolerance data presented on page 3 of the folder was obtained from a mixture of patients, some of whom had been treated within the terms of the summary of product characteristics (SPC) because they had received a previous anthracycline and some of whom had not because they had not received a previous anthracycline.

Rhône-Poulenc Rorer alleged that the folder clearly promoted the use of Navelbine in patients with breast cancer who had not previously received an anthracycline and therefore was in breach of Clause 3.2 of the Code.

RESPONSE

Pierre Fabre stated that the folder presented a summary of the paper in a format that was commonly used.

Pierre Fabre stated that the use of this folder was immediately suspended on 6 November. Following continued correspondence with Rhône-Poulenc Rorer to clarify its (commercial) interpretation of the highlighted data, an external clinical review of this item was sought. It became apparent that the data could be interpreted in a way that was different from that intended by the company. Rhône-Poulenc Rorer was informed on 16 December that Pierre Fabre was reviewing the material to exclude specific data relating to patients who had not received previous anthracycline treatment.

Pierre Fabre submitted that it had acted promptly and in the spirit of the Code to rectify inadvertent errors in this item and avoid any further misinterpretation. It considered that there was nothing further to add in this matter and it should be closed.

PANEL RULING

The Panel noted the action taken by Pierre Fabre, nevertheless the complaint had been made and the Panel therefore had to make a ruling. The Panel noted that the Navelbine SPC gave the therapeutic indications for breast cancer as the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The Panel noted that the study detailed in the folder (Fumoleau *et al* (1993)) was a phase II trial of weekly intravenous vinorelbine in advanced breast cancer. The section of the folder referring to patient characteristics gave details of prior treatment with adjuvant chemotherapy. It was stated that 29% of patients so treated had received an anthracycline and that 14% had not. The Panel assumed that the remaining 57% of patients had received no prior adjuvant chemotherapy. Thus a total of 71% of patients had not been pre-treated with an anthracycline. The data therefore included patients who had not been treated in accordance with the SPC. The folder in effect promoted Navelbine for patients who had not relapsed after, or were refractory to, an anthracycline containing regimen. The Panel therefore ruled a breach of Clause 3.2 of the Code.

2 Folder 'Metastatic Breast Cancer Navelbine + Doxorubicin'

The folder (ref PFO 23) referred to a study by Spielmann *et al* (1994) which was a phase II trial of vinorelbine/doxorubicin in advanced breast cancer. Details of the inclusion criteria, patient characteristics and response to therapy were given.

COMPLAINT

Rhône-Poulenc Rorer pointed out that the folder identified that only 22% of patients in the study had been exposed to anthracyclines. The remaining 78% of patients had therefore not relapsed after or were refractory to an anthracycline and therefore most of the patients treated in this study were treated outside the terms of the SPC for Navelbine.

Virtually all of the data presented comprised a mixture of data from patients treated within and outside the terms of the marketing authorization for Navelbine because some had received a previous anthracycline and some had not. It was claimed that the response rate to Navelbine plus doxorubicin was not affected whether a patient had had prior anthracycline chemotherapy or not, and figures were quoted to justify this.

As a result, the folder promoted the use of Navelbine (+doxorubicin) in patients who had not previously received an anthracycline and who were refractory to it or had relapsed after it, and it was therefore a breach of Clause 3.2 of the Code.

RESPONSE

Pierre Fabre referred to its response in point 1 above. The use of the folder and the process for dealing with the complaint and the withdrawal of the item were similar to that in point 1 above.

PANEL RULING

The Panel noted that in the section of the folder referring to patient characteristics it was stated that 22% of the patients in the study by Spielmann *et al* had previously received anthracycline treatment; 78% of patients presumably had not. The data presented was from the whole study population. In a section detailing response it was stated that response was not altered by prior adjuvant chemotherapy or prior anthracycline therapy. An overall response rate for those patients who had not been previously exposed to anthracyclines was given. The Panel considered that this was similar to point 1 above. The folder in effect promoted Navelbine for patients who had not been treated in accordance with the SPC. The Panel therefore ruled a breach of Clause 3.2 of the Code.

3 Folder 'Metastatic Breast Cancer Navelbine + 5 FU'

The folder (ref PFO 22) referred to a study by Dieras *et al* (1996) which assessed the efficacy and tolerability of a combination of vinorelbine and fluorouracil (5 FU) therapy in advanced breast cancer. Details of the eligibility criteria, patient characteristics and response were given.

COMPLAINT

Rhône-Poulenc Rorer pointed out that the folder clearly identified that patients in the study had received no prior chemotherapy for metastatic disease and that only 54% of the patients had received an anthracycline in the adjuvant setting. Therefore, nearly half of the patients in this study were treated outside the terms of the marketing authorization for Navelbine.

Page 3 of the folder claimed that Navelbine was valuable in 'Patients unable to receive anthracyclines' and three sub-groups of such patients were identified, resistance, cardiac toxicity and patient refusal. The folder did not refer to patients unable to continue to receive anthracyclines. Whilst Rhône-Poulenc Rorer would accept that resistance to anthracyclines might imply that the patients had been previously treated with anthracyclines and had failed (though resistance could also be tested *in vitro*), cardiac toxicity might arise from a number of causes other than anthracycline therapy (for example radiotherapy to the heart area) and most significantly, patient refusal to receive an anthracycline (for whatever reason) indicated that the patients had not received one. Rhône-Poulenc Rorer alleged that the folder clearly constituted promotion of Navelbine for patients who had not received a previous anthracycline. Furthermore, virtually all of the data presented on pages 2 and 3 were obtained from a mixture of patients, some of whom had been treated within the terms of the marketing authorization for Navelbine (because they had relapsed after or were refractory to an anthracycline containing regimen) and some of whom were outside those terms (because they had not).

On page 4, the most prominent claim was that Navelbine + 5FU was '…an effective alternative treatment for patients in whom anthracyclines are contra-indicated'. Rhône-Poulenc Rorer believed that the use of a medicine as an alternative to a contraindicated therapy was not the same as the use of that medicine after the therapy had been tried and had failed. Such patients had, by definition, not received a previous anthracycline, and therefore this constituted promotion of Navelbine outside the terms of its SPC and must therefore also be in breach of Clause 3.2 of the Code.

RESPONSE

Pierre Fabre stated that the use of the folder and the process for dealing with the complaint and withdrawal of the item were similar to point 1 above. With regard to the patient selection, Pierre Fabre referred to its response in point 4 below.

With regard to the claim that Navelbine + 5FU was '…an effective alternative treatment for patients in whom anthracyclines are contra-indicated'. It should be noted that this had not been mentioned in any previous correspondence with Rhône-Poulenc Rorer.

Doxorubicin was the most commonly used anthracycline in the UK. The stated contraindications for doxorubicin, taken from the SPC for doxorubicin hydrochloride for injection (ABPI Compendium of data sheets and summaries of product characteristics 1998-99), were that dosage should not be repeated in cases of bone marrow depression or buccal ulceration or buccal burning sensation, which could precede ulceration. The statement '…should not be repeated…' clearly implied that doxorubicin had already been administered to the patient. If treatment

was contraindicated and therefore not given, the disease would progress and the patient would effectively relapse having previously had an anthracycline. In this context, Pierre Fabre was satisfied that Navelbine + 5FU was an effective alternative treatment for these patients and that this remained within the marketing authorisation for Navelbine in the UK and within the Code.

PANEL RULING

The Panel noted that in the section of the folder detailing patient characteristics in the Dieras study it was stated that 54% had been treated with an anthracycline; 46% presumably had not. The data presented was from the whole study population. The Panel considered that this was similar to points 1 and 2 above. The folder in effect promoted Navelbine for patients who had not been treated in accordance with the SPC. The Panel therefore ruled a breach of Clause 3.2 of the Code.

The Panel considered that the claim 'Patients unable to receive anthracyclines – resistance – cardiac toxicity – patient refusal' could be interpreted as including patients who had never received anthracyclines. The Panel considered that the specialist audience might not interpret the claim in the same way. Nevertheless the folder was not clear about the use of the product. The Panel decided that the claim was not consistent with the indications for Navelbine given in the SPC and ruled a breach of Clause 3.2 of the Code.

The Panel noted Pierre Fabre's submission that '…patients in whom anthracyclines are contra-indicated' were, with regard to doxorubicin, those patients in whom dosage should not be repeated, suggesting therefore some prior exposure to the medicine. The Panel noted, however, that the contraindications for epirubicin, another anthracycline, were patients with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy and those with a current or previous history of cardiac impairment. In the Panel's view, therefore, some patients could be excluded from therapy with epirubicin without ever having received a dose of it or any other anthracycline. The Panel thus considered that the claim 'It is an effective alternative treatment for patients in whom anthracyclines are contra-indicated' was not within the terms of the SPC, as alleged. A breach of Clause 3.2 of the Code was ruled.

4 Booklet 'Navelbine Regimens Non-small cell lung cancer Advanced breast cancer'

Pages 4 and 5 of the booklet ref (PFO 21) referred to Navelbine in combination with other agents in the treatment of advanced breast cancer. The final part of this section referred to patient selection in advanced breast cancer stating 'Early relapse after adjuvant anthracycline therapy' and 'Problems related to anthracycline use – resistance – cardiac risk – patient refusal'.

COMPLAINT

Rhône-Poulenc Rorer pointed out that the claim in the booklet was similar to the claim referred to in point 3 above. The company accepted that anthracycline resistance probably implied previous exposure to an anthracycline, cardiac risk was a broad term, which might occur as a result of many unrelated clinical issues and did not imply that the patient had received a previous anthracycline.

Finally, patient refusal to receive an anthracycline at all, not refusal to continue with an anthracycline, was not consistent with a patient having received a anthracycline and either failed to respond to it or relapsed after it. Rhône-Poulenc Rorer alleged that the booklet was also in breach of Clause 3.2 of the Code.

RESPONSE

Pierre Fabre submitted that patients relapsing after adjuvant anthracycline use could be considered for a repeat treatment with anthracycline if the disease-free interval was sufficiently long and the cumulative lifetime dose had not been exceeded. The decision to use a second course of anthracycline (or not) was a clinical decision based on a careful assessment of potential risk and benefits. Common reasons why patients might not receive a second course of anthracycline were that the disease free interval was short and the likelihood was that response might be less than expected due to anthracycline resistance. The proximity of the cumulative lifetime dose limit, or, changes to the patients' ECG since, or because of, the previous course of anthracycline, might limit the duration of treatment and compromise response and outcome. Some toxicity associated with anthracycline use was unpleasant and patients, who had a right to participate in their own treatment decisions, might choose not to repeat this treatment.

Although this was a complaint from Rhône-Poulenc Rorer that had not been discussed, Pierre Fabre had already reviewed all its promotional material as a consequence of previous correspondence. The booklet (PFO 21) had been replaced with an updated version, (PFO 36). The company pointed out that the wording had been simplified to reduce any possibility of misinterpretation from any source and subjected to an external clinical expert review to check the meaning, clinical intent and compliance to the marketing authorization.

PANEL RULING

The Panel considered that the booklet was less likely to be misinterpreted than the folder at issue in point 3 above. The folder in point 3 referred to 'patients unable to receive anthracyclines' whereas the booklet (PF021) now at issue stated 'Problems related to anthracycline use'. The Panel considered that on balance this section was not unacceptable and no breach of Clause 3.2 of the Code was ruled.

Complaint received **8 February 1999**

Case completed **5 May 1999**

CASE AUTH/842/2/99

GENERAL PRACTITIONER v WHITEHALL LABORATORIES

Traxam Gel journal advertisement

A general practitioner complained about a journal advertisement for Traxam Gel (felbinac). Traxam Gel, a topical non-steroidal anti-inflammatory drug (NSAID), was indicated for the relief of symptoms associated with soft tissue injury and was marketed by Whitehall Laboratories. The advertisement compared the cost of therapy with either an oral NSAID (ibuprofen) or a topical NSAID (Traxam Gel). The advertisement was headed 'Effective felbinac' with a sub-heading 'Traxam is as effective as oral ibuprofen – and is a cost effective alternative'. A box was headed 'Comparison of total costs associated with the treatment of 1000 patients for one month with oral ibuprofen or Traxam'. For ibuprofen the total cost given was £41,408 (initial cost £2,160 shadow cost £39,248). For Traxam the total cost given was £7,319 (initial cost £7,000 shadow cost £319). Shadow cost was stated to be the cost of managing side effects. The complainant alleged that the advertisement was totally misleading regarding cost comparisons. Also the clarity of the information presented (shadow costs) was in his view misleading.

The Panel noted that shadow cost was the cost of managing side effects, namely a peptic ulcer induced by an oral NSAID. The cost comparison was based on an economic model published in 1993 using prices which were current at the time. The Panel noted that since the publication of the paper the cost of oral ibuprofen had been reduced. The Panel was unsure as to whether the costs other than changes in the price of the medicine would have merely risen in line with inflation as submitted by Whitehall. The costs quoted appeared to be based on a 1992 paper which was an economic evaluation of an oral NSAID in the treatment of arthritis. The Panel queried whether the same model could equally be applied to the short-term administration of NSAIDs for soft tissue injuries. The basis for the clinical comparison of Traxam and oral ibuprofen in soft tissue injuries was a paper which showed that the two had similar efficacy in the treatment of lower back injury.

The Panel considered that overall the cost comparison was inaccurate, ambiguous and not based on up-to-date information. A breach of the Code was ruled.

A general practitioner complained about a journal advertisement for Traxam Gel (felbinac). Traxam Gel was a topical non-steroidal anti-inflammatory drug (NSAID). The advertisement, prepared in February 1998, had been issued by Cyanamid of Great Britain Limited. Traxam was marketed by Whitehall Laboratories Ltd and Whitehall responded to the complaint.

The advertisement compared the cost of therapy with either an oral NSAID (ibuprofen) or a topical NSAID (Traxam Gel). The advertisement was headed 'Effective felbinac' with a sub-heading 'Traxam is as effective as oral ibuprofen – and is a cost effective alternative'. A box was headed 'Comparison of total costs associated with the treatment of 1000 patients for one month with oral ibuprofen or Traxam'. For ibuprofen the total cost given was £41,408 (initial cost £2,160 shadow cost £39, 248). For Traxam the total cost given was £7,319 (initial cost £7,000 shadow cost £319). Shadow cost was stated to be the cost of managing side effects.

COMPLAINT

The complainant alleged that the advertisement was totally misleading regarding cost comparisons. Also the clarity of the information presented (shadow costs) was in his view misleading.

RESPONSE

Whitehall stated that the reference used to substantiate the cost comparisons claims and shadow costs to which the complainant was objecting was as cited in the advertisement, a paper by Peacock and Rapier in the British Journal of Medical Economics 1993. This paper illustrated a cost-effectiveness analysis using an established and proven cost-benefit decision tree model and accurately reflected the claims made in the advertisement. Whitehall pointed out that examples of economic models were widely available in the pharmacoeconomic literature and the reference cited had been appropriately refereed.

Whitehall noted that the complainant had stated that 'the clarity of the information presented (shadow costs) was misleading'. However, the advertisement clearly explained what was meant by shadow cost, namely the cost of managing side effects in this economic analysis context. As demonstrated in the reference, shadow cost related to the cost of managing side effects, namely a peptic ulcer induced by an oral NSAID. The cited reference explained the treatment decision tree as well as the calculations of shadow costs.

As the economic model was formulated in 1993, Whitehall had to reflect the costs as calculated and detailed in the reference. It would be appreciated that all the costs incurred due to the management of a peptic ulcer induced by an oral NSAID would have had to be adjusted for inflation if Whitehall was to have reflected 1998 prices [the year the advertisement was prepared]. Therefore, the 1993 price of ibuprofen was quoted and duly acknowledged in the advertisement. Whitehall conceded that the 1998 Drug Tariff price of generic ibuprofen was lower than the 1993 prices. However, this was not significant compared to the current cost of managing a peptic ulcer induced by an oral NSAID. The price of Traxam was the same now as it was in 1993.

Whitehall did not believe that it was in breach of Clause 7.2 of the Code. It used the material as

outlined in the reference appropriately and, therefore, it maintained that it did not mislead physicians with the cost comparisons in the advertisement as the latter accurately reflected the pharmacoeconomic model.

Whitehall stated that it had since reviewed its advertising strategy for the brand and did not propose to use the advertisement in this format again.

PANEL RULING

The Panel noted that the boxed cost comparison was headed 'Comparison of total costs associated with the treatment of 1000 patients for one month with oral ibuprofen or Traxam'. Beneath the box it was stated that 'Treatment costs for ibuprofen at minimum dosage (1200mg/day) for 28 days is £2.16 (Drug Tariff, October 1993). Traxam, 1200mg/day for 14-28 days equivalent costs £7.00 per tube (MIMS March 1997)'. The Panel considered that it was thus unclear as to what duration of treatment with Traxam Gel formed the basis of the price comparison.

The Panel noted that Traxam Gel was indicated for the relief of symptoms associated with soft tissue injury. Up to 4g of gel (120mg of felbinac) could be applied to the affected area each day. If symptoms did not resolve within 14 days, the patient should be reviewed. The Panel noted that, according to the heading, the cost comparison had shown the cost of treating 1000 patients for one month (28 days) with 4g Traxam Gel applied each day. The Panel noted that the cost comparison had assumed that one tube (100g – cost £7) of Traxam Gel would provide one month's therapy for each patient. With the use of 4g of Traxam Gel each day, however, 112g of gel would be needed, necessitating the purchase of two tubes for each patient thus doubling the stated initial cost of £7000. In contrast one tube of Traxam Gel would have been more than sufficient for the 14 days' treatment recommended in the prescribing information. The initial cost of treatment would not be reduced, however, as one whole tube had to be purchased whether or not the whole amount was required. Text beneath the cost comparison referred to 14-28 days' treatment with Traxam.

The Panel noted that the authors of the paper cited in support of the claim that Traxam was a cost effective alternative to oral ibuprofen, had taken a previously published economic model and applied it to ibuprofen and Traxam in the treatment of rheumatic conditions. The Panel noted that the authors viewed soft tissue injuries as a type of rheumatic condition. The authors explained that with soft tissue injuries treatment with an NSAID was required for less than four weeks. The cost of treating patients with oral ibuprofen for only 14 days was thus calculated and stated to be £10,892 in total with a shadow cost of £9,812 associated with an assumed incidence of ulcer of 2.5%. If 28 days' treatment was required, however, the ulcer rate was assumed to be 10% giving a shadow cost of £39,248 and a total cost of £41,408. The Panel noted that it was the 28 day cost of ibuprofen which had been given in the advertisement although the incidence of peptic ulcer had been incorrectly quoted as 20% in the advertisement. Given that Traxam Gel and oral ibuprofen could only be compared in the treatment of soft tissue injuries, and that patients treated with Traxam Gel should have been reviewed after 14 days' therapy if their symptoms had not resolved, the Panel considered that the 14 day cost would have been more appropriate.

The Panel noted that the cost comparison was based on an economic model published in 1993 using prices which were current at the time. The Panel noted that since the publication of the paper the cost of oral ibuprofen had been reduced. The Panel was unsure as to whether the costs other than changes in the price of the medicine would have merely risen in line with inflation as submitted by Whitehall. The costs quoted by Peacock and Rapier appeared to be based on a paper by Knill-Jones *et al* (1992) which was an economic evaluation of an oral NSAID in the treatment of arthritis. The Panel queried whether the same model could equally be applied to the short-term administration of NSAIDs for soft tissue injuries. The basis for the clinical comparison of Traxam and oral ibuprofen in soft tissue injuries was a paper by Hosie (1993) which showed that the two had similar efficacy in the treatment of lower back injury.

The Panel considered that overall the cost comparison was inaccurate, ambiguous and not based on up-to-date information. A breach of Clause 7.2 was ruled.

Complaint received **15 February 1999**

Case completed **19 April 1999**

CASE AUTH/843/2/99

3M HEALTH CARE v GLAXO WELLCOME

Conduct of representative

3M Health Care alleged that during a discussion with a hospital drug information pharmacist an Allen & Hanburys representative had made inaccurate claims about, and thus disparaged, 3M's product Qvar. Qvar was beclomethasone dipropionate (BDP) in a chlorofluorocarbon free (CFC-free) breath actuated inhaler. The propellant was hydrofluoroalkane (HFA) – 134a. 3M submitted a copy of a letter from the pharmacist involved.

The representative was said to have stated that 3M used alcohol to 'dissolve' BDP after addition of a surfactant. The alcohol reduced the particle size to such a degree that it was deposited in the alveoli. The representative had inferred that this was a problem as deposition in the alveoli would increase systemic steroid absorption, leading to long-term safety problems. 3M said that there was no surfactant in Qvar. The suggestion that deposition led to long-term safety problems was not supported by the summary of product characteristics (SPC) or any data in 3M's possession and was unsubstantiated. It was alleged that this was inaccurate and disparaging of Qvar. The Panel noted that the parties provided different accounts of what the representative had said. There was no mention of a surfactant in relation to Qvar in the representatives' briefing material and the Panel ruled no breach in that regard.

With regard to long-term safety problems, the Panel noted that similar comments were made in the briefing material. For example, one document stated that 'The change in particle size of 3M's CFC-free BDP may have significant implications for the systemic safety profile of the product.' The Panel considered that the briefing material was inaccurate regarding safety issues and ruled it in breach of the Code. Given the briefing material, the balance of probabilities was that the representative had made the statements in question and a breach was ruled in that regard also. It was also ruled that there had been a breach because Qvar had been disparaged. Upon appeal by Glaxo Wellcome, the opinion of the Appeal Board was that the briefing material would raise doubts regarding the safety profile of Qvar in the minds of its representatives. The Appeal Board considered that overall the briefing material was unbalanced because it failed to convey that at licensed doses there was no evidence that BDP deposition from Qvar led to long-term safety problems. The Appeal Board upheld the Panel's ruling of a breach in that regard and also upheld the Panel's ruling that Qvar had been disparaged. The Appeal Board considered it inappropriate to make a ruling upon the conduct of a representative who had simply been following the briefing material and overturned the Panel's ruling of a breach in that respect.

The representative was said to have referred to the problem of halving the dose of Qvar and how patients and general practitioners would find this confusing. 3M said that there was no evidence to support this and evidence to the contrary could be supplied. The Panel noted that the representative recalled saying that confusion might arise if a prescription for a CFC-free inhaler was not accurately or consistently written so that an inhaler was dispensed which was not bioequivalent to the one being used by the patient. The Panel considered that what was important to the patient was the number of puffs needed. For patients on two puffs twice daily of CFC-BDP this would not change. The Panel did not consider that patients would find the changeover confusing as stated in the briefing material. The Panel considered that the briefing material was misleading in its inference that the dosing of Qvar was confusing and ruled it in breach. It was not clear what the representative had said and no breach was ruled in that regard. Upon appeal by Glaxo Wellcome, the Appeal Board noted that there were differences between CFC-BDP and Qvar but, contrary to the impression created by the briefing material, did not consider that these were such as to cause confusion and upheld the Panel's ruling of a breach of the Code.

Another statement said to have been made by the representative was that she was concerned about how the new products would look and taste, the inference being that as Qvar looked and tasted very different this was confusing. 3M said that the taste difference was common to all hydrofluoroalkane-134a inhalers, as was stated in Glaxo Wellcome's Evohaler material. The Panel noted that the briefing material did not refer to the taste of Qvar. The allegation came down to one person's word against another and in the circumstances the Panel ruled no breach of the Code.

The pharmacist had recalled that the representative said that the date for changeover was 2003 and gave the impression that other inhaler manufacturers were giving misleading information by saying that the changeover was earlier than that. The Panel noted that the position was complicated as essential use exemptions were in operation. It appeared that the use of CFCs in inhalers was reviewed on an annual basis and it was not possible to be certain as to the date for change. The Panel considered that by simply saying that the transition date was likely to be 2003 the representative had been ambiguous and misleading and a breach of the Code was ruled. Upon appeal by Glaxo Wellcome, the Appeal Board noted that the representative denied making the statement and noted also the statements in the briefing material. The Appeal Board considered that given that Glaxo Wellcome's CFC-free salbutamol had already been launched, it was unlikely that the representative would have created the impression that the transition would not take place until 2003. The Appeal Board overturned the Panel's ruling of a breach of the Code.

The representative was alleged to have used Qvar's brand name during the discussion with the pharmacist without 3M's permission. The Panel noted the representative's statement that she might

have lapsed into using the name in response to the pharmacist's use of it. A breach of the Code was ruled. Upon appeal by Glaxo Wellcome, the Appeal Board noted that whilst the briefing material strongly recommended that representatives did not refer to Qvar by brand name, it omitted to mention that use of other companies' brand names was contrary to the Code. However, the Appeal Board considered that it was not possible to determine precisely what had been said by the representative and overturned the Panel's ruling of a breach of the Code.

It was alleged by 3M that the representative was untrained on Qvar, and therefore by definition was acting unethically, and was highly unlikely to have been in possession of the Qvar SPC. The Panel considered that the Code did not require representatives to have available SPCs for competitor products which they referred to. Although the Code required representatives to be trained, the Panel did not accept that the Code meant that the representative should have received training on Qvar. No breach of the Code was ruled in these respects.

3M further claimed that by discussing a competitor product in the manner reported the representative was clearly not fully trained. The inaccuracy of the discussion had plainly led to confusion and a reduction in confidence in the industry. A breach of Clause 2 of the Code was alleged. The Panel noted that Clause 2 was used as a sign of particular censure. It did not accept that the circumstances were such as to warrant a ruling of a breach of that clause. Upon appeal by 3M, the Appeal Board noted its rulings as above and considered that overall the representatives' briefing material sought to cast unjustified doubts on Qvar, which was the only CFC-free BDP available. The Appeal Board considered that Glaxo Wellcome's actions had brought discredit upon, and reduced confidence in, the pharmaceutical industry and ruled that there had been a breach of Clause 2 of the Code.

3M Health Care Limited complained about a representative of Glaxo Wellcome UK Limited. 3M alleged that, during a conversation with a hospital drug information pharmacist, the representative had made inaccurate claims about and thus disparaged 3M's product, Qvar. Qvar was beclomethasone dipropionate (BDP) in a chlorofluorocarbon free (CFC-free) breath actuated inhaler. The propellant used in Qvar was hydrofluoroalkane (HFA) – 134a. In support of its complaint, and with her permission, 3M submitted a letter that the pharmacist had written to the company and which read:

'I recently met with our local Allen & Hanburys representative. I have known her for a long time, and have respect for what she tells me. We were talking about the launch of Flixotide nebules.

I asked her about the CFC-free issue as I (and all other pharmacists) had just received a large package of information from Allen & Hanburys through the post. She started by telling me that the date for changing to CFC-free inhalers was in fact 2003, and gave me the impression that other inhaler manufacturers (eg 3M) were giving misleading information by saying the change over was earlier than this.

We talked about Qvar in some detail. We talked about the problem in formulating a CFC-free beclomethasone product. She explained that 3M use alcohol to dissolve the drug, after the addition of a surfactant. This alcohol reduces the drug particle size to such a degree that the drug is deposited in the alveoli. Not being an expert on alveoli function, I questioned whether this was a problem. She inferred that it was, as the beclomethasone anti-inflammatory action needs to have an effect higher up the bronchial tree, and that deposition in the alveoli would increase systemic steroid absorption, leading to long-term safety problems.

She then went on at length about how Allen & Hanburys are trying to formulate a CFC-free product without alcohol, but are having problems due to drug clumping. Apparently this is not a problem with salbutamol, which is why the Evohaler exists already.

She then talked about the problem of halving the dose, and how patients (and general practitioners) would find this confusing. Allen & Hanburys want to produce an equivalent dose product to swap one for one. She was also concerned about how the new products would look and taste. Again, the inference was as Qvar looks (and tastes?) very different, this is confusing.

My concern is that both this representative, and our 3M representative – give very credible, but conflicting, information.'

COMPLAINT

3M said that the substance of its complaint against Glaxo Wellcome was that the detailed discussions constituted breaches of the following clauses of the Code:

1 Clause 2 – by discussing a competitor product in this manner the representative was clearly not fully trained. The inaccuracy of the discussion had plainly led to confusion and a reduction in confidence in the pharmaceutical industry. 3M referred particularly to paragraphs 5 and 6 of the letter from the hospital pharmacist.

2 Clause 7.2 – the representative made inaccurate statements concerning Qvar.

- There was no surfactant in the product. Ethanol as described by the representative was the sole co-surfactant.
- The suggestion that the drug deposition from Qvar led to long-term safety problems was not supported by the summary of product characteristics (SPC) or any data in 3M's possession and was unsubstantiated.
- There was no evidence to support the inference that the dosing was confusing (evidence to contrary could be supplied if required).
- The taste differences were common to all HFA inhalers and this was stated in Glaxo Wellcome's Evohaler material.
- The details on CFC-free transition were incorrect.

3 Clause 7.10 – no permission had been given to any employee of Glaxo Wellcome to use the Qvar brand name in its promotional activities (paragraph 3 of the letter).

4 Clause 8.1 – the suggestion that the beclomethasone deposition from Qvar led to long-term safety problems was a disparaging statement.

5 Clauses 15.1, 15.2, 15.8 – the representative was untrained on Qvar, therefore by definition was acting unethically, and was highly unlikely to have been in possession of the Qvar SPC.

3M stated that in addition to this specific letter, the company had a large number of reports from its own personnel and contract representatives from throughout the UK that indicated that these comments by Glaxo Wellcome personnel were widespread and consistent in their nature.

3M suggested that a detailed briefing might have occurred and that under Clause 15.9 any such material used by Glaxo Wellcome should be scrutinised as part of the complaint.

RESPONSE

Glaxo Wellcome stated that the most convenient way to address the issues was to describe the meeting between the drug information pharmacist and the Allen & Hanburys representative, as described by the representative. Glaxo Wellcome was more than a little disappointed that the pharmacist did not write to Allen & Hanburys to express the concerns described in the final paragraph of her letter. Glaxo Wellcome would not be able to address any of her concerns now as she had emigrated within two weeks of writing the letter to 3M.

The representative visited the pharmacist on Thursday, 14 January, to discuss Flixotide Nebules (fluticasone propionate) which had just been launched. There had been a long discussion about Flixotide Nebules and as the representative was putting away her materials the pharmacist brought up the topic of CFC-free transition. Apparently, she had recently received a letter and an information folder from Allen & Hanburys on this topic, but the representative was also led to believe that someone was going to be visiting the hospital to discuss CFC-free issues in the near future and the pharmacist wished to be prepared. After their long discussion on Nebules, they talked for not more than five minutes about the whole issue of CFC-transition, although much ground was covered in that time. In fact so much was discussed in this short period of time that the representative checked with the pharmacist that she had understood everything. Although she said that she had, it now appeared that the representative's fears had been confirmed.

The issue of the timing of transition did come up and the representative commented that she knew one local consultant who said that he had been informed by his 3M representative that the transition should be over by April 1999. She had said, supported by Hansard, that transition was likely to take until the year 2003 as it would take longer with some molecules than with others. She knew that the phasing out of different CFC-containing products would take place when appropriate CFC-free formulations were available.

They had talked about Ventolin Evohaler (salbutamol) as this was the only Allen & Hanburys CFC-free product currently available in the UK. The representative explained that the Ventolin Evohaler made use of a specially coated can and valve in order to obtain the same performance from salbutamol in HFA-134a (the CFC-free propellant) as from the CFC-containing inhaler. When discussing 3M's CFC-free salbutamol product, she had commented, quite accurately, that 3M had adopted a different approach and used a surfactant to optimise the inhaler's performance, but that the surfactant had to be dissolved in alcohol as it was itself insoluble in HFA-134a.

The pharmacist was particularly interested in discussing any problems surrounding CFC-free inhaled corticosteroids, including 3M's CFC-free BDP (Qvar). Glaxo Wellcome's representative explained that Allen & Hanburys had found the BDP question to be more challenging than that with salbutamol. It was well known that 3M had addressed the problem by dissolving the BDP in alcohol. The representative explained that the use of alcohol in this situation was for a different reason to when it was used in 3M's CFC-free salbutamol inhaler. In this situation it was because BDP was itself unstable when attempts were made to suspend it in HFA-134a, so it was dissolved in alcohol to produce a solution of BDP, which yielded very fine particles on firing, compared with those from a CFC-containing inhaler. There was therefore no need for any surfactant.

The representative concerned was very experienced and used the term '3M's CFC-free BDP', but might possibly have lapsed into calling it Qvar in response to the pharmacist's use of that term. When responding to the pharmacist's comments on the properties of Qvar, the representative had confirmed that it was licensed to be used at half the dose of CFC-containing BDP inhalers because its very small particles were associated with greater total lung deposition. However, increased deposition potentially had disadvantages as well as advantages as the smaller particles allowed more deposition in the very small airways and alveoli, the latter being associated with greater systemic absorption, as was well described in 3M's published studies. As the inflammation of asthma was widespread throughout the bronchial tree this increased peripheral deposition of corticosteroid was not necessarily linked to an equivalent increase in efficacy. While the representative said that this altered the efficacy:safety ratio of CFC-free BDP compared with CFC-containing preparations, she certainly did not say that this would lead to long-term safety problems.

They discussed dosing recommendations, but the representative only said that confusion might arise if a prescription for a CFC-free preparation was not accurately nor consistently written, so that an inappropriate inhaler was dispensed to the patient, ie one that was not bioequivalent to the one being used by the patient. She had confirmed Allen & Hanburys' commitment, expressed in the folder described by the pharmacist, to providing CFC-free replacements

which had the same performance as the CFC-containing formulations that they replaced. She agreed with the statement in the folder that the taste, sound and feel of CFC-free inhalers might be different to the patient. While she confirmed that the Allen & Hanburys' CFC-free inhalers (Evohaler) looked the same as the inhaler they replaced and that this would be reassuring for patients, she did not comment that the Qvar inhaler looked different to previous 3M inhalers as she was not aware of any differences. She did not say or imply that Qvar looked and tasted different nor that this would create confusion.

The representative left the pharmacist on very good terms and was very surprised and hurt to hear of this complaint.

Addressing the complaints from 3M:

1 It appeared from her letter that the drug information pharmacist had not fully understood what was being discussed with this very experienced and well-informed representative. From the representative's account the pharmacist had expressed herself as having been happy with the results of their discussion. She had not availed herself of the opportunity to revise some of the points over which she appeared not to have been clear. Her subsequent uncertainty might not have been helped by the twelve day delay before she wrote her letter to 3M. Glaxo Wellcome's representative had responded accurately, factually and appropriately to direct questions from the pharmacist. Glaxo Wellcome did not believe that the representative's behaviour was in any respect in breach of Clause 2 of the Code.

2 The representative did not state that there was a surfactant in Qvar. She had a complete grasp of the reasons why a surfactant was not required in Qvar. Ethanol was described only in its role as a solvent for the BDP. However, she and the pharmacist had already discussed CFC-free salbutamol inhalers and the fact that there was a surfactant (oleic acid) in 3M's CFC-free salbutamol inhaler. This presumably explained the confused memory of the pharmacist when she wrote her letter?

It was neither stated nor suggested by the representative that beclomethasone deposition from Qvar led to long-term safety problems. Glaxo Wellcome noted from the pharmacist's letter that this was one of the inferences that she had later drawn from their discussion. The representative had only repeated what was stated in the Qvar SPC, that there was greater systemic absorption, dose for dose from Qvar than from a CFC-containing BDP inhaler. This was stated as the rationale for investigating the use of lower total daily doses of Qvar compared with CFC-containing BDP inhalers (Section 5.2 of the Qvar SPC).

The representative had discussed the possibility of confusion in the context of the inaccurate prescribing of BDP inhalers when the 3M CFC-free BDP and CFC-containing BDP inhalers were not directly equivalent at the same dose. There was no implication on her part that the dosing recommendations themselves were confusing.

The representative never suggested that the Allen & Hanburys CFC-free inhaler might not have a different taste to the CFC-containing inhaler. This was clearly stated in all materials including those received by the pharmacist.

The representative's account of CFC-free transition reflected the facts. It was likely that a complete phasing out of CFC inhalers would not take place before 2003. The use of CFCs in inhalers for medical use was reviewed on an annual basis.

Glaxo Wellcome did not believe that there was a breach of Clause 7.2 of the Code in any respect, as the representative presented the information factually and accurately.

3 The pharmacist's letter used the name Qvar when describing her discussions with the representative. As the pharmacist raised the topic, it was fair to assume that it was she who introduced the name Qvar into the conversation. It was not in the interests of Allen & Hanburys to increase the usage of the name Qvar, and therefore, in addition to the content of Clause 7.10, Glaxo Wellcome's representatives had all been instructed to use the term '3M's CFC-free BDP' and not the name Qvar. They were instructed to provide succinct responses when customers raised the issue of CFC-free BDP, to allow them to return to their product focus (representatives' briefing materials).

4 Glaxo Wellcome did not believe that there was a breach of Clause 7.10, in that the representative would only have used the name Qvar in response to its use by the pharmacist.

5 The representative did not state nor suggest that the deposition characteristics of Qvar led to long-term safety problems. She did state that the greater lung deposition was associated with greater systemic absorption than for the same dose of CFC-containing BDP inhalers, as was stated in the SPC for Qvar. The fact that this altered the efficacy:safety ratio was acknowledged in the SPC, in that this was the rationale behind the use of lower doses of Qvar than in the CFC-containing BDP inhalers. The Medicines Control Agency (MCA) had itself only recently addressed the issue of the safety of inhaled corticosteroids in 'Current Problems in Pharmacovigilance'.

The representative's accurate presentation of the facts could not be taken as disparaging and Glaxo Wellcome did not believe there was a breach of Clause 8.1 of the Code.

6 Glaxo Wellcome did not believe that there was a breach of Clause 15.1 of the Code as the representative was not promoting Qvar, although she did display sufficient scientific knowledge to be able to provide accurate information, in response to the pharmacist's questions.

Glaxo Wellcome did not believe that there was a breach of Clause 15.2 of the Code as the representative had at all times maintained a high standard of ethical conduct, indeed the pharmacist's letter stated 'I… have respect for what she tells me'.

Glaxo Wellcome did not believe that there was a breach of Clause 15.8 of the Code because the representative did not initiate this discussion about

CFC-free inhalers, which included Qvar. The pharmacist's letter stated 'I asked her about the 'CFC-free' issue…', indicating that the pharmacist had herself initiated the discussion.

Glaxo Wellcome stated that it was clearly the policy of 3M, as expressed by the company at a recent symposium hosted by the Department of Medicines Management of Keele University, to 'encourage healthcare professionals to begin switching now, citing patient confusion and escalating costs as potential implications of delay'. The consensus view expressed by the participants was that 'The beclomethasone switch is significantly more complex (than salbutamol). Bioequivalence is a concern. The majority of prescribers believe that they should delay the switch until there are two bioequivalent CFC-free MDIs.' A preliminary report of this important symposium had been published in The Pharmaceutical Journal and it was understood that the full report was to be published shortly.

While the representative did not discuss possible confusion caused by the dosing recommendations, Glaxo Wellcome considered that some of the advice in the Qvar SPC was indeed confusing. While the advice for switching patients with well controlled asthma was clear, Glaxo Wellcome believed that there was the possibility of confusion for the prescriber when transferring patients with poorly controlled asthma from a CFC-containing BDP inhaler to 3M's CFC-free BDP. The licensed dose of Qvar was up to 800 micrograms daily, taken in two divided doses, and it was suggested that patients with poorly controlled asthma might be switched to Qvar at the same microgram dose up to 800 micrograms daily. As an alternative, it was suggested that the dose of CFC-containing BDP could be doubled and this dose converted to Qvar according to the table shown. There was not a problem at doses of CFC-containing BDP up to 1000 micrograms daily, which doubled to 2000 micrograms and so was covered by the table. But what was the prescriber to do when patients were not controlled on, say, 1500 to 2000 micrograms of CFC-containing BDP, which doubled to 3000 and 4000 micrograms respectively, which were not covered by the switching advice?

In conclusion, Glaxo Wellcome assured the Authority that its representatives were behaving correctly in their contacts with customers and not inappropriately, as was implied by 3M. Naturally 'detailed briefing' had occurred, as was appropriate to any pharmaceutical company, but Glaxo Wellcome did not consider that it had been in any way improper.

PANEL RULING

The Panel noted that Evohaler was the name given to the CFC-free metered dose inhaler (MDI) from Allen & Hanburys. CFC-free Ventolin inhaler was available as Ventolin Evohaler. The Panel noted that Qvar was the first CFC-free BDP product.

The Panel noted that the parties had provided differing accounts of the conversation between the representative and the drug information pharmacist. It was difficult in such cases to determine exactly what had been said. A judgement had to be made on the available evidence. Companies had to provide detailed briefing material for their medical representatives. This consisted of both the training material used to instruct representatives about a medicine and the instructions given to them as to how the medicine should be promoted. Clause 15.9 of the Code required that briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel noted that Glaxo Wellcome had provided extensive briefing material with its response. It had requested that the materials were not passed to 3M.

The Panel noted that 3M had made a number of allegations of breaches of Clause 7.2 of the Code in relation to the discussion between the representative and the pharmacist. The Panel considered that as these allegations were in relation to what the representative had said Clause 15.2 was the more appropriate clause.

The Panel took each of the points raised by 3M in turn.

With regard to the reference to surfactant, the Panel noted that the parties provided differing accounts of what was said by the representative. The letter from the pharmacist referred to the representative saying that a surfactant was required in formulating CFC-free BDP whereas the representative said that she had not described CFC-free BDP as needing a surfactant. The briefing material appeared not to refer to a surfactant in Qvar. One document, dated October 1998, in a section headed 'Qvar General Information' stated that CFC-BDP contained the active drug, a surfactant and two CFC propellants, and that 3M's CFC-free BDP contained a propellant called HFA-134a and ethanol, which acted as a solvent, as well as the active drug. The Panel considered that it was not possible to determine precisely what was said. The Panel noted that it was unable to find any mention of a surfactant with regard to CFC-free BDP in the briefing material. In the circumstances the Panel ruled that there was no breach of Clause 15.2 of the Code.

With regard to the alleged comments about the beclomethasone deposition from Qvar leading to long-term safety problems, the Panel noted that similar comments were made in the briefing material. One document entitled 'CFC-free beclomethasone dipropionate (BDP) – what are the issues?' stated that 'Changing the particle size profile of CFC-free BDP may have implications for the safety profile of the product…' A post launch briefing document dated October 1998 referred to 'The change in particle size of 3M's CFC-free BDP may have significant implications for the systemic safety profile of the product'. This document also stated that because the drug particles were smaller they passed freely down the lower airways and were deposited in the alveoli creating the potential for greater systemic absorption and therefore concern over safety. The Panel considered that the briefing material was inaccurate regarding safety issues. If the representative had followed the briefing material this would have led to a breach of the Code. The Panel considered that the briefing material failed to comply with the Code. A breach of Clause 15.9 was ruled. Given the content of

the briefing material the Panel decided that on the balance of probabilities the representative would have made the statements in question. The Panel ruled a breach of Clause 15.2 of the Code.

The Panel accepted the allegation that the impression given by Glaxo Wellcome that the deposition from Qvar led to long-term safety problems was disparaging. A breach of Clause 8.1 of the Code was ruled.

With regard to the allegation regarding the dosing of Qvar, the Panel noted that the pharmacist stated that the representative had talked about the problems of halving the dose and how patients and doctors would be confused. The representative recalled saying that confusion might arise if a prescription for a CFC-free preparation was not accurately nor consistently written so that an inappropriate inhaler was dispensed ie one that was not bioequivalent to the one being used by the patient. The Panel examined the briefing material. The post launch briefing document dated October 1998 in a section headed 'Qvar General Information' referred to transferring patients from CFC-BDP to Qvar. It stated that a simple switch would be one where the dose, product name, appearance, safety and efficacy were the same, ie to an inhaler which was as similar as possible in as many respects as possible. However patients and prescribers would have to adjust to a different dose (and therefore different efficacy profile), different product name, different coloured inhaler and different aerosol characteristics compared with CFC-BDP. In addition the complicated dosage recommendations in the SPC did not make for a simple switch. This document also stated that transition to 3M's CFC-free BDP would cause unnecessary confusion and disruption for both patients and healthcare professionals. The Panel considered that the briefing material was misleading regarding the inference that the dosing of Qvar was confusing. Changing patients to Qvar would mean a change in dose but this was not necessarily confusing as implied by the briefing material. In the Panel's view the change in the product name might help to reinforce the change of dose. From the patients' perspective it was important to know how many puffs to inhale per day. The amount of medicine in each actuation of an inhaler was less important. The Panel noted that the Qvar SPC explained that patients on 2 puffs twice daily of CFC beclomethasone 100 micrograms would change to 2 puffs twice daily of Qvar 50 micrograms. The Panel did not consider that patients would find this change over confusing as stated in the briefing material. A breach of Clause 15.9 of the Code was ruled. The Panel was not sure whether the representative had been discussing prescribing after a patient had been switched to CFC-free BDP or the process of switching from CFC-BDP to CFC-free BDP. The Panel considered that the representative should have been clearer about what was meant. It decided, however, that there was not sufficient evidence on which to base a ruling of a breach and therefore ruled no breach of Clause 15.2 of the Code.

With regard to the allegation regarding differences in taste, the Panel noted that the pharmacist stated that the representative was concerned about how the new products would look and taste, inferring that as Qvar tasted very different this would cause confusion. Glaxo Wellcome stated that the representative had agreed with the statement in the Allen & Hanburys information folder that the taste, sound and feel of CFC-free inhalers might be different to the patient. The Panel noted that the information file stated that some patients might notice a slightly different taste with the Evohaler compared to the MDI it replaced. This was due to the new propellant and did not affect the way the medicine worked. The Panel was unable to find any mention in the briefing material that the taste of Qvar would be confusing. The Panel considered that this allegation came down to one person's word against another. In the circumstances the Panel ruled no breach of Clause 15.2 of the Code.

With regard to the date for changing to CFC-free inhalers, the Panel noted that the pharmacist recalled that the representative said that the date for changeover was 2003 and gave the impression that other inhaler manufacturers were giving misleading information by saying that the changeover was earlier than that. The Panel noted that the representative stated she had said that the transition was likely to take until the year 2003. The Panel examined the briefing material. A question and answer document entitled 'Allen & Hanburys managing the transition to CFC-free metered dose inhalers' included a section on legislation. The section referred to the Montreal protocol and referred to the recognition that MDIs for the treatment of asthma and chronic obstructive pulmonary disease were an essential use of CFCs which meant that exemptions might be granted allowing the continued use of CFCs in MDIs (metered dose inhalers) while CFC-free MDIs were being developed. Nominations for exemptions had been accepted for 1998 and 1999 and submitted for 2000. It was hoped that CFC MDIs would continue to be given exemptions until such time as alternative CFC-free MDIs were widely available for patient use. The document also stated that the essential use exemption allowing CFCs to be used in the manufacture of MDIs would continue to be provided until an adequate range of CFC-free alternatives were available. CFC-containing MDIs were likely to remain available in the EU up to 2003. A document dated July to September 1998 referred to the UK strategy document that the transition process was likely to be completed within the next three years ie 2001. The Panel noted that neither 3M nor Glaxo Wellcome had clearly set out what the position was with regard to the transition to CFC-free MDIs. The Panel considered that the pharmacist had been left with the impression that the date for change was 2003. Nominations for exemptions had been accepted for 1999 and submitted for 2000. It appeared that the use of CFCs in inhalers was reviewed on an annual basis. It was not therefore possible to be certain as to the date for change. The Panel considered that the matter was complicated and it was important for representatives to be clear about the position when discussing transition dates with health care professionals. The Panel considered that by simply saying that the transition date was likely to be 2003 the representative had been ambiguous and inaccurate. The Panel ruled a breach of Clause 15.2 of the Code.

With regard to the alleged use by the representative of 3M's brand name, Qvar, the Panel noted that the representative's statement that she might have lapsed into calling it Qvar in response to the pharmacist's use of the word. The Panel ruled a breach of Clause 7.10 as permission had not been given to Allen & Hanburys to use the Qvar brand name. The Panel noted that the briefing material clearly instructed representatives to use the term 'CFC-free BDP' when referring to Qvar.

The Panel noted that Clause 15.8 of the Code required that representatives had an SPC to provide, or available to provide if requested, when initiating a discussion on a medicine. It was assumed that this clause referred to the medicines being promoted by the representative and not competitor medicines, although the Panel noted this was not clear in the Code as drafted. The Panel noted that The Medicines (Advertising) Regulations 1994 clearly referred to medicines being promoted by representatives. No breach of Clause 15.8 was ruled. Clause 15.1 referred to representatives being trained on the products they promoted. The Allen & Hanburys representative was not promoting Qvar. The Panel considered that representatives needed to be trained on competitor products if the promotion of their companies' products included comparisons with competitors etc, but did not accept that the representative needed to be trained on Qvar as meant by Clause 15.1 of the Code and so ruled no breach of that clause. With regard to the allegation that as the representative was not trained on Qvar she was acting unethically, the Panel decided that as there was no breach of Clause 15.1 of the Code there could not be a breach of Clause 15.2 as alleged. The Panel ruled accordingly.

The Panel noted that Clause 2 was used as a sign of particular censure. It did not accept that the circumstances were such as to warrant a ruling of a breach of that clause and no breach of Clause 2 was ruled.

APPEAL BY GLAXO WELLCOME

Glaxo Wellcome stated that it had interviewed at length and in detail the representative involved and had also reviewed its briefing material and the supporting evidence.

Glaxo Wellcome submitted that it should be noted that the discussion on the CFC-free transition was initiated by the pharmacist, and the topics for discussion were driven by the pharmacist, not by the representative. The representative was responding to specific enquiries by the pharmacist and the whole discussion lasted for no more than 5 minutes.

Alleged comments by the representative about the beclomethasone dipropionate deposition from Qvar leading to long-term safety problems

The phrase used in the briefing document relating to this stated 'potential for greater systemic absorption and concern over safety' (underlining added). If a drug was deposited in the smaller airways and alveoli in greater quantities, as was the case with 3M's CFC-free BDP, it would seem clear that this potential existed. Indeed the Qvar SPC stated that the reason for the investigation of the efficacy of lower doses of Qvar compared to CFC-containing BDP, was the pharmacokinetic data which showed that CFC-free BDP achieved the same blood levels as twice the dose of CFC-containing BDP. In the study from 3M on which this statement was based 200 micrograms CFC-free BDP was shown to achieve maximum serum levels of total beclomethasone products more than twice as high and more than three times as quickly as 200 micrograms of CFC-BDP.

Current Problems in Pharmacovigilance stated that 'the increased lung delivery results in 2-2.5 fold greater potency of Qvar when compared with CFC-BDP. The use of high doses of inhaled corticosteroids has been associated with systemic side effects'. The article went on to say 'Prescribers should remain vigilant to the risk of systemic adverse effects, particularly with prolonged high dose inhaled corticosteroids including CFC-free products'.

Jackson and Lipworth (1995) stated that the risk of developing side effects related to the amount of drug reaching the systemic circulation. It was understood that enhanced deposition, especially to the alveolar region, might result in increased systemic availability and a higher risk of systemic side effects.

An article in Respiratory Medicine by Chrystyn (1997) stated that 'There may be greater systemic absorption from alveolar deposition (following inhalation from [CFC-free] MDIs) which could give rise to an increase in extra-pulmonary effects'.

An editorial in Chest (Taskin (1999)) stated that 'This enhanced lower respiratory deposition could result in an actual increase in systemic bioavailability of the BDP from the [CFC-free] preparation owing to greater absorption from the lung, as suggested by data from pharmacokinetic studies that imply the potential for equivalent or even increased systemic side effects from half doses [CFC-free]-BDP compared with CFC-BDP'.

A supplement in The Pharmaceutical Journal on CFC-free inhalers stated:

'Therefore, while the supra-bioavailability of some of the newer CFC-free aerosols may be marketed as an advance, this might turn out to be a health problem. Unfortunately we shall not know this until millions of patients have been exposed to the new products. Downward dose titration of supra-bioavailable corticosteroid products will generally be needed to minimise or avoid this risk.'

In view of the pharmacokinetic data on Qvar and the statements and comments quoted above regarding the implications of these factors, Glaxo Wellcome felt that the note of caution in its briefing materials was justified. If reflected the opinions of independent authorities, but only to the extent of saying **potential** for greater systemic absorption and concern over safety. This echoed the note of caution in most publications covering the subject.

Glaxo Wellcome therefore appealed against the rulings of breaches of Clauses 15.2 and 15.9 in this respect.

Disparaging impression regarding the deposition from Qvar and long-term safety problems

As Glaxo Wellcome believed that the comments in the briefing materials were correct and reflected current opinion, it did not believe that the briefing material could be viewed as disparaging. Nothing in the briefing material was designed to disparage Qvar, only to point out the implications of the particular particle size and deposition characteristics of the preparation, as stated above, and supported by independent opinion.

No attempt was made by the representative to disparage Qvar.

Glaxo Wellcome therefore appealed against the ruling of a breach of Clause 8.1 in this respect.

Statement by the representative that patients and doctors might be confused at the change in dose

Glaxo Wellcome stated that the representative only said that confusion might arise if a prescription for CFC-free BDP was not accurately nor consistently written, so that an inappropriate inhaler was dispensed to the patient, one that was not bioequivalent to the inhaler currently being used. She made no comment regarding the appearance of Qvar in relation to previous 3M inhalers and did not say nor imply that Qvar looked and tasted different nor that this would cause confusion.

Statement in briefing document: 'The change in dose recommended in the Qvar SPC may be regarded as confusing for both the patient and the doctor.'

The patient

There were many aspects of the CFC-free transition which might be regarded as potentially confusing for the patient, regardless of the actual product and manufacturer.

Appearance of the inhaler

Glaxo Wellcome noted that patients became accustomed to the size, shape, colour and general appearance of their inhaler and changes to these had the potential to cause confusion. This confusion had been seen when patients had received different brands of generic inhaler containing the same medication. The prescribing of a new inhaler with a different appearance was clearly a potential cause of confusion for a patient. A recent article in Practice Nurse endorsed this view in stating:

'So, with non-compliance already an established problem in asthma treatment, the different shapes, weight, aerosol delivery and oropharyngeal impact of the new CFC-free inhalers, in addition to their distinctive tastes are clearly potential causes for further disruption to asthma management.'

The Department of Health had advised that the overall aim of the transition process should be that the change to CFC-free MDIs should be managed with the minimum of disruption to patients. It suggested that 'most patients will be able to transfer directly to a CFC-free version of their current MDI(s) and should not be changed to different drugs or delivery systems unless, as part of normal clinical management this is required for optimum disease control'. It was well known that even the smallest changes in medication might affect acceptability of therapy for patients. Any lack of confidence on the patients' behalf was likely to affect their compliance.

Dose of medication

The SPC recommended that well-controlled patients might be transferred simply by instructing them to take the same number of inhalations from the Qvar as they were taking from their CFC-BDP.

However, in a table in the SPC it was made clear that all patients could not necessarily be directly transferred to Qvar at the same number of doses.

The table recommended that patients receiving 1600 micrograms of CFC-BDP (generally taken as four puffs twice daily) were switched to the same number of puffs of Qvar (eg four puffs twice daily) as those receiving 2000 micrograms of CFC-BDP (which might be administered as five puffs twice daily). This prescribing of the same dose of Qvar for patients previously managed with different doses of CFC-BDP in different regimes would clearly seem to have the potential for confusion.

The doctor

Apart from the difficulties which might arise for the health professional who might have to explain changes in appearance, shape and colour of their new inhaler to a patient, further confusion might arise in the dosing recommendations.

The Qvar SPC provided a table recommending that for well-controlled patients the transition be made at 2:1 for some doses and at 2.5:1 for others. The different ratio recommendations were not made on clinical presentation of the patient, but purely on their previous dose of CFC-BDP. The comments made in the previous section relating to the difference in the number of puffs that might be prescribed when switching from CFC-BDP to CFC-free-BDP applied here as well.

For patients who were poorly controlled, the Qvar SPC recommended a change at the same microgram for microgram dose of BDP up to 800 micrograms daily. However there was little advice as to how to prescribe for patients who were poorly controlled at doses of CFC-BDP over 800 micrograms. It was simply suggested that the patient's current dose was doubled and this dose be converted to the Qvar dose according to the table.

However, following this advice would mean (for patients poorly controlled at doses of CFC-BDP over 800 micrograms) prescribing Qvar at doses above the recommended maximum dose of 800 micrograms per day. As about 20% of patients on BDP were taking doses in excess of 800 micrograms daily there was a large group in whom a potential for confusion regarding dose might arise with health professionals prescribing for these patients.

A symposium was held at Keele University recently to discuss the CFC-free transition. The meeting and its conclusions were reported in The Pharmaceutical Journal. In the summary of the meeting it was stated that 'One of the concerns for patient switches was the dosage adjustment required for Qvar'.

There were two conclusions drawn at the end of the meeting following an interactive session. They were as follows:

- 'The salbutamol switch is relatively straightforward – start the transition now
- The beclomethasone switch is significantly more complex. Bioequivalence is a concern. The majority of prescribers believe that they should delay the switch until there are two bioequivalent CFC-free metered dose inhalers.'

As there were dose differences between Qvar and CFC-BDP, there was also potential for confusion if doctors and pharmacists did not follow guidelines which discouraged switching patients back and forth between CFC-free and CFC-containing inhalers. Such switches might even happen inadvertently.

Thus Glaxo Wellcome believed that the statements made by the representative and in the briefing document were borne out by the change in appearance of the Qvar inhaler compared with previous beclomethasone inhalers and by the dosing recommendations as laid out in the SPC.

This view of the potential for confusion would appear to be borne out by opinions of doctors, nurses and pharmacists.

Glaxo Wellcome therefore appealed against the ruling of a breach of Clause 15.9 in this respect.

'By saying that the transition date was likely to be 2003 the representative had been ambiguous and inaccurate'

The letter from the pharmacist stated that the representative had said that the date for the transition was 2003. The representative had stated that she did not say this.

At the time of the interview Glaxo Wellcome had already launched its CFC-free inhaler containing salbutamol, it was therefore most unlikely that the representative would have given the impression that the transition would not take place until 2003. The representative tried to communicate that the transition was gathering pace but was unlikely to be complete until about the year 2003. This information appeared in all Glaxo Wellcome's briefing material and reflected the current generally accepted view of the timetable for the CFC-free transition.

This view was drawn from a report in Hansard, which stated that the transition to CFC-free inhalers was likely to take until the year 2003 or at the very least the end of 2002. Nothing had happened in the time since that statement was made to affect its accuracy.

Looking at the individual elements of the transition:

The transition to CFC-free salbutamol was likely to be complete by the early or middle part of the year 2000.

With respect to inhaled corticosteroids and other molecules the transition process was likely to take much longer and was unlikely to be complete until the year 2002 or 2003, including the MCA's recommended monitoring period.

There was a difference between the yearly review of CFC licences and the proposed date for the completion of the transition process.

Glaxo Wellcome acknowledged that the transition process was ongoing, and refuted the claim that the representative was making statements that were ambiguous or unbalanced.

Glaxo Wellcome therefore appealed against the ruling of a breach of Clause 15.2 in this respect.

Alleged use of 3M's brand name Qvar by the representative

Glaxo Wellcome noted that there was no allegation in the letter from the pharmacist that the representative used the name Qvar at any time. She only stated 'We talked about Qvar in some detail'.

The representative had stated that she used the phrase CFC-free BDP as advised in the briefing document. She stated that she would not remember using the word Qvar, but admitted, when faced with the charge, that she might have inadvertently lapsed into using the name in response to the pharmacist's use of the word. The representative was very experienced and was fully aware of the briefing material. In this it stated in bold and underlined that 'we strongly recommend that you do not refer to the brand name but use the generic title'.

The complaint regarding use of the name Qvar appeared to have been generated in the letter of complaint from 3M, rather than from any statement made by the pharmacist.

In view of the lack of any accusation by the pharmacist and the statement by the representative that she could not remember using the name Qvar, Glaxo Wellcome appealed against the ruling of a breach of Clause 7.10.

Glaxo Wellcome reiterated that all the discussions referred to took place within a five-minute period, at the end of a discussion about Flixotide Nebules.

APPEAL BY 3M HEALTH CARE

3M Health Care appreciated fully the difficulties that the Panel faced in dealing with this matter where much of the evidence relied upon 'who said what' and it accepted the rulings of the Panel with one exception. It wished to appeal the ruling of no breach of Clause 2.

This was not withstanding the seriousness with which a breach of Clause 2 was regarded. 3M did not accept that the seriousness of a breach of this clause was a consideration in judging whether any breach was committed.

The adjudications of the Panel on breaches of Clauses 7.10, 8.1,15.2 and 15.8 were clear evidence of the presence of inaccurate, ambiguous and misleading

competitor activity. In considering this and the size of the Glaxo Wellcome sales and marketing forces in the respiratory area, 3M felt that its suspicions of widespread misinformation about Qvar and the global and UK CFC transition strategies were well founded. It was entirely reasonable to assume that some thousands of calls had been made on GPs, secondary care specialists and health authority personnel disseminating the demonstrably ambiguous and inaccurate Glaxo Wellcome messages.

Glaxo Wellcome considered that the conduct of the representative in question was in line with the information in the briefing materials prepared by the parent company, Glaxo Wellcome. In 3M's view, at best, the representative's presentation of that briefing led to confusion for the pharmacist. At worst, faced with an apparent major divergence in the 'facts' pertaining to both Qvar and the United Nations Montreal Protocol on transition to non-CFC inhalers, it was entirely reasonable that the pharmacist's trust and confidence in the companies involved and the wider pharmaceutical industry had been undermined. Thus 3M continued to believe that a breach of Clause 2 had occurred.

In specifically examining the cause behind the evident confusion of the pharmacist, the Panel's ruling had already adjudged that the Glaxo Wellcome briefing materials were inaccurate with regard to the safety of Qvar and failed to comply with the Code. On the 'balance of probabilities' described in the Panel's ruling the representative was led into breaching Clause 15.2. Again the briefing materials led the representative into a breach of Clause 15.9 when she discussed the 'confusing' dosing information provided with Qvar. Finally the briefing materials led the representative into 'ambiguous and inaccurate' statements about the timing of the phase out of CFC inhalers.

In addition 3M was surprised to find that the representative was discussing doses of 3000-4000 micrograms of beclomethasone when the maximum recommended daily dose of Allen & Hanburys' Becloforte was 2000 micrograms.

In conclusion, misleading briefing documents appeared to have led this well respected and experienced representative to present inaccurate data which discredited Qvar in a serious way. Since the pharmacist had also been visited by 3M sales representatives, who would have given a factually correct presentation of the Qvar data, 3M was in no doubt that the pharmacist, faced with divergent views about something as fundamental as drug safety, would have reduced confidence in the veracity of the industry and it representatives.

Since the root cause of this complaint appeared to be failings in the company briefing materials, it was reasonable to assume that less experienced Glaxo Wellcome representatives might have made equally inaccurate and ambiguous statements. 3M therefore believed that the breaches of the Code by this representative were widespread amongst the large Glaxo Wellcome sales force.

Such a series of Code breaches could also undermine not only the clear messages conveyed by 3M representatives, but also the United Nations initiative to phase out CFCs and communications from the Department of Health on this matter. The widespread nature of the inaccurate information, in direct conflict with 3M's own communications, led 3M to request that the Appeal Board reconsider the possibility that a breach of Clause 2 had occurred in this case.

RESPONSE FROM GLAXO WELLCOME

Glaxo Wellcome said that the case had been made particularly difficult by the fact that the initial letter from the hospital pharmacist to 3M was written over two weeks after the visit by the Glaxo Wellcome representative and shortly before the pharmacist emigrated. Apart from the ruling of a breach of Clause 7.10, the rulings of breaches of the Code had been based largely upon the Glaxo Wellcome briefing materials. The letter of appeal from 3M concentrated on this fact.

From the outset, Glaxo Wellcome utterly refuted the suggestion by 3M, based on its 'suspicions', that Glaxo Wellcome was operating an orchestrated campaign aimed at 3M's Qvar, UK CFC transition and the United Nations.

Glaxo Wellcome stressed that it was entirely supportive of the efforts of the UK Government and the European Community in progressing CFC transition within the framework of the Montreal Protocol. Nothing in Glaxo Wellcome's materials was incompatible with that position. Glaxo Wellcome took its corporate responsibilities in this area very seriously and, as recommended in the Government's draft Transition Strategy, it had produced a range of informational materials for both patients and health professionals. All of Glaxo Wellcome's internal briefing materials and educational materials for health professionals and patients were written positively, as befitted a company that would have removed 25% of the UK's essential, medicinal use of CFCs when the transition of Ventolin (salbutamol) inhaler to Ventolin Evohaler was completed later this year.

Set against this, Glaxo Wellcome found some of 3M's tone, language and behaviour to be, at best, disingenuous, for example when suggesting that Glaxo Wellcome was undermining the clear messages conveyed by 3M representatives, the United Nations and the Department of Health. It was the policy of Glaxo Wellcome to comply with all legislation regarding CFC transition, while at the same time maintaining continuity of patient care and minimising the extra workload that transition inevitably created for healthcare professionals. As the largest supplier of medicines for respiratory diseases in the UK, with over one million patients using its metered dose inhalers, Glaxo Wellcome was affronted by 3M's accusations.

The statement used by Glaxo Wellcome's representative, in its briefing materials and even in the folder received by the hospital pharmacist, reflected the Government's position in clearly stating that 'It is unlikely the transition will be completed before 2003.' There was neither ambiguity nor inaccuracy in this statement. Both Hansard and more recently the draft UK Transition Strategy stated that transition for most

types of MDI was likely to occur within the next 3 years (ie up to the end of 2002). This clearly meant that a small minority of products was unlikely to be available in CFC-free form within that time frame. Glaxo Wellcome stated that the issue of 'exemptions' for the continued use of CFCs was related, but involved reviews with rolling datelines, as was clearly stated in its briefing materials and the folder for pharmacists.

Glaxo Wellcome found it remarkable and totally unreasonable that 3M should state in its letter that 'It is entirely reasonable to assume that some thousands of calls had been made on GPs, secondary care specialists and health authority personnel disseminating the demonstrably ambiguous and inaccurate Glaxo Wellcome messages'. In spite of 3M's assertions to the contrary, it was not in the interests of Glaxo Wellcome to have its representatives pro-actively raising the subject and names of products, such as 3M's CFC-free BDP, which might be viewed as potential competitors. Representatives were specifically instructed in the briefing materials, if drawn into conversation with customers, not to refer to 3M's CFC-free BDP by its brand name. Briefing materials relating to 3M's CFC-free BDP were only to provide up-to-date information to enable representatives to address succinctly any questions raised by customers, before they 'rapidly return to selling Serevent and Flixotide'. This was indeed the case in the interview which was the subject of the original complaint. After Glaxo Wellcome's representative had completed her discussion on Flixotide Nebules, the pharmacist, for her own benefit, set off a series of questions on CFC transition and then asked specifically about 3M's CFC-free BDP.

The Panel's ruling on the possibility of confusion over dosing concentrated on the possible impact on the patient. This was probably because the representative remembered discussing the possible problems that might arise when different BDP inhalers, e.g. Becotide, generic beclomethasone and Qvar, which were not bio-equivalent and should not be interchanged, were prescribed inconsistently. The letter of appeal from 3M was somewhat confused when it referred to the representative having discussed doses of 3000-4000 micrograms of beclomethasone. There was never any suggestion that she had had such a discussion. This item came near to the end of Glaxo Wellcome's letter when it was expressing its view that the instructions in the Qvar SPC for transferring patients with poorly-controlled asthma to Qvar could possibly result in confusion for the prescriber. Glaxo Wellcome still believed that to be the case, as expressed in its original response.

Where the briefing documents referred to the systemic absorption of 3M's CFC-free BDP, Glaxo Wellcome believed that they were factual and not misleading. Any safety concerns regarding inhaled corticosteroids were related to their effects after systemic absorption. Section 5.2 of the SPC for Qvar clearly stated that the rationale for the investigation of lower total daily doses was related to the fact that there was twice the systemic absorption of corticosteroid with Qvar compared with CFC-BDP inhalers. When the Glaxo Wellcome briefing materials were written, 3M was promoting Qvar as 'improving the therapeutic ratio' and having 'no clinically significant effects on adrenal function' compared with conventional CFC-BDP formulations. In an environment where the vigilance of prescribers of inhaled corticosteroids was being encouraged (Current Problems in Pharmacovigilance, May 1998), Glaxo Wellcome thought that it was appropriate to express caution, which it did in its briefing materials. It believed that it had been vindicated.

When Glaxo Wellcome submitted its response to the original complaint from 3M it did so after requesting a copy of the most recent SPC for Qvar. On 23 February 1999 it received a copy of the Qvar SPC (0398/QV/009/002), partially revised in September 1998, which it presumed had been used by 3M when it framed its complaint. 3M referred to it in point 2, regarding the safety of Qvar and point 5, referring to the Glaxo Wellcome representative being unlikely to be in possession of the Qvar SPC.

As the result of 3M's appeal Glaxo Wellcome recently requested a further copy of the SPC for Qvar. It had on 4 May 1999 received the latest Qvar SPC (0199/QV/009/028) – partially revised in December 1998. Glaxo Wellcome was somewhat surprised to read a change in Section 5.1 where 'without significant systemic activity' had been replaced by 'with fewer systemic effects than oral steroids'. A not insignificant amendment.

3M's original complaint had been made after the December 1998 revision of the SPC and referred to an event which had also taken place after the December revision. This suggested that if 3M was supplying an out-dated SPC in response to external requests, it was likely that its own representatives were using the old SPC with customers and that it had used this old text to substantiate some of the statements in its complaint. Glaxo Wellcome took this matter seriously, especially as it involved a statement on the safety of the product. This was at odds with the claim from 3M that its representatives had been giving a 'factually correct presentation of the Qvar data'. The March 1999 issue of Current Problems in Pharmacovigilance had re-emphasised the need to show the same levels of concern with Qvar as with other inhaled corticosteroids. Glaxo Wellcome felt that it was most unfair of 3M to accuse Glaxo Wellcome of expressing what was no more than a reasonable level of concern in its briefing materials, when 3M had amended the Qvar SPC for the same reasons.

Glaxo Wellcome denied that its representative presented any inaccurate data to the pharmacist or that its briefing materials were misleading. The data on 3M's CFC-free BDP were all taken from studies carried out by 3M, which had either been published or presented at meetings. Glaxo Wellcome stated that to have accused its representative of having reduced the pharmacist's confidence in the pharmaceutical industry did not fit well with a company whose representatives were possibly using out-dated SPCs at the time.

In conclusion, Glaxo Wellcome strongly believed that it had not breached Clause 2 of the Code and that

Glaxo Wellcome and its representative had behaved in an ethical and professional manner throughout.

FURTHER COMMENTS FROM 3M HEALTH CARE

3M said that the basis of its appeal and its opinion that the activities of Glaxo Wellcome constituted a breach of Clause 2 of the Code was that the Panel's initial ruling clearly revealed evidence of inaccurate, ambiguous and misleading representative briefing materials which, having been distributed widely, demonstrated an unequivocal campaign of misinformation against Qvar. For briefing material to be prepared in this depth could only be for the purpose of combating a competitor and inaccurate statements must therefore be disparaging to that competitor product and company.

The emotive tone of Glaxo Wellcome's response to 3M's appeal struck 3M as an attempt to utilise its reputation and standing to quell 3M's claims of a breach of Clause 2 in the absence of any convincing arguments in Glaxo Wellcome's defence and in the face of compelling evidence against it.

3M's response would focus on the facts and provide further evidence that supported its case. 3M would like to provide the following additional information to demonstrate the extent of the Glaxo Wellcome activity in this case:

1 Key issues for prescribers. Research and motivations to prescribe inhaled steroids and the importance of safety to the prescriber.

In 1996 a market research company undertook 40 in-depth interviews with 10 chest physicians, 15 GPs, 10 practice nurses and 5 hospital asthma clinic nurses to identify for 3M the key issues in deciding asthma therapy.

In the profile of the ideal inhaled steroid therapy, systemic side effects came up as a key issue. Promotional activity in this sensitive area would be of great importance to prescribers. Doctors also indicated that those companies that had an established presence in the inhaled steroid field would have greater credibility.

3M believed Glaxo Wellcome was fully aware of these issues and selected this area to undermine confidence of the prescriber in Qvar.

2 Relative organization size and commercial motivation for GW

Glaxo Wellcome recently stated at an open meeting at a health authority that it had 500 representatives and 100 nurses working on respiratory products in the UK. It was therefore obvious that the Glaxo Wellcome activities of which 3M complained might have, indeed, been repeated in some thousands of representative calls. Glaxo Wellcome pharmaceutical sales in the UK (reference IMS Feb 99) were approximately £583 million with respiratory sales of £401 million against 3M's pharmaceutical sales of £28 million. It was some 20 times larger and therefore its voice in the market place was much greater than that of 3M. 3M would suggest with such a large share of respiratory business, threatened by CFC-free alternatives, that Glaxo Wellcome had a very strong interest in maintaining its market share. 3M now felt that there was ample evidence of a widespread misinformation campaign.

3 Reports that indicate how widespread the misinformation campaign was from Glaxo Wellcome

3M had taken the following extracts from its own and its contract representatives/sales management's monthly reports. These comments were made under the section the company had in these reports for 'competitor activity' and were direct quotes:

'[four representatives named] are finding customers continuing to bring up the alveoli problems issue. Allen & Hanburys is using this without evidence and as a hypothesis.'

'Small particles and alveolar deposition, and minimum effective particle size. This point came from …… and……; there seems to have been some discussion about work being done by Allen & Hanburys on the minimum sized effective particles in this area.'

'Professor … has got concerns that the particles are so small they may adversely affect the alveoli. This is a line that has been mooted at Glaxo Wellcome meetings and seems to be a strategy of the company.'

'Allen & Hanburys is definitely going for the safety profile of Qvar…'

'Allen & Hanburys has recently put a new sales force on the road selling Seretide. It is also continuing to focus on doubts about the safety aspects of Qvar.'

- Glaxo Wellcome Associate Medical Director – during a meeting on CFC transition at Keele University organised by the West Midlands NHS regional office on 21 January 1999 (based on a report from 3M attendee)

The doctor '…from Glaxo Wellcome commented that Qvar was deposited at the alveolar level where there would be no efficacy and where the drug would be rapidly absorbed into the systemic circulation with the possible implications on systemic safety'.

In addition to this the doctor had repeatedly made the same comments during poster discussions at international meetings throughout 1998 and 1999. (European Respiratory Society '98, World Asthma Meeting '98 and American Thoracic Society '99).

A Safety of Qvar

3M referred to statements in Glaxo Wellcome's briefing material that 'changing the particle size of 3M's CFC-free BDP may have implication for the safety profile of the product' and that 'particles… were deposited in the alveoli creating the potential for greater systemic absorption and therefore concern over safety'. Glaxo Wellcome had not provided any evidence to support its claims. Nor did 3M accept that the obfuscation in the Glaxo Wellcome response, referring to recent changes in the Qvar SPC, was any justification for its statements.

3M stated that the correct version of its SPC had been used by the company at all times. This amendment was made in consultation with the MCA to ensure consistency across all prescribing information within the inhaled steroid class. Nothing in the Qvar SPC referred to any decrease in safety when compared with other members of the inhaled steroid class. To the contrary, the current MCA approved Qvar SPC stated 'At a daily dose of 800 micrograms Qvar, suppression of urinary free cortisol was comparable with that observed with the same dose of CFC-containing beclomethasone dipropionate, indicating a wider safety margin, as Qvar was administered at lower doses than the CFC product' [underlining added]. The removal of the statement 'without significant systemic activity' was at the request of the MCA as part of its campaign to ensure that health care professionals continued to be vigilant when prescribing any inhaled steroid.

3M found the clear evidence of Glaxo Wellcome's comments on Qvar's safety in its briefing material disparaging, inaccurate and malicious. That 3M had had widespread feedback that Glaxo Wellcome was making these claims throughout the UK and at international medical meetings, attested to its activities aimed at discrediting Qvar, 3M and therefore the industry. 3M considered that the tone of the response to its complaint and to its subsequent appeal and the apparent lack of contrition indicated to 3M that only a finding of a breach of Clause 2 would make Glaxo Wellcome appreciate the extent and effect of this campaign.

To provide further evidence of the safety of Qvar 3M referred to two recent publications: Inhaled corticosteroids for adult asthma. Impact of formulation and delivery device on relative pharmacokinetics, efficacy and safety. R Shaw, Respiratory Medicine 1999, and, Long term safety of BDP extrafine aerosol. Cohen *et al*. Results of 12 month safety study. Poster presented at the American Thoracic Society; AJRCCM 1999. In both of these papers, the continued safety of beclomethasone as Qvar was well supported.

B Confusing dosing

3M noted that Glaxo Wellcome again provided no evidence to support its claims that the dosing schedule for Qvar was confusing. 3M referred to a randomized open study performed as part of a multicentre, 1 year safety study of Qvar, at half the daily dose compared with CFC-BDP, as evidence to support the ease of switch and acceptance. 354 asthma patients who currently used inhaled steroid (77% of whom used CFC-BDP) were randomized to CFC-free BDP and 119 to CFC-BDP. During the run in phase of the study all patients completed a questionnaire about their current CFC inhaler. After 1 month of treatment with Qvar 267 patients then completed the same questionnaire on their Qvar inhaler, having been switched from CFC at half the dose.

The results showed that 96% of patients switching found it easy or very easy, 76% found it very easy. These data did not appear to support any conclusions that switching to Qvar was difficult or confusing for patients. The Panel's ruling had already pointed out that switching to Qvar was facilitated by patients remaining on then same number of puffs from their inhaler but receiving a lower strength inhaler. Again, there were no data to suggest that prescribers found this concept at all confusing.

C Date of transition

3M said that it concurred with previous conclusions but noted that the recent evidence Glaxo Wellcome brought to bear was the consultation document just re-released. It used the same words as in the draft released in 1998 'that the transition process is likely to be complete in the next 3 years'. 3M suggested that this same statement appearing in such a policy a year apart indicated there was no certainty. It was also clear from recent EU correspondence that CFCs would not be made available for salbutamol for the year 2000 allocations.

Glaxo Wellcome also failed to point out one of the key principles outlined in this document to guide CFC phase out. This was 'all those involved will promote transition'. It appeared to 3M that Glaxo Wellcome was selecting the circumstances, based on its own product availability, when it supported or refuted this principle.

Glaxo Wellcome had not provided further evidence to support a date of 2003 and 3M maintained this was inappropriate.

D Brand name

The representative concerned appeared to acknowledge she might have used this brand name. 3M again saw no additional evidence to support the appeal against the Panel's ruling on this point.

In conclusion, 3M believed that there was indisputable evidence of a campaign of misinformation by Glaxo Wellcome against 3M and its product Qvar and that the inaccurate, ambiguous and misleading briefing document from Glaxo Wellcome was merely an example of more widespread activity. Furthermore, Glaxo Wellcome had provided no convincing evidence to support any appeal against the original rulings and the intimidating nature of response indicated its lack of respect for opinions other than its own. This lack of contrition by a UK industry giant, and the malicious campaign against a competitor, in an attempt to damage the reputation of both Qvar and 3M, must, in 3M's view, be subject to serious censure by the Authority. Thus 3M alleged that, notwithstanding the seriousness of the offence, a breach of Clause 2 had taken place.

APPEAL BOARD RULING

With regard to alleged comments concerning long-term safety problems, the Appeal Board noted Glaxo Wellcome's submission that there was potential for systemic side effects at both licensed and unlicensed doses of Qvar. In the opinion of the Appeal Board the briefing material would raise doubts regarding the safety profile of Qvar in the minds of the

representatives. The Appeal Board considered that overall the briefing material was unbalanced because it failed to convey that at licensed doses there was no evidence that beclomethasone deposition from Qvar led to long-term safety problems. The Appeal Board upheld the Panel's ruling of a breach of Clause 15.9 of the Code. The appeal on this point was thus unsuccessful.

The Appeal Board acknowledged that it was difficult to determine precisely what the representative had said regarding long-term safety problems. However, given that the representative's briefing material was itself in breach of the Code the Appeal Board considered it inappropriate to make a ruling upon the conduct of a representative who had simply been following the briefing material. The Appeal Board ruled no breach of Clause 15.2 of the Code. The appeal on this point was therefore successful.

The Appeal Board considered that the briefing material was also disparaging and upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal in this regard was thus unsuccessful.

With regard to the allegation concerning the dosing of the products, the Appeal Board noted that there were differences between CFC-BDP and Qvar but, contrary to the impression created by the briefing material, did not consider that these were such as to cause confusion. The Appeal Board upheld the Panel's ruling of a breach of Clause 15.9 of the Code. The appeal in this regard was therefore unsuccessful.

With regard to the date for changing to CFC-free inhalers, the Appeal Board noted that the representative denied making the statement in question and noted the statements in the briefing material and Hansard regarding the expected transition date. The Appeal Board considered that given the Glaxo Wellcome CFC-free inhaler containing salbutamol had already been launched it was unlikely that the representative would have created the impression that the transition would not take place until the year 2003. The Appeal Board ruled no breach of Clause 15.2 of the Code. The appeal in this regard was successful.

With regard to the alleged use of 3M's brand name, Qvar, the Appeal Board noted that whilst the briefing material strongly recommended that representatives did not refer to Qvar by brand name it omitted to mention that use of other companies' brand names was prohibited under Clause 7.10 of the Code. However the Appeal Board considered that it was not possible to determine precisely what had been said by the representative and ruled no breach of Clause 7.10 of the Code. The appeal was therefore successful on this point.

The Appeal Board noted that it had had the benefit of seeing Glaxo Wellcome's briefing material referring to 3M's CFC-free BDP whereas 3M had not. The briefing material contained the company's rebuttal of 3M's claims for Qvar. The Appeal Board noted from some slides used by Glaxo Wellcome at representatives' briefing meetings that Regional Medical Advisers were to proactively discuss with key opinion leaders the clinical data on Qvar and 'Inadequacy and issues with 3M evidence'. The Appeal Board noted its rulings above and considered that overall the representatives' briefing material sought to cast unjustified doubts about Qvar which was the only CFC-free BDP available. The Appeal Board considered that Glaxo Wellcome's actions brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The appeal on this point was thus successful.

Complaint received **18 February 1999**

Case completed **17 June 1999**

RESEARCH ETHICS COMMITTEE CHAIRMAN v SERVIER

Promotion of Natrilix SR

The chairman of a research ethics committee complained about a 'Dear Doctor' letter headed 'HYVET Hypertension in the very elderly trial' with the subheading 'The first morbidity/mortality trial in very elderly hypertensives' which he had received from Servier. The letter stated that Natrilix SR 1.5mg (indapamide) had been selected as the drug treatment for the HYVET study and referred to, and had been accompanied by, an article from Prescriber which set out the aims of the HYVET study. It was explained that the active treatment group would receive Natrilix SR, with Coversyl (perindopril, also marketed by Servier) added later if needed to achieve target blood pressure. Also the subject of complaint was a Natrilix SR leaflet, the front of which listed the key features of the design and objectives of the HYVET study.

The complainant said that the letter and the leaflet made a clear association between the HYVET study and the 'choice' of indapamide. To the casual reader the impression was that indapamide had special properties that led to its selection for the study and was therefore of special benefit in elderly hypertensives over other diuretic agents. While it was true that this proposition was not explicit, the clear linking of the trial with the medicine being promoted left little doubt that this association was being suggested. The choice of indapamide reflected no more than the willingness of Servier to co-sponsor the trial and not any superiority of indapamide over any other diuretic, such as the much cheaper bendrofluazide.

The Panel noted that no reason was given in the 'Dear Doctor' letter for the choice of Natrilix SR. The article in Prescriber gave a detailed rationale for the chosen treatments. It stated that diuretics had been shown to be effective in patients aged 60-80 years old. Indapamide SR produced a smooth absorption with a lower peak concentration than the instant release preparation which translated into a long hypotensive effect and less disturbance of potassium balance and other metabolic effects. Perindopril was to be added later to achieve a target systolic blood pressure of less than 150mmHg and a diastolic of less than 80mmHg. The article stated that the study was supported by the British Heart Foundation and Servier. The leaflet included a double page headed 'Rationale for choice…' the reasons given were that Natrilix SR was as effective as amlopidine, it was a well tolerated, low dose diuretic and was suitable for hypertensive patients with a wide range of co-existing diseases and concomitant medications.

The Panel did not accept that readers of the material would conclude that the selection of Natrilix SR meant that it was of special benefit in elderly hypertensives over other diuretics. In the Panel's view the reason for the choice of indapamide was more than merely the willingness of Servier to co-sponsor the trial. The Panel ruled no breach of Clause 7.8 of the Code.

The chairman of a research ethics committee complained about a 'Dear Doctor' letter headed 'HYVET Hypertension in the very elderly trial' with the subheading 'The first morbidity/mortality trial in very elderly hypertensives' which he had received from Servier Laboratories Ltd. The letter, from a group product manager, stated that Natrilix SR 1.5mg (indapamide) was selected as the drug treatment for the HYVET study. On the reverse was prescribing information for Natrilix SR and for Coversyl (perindopril – also marketed by Servier). The letter referred to, and had been accompanied by, an article from Prescriber, 5 September 1998, which set out the aims of the HYVET study. It was explained that the active treatment group would receive Natrilix SR, with Coversyl added later if needed to achieve target blood pressure.

Also the subject of complaint was a four page Natrilix SR leaflet (ref 99NXIC101), the front of which listed the key features of the design and objectives of the HYVET study. The middle two pages of the leaflet were headed 'Rationale for choice…' and set out some clinical properties of Natrilix SR.

COMPLAINT

The complainant said that the 'Dear Doctor' letter and the leaflet made a clear association between the HYVET study and the 'choice' of indapamide. To the casual reader, the impression was that indapamide had special properties that led to its selection for the study and was therefore of special benefit in elderly hypertensives over other diuretic agents.

While it was true that this proposition was not explicit, the clear linking of the trial with the medicine being promoted left little doubt that this association was being suggested.

The complainant stated that because the ethics committee had been in the position of reviewing this trial for ethical approval, it was aware that the choice of indapamide reflected no more than the willingness of Servier to co-sponsor the trial and not any superiority of indapamide over any other diuretic, such as the much cheaper bendrofluazide. This was hardly privileged information – the same conclusion could very reasonably have been reached by any interested, critical observer.

The committee was also aware, of course, that at the time of this mailing the trial had not even received ethical approval – a fairly crucial decision in whether it went ahead. (This too was not privileged information, as all the committee's approvals were in the public domain.)

The complainant stated that there could be no objection to publishing details of a trial before it was approved as large multi-centre studies needed to recruit investigators quickly. Such details were published in the case of the HYVET study in Prescriber on 5 September 1998. This was not the issue.

The complainant did not know what the Authority's powers were to enforce acceptable standards of advertising, but in the view of the members of his committee the 'Dear Doctor' letter and the leaflet fell below acceptable ethical standards. The complainant had copied his letter of complaint to Servier.

RESPONSE

Servier stated that the complainant referred to three items of promotional material:

- 'Dear Doctor' letter from Servier group product manager;
- article on HYVET study from Prescriber, 5 September 1998;
- leaflet 99NXIC101.

The first two items were mailed together to selected general practitioners, hospital doctors and drug information pharmacists in October 1998. The leaflet was distributed to GPs and hospital doctors by representatives from September to December 1998. Servier understood that there was no complaint about the Prescriber article and would not address this further.

The HYVET study was the first morbidity/mortality trial in very elderly hypertensives. It was an international study with over 2,000 patients to be recruited from 18, mainly European, countries.

Servier agreed that the promotional material made an association between the study and Natrilix SR. It also agreed that the impression given was that Natrilix SR was selected for the study – in fact this was clearly stated.

Servier strongly disagreed with the suggestion that the selection of Natrilix SR was solely related to the funding of the study, rather than to relevant clinical properties of the medicine. These properties were stated in the leaflet, the HYVET study protocol and the Natrilix SR summary of product characteristics. They included: full 24 hour hypotensive effect; efficacy in elderly hypertensives at least equivalent to the calcium channel blocker amlodipine 5mg and hydrochlorthiazide 25mg; no interference with carbohydrate metabolism even in diabetic hypertensive patients; no interference with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol; and reduction of left ventricular hypertrophy.

These properties were particularly relevant given that the intended patient population was elderly (≥80 years) and likely to have significant co-existing disease. It was primarily for these reasons that Natrilix SR was selected for the HYVET study.

Servier considered that the property claims for Natrilix SR suggested by this promotion were fully substantiated and did not consider these promotional pieces misleading. Servier therefore denied any breach of the Code.

PANEL RULING

The Panel noted that it was true to state that Natrilix SR 1.5mg had been selected for the HYVET study. No reason was given in the 'Dear Doctor' letter for the choice of Natrilix SR. The article in Prescriber gave a detailed rationale for the chosen treatments. It stated that diuretics had been shown to be effective in patients aged 60-80 years old. Indapamide SR produced a smooth absorption with a lower peak concentration than the instant release preparation which translated into a long hypotensive effect and less disturbance of potassium balance and other metabolic effects. Perindopril was to be added later to achieve a target systolic blood pressure of less than 150mmHg and a diastolic of less than 80mmHg. The article stated that the study was supported by the British Heart Foundation and Servier. The leaflet included a double page headed 'Rationale for choice…' the reasons given were that Natrilix SR was as effective as amlodipine, it was a well tolerated low dose diuretic and was suitable for hypertensive patients with a wide range of co-existing diseases and concomitant medications.

The Panel considered that the audience would be familiar with the concept of companies sponsoring trials which included their products. The Panel noted that the leaflet and the Prescriber article referred to the clinical properties of Natrilix SR which had contributed to its selection. The benefits of Natrilix SR were not compared with those of any other diuretic.

The Panel did not accept that readers of the material would conclude that the selection of Natrilix SR meant that it was of special benefit in elderly hypertensives over other diuretics. In the Panel's view the reason for the choice of indapamide was more than merely the willingness of Servier to co-sponsor the trial. The Panel ruled no breach of Clause 7.8 of the Code.

Complaint received **24 February 1999**

Case completed **21 April 1999**

CASE AUTH/846/3/99

GENERAL PRACTITIONER v GLAXO WELLCOME

Seretide news item on Radio 4

A general practitioner complained about an item on the Radio 4 Today programme relating to Allen & Hanburys' Seretide (salmeterol/fluticasone). The complainant said that this had been initiated by Glaxo Wellcome to promote its product in the guise of a news item. He wished to express his disquiet about the promotion of new prescription only medicines to members of the public by means of radio interviews.

The Panel noted that the doctor interviewed on the radio programme had been an eminent, independent physician expressing his own views. He was chairing the media launch for Seretide and had agreed to make himself available for radio interviews. Detailed briefing notes had been prepared for each of the speakers at the launch. The notes for the physician in the Today interview included a number of messages about Seretide such as 'Seretide helps achieve highly effective asthma control', 'Patients poorly controlled on 400mcg of beclomethasone or equivalent are going to benefit from Seretide' and 'Seretide is a considerable step forward in asthma management'. The briefing notes also stated that the launch was an exciting milestone marking the introduction of Seretide which was a significant step forward in the management of asthma.

The Panel noted that some of what the physician had said in the interview was included in the Seretide press pack. In this regard the Panel noted the statements about convenience of the combination and the fact that it was cheaper than the two separate inhalers and would be cheaper for patients who paid for their prescriptions. In the radio interview the physician stated that Seretide gave better control of asthma than each medicine used separately. The press release stated that Seretide was at least as effective as salmeterol and fluticasone given through two inhalers at improving lung function and controlling symptoms across a wide range of doses. In response to a suggestion in the interview that patients should ask for the new inhaler because for many people it was going to be an advance, the physician agreed as he thought that it was going to make control of asthma much easier for the patient and for the GPs who were treating asthma.

The Panel considered that although the doctor interviewed was an independent physician, he had been briefed by the company and the company had facilitated his appearance on the Today programme. It was therefore not possible for Glaxo Wellcome to completely disassociate itself from what he had said during the interview. If Glaxo Wellcome was not responsible then the effect would be for companies to use independent experts as a means of avoiding the restrictions in the Code.

The Panel acknowledged that the physician was expressing his own opinion but considered that the material provided by Glaxo Wellcome was too positive and more suited to promoting Seretide than providing factual, balanced non promotional information as required by the Code. A breach of the Code was ruled. The Panel considered that Glaxo Wellcome had in effect advertised a prescription only medicine to the general public and therefore also ruled breach of the Code in that regard.

A general practitioner complained about an item on Radio 4 relating to Allen & Hanburys' Seretide (salmeterol/fluticasone). Seretide was indicated in the regular treatment of asthma where use of a combination (bronchodilator and inhaled corticosteroid) had been found to be appropriate.

COMPLAINT

The complainant said that he wished to express his disquiet about the promotion of new presentations for prescription only medicines via radio interviews to members of the public. The latest offender was Glaxo Wellcome which initiated an item on the Radio 4 programme Today on Monday, 1 March, promoting its product Seretide in the guise of a news item. The complainant said that he would be grateful for any action the Authority could take to prevent any recurrence of such an unethical event.

RESPONSE

Glaxo Wellcome UK Limited said that Seretide was launched on 1 March. The interview under investigation took place between one of the programme's presenters and an eminent and independent physician, well respected by his peers. It was a short interview and a transcript was provided.

Glaxo Wellcome noted that the complainant had expressed disquiet that Seretide was being promoted under the guise of a news item and regarded this as unethical, although he did not make further specific accusations. Glaxo Wellcome was of course very aware of the potential problems that radio interviews around the launch of a new product could raise. Indeed, it would be recalled that in 1998, in Case AUTH/678/2/98, Glaxo Wellcome had lodged a complaint about the launch of a new product. In the ruling on the case, in which it had been suggested that patients might wish to visit their doctor and request the new treatment, a breach of Clause 20.2 of the Code was ruled. The media information pack and the video newsreel provided by the company concerned were considered not to be in breach of Clauses 20.1 or 20.2 of the Code.

Glaxo Wellcome considered that this launch was indeed a news item, as did the editor of the Today programme, and one considered important by many leading experts in respiratory medicine. The specific interview complained of took place live early on Monday morning, 1 March. No member of Glaxo Wellcome was present in the studio at the time of the interview. The whole tenor of the interview was one of excitement and enthusiasm for this new product, which reflected the physician's genuine views.

The physician had already agreed to chair the media launch for Seretide, planned for 1 March, and also to

make himself available for radio interviews. He was briefed on the technical aspects of the medicine and the results of the clinical trials.

The physician was also made aware of what the company was, and was not, allowed to say, and that he would be seen to be acting on behalf of the company in any such interview, albeit as an independent spokesperson. Glaxo Wellcome provided details from its public relations agency detailing the logistics of how the physician was approached for this interview. The briefing material that it sent to him was provided, which Glaxo Wellcome considered fully conformed to the requirements of the Code.

Glaxo Wellcome briefed journalists both from newspapers and radio, prior to any interviews taking place, and it provided an example of its media information pack. It was then up to the journalists themselves, if interested, to request interviews with either company representatives or independent experts. The Today programme subsequently requested the interview with the physician in question.

The various company personnel involved in the launch of this product to the media and more widely, to prescribing doctors, had all been trained specifically on the Code. They were fully aware of the issues of advertising to the public and of the ruling made last year, and of the potential pitfalls when a new product, that might cause excitement in the public arena, was under discussion. There was considerable effort paid internally therefore to ensure that in briefing doctors, both verbally and with written material, these guidelines were adhered to. Great attention was paid to ensuring that this briefing material remained strictly within the Code. Ultimately however, especially in live interviews, the company had no direct control over what the presenter asked or how an independent expert responded, as in this case.

In conclusion therefore Glaxo Wellcome denied any breach of Clauses 20.1 or 20.2 of the Code.

PANEL RULING

The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company or its agent to the journalists. When interviews with company representatives were reported a judgement would be made on what the representative had said.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel noted that the interview was between one of the presenters of the Today programme and a physician. The Panel noted Glaxo Wellcome's submission that he was an eminent and independent physician. He was chairing the media launch for Seretide and had agreed to make himself available for radio interviews.

The Panel noted that at the media launch of Seretide there were a number of independent speakers delivering short presentations on various aspects of asthma management and a presentation from a member of the company's medical department. Glaxo Wellcome's public relations agency had briefed all the speakers in advance of the media launch stressing that presentations should not be overly promotional and that their views were their own. After hearing the interview with the physician, the agency commented that it had been overly positive about Seretide but those were his views and he certainly was not briefed that way. Neither the agency nor Allen & Hanburys had any idea of the responses he would make.

The Panel noted that detailed briefing notes had been prepared for each of the speakers at the media launch. The notes for the physician included a number of messages about Seretide such as 'Seretide helps achieve highly effective asthma control', 'Patients poorly controlled on 400mcg of beclomethasone or equivalent are going to benefit from Seretide' and 'Seretide is a considerable step forward in asthma management'. The briefing notes also stated that the launch was an exciting milestone marking the introduction of Seretide which was a significant step forward in the management of asthma.

The Panel examined the press pack. Journalists from pharmaceutical and medical publications had been invited to the launch as had journalists from the lay media, newspapers, women's magazines and radio stations, as well as freelance journalists. Press packs had been provided to those attending the launch and sent to a number of invitees. A number of documents were included in the press packs; some discussed the prevalence, diagnosis, treatment and management of asthma in general terms and others discussed Seretide. The press release was headed 'Seretide – Great Control for Asthma Sufferers in One Inhaler'. The press release referred to Seretide as a '…new advance in asthma management' and bringing '…new control and fresh hopes to the UK's 3.5 million asthma sufferers'. It also stated that for the first time asthma sufferers would be able to receive comprehensive control of their asthma from just one inhaler. The press release quoted the physician as saying 'Seretide is an evolutionary milestone in the treatment of asthma. It will help to ensure that patients receive the important therapies that they need to keep their asthma under control in one convenient inhaler'.

The Panel noted that some of what the physician had said in the interview was included in the press pack. In this regard the Panel noted the statements about convenience of the combination and the fact that it was cheaper than the two separate inhalers and would be cheaper for patients who paid for their prescriptions. In the radio interview the physician stated that Seretide gave better control of asthma than each medicine used separately. The press release stated that Seretide was at least as effective as

salmeterol and fluticasone given through two inhalers at improving lung function and controlling symptoms across a wide range of doses. In response to a suggestion in the interview that patients should ask for the new inhaler because for many people it was going to be an advance, the physician agreed as he thought that it was going to make control of asthma much easier for the patient and for the GPs who were treating asthma.

The Panel noted that the physician in question had agreed to chair Glaxo Wellcome's launch meeting for Seretide and to give radio interviews. The Panel considered that although he was an independent physician he had been briefed by the company and the company had facilitated his appearance on the Today programme. It was therefore not possible for Glaxo Wellcome to completely disassociate itself from what he had said during the interview. If Glaxo Wellcome were not responsible then the effect would be for companies to use independent experts as a means of avoiding the restrictions in the Code.

The Panel acknowledged that the physician was expressing his own opinion but considered that the material provided by Glaxo Wellcome was too positive and more suited to promoting Seretide than providing factual, balanced non promotional information as required by Clause 20.2 of the Code. A breach of Clause 20.2 of the Code was ruled. The Panel considered that Glaxo Wellcome had in effect advertised a prescription only medicine to the general public and therefore ruled breach of Clause 20.1 of the Code.

Complaint received **2 March 1999**

Case completed **11 May 1999**

CASE AUTH/847/3/99

LILLY v WYETH

Premique journal advertisements

Lilly complained about Wyeth's promotional campaign for Premique (conjugated oestrogens and medroxyprogesterone), referring to two particular journal advertisements representative of the campaign.

One advertisement was headed 'Premique Period-free HRT' and the other '54 and period-free'. Lilly stated that the term 'period' was colloquially applied to the normal flow of blood that occurred during menstruation. However, the advertisements clearly tried to differentiate Premique from other forms of hormone replacement therapy (HRT) and in so doing inferred that its effect on the uterus was similar to medicines like Evista (Lilly's product raloxifene). It was well established that women given cyclical HRT would get a scheduled vaginal bleed; however this was clearly referred to as a withdrawal bleed and not a period. By referring to Premique as being period-free HRT, Wyeth was implying to any prescribing physician that it was bleed free. Vaginal bleeding was included in the side effects section of the data sheet for Premique and occurred in 27% of women receiving the generic components of the drug in a clinical study. Lilly alleged that to state that Premique represented period-free HRT was an all-embracing claim that was exaggerated, misleading and inaccurate and clearly in breach of the Code.

The Panel accepted that the words 'menstruation' and 'period' were commonly used by clinicians and by patients when referring to the bleed associated with HRT. In the Panel's view it would be unusual for a withdrawal bleed to be referred to in its correct physiological terms. A number of continuous combined HRT preparations were promoted using the phrase 'period-free HRT' or similar. The Panel did not consider that the phrase 'period-free HRT' was in breach of the Code as alleged. There was no claim that Premique was bleed-free.

Lilly also alleged that one of the advertisements did not include prescribing information. It was too big to be an abbreviated advertisement because, although an internal box fell just within the permitted maximum size of 420sq cm, the rest of the page was blank and so the whole of the page had to be counted. Wyeth had accepted this and the Panel ruled that there had been a breach of the Code.

Eli Lilly and Company Limited complained about Wyeth Laboratories' promotional campaign for Premique (conjugated oestrogens and medroxyprogesterone acetate) referring to particular advertisements which were representative of those which had appeared in many publications.

1 Period-free HRT

Advertisement Z755020/0597 was headed 'Premique Period-free HRT' and Z753660/1095 was headed '54 and period free.'

COMPLAINT

Lilly stated that the term 'period' was colloquially applied to the normal flow of blood that occurred during menstruation. However, this advertisement clearly tried to differentiate Premique from other forms of hormone replacement therapy (HRT) and in so doing inferred that its effect on the uterus was similar to medicines like Evista (Lilly's product raloxifene). It was well established that women given cyclical HRT would get a scheduled vaginal bleed; however this was clearly referred to as a withdrawal bleed and not a period. According to the above definition, postmenopausal women did not get periods. Premique was a form of continuous combined HRT and by referring to the product being period-free HRT, Wyeth was implying to any prescribing physician that it was bleed-free.

Vaginal bleeding was included in the side effects section of the data sheet for Premique and occurred in 27% of women receiving the generic components of the drug in a clinical study. Lilly alleged that to state that Premique represented period-free HRT was an all-embracing claim that was exaggerated, misleading and inaccurate and clearly in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Wyeth said that the phrase 'period-free HRT' had been used by all the manufacturers of continuous combined HRT in all their advertising for a number of years. Wyeth was not aware of any previous complaints against the use of this phrase and did not consider its use to be misleading, or in breach of Clauses 7.2 and 7.8 of the Code.

The use of the phrase 'period free' was to indicate that the monthly withdrawal bleed associated with cyclical HRT regimens need no longer happen. Wyeth was fully aware that many women would experience abnormal or breakthrough bleeding during the first 3-6 months of cyclical HRT use, and this was highlighted in the appropriate sections of the data sheet and patient information leaflet. Wyeth made no claim that Premique was bleed-free.

'Period-free HRT' was consistently used by all the manufacturers of continuous combined HRT; it was also a term used by the medical profession. The recent Journal of the British Menopause Society included treatment protocols and guidelines issued by the West Midlands Menopause Society and clearly referred to period-free HRT. The phrase also appeared in medical literature, items produced by the Amarant Trust and in items approved by the Medicines Control Agency as being in line with Wyeth's marketing authorization.

PANEL RULING

The Panel accepted that the words 'menstruation' and 'period' were commonly used by clinicians and by patients when referring to the bleed associated with HRT. In the Panel's view it would be unusual for a withdrawal bleed to be referred to in its correct physiological terms. The Panel noted that a number of continuous combined HRT preparations were promoted using the phrase 'period-free HRT' or similar. The Panel noted that women on Premique might experience breakthrough bleeding and spotting in the early stages of therapy. Reference was made to this in the data sheet.

The Panel did not consider that the phrase 'period-free HRT' was in breach of the Code as alleged. There was no claim that Premique was bleed-free. The Panel ruled no breach of Clauses 7.2 and 7.8 of the Code.

2 Advertisement without prescribing information

COMPLAINT

Lilly stated that one of the advertisements (Z753660/1095), which appeared in The Journal of the British Menopause Society in December 1998, did not have any prescribing information. Lilly stated that this was because Wyeth assumed that it was an abbreviated advertisement and therefore exempt from this requirement as defined in Clause 5.1. The internal box around the advertisement fell just within the size allowed in Clause 5.3 (it was 419 square centimetres). It was, however, the only advertisement in the centre of a page. Lilly stated that the whole page made up the size of the advertisement and alleged that this was in breach of Clause 5.3.

RESPONSE

Wyeth stated that the inappropriate placement of an abbreviated advertisement had already been brought to its attention, and the recent March edition of The Journal of the British Menopause Society carried a full-page advertisement with prescribing information.

PANEL RULING

The Panel noted that while the advertisement in question was boxed by a thin black line such that it appeared to have a surface area of 419 square centimetres it was the only item on an A4 page (613 square centimetres). It was the view of the Panel that when an advertisement occupied only part of a page in a journal, the rest being blank, the whole of the page nonetheless had to be considered when calculating the size of the advertisement so as to see whether it exceeded the maximum allowable size for an abbreviated advertisement which was 420 square centimetres.

The maximum size had been exceeded and so the advertisement was a full advertisement and not an abbreviated advertisement. The Panel ruled a breach of Clause 4.1 of the Code as prescribing information had not been included.

Complaint received **3 March 1999**

Case completed **21 April 1999**

BRISTOL-MYERS SQUIBB AND SANKYO PHARMA v MERCK SHARP & DOHME

Zocor detail aid

Bristol-Myers Squibb and Sankyo Pharma complained jointly about cost comparisons used by Merck Sharp & Dohme to promote Zocor (simvastatin).

It was alleged that the data used in a bar chart comparing the estimated costs of lowering total cholesterol by at least 20% from baseline using the minimum dose of statin were not from similar groups of patients. The pravastatin data (40mg dose) was from a study in patients with average baseline cholesterol levels and the Zocor study was in hypercholesterolaemic patients. The Panel noted that in general it could be misleading not to compare similar groups. However, if the pravastatin data had been based on patients with hypercholesterolaemia, as it was for Zocor, then the minimum dose of pravastatin would still be 40mg. No breach of the Code was ruled.

It was alleged that the claim 'Zocor is a proven, cost effective way to save the lives of your post-MI and angina patients', which appeared on a page discussing the use of the 10mg dose of Zocor, implied that this dose of Zocor was approved to save the lives of post-MI and angina patients. This was outside the licence. The Panel noted that the summary of product characteristics (SPC) stated that patients with coronary heart disease could be treated with a starting dose of 20mg/day. Reference was made to reducing the dose depending on the patient's individual response and to reducing the dose in hyperlipidaemia. The Panel did not accept that the use of the 10mg dose was outside the SPC recommendations as alleged. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited and Sankyo Pharma UK Limited complained jointly about cost comparisons used by Merck Sharp & Dohme Limited to promote Zocor (simvastatin). Two detail aids had given rise to similar concerns. The companies confined their attention to the most recent which was headed 'Proven life saver' (ref 09-99 ZCR. 98. GB. 702 08.B.6c.HO.998).

1 Cost comparisons of statins

The page in question was headed 'How much does it cost to lower cholesterol?' and referred to the Government Standing Medical Advisory Committee (SMAC) statement on the use of statins which recommended a total cholesterol reduction of 20-25%. The page featured a bar chart comparing the estimated costs of lowering total cholesterol by at least 20% from baseline using the minimum doses necessary of five different statins. The five statins shown were cerivastatin 0.3mg (£18.20), fluvastatin 80mg (£29.80), pravastatin 40mg (£46.48), atorvastatin 10mg (£18.88) and Zocor 10mg (£18.29). The doses of cerivastatin, fluvastatin, and pravastatin were, according to the bar chart, the 'top licensed dose' whereas the doses of atorvastatin and Zocor were the 'starting dose'.

COMPLAINT

Bristol-Myers Squibb and Sankyo stated that the only pravastatin data referred to in the bar chart was from the CARE study which was in patients with average baseline cholesterol levels. The simvastatin study used for comparison was in hypercholesterolaemic patients. Since the comparison was not made for similar groups of patients, it was misleading and in breach of Clause 7.2 of the Code.

The detail aid gave the impression that 40mg pravastatin was required to lower total cholesterol by at least 20% from baseline. However, data from only one study with pravastatin was cited and selective use of this paper hid the fact that there were numerous studies with the 10 and 20mg doses of pravastatin in which total cholesterol had been reduced by at least 20%. For this reason the comparison was misleading, not a fair representation of the available data and was disparaging to pravastatin. It was alleged that the comparison was therefore in breach of Clauses 7.2 and 8.1 of the Code.

Should Merck Sharp & Dohme renew this detail piece selectively using data from another study, as it had suggested in a letter, it was the complainants' belief that this comparison would also be in breach of the Code.

RESPONSE

Merck Sharp & Dohme considered that it was important that clinicians were made aware of how much it cost to reduce cholesterol with each lipid lowering agent as the medicines were not of equal potency. Naturally such cost comparisons were often contentious and therefore it was necessary to use a nationally accepted target as a basis on which to compare effects.

In this case Merck Sharp & Dohme used the guidelines produced by the SMAC.

Given that a 20% reduction in total cholesterol was a desirable endpoint in high risk patients according to these guidelines, Merck Sharp & Dohme examined the totality of the evidence supporting each statin's ability to reduce cholesterol by that amount at differing dosages. Having reviewed the data in light of the complaint, Merck Sharp & Dohme had no reason to alter its view that it had presented the cost comparison with pravastatin accurately.

The complainants had referenced six studies as showing that doses of pravastatin between 10mg and 20mg achieved total cholesterol reductions of over 20%. The number of patients within these studies receiving pravastatin was approximately 650.

Most data on pravastatin however was at the 40mg dosage. The detail aid quoted the CARE study which

included some 2081 patients on 40mg pravastatin. This dose produced a 20% reduction in total cholesterol. To Merck Sharp & Dohme's knowledge no study had shown 20mg pravastatin to be equivalent to 40mg in cholesterol reducing ability and therefore it was to be expected that 20mg would produce less than a 20% reduction in total cholesterol.

In addition to this, other large studies had shown that 40mg of pravastatin only just achieved the target of 20% cholesterol reduction including WOSCOPS (3302 patients on 40mg pravastatin) and REGRESS (450 patients on 40mg pravastatin). Another large study, LIPID, showed a 21% reduction at six months in 4512 patients taking 40mg of pravastatin.

There was ample evidence in over 10,000 patients that pravastatin at a dose of 40mg would only just produce a 20% reduction in total cholesterol.

If one looked at the evidence for 10mg and 20mg of pravastatin, several studies, including greater numbers of patients than those quoted by the complainants, showed these doses failed to achieve a 20% reduction in total cholesterol.

In one of these studies, CURVES, which included a direct comparison of pravastatin and simvastatin, it could be seen that both 10mg and 20mg doses of pravastatin failed to achieve a 20% reduction in total cholesterol.

Thus Merck Sharp & Dohme considered that its data was representative of the totality of the evidence on the cholesterol reducing ability of pravastatin. The weight of evidence supported the fact that 40mg was required to achieve a 20% reduction in total cholesterol and therefore the cost comparison was fair. The claim could be substantiated and was not disparaging to pravastatin.

PANEL RULING

The Panel examined the CARE study which was designed specifically to study the effectiveness in a typical patient population of lowering LDL cholesterol levels to prevent coronary events after myocardial infarction. The entry criteria were patients with myocardial infarction who had plasma cholesterol levels of less than 6.2mmol/l and an LDL cholesterol level of 3-4.5mmol/l. The dose of pravastatin used was 40mg. The results showed that reducing LDL cholesterol with pravastatin from average to low levels significantly reduced the number of recurrent coronary events. However there was no significant reduction in overall mortality.

The Panel noted that the data for Zocor came from a study by Dart *et al* on patients with hypercholesterolaemia.

The Panel noted that the SMAC Guidelines referred to using a dose of statin to reduce total cholesterol to 5mmol/l or by 20-25% in those high risk patients (eg those with a previous myocardial infarction) who had serum cholesterol below 6.3mmol/l before starting treatment.

The Panel noted that the comparison was not of similar patients. The data for Zocor at 10mg was for hypercholesterolamia patients whereas the data for pravastatin at 40mg was from patients with average cholesterol levels.

The Panel noted that the bar chart implied that a 40mg dose of pravastatin was necessary to lower total plasma cholesterol by at least 20%. The complainants had referred to six studies in which lower doses of pravastatin (10 or 20mg) could similarly lower total cholesterol. The Panel noted that together these studies had involved 576 patients. Conversely, Merck Sharp & Dohme had referred to thirteen studies involving 1434 patients, in which pravastatin 10 or 20mg had failed to reduce total cholesterol by as much as 20%. Substantiation that a 40mg dose of pravastatin lowered total cholesterol by at least 20% came from 6 studies, three of which involved a total of 9895 patients. The Panel noted, therefore, that although a few studies had shown a reduction in total cholesterol of at least 20% with pravastatin 10 or 20mg the balance of the data at these doses showed a reduction of less than 20%. In comparison the large amount of data for 40mg showed reductions of at least 20%. In the Panel's view the cost comparison, by referring to a 40mg dose of pravastatin, was neither misleading nor disparaging as alleged. No breach of Clauses 7.2 and 8.1 was ruled.

With regard to the choice of patient populations, the Panel considered that in general it could be misleading not to compare similar groups. However, if the pravastatin data in the detail aid had been based on patients with hypercholesterolaemia, as it was for Zocor, then the balance of the data would still point to the use of a 40mg dose of pravastatin (eg WOSCOP study). The Panel therefore ruled no breach of Clause 7.2 of the Code.

2 Claim 'Zocor is a proven, cost effective way to save the lives of your post-MI and angina patients.'

The above claim appeared immediately below the bar chart at issue in point 1 above.

COMPLAINT

Bristol-Myers Squibb and Sankyo stated that it was not the unqualified nature of this statement that concerned them but rather the fact that it appeared on a page that had specifically discussed the use of the 10mg dose of simvastatin. This gave the overall impression that the 10mg dose of simvastatin was approved to save the lives of post-MI and angina patients. This could not be substantiated and was outside the licensed indication for the 10mg dose of simvastatin. It was alleged that the page was therefore in breach of Clauses 7.2 and 3.2 of the Code.

RESPONSE

Merck Sharp & Dohme maintained that this was a stand-alone statement of fact which did not require further qualification. However, this was largely beside the point as the licence did not stipulate a dosage at which Zocor was proven to have effects on mortality. The therapeutic indications section of the summary of product characteristics (SPC) stated that 'In patients with coronary heart disease with a plasma

cholesterol level of 5.5mmol/l or greater, 'Zocor' is indicated to:- reduce the risk of mortality'.

The section to which the complainants referred, under 'Coronary heart disease', stated 'Patients with coronary heart disease can be treated with a starting dose of 20mg/day given as a single dose in the evening. Adjustment of dosage, if required, should be made as specified above.' The word 'can' indicated this was an advisory statement, and in referring to the paragraph above made it clear that doses could be reduced below 20mg.

The SPC did not stipulate that only doses above 20mg of simvastatin were licensed to reduce mortality and Merck Sharp & Dohme was not in breach of Clauses 3.2 or 7.2 of the Code.

Merck Sharp & Dohme believed that the complainants had made an error in the interpretation of the SPC.

PANEL RULING

The Panel noted from the SPC that Zocor was indicated to reduce the risk of mortality in patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater. The SPC stated that patients with coronary heart disease could be treated with a starting dose of 20mg/day and that adjustment of dose if required should be made at intervals of not less than four weeks depending on the patient's individual response. Reference was made in the SPC to the dosing in hyperlipidaemia (10mg to 40mg per day). This section also referred to the need to consider reducing the dose of Zocor if lipid levels fell below specified values.

The Panel considered that although a 20mg starting dose of Zocor was given for coronary heart disease, the use of the word 'can' meant that the recommendation was not an absolute instruction. This was reinforced by the cross reference to the previous paragraph in the SPC which dealt with reducing the dose of Zocor. The Panel did not accept that the use of 10mg of Zocor in such circumstances was outside the SPC recommendations as alleged.

The Panel did not accept that the claim was in breach of the Code as alleged and ruled no breach of Clauses 3.2 and 7.2.

Complaint received **11 March 1999**

Case completed **16 June 1999**

CASE AUTH/857/3/99

ZENECA PHARMA v GLAXO WELLCOME

Naramig journal advertisements

Zeneca complained about advertisements for Naramig (naratriptan) issued by Glaxo Wellcome. The advertisements featured a photograph of a smiling woman's face with the words 'Feeling Brilliant!' superimposed on it. Zeneca alleged that the claim 'Feeling Brilliant' was an exaggerated claim that could not be substantiated.

The Panel considered that the data was not sufficient to justify the use of the strong claim that patients would be 'Feeling Brilliant'. The Panel considered that the claim was exaggerated and a breach of the Code was ruled.

Zeneca Pharma complained about two advertisements (ref GEN 25891 December 1998) for Naramig (naratriptan), placed by Glaxo Wellcome UK Limited, which had appeared in Pulse, 30 January 1999. Each advertisement featured a photograph of a smiling woman's face with the words 'Feeling Brilliant!' superimposed on it.

COMPLAINT

Zeneca said that it had previously complained about the Naramig promotional claim 'It's Brilliant' (Case AUTH/800/11/98). On that matter, the Panel ruled that the claim 'It's Brilliant' was exaggerated in breach of Clause 7.8 of the Code.

Zeneca regarded the change of only one word of the claim from 'It's Brilliant' to 'Feeling Brilliant' to be nothing more than a cynical disregard for the adjudication in Case AUTH/800/11/98 and a determination to continue using a misleading claim. Zeneca had been unable to resolve this matter with Glaxo Wellcome and, regrettably, it must now bring the matter before the Authority.

Zeneca alleged that the claim 'Feeling Brilliant' was an exaggerated claim which was not capable of substantiation and therefore in breach of Clause 7.8.

1 In its defence in Case AUTH/800/11/98, Glaxo Wellcome submitted data on the efficacy and tolerability of Naramig. It also stated that the Naramig advertisement deliberately depicted the statement 'It's Brilliant' within quotation marks as it was intended to convey what the patient thought of Naramig and submitted, in support of this, market research data where 51% of patients rated Naramig as excellent.

The current Naramig advertisements depicted the statement 'Feeling Brilliant' within quotation marks. Zeneca must therefore conclude that this was intended to convey what patients felt after treatment with Naramig.

2 To claim that patients felt brilliant following treatment with Naramig for migraine was, indeed, remarkable. In the postdromal phase of migraine (eg following resolution of the attack) patients felt lethargic, tired, washed out, lacking energy and drive; concentration and attention spans were limited,

speech, bowel function and fluid balance might be altered and head tenderness was common. For a claim that, following treatment with Naramig, patients felt brilliant, to be supportable, a considerable burden of proof was required. Zeneca contended that Glaxo Wellcome could furnish none.

3 In response to Zeneca's request for evidence to support the claim 'Feeling Brilliant', Glaxo Wellcome provided essentially the same data which it cited in Case AUTH/800/11/98 to support the claim that patients assessed Naramig as 'It's Brilliant'.

Glaxo Wellcome provided data to show that Naramig was effective and well tolerated. Zeneca accepted that. However, Zeneca did not accept that the market research data, based on an analysis of over 100 questionnaires returned from Naramig sample packs, demonstrated that patients felt brilliant following Naramig treatment. Glaxo Wellcome had not provided Zeneca with details of the questionnaire. However, it understood that the data had been generated from a questionnaire supplied to patients with sample packs of Naramig, a copy of which was provided. Zeneca regarded data gathered in this manner to be uncontrolled and unscientific and did not accept that promotional claims could be derived from such a small and unrepresentative sample of patients. It was important to note that this questionnaire contained questions relating only to efficacy. There were no questions relating to tolerability or how patients felt. The results of this exercise did not, in any way, support the claim that patients felt brilliant.

Glaxo Wellcome had also made reference to preliminary results from an open label study evaluating the impact of Naramig on quality of life and economic costs. Reference was made to improvements in the domains of role physical, bodily pain, general health, vitality and social function. No information was given on what the improvement was measured against or on any other details of the study except that it would be presented in full later in the year. Clearly, none of the information which Glaxo Wellcome was prepared to give on this study supported the claim that patients felt brilliant.

4 Zeneca stated that Glaxo Wellcome appeared to concede that it did not have specific evidence to support the claim that patients felt brilliant following treatment with Naramig.

In response to Zeneca's request for evidence to support the claim, Glaxo Wellcome stated:

'The use of the term 'feeling brilliant' in our advertisement conveys how patients are likely to feel after taking Naramig…' (Zeneca's underlining)

'The statement is depicted within quotation marks as it conveys what the patients might feel and is not a scientific statement' (Zeneca's underlining).

It was clear that this powerful and all embracing claim that patients feel brilliant was nothing more than supposition on the part of Glaxo Wellcome.

RESPONSE

Glaxo Wellcome stated that the term 'Feeling Brilliant!' was clearly used on the advertisement to reflect what the majority of patients were likely to feel after taking Naramig.

The term 'brilliant' was a commonly used phrase in everyday language, used when people were very pleased about something, or thought that it was very good.

The use of the term 'Feeling Brilliant' conveyed how patients were likely to feel after experiencing relief from the burden of their migraine attack following treatment with Naramig. It was a reflection of the proven clinical efficacy of Naramig, with a tolerability similar to placebo, and was supported by both market research data and clinical trial data showing that the majority of patients who took Naramig:

- rated Naramig as good or excellent
- experienced headache relief which was maintained for at least 12 hours
- had little or no clinical disability 2-4 hours after treatment.

The statement on the advertisement was depicted within quotation marks as it conveyed what the patient was likely to feel and was not a scientific statement.

a) Market research data – over 50% of patients rated Naramig as excellent

Analysis of over 100 questionnaires returned from Naramig sample packs found that:

- 51% of patients rated Naramig as excellent, with 81% of patients rating it as good or excellent
- 93% of patients found that Naramig got rid of their migraine attack
- 87% of patients would take Naramig again
- 77% of patients rated Naramig as better than the treatments they had tried previously.

b) Long-term treatment – patients rated Naramig as good or excellent in the majority of attacks

In a long-term study of Naramig over 6 months, treating 7,566 attacks, patients rated Naramig as good or excellent in a mean of 61% of attacks. Patients' global assessment of treatments such as this were useful as they took into account both efficacy and tolerability.

c) Clinical profile

Naramig was a fast acting and highly effective acute treatment for migraine. The clinical efficacy of Naramig was evaluated in eight studies in which over 4,000 migraine patients treated over 15,000 migraine attacks.

In common with other medicines in its class (5-HT1 agonists), Naramig started working within an hour and was highly effective. Up to 76% of patients experienced headache relief at four hours after a single dose of Naramig 2.5mg.

- Low rate of return of migraine symptoms

Naramig had a half-life longer than any other available 5-HT_1 agonist and this might account for its long duration of action. Few patients (17-28%) taking

Naramig experienced a recurrence of their migraine attack.

- Excellent tolerability profile

Data from double-blind, placebo controlled studies demonstrated that Naramig tablets were very well tolerated with an adverse event profile similar to placebo. This was confirmed in the summary of product characteristics (SPC) for Naramig which stated that the incidence of side effects reported in clinical trials was similar to placebo. Naramig was the only $5HT_1$ agonist to carry this statement on its SPC.

d) Improvements in quality of life

Results from a recently completed open label study evaluating the impact of Naramig on quality of life and economic costs found that patients taking Naramig experienced significant improvements in their quality of life (measured using the SF-36 Health Survey) compared with their customary therapy (data from across at least 6 attacks). The significant improvements were found in the domains of: role physical ($p=0.004$), bodily pain ($p=0.002$), general health ($p=0.004$), vitality ($p<0.001$) and social function ($p=0.006$). Patients were also significantly more satisfied with Naramig than their customary therapy. This data would be presented in full later in the year.

In response to the specific points raised by Zeneca in its correspondence:

e) Lethargy and tiredness after a migraine – the postdrome

Although Zeneca stated that patients were described as often experiencing lethargy and tiredness after a migraine attack, the phenomenon of a postdrome was described prior to the advent of the $5\text{-}HT_1$ agonists. Malaise and fatigue were reported by only 2-4% of patients taking Naramig during the clinical trial programme. In addition, as mentioned previously, the majority of patients taking Naramig reported little or no clinical disability 2-4 hours after treatment.

f) Previous ruling

Previously the Panel had ruled that the claim 'It's brilliant!' was in breach of Clause 7.8 as it would be: '…read as a general statement rather than be attributed specifically to what patients might think of Naramig'.

The concept of patient perception, using up-to-date colloquial terminology, was intended previously, but obviously poorly put across in view of the previous ruling relating the statement specifically to the drug.

In Glaxo Wellcome's opinion this advertisement, with the term 'Feeling Brilliant!' positioned across a patient and in quotation marks, addressed this concern as it clearly reflected what a patient might feel after taking Naramig rather than any claim that the product was brilliant.

In conclusion, Glaxo Wellcome believed the data supported that Naramig was a highly effective long lasting migraine treatment with an excellent tolerability profile. Up to three-quarters of patients experienced relief with Naramig, and of these patients about three-quarters did not experience their migraine symptoms returning and very few experienced an adverse event.

Consequently, Glaxo Wellcome believed that the use of the term 'Feeling Brilliant' accurately described in colloquial terms how a patient would feel when they had gained relief from their migraine with Naramig. As such Glaxo Wellcome believed that this term was not a superlative, and refuted any allegation of a breach of Clause 7.8.

PANEL RULING

The Panel noted that the advertisements at issue were almost identical to those considered in Case AUTH/800/11/98. The only change was the claim from 'It's Brilliant!' to 'Feeling Brilliant!'. In the previous case Glaxo Wellcome had submitted that 'It's Brilliant!' was an accurate reflection of how patients viewed Naramig and of the clinical data on tolerability. The phrase reflected the benefits of Naramig and how patients felt after taking the product and experiencing relief from a migraine attack. The Panel, however, had considered that the claim would be read as meaning the product was excellent or superb; it would be seen as a general statement rather than being attributed specifically to what patients might think of Naramig. The Panel had considered the claim 'It's Brilliant!' was exaggerated and had ruled a breach of Clause 7.8. The Panel noted that its comments that the claim would not be attributed to how patients viewed Naramig was in response to Glaxo Wellcome's submission to the contrary and not due to a concern that the concept of patient perception had been poorly portrayed.

The Panel considered that in the case now before it the claim 'Feeling Brilliant' was a strong claim. One definition of brilliant was excellent. The data to substantiate the claim provided by Glaxo Wellcome was market research data, clinical trial data and the proven clinical efficacy of Naramig which had a tolerability similar to placebo. The Panel noted that the market research data was based on questionnaires contained in Naramig sample packs. In response to the question 'What is your overall rating of this treatment? Excellent/Good/OK/Poor', 51% of the first 102 patients to respond rated Naramig as excellent. In a clinical study treating 7,566 attacks, patients rated Naramig as good or excellent in 61% of attacks. The study did not record the percentage of attacks in which Naramig was rated as excellent.

The Panel considered that the data was not sufficient to justify the use of the strong claim that patients would be 'Feeling Brilliant'. The Panel considered that the claim was exaggerated and a breach of Clause 7.8 of the Code was ruled.

Complaint received **15 March 1999**

Case completed **7 May 1999**

CASE AUTH/860/3/99

NEXSTAR v THE LIPOSOME COMPANY

Abelcet journal advertisement

NeXstar complained about a claim 'Fact: Abelcet is the least expensive lipid based formulation of amphotericin B' which was used in an advertisement for Abelcet issued by The Liposome Company.

The Panel noted that the claim was very broad and implied in every circumstance that Abelcet was the least expensive lipid based formulation of amphotericin B. Given that NeXstar's product could be administered in a range of doses this might not always be the case. The Panel ruled that the claim was misleading as it was not sufficiently qualified.

NeXstar Pharmaceuticals Limited complained about an advertisement for Abelcet (a lipid-based formulation of amphotericin B) which had been placed by The Liposome Company Ltd. NeXstar was the supplier of an alternative lipid-based formulation of amphotericin B (AmBisome); a third formulation was also available from another pharmaceutical company.

The advertisement featured three claims, the first dealt with the efficacy of Abelcet in aspergillosis and severe candidiasis and the second with the fact that Abelcet was the only lipid based formulation of amphotericin B indicated for the treatment of severe invasive candidiasis. The third claim was the claim at issue, 'Fact: Abelcet is the least expensive lipid-based formulation of amphotericin B'.

COMPLAINT

NeXstar stated that the advertisement had appeared in UK journals. The advertisement included the claim in question 'Fact: Abelcet is the least expensive lipid-based formulation of amphotericin B', citing MIMS, December 1998, as a reference. MIMS quoted prices as follows: Abelcet: £860 for 10 x 100mg vials; AmBisome £1,450 for 10 x 50mg vials. Whilst this made Abelcet less expensive on a mg-for-mg basis, it ignored the crucial fact that the licensed dose for Abelcet was 5mg/kg/day whilst the licensed dose for AmBisome was a range from 1 to 3mg/kg/day. It was thus very clear that at a dose of 1mg/kg/day, AmBisome was substantially less expensive than Abelcet. A 1mg/kg dose in an average 70kg patient would cost £203, whilst a 5mg/kg dose of Abelcet would cost £301.

NeXstar alleged that this was a clear breach of Clause 7.2 of the Code. The supplementary information was very explicit on this point, stating that '…a price comparison should be made on the basis of the equivalent dosage requirement for the same indications'.

NeXstar believed that this was a deliberate attempt to mislead prescribers as to the relative costs of Abelcet and AmBisome.

RESPONSE

The Liposome Company said that the Abelcet advertisement appeared in the Abstract Book of the 25th Annual Meeting of the European Group for Blood and Bone Marrow Transplantation, Hamburg 21-24 March 1999. The same advertisement had been used in 1996 and 1997 in UK publications.

The advertisement referred to the use of Abelcet for severe systemic fungal infections which was generally recommended at 5mg/kg for at least 14 days. In this context the advertisement claimed that Abelcet was the least expensive lipid-based formulation of amphotericin B based on data in MIMS. The complaint concerned the price comparison made on the basis of the equivalent dosage requirement for the same indication and went on to compare 1mg/kg AmBisome (of a licensed range 1-3mg/kg) with the sole licensed dose of 5mg/kg Abelcet. NeXstar's assertion was that 1mg of AmBisome was equivalent to 5mg of Abelcet when used clinically to treat severe systemic fungal infections.

The question therefore remained what were the equivalent doses of Abelcet and AmBisome in the treatment of severe systemic fungal infections?

The AmBisome summary of product characteristics (SPC) stated that 'Data are presently insufficient to define the total dosage requirements and duration of treatment necessary for resolution of mycoses'.

In a seminal study of AmBisome (Ringdén *et al* 1991) the dose per day of AmBisome for proven invasive infection in 64 cases was 2.4 ± 0.8mg/kg with a duration of 29 ± 18 days. More up-to-date information from some of the same authors stated that 'With more experience, the initial dose was increased to 3-4mg/kg/d if [invasive fungal infection] was suspected or verified in the lung. At other sites of infection, the initial dose was 2-3mg/kg/d.' (Ringdén *et al* 1997).

Further information was also available in the public domain from the US Product Insert which indicated that 3-5mg/kg AmBisome was required to treat a systemic invasive fungal infection. The average dose of AmBisome used to treat a severe systemic fungal infection was therefore greater than 1mg/kg and so the level of 1mg/kg AmBisome could not be considered 'the equivalent dosage requirement' for any comparison between AmBisome and Abelcet in this indication.

On what basis did NeXstar suggest that 1mg AmBisome was equivalent to 5mg of Abelcet?

The SPC for AmBisome under section 4.2 Posology, subheading Treatment of Mycoses, stated that 'Therapy is usually instituted at a daily dose of 1.0mg/kg body weight, and increased stepwise to 3.0mg/kg, as required'. The language used could only mean that 1mg/kg was the initial dose for the treatment of severe systemic mycoses and not the dose commonly used in confirmed systemic mycoses. Further, the stated recommended dose under Section 4.2 Posology, subheading Empiric Treatment of Febrile Neutropenia (ie where a mycosis had not been established), was 3mg/kg body weight per day. It

defied scientific and medical reasoning to alternatively suggest that the treatment dose of AmBisome for a confirmed severe invasive fungal infection, in the general case, was a third of the empiric 3mg/kg dose required for a neutropenic fever unresponsive to broad spectrum antibiotics.

The Liposome Company stated that the cost comparison example given by NeXstar raised a fundamental issue. The letter of complaint stated that 'A 1mg/kg dose of AmBisome in an average 70kg patient would cost £203, whilst a 5mg/kg dose of Abelcet would cost £301'. This was incorrect, misleading and potentially dangerous for the patient. Neither Abelcet nor AmBisome contained preservative. Therefore both licences were granted on the basis of single use vials. The SPC for AmBisome under Section 6.4 stated '**DO NOT STORE** partially used vials for future patient use'. So for the hypothetical case of a 70kg patient taking an initial dose of 1mg/kg, 2 vials would be needed costing £290. Similarly, 4 vials of Abelcet would be needed for a treatment dose of 5mg/kg in a 70kg patient costing £344. In both cases, the residual amounts should be discarded. Failure so to do could leave the patient at risk of infection from a contaminated product. If NeXstar in a presumably carefully drafted letter signed by chief executives of the company was communicating that the cost of AmBisome for a 70kg patient with an initial dose of 1mg/kg was £203, which could only mean multiple use of vials, then this would be a serious deviation from the SPC.

The complaint also implied by this erroneous reckoning that in every case an initial dose of 1mg/kg of AmBisome was less expensive than the treatment dose of 5mg/kg Abelcet. This was misleading. For weights between 51 and 60kg, common values in severely ill patients and those undergoing cancer chemotherapy, 2 vials of AmBisome were required at a cost of £290, whereas the administration of the necessary 3 vials of Abelcet would cost £258. Similarly in children under 20kg, the cost would be £145 and £86 per day for AmBisome and Abelcet respectively. A further range applied to obese patients. Therefore the selection of 70kg patient weight for the 'comparison' did not show the whole picture.

A proper comparison would be to compare the average dose of AmBisome with the treatment dose of 5mg/kg Abelcet. Assuming the published average dose of 2.4mg/kg quoted above for AmBisome, the 70kg patient example of NeXstar would require 168mg or 4 x 50mg vials at a cost of £580 compared with £344 for Abelcet, 350mg from 4 x 100mg vials.

The Liposome Company's view was that the complaint from NeXstar was without merit and itself misleading on at least two counts. The first misleading aspect was that 1mg/kg of AmBisome was the normal dose, not the initial dose, for treatment of severe systemic mycoses and that this was somehow equivalent to a treatment dose of 5mg/kg Abelcet. The second misleading part related to the fact that the complainant had failed to appreciate the fundamentals of administration of injectable products which contained no preservative and the associated cost implications for the safety measures which the Medicines Control Agency had put in place.

The Liposome Company believed that the comparison was accurate, balanced, fair, objective and based on an up-to-date evaluation. Its statement that Abelcet was the least expensive lipid-based formulation of amphotericin B, in the context of severe systemic fungal infection, was true. The Liposome Company rejected this contrived complaint which had no medical or scientific basis.

PANEL RULING

The Panel noted that NeXstar had complained about an advertisement that had appeared in UK journals but had enclosed an advertisement that had appeared in the Abstract Book of the 25th Annual Meeting of the European Group for Blood and Marrow Transplantation and 15th Meeting of the Nurses Group held in Hamburg. The book had been distributed at the congress to officially registered participants. The Liposome Company did not know whether the publishers of the Abstract Book had made it available elsewhere. The Panel was not certain whether the advertisement in the Abstract Book was one that was subject to the Code or not. The Panel noted, however, that The Liposome Company stated that the advertisement had appeared in UK based publications in 1996 and 1997. The Panel considered that it could make a ruling as the advertisement had appeared in the UK. The costs of Abelcet and AmBisome had not changed since 1996.

The Panel was concerned that NeXstar included a calculation of the cost of treating a 70kg patient based on using part vials. Even if only part of a vial was used, the whole of it had to be paid for. Treating a 70kg patient with AmBisome would require 2 x 50mg vials and cost £290 and not £203 as stated by NeXstar. Similarly treating a 70kg patient with Abelcet would require 4 x 100mg vials and cost £344 not £301 as stated by NeXstar.

The Panel noted the submission from the Liposome Company regarding the cost of treating patients who weighed between 51kg and 60kg and children.

The Panel noted that the AmBisome SPC stated that therapy was usually initiated at a daily dose of 1mg/kg and increased to 3mg/kg as required. A clinical study had shown that the mean dose for proven invasive infection was 2.4mg/kg. Although the US Product Insert stated a dose of 3-5mg/kg to treat systemic invasive fungal infection, the Panel noted that the UK SPC took precedence.

The Panel noted that the claim at issue was very broad and implied that in every circumstance Abelcet was the least expensive lipid-based formulation of amphotericin B. Given that AmBisome could be administered in a range of doses, and there was not a single stated dose for the treatment of severe systemic infections, this might not always be the case. The Panel considered the claim was misleading as it was not sufficiently qualified as to the basis of the comparison. A breach of Clause 7.2 was ruled.

Complaint received **18 March 1999**

Case completed **3 June 1999**

MEDICINES CONTROL AGENCY v SEARLE AND PFIZER

Advertisement for COX-2 technology

The Medicines Control Agency (MCA) complained about an advertisement for COX-2 technology produced by Searle and Pfizer. The advertisement was headed 'COX-2 technology: a landmark discovery in molecular biology' and discussed two forms of cyclooxygenase, COX-1 and COX-2. The strapline at the bottom of the advertisement stated 'COX-2 specific inhibition. Intelligent medicine with specific direction'. The MCA stated that it had recently received complaints concerning the publication of the advertisement about COX-2 technology and media publicity about celecoxib. The complainants had alleged that the advertisement was a 'teaser' advertisement and was in breach of the Advertising Regulations. The MCA did not consider that there had been a breach of the Regulations. The MCA noted that the Regulations did not refer specifically to the issue of teaser advertisements. Clause 9.1 of the Code prohibited the issue of teaser advertising which was intended to elicit an interest in something which would be available at a later date. In the opinion of the MCA, the advertisement appeared to fall within this definition.

The Authority informed the MCA that a complaint about the advertisement had been considered previously and no breach of the Code had been ruled (Cases AUTH/833/1/99 and AUTH/834/1/99). There had been no appeal in these cases and, as provided for in the Constitution and Procedure, the new complaint was allowed to proceed. Either party, as appropriate, would be able to appeal the Panel's ruling.

In the previous cases, the Panel had noted that the advertisement was not about a medicine, it was a corporate advertisement about an area of research. The Panel had considered that given the amount of general information about the research and development of COX-2 inhibition, the advertisement was not a teaser as alleged. No breach of the Code had been ruled. The Panel considered that its ruling in Cases AUTH/833/1/99 and AUTH/834/1/99 also applied to the new complaint. The Panel therefore ruled no breach of the Code.

The Medicines Control Agency (MCA) submitted a complaint about an advertisement for COX-2 technology produced by Searle and Pfizer Limited. The advertisement was headed 'COX-2 technology: a landmark discovery in molecular biology' and discussed two forms of cyclooxygenase, COX-1 and COX-2. The strapline at the bottom of the advertisement stated 'COX-2 specific inhibition. Intelligent medicine with specific direction'.

The Authority informed the MCA that a complaint about the advertisement had been considered previously and no breach of the Code had been ruled (Cases AUTH/833/1/99 and AUTH/834/1/99). Paragraph 5.1 of the Constitution and Procedure for the Authority said that the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which had not been the subject of an appeal to the Code of Practice Appeal Board. The MCA was told that the Director had decided that, as there had been no appeal in the previous cases, the complaint would proceed with the Panel making a ruling in the first instance as usual. Following that, either party could appeal the decision to the Appeal Board.

COMPLAINT

The MCA stated that it had recently received complaints concerning the publication of the advertisement about COX-2 technology and media publicity about celecoxib. The MCA stated that the complainants had alleged that the advertisement was a 'teaser' advertisement and was in breach of Regulation 3(1) of The Medicines (Advertising) Regulations 1994 (SI 1994 No.1932, as amended).

The MCA had reviewed the material, and did not consider that there had been a breach of Regulation 3(1). The MCA noted that the Advertising Regulations did not refer specifically to the issue of teaser advertisements.

Clause 9.1 of the Code prohibited the issue of teaser advertising which was intended to elicit an interest in something which would be available at a later date. In the opinion of the MCA, the advertisement cited above would appear to fall within this definition.

RESPONSE

Searle replied on behalf of both itself and Pfizer.

Searle noted that the advertisement was the same as that involved in Cases AUTH/833/1/99 and AUTH/834/1/99 in which the Panel had previously ruled no breach of Clause 9.1.

The advertisement had appeared in a member of publications including the BMJ 23 January.

Searle did not agree that the advertisement elicited an interest in any product that would be available at a later date.

The purpose of this corporate advertisement was to publicise the partnership of Searle and Pfizer in their commitment to research in the area of COX-2 inhibition, following on from the important scientific discovery of the existence of two isoforms of cyclooxygenase.

The overall message of the advertisement was science based and general. The text stated that 'Searle and Pfizer are working together to determine the clinical significance of COX-2 specific inhibition and how this new approach may influence the development of treatments for diseases that include an inflammatory component'.

There was nothing in the content or the overall presentation of this advertisement to indicate, either directly or indirectly, a particular product that would be following or would be available at a later date. Searle therefore believed that it did not contravene Clause 9.1 of the Code.

Searle provided copies of the three papers it supplied in response to requests for further information elicited by the advertisement.

PANEL RULING

The Panel noted that the advertisement had been subject to a similar complaint, Cases AUTH/833/1/99 and AUTH/834/1/99.

Previous ruling in Cases AUTH/833/1/99 and AUTH/834/1/99 The Panel had noted that the advertisement was not about a medicine, it was a corporate advertisement about an area of research. The Panel had considered that given the amount of general information about the research and development of COX-2 inhibition the advertisement was not a teaser as alleged. No breach of Clause 9.1 had been ruled.

Panel ruling in Cases AUTH/861/3/99 and AUTH/862/3/99 The Panel considered that its ruling in Cases AUTH/833/1/99 and AUTH/834/1/99 also applied to the new complaint. The Panel therefore ruled no breach of Clause 9.1 of the Code.

Complaint received **22 March 1999**

Case completed **14 May 1999**

CASE AUTH/866/4/99

MERCK SHARP & DOHME v GLAXO WELLCOME

Seretide leavepiece

Merck Sharp & Dohme complained about a Seretide leavepiece issued by Allen & Hanburys. The Panel ruled a breach of the Code in relation to the presentation of three graphs. The Panel considered that visually the graphs invited direct comparison of mean improvement in FEV1 following a therapy change in patients symptomatic on beclomethasone 400mcg/day or equivalent. The three graphs were from separate studies. The first graph showed the effect of adding montelukast, Merck Sharp & Dohme's product, the second graph showed the effect of either doubling the dose of beclomethasone or adding salmeterol and the third graph showed the effect of switching patients to Seretide. Readers would be left with the impression that Seretide increased mean FEV_1 to a significantly greater degree than any of the other treatment options. There was no direct comparative data to support this.

The claim 'The first preventative medication to improve lung function on day one' was alleged to be misleading and incapable of substantiation. Seretide was a combination of salmeterol and fluticasone each of which had been available separately for a number of years. Glaxo Wellcome accepted that Seretide might not be the first preventative medication to improve lung function on the first day of treatment. The Panel ruled that the claim was misleading and not capable of substantiation.

Merck Sharp & Dohme Limited complained about a Seretide leavepiece (ref 20152224 – BP/February 1999) issued by Allen & Hanburys Limited. Seretide was presented as an Accuhaler in three different strengths each containing salmeterol 50mcg and varying doses of fluticasone. Seretide 100 denoted a combination of salmeterol 50mcg and fluticasone 100mcg. Merck Sharp & Dohme marketed Singulair (montelukast).

1 Page 3 headed 'Improvements in lung function after low dose inhaled steroids'

COMPLAINT

Merck Sharp & Dohme noted that a series of graphs invited the reader to compare the effects of various strategies in patients whose asthma remained uncontrolled despite 400mcg per day of inhaled beclomethasone. The strategies included adding montelukast, doubling the dose of inhaled corticosteroid, adding salmeterol or switching the patient to Seretide 100. The company noted that the four graphs were drawn from three separate studies and were therefore not comparable whatever the seeming similarities which might be drawn when one looked at the studies on paper. Merck Sharp & Dohme stated that such indirect comparisons of different trials did not allow the clinician to judge the statistical power of any differences seen and simply created a general impression which might well prove to be false when direct clinical trial comparisons took place.

Merck Sharp & Dohme stated that indirect comparisons of studies had a limited place when supported by direct comparisons or a large body of consistent evidence. In this instance this was not the case. Drawing the graphs side by side on the same scale was to invite a comparison which was clearly misleading. It was not sufficient to state the graphs were labelled as coming from separate studies. There would be little point including the graphs if it was expected that doctors would immediately appreciate the failings of the comparison and disregard them.

Merck Sharp & Dohme alleged that the comparison lacked scientific rigour, was invalid and was misleading in breach of Clauses 7.2 and 7.6 of the Code.

RESPONSE

Glaxo Wellcome stated that the page in question presented some of the options available for the treatment of patients whose asthma was inadequately controlled on low doses of inhaled steroid (eg beclomethasone 400mcg/day or equivalent). The company agreed with Merck Sharp & Dohme that comparisons should not be drawn across different studies, However, there were no data directly comparing all the options presented although each of them had been studied separately. In the absence of direct comparative data it was still necessary to discuss the different therapeutic strategies that might be used in such patients as clinical decisions would be taken on the evidence available.

Glaxo Wellcome stated that it ensured that the studies had similar inclusion and exclusion criteria and used the same endpoint (mean % improvement in FEV_1) and that the patients were receiving similar medication on entry. The company had quite clearly and explicitly labelled the three studies separately and inserted the results in individual boxes to highlight this. No doctor could be misled into thinking that these data were from the same trial.

Glaxo Wellcome entirely disagreed with Merck Sharp & Dohme's assertion that to present the graphs side by side on the same scale invited a comparison which was misleading. The company had simply presented the lung function results from these studies in a graphical manner. The same scale had been used across all four graphs to ensure that the size of the improvement in FEV_1 was not misrepresented.

Glaxo Wellcome specifically noted that it had not made any comparative claims between the different treatments or studies. The company simply claimed in the two sub bullet points below that Seretide 'provides substantial improvements in lung function' and 'provides considerable reductions in symptoms' in this type of patient, which were valid conclusions.

Glaxo Wellcome did not believe that there was a breach of either Clause 7.2 or 7.6 of the Code.

PANEL RULING

The Panel noted that the three graphs had been presented in three separate boxes labelled Study 1, Study 2 and Study 3 respectively. The graphs depicted the mean percentage improvement in FEV_1 following a therapy change in patients symptomatic on beclomethasone 400mcg/day or equivalent. The three graphs were on the same horizontal plane and all drawn to the same scale. The first graph showed that adding montelukast 10mg/day improved FEV^1 by a mean of 5.4%. The second graph showed that either doubling the dose of beclomethasone or adding salmeterol 50mcg twice daily improved mean FEV_1 by 9.5% and 15.5% respectively. The third graph showed that switching patients to Seretide 100 bd improved mean FEV_1 by 27.2%. The Panel considered that visually the graphs invited direct comparison of the results contained therein and that some readers would be left with the impression that Seretide increased mean FEV_1 to a significantly greater degree than any of the other treatment options. There was no direct comparative data to support this.

The Panel considered that the data presented in the graphs and layout of the graphs invited a direct comparison of the results which was misleading. A breach of Clauses 7.2 and 7.6 was ruled.

The Panel considered that it was confusing to show data where 30% of patients had not received inhaled steroids on entry to a study beneath a heading 'improvements in lung function after low dose inhaled steroids'. The Panel requested that its concerns be drawn to Glaxo Wellcome's attention.

2 Page 5 headed 'The first preventative medication to improve lung function on day one'

COMPLAINT

Merck Sharp & Dohme stated that in correspondence with Glaxo Wellcome it had argued that montelukast, a leukotriene receptor antagonist, had ample evidence of efficacy on day one. In reply Glaxo Wellcome had stated that rather than being a 'preventer', montelukast was a 'controller' of asthma on the grounds that it was not instigatable at step 2 of the British Thoracic Society (BTS) Guidelines. A copy of the correspondence was provided.

Merck Sharp & Dohme stated that even by the definition of 'preventative medication' supplied by Glaxo Wellcome the statement above was clearly invalid. Though not in the guidelines (developed before the medicine was licensed) montelukast was 'instigatable' at step 2 for the management of exercise induced asthma according to its licence. Zafirlukast, another leukotriene receptor antagonist and also with evidence of efficacy on day one, could be instigated as first line preventative therapy (what would be step 2 of the BTS Guidelines), again within licence. Both products were available before Seretide.

Furthermore, Merck Sharp & Dohme stated that Seretide was simply a combination of two products which themselves had been prescribed individually for several years. As the salmeterol component of this combination was not a preventer, by Glaxo Wellcome's own definition, the preventer part of this product must come from the fluticasone component (an inhaled steroid). The graph below the claim would appear to demonstrate that fluticasone had beneficial effects on lung function on day one. Thus, by Glaxo Wellcome's own logic, Seretide could not be the first 'preventative medication' to act within 24 hours.

Merck Sharp & Dohme stated that several preventer compounds available before Seretide had shown efficacy on day one of dosing including montelukast, zafirlukast and, it would appear, fluticasone. The above claim was therefore misleading in breach of Clause 7.2 and incapable of substantiation in breach of Clause 7.3.

RESPONSE

Glaxo Wellcome stated that on further consideration of the evidence presented by Merck Sharp & Dohme,

it conceded that Seretide might not be the first preventative medication to improve lung function on the first day of treatment. The company therefore accepted that this claim represented an inadvertent breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that Glaxo Wellcome had accepted that Seretide was not the first preventative medicine to improve lung function on day one. The claim that it was such was, therefore, misleading and could not be substantiated. A breach of Clauses 7.2 and 7.3 was ruled.

Complaint received **15 April 1999**

Case completed **22 June 1999**

CASE AUTH/871/4/99 *NO BREACH OF THE CODE*

LOCAL MEDICAL COMMITTEE v YAMANOUCHI PHARMA

Men's Health Matters – public awareness leaflet

The British Medical Association forwarded a complaint it had received from the secretary of a local medical committee. The complaint concerned a leaflet with the title 'Male Over 50 Prostate Problems?' funded by Yamanouchi Pharma. The complainant had serious doubts about the propriety of a pharmaceutical company sponsoring such leaflets.

The Authority informed the complainant that complaints about a similar leaflet had been considered previously and no breach of the Code had been ruled (Cases AUTH/802/11/98 and AUTH/841/2/99). There had been no appeal in those cases and, as provided for in the Constitution and Procedure, the new complaint was allowed to proceed. Either party, as appropriate, would be able to appeal the Panel's ruling.

In the previous cases, the Panel had considered that the leaflet raised public awareness about prostate problems and the fact that they could be treated with medicines. Although the leaflet might facilitate the market development of Yamanouchi's product, Flomax MR, the Panel did not consider that the leaflet was an advertisement for the product to the general public. The leaflet might encourage patients to discuss prostate problems with their doctor but it did not encourage them to ask their doctor to prescribe a specific medicine. No breach of the Code was ruled. The Panel considered that this ruling also applied to the new complaint.

The Panel considered that the provision of such leaflets *per se* did not fail to recognise the special nature of medicines and no breach of the Code was ruled.

The British Medical Association forwarded a complaint which it had received from the medical secretary of a local medical committee. The subject of the complaint was a leaflet which had the title 'Male Over 50 Prostate Problems?'. The leaflet, in a series of questions to the reader, gave the symptoms of prostate problems and stated 'No, it isn't 'your age', and something simple can be done about it. Most prostate problems can be treated with medicines. Your doctor will be able to help. Ring the surgery NOW to make an appointment'. At the bottom of the leaflet was a logo, MHM, and 'Men's Health Matters'.

The Authority informed the complainant that complaints about a similar leaflet funded by Yamanouchi Pharma Ltd had been considered previously and no breach of the Code had been ruled (Cases AUTH/802/11/98 and AUTH/841/2/99). Paragraph 5.1 of the Constitution and Procedure for the Authority stated that the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which had not been the subject of an appeal to the Code of Practice Appeal Board. The complainant was told that the Director had decided that, as there had been no appeal in either of the previous cases, the complaint would proceed with the Panel making a ruling in the first instance as usual. Following that, either party could appeal the decision to the Appeal Board.

COMPLAINT

The complainant stated that the leaflet was circulated to the entire population of a town in a copy of the local free newspaper. One of the complainant's constituent doctors, so incensed by the leaflet and the influx of men at his surgery as a result, did some research which led him to Yamanouchi, the makers of Flomax MR. The complainant stated that it appeared that Yamanouchi might be sponsoring the production of and circulation of these leaflets. The complainant could not believe that the town in question was the only place in England likely to be targeted with these leaflets.

The complainant stated that he raised the matter because he had serious doubts about the propriety of a pharmaceutical company sponsoring leaflets of this sort.

RESPONSE

Yamanouchi explained that the Men's Health Matters (MHM) educational campaign could only be launched and implemented in a particular health authority after consent and full agreement by the local hospital urology team. Once this had been obtained, all the local GPs who routinely referred patients to the

hospital urology department were sent a Dear Doctor letter and the 'Male Over 50…?' leaflet. The Dear Doctor letter advised GPs of the existence of a prostate assessment clinic at their local hospital and explained the benefits of the campaign as a whole. The 'Male Over 50…?' leaflet was then distributed to the public in that particular area as an enclosure in local newspapers.

Yamanouchi stated that the purpose of the leaflet was educational, and aimed to improve the general public's awareness of prostate diseases. Symptoms might severely impair patients' quality of life and it encouraged men with problems to seek medical attention. A 1997 Gallup survey conducted in the UK had shown that the majority of men with health issues did not seek medical attention despite having symptoms because they were either too embarrassed to visit their family doctor or they considered that associated symptoms were part of the normal ageing process.

Yamanouchi stated that it had reviewed the 'Male Over 50…?' leaflet again in view of the current complaint and remained satisfied that it was not in breach of the Code, specifically Clauses 9.1 and 20.

Yamanouchi stated that lower urinary tract symptoms could have serious detrimental effects on the patient's quality of life. Recognising this, and conscious that men could sometimes feel very embarrassed about their urinary problems, the company was careful to ensure that all of its publications relating to this therapy area were in good taste and treated the subject in a suitably serious manner. Yamanouchi did not consider that the imagery, text or style of the 'Male Over 50…?' leaflet was in any way frivolous or lacking in taste, or that it would be likely to cause offence to the potential readership. Consequently the company considered that the leaflet was not in breach of Clause 9.1 of the Code.

Yamanouchi did not consider that the leaflet was in breach of Clause 20, as it did not promote any product but merely provided information on a therapeutic area. Provision of information on a therapeutic area to the general public was not against the Code. Yamanouchi noted that this was also the Panel's view in its adjudication of two previous complaints.

PANEL RULING

With regard to the provisions of Clause 20 the Panel noted that its rulings in the previous two cases, Case AUTH/802/11/98 and Case AUTH/841/2/99 had not been appealed.

Previous ruling in Cases AUTH/802/11/98 and AUTH/841/2/99 The Panel noted that the leaflet 'Male Over 50 Prostate Problems?' encouraged readers who had answered 'yes' to the series of questions about the symptoms of prostate problems to go to see their doctor for help. The leaflet stated 'Most prostate problems can be treated with medicines'. No specific medicine or class of medicine was mentioned on the leaflet. There was no other reference to medicines in the leaflet. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. Yamanouchi had sponsored the leaflets in question and also marketed Flomax MR (tamsulosin), a POM for the treatment of functional symptoms of benign prostatic hyperplasia. The Panel considered that the leaflet raised awareness about prostate problems and the fact that they could be treated with medicines. The leaflet might facilitate the market development of Flomax MR. The Panel did not consider that the leaflet was an advertisement for the product to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public 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. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel accepted that the leaflet might encourage patients to discuss prostate problems with their doctor but the leaflet in question did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of Clause 20.2 of the Code.

Panel ruling in Case AUTH/871/4/99 The Panel considered its ruling in Cases AUTH/802/11/98 and AUTH/841/2/99 would also apply to the new complaint. The Panel, therefore, ruled no breach of Clauses 20.1 and 20.2 of the Code.

The Panel noted that the complainant had serious doubts about the propriety of a pharmaceutical company sponsoring the leaflet. The Panel considered that the provision of such leaflets was not unacceptable *per se* and did not fail to recognise the special nature of medicines. No breach of Clause 9.1 was ruled.

The Panel noted that as a result of previous cases the leaflet would in future include a reference that it was sponsored by Yamanouchi.

Complaint received **23 April 1999**

Case completed **28 June 1999**

CASE AUTH/872/4/99

DOCTOR v JANSSEN-CILAG

Sporanox advertisement

A doctor complained about an advertisement for Sporanox liquid (itraconazole) issued by Janssen-Cilag. The complainant alleged that the claim 'When Sporanox pours fungi cannot reign' implied that Sporanox was capable of preventing all fungal infections and this was not so. The complainant drew attention to two statements in the small print that Sporanox might be effective 'As prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy is considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplantation' and that 'At present there are insufficient clinical efficacy data in the prevention of aspergillosis'.

The Panel considered that the headline was misleading as alleged. A breach of the Code was ruled. It was immaterial that additional data had been included in footnotes as it was an accepted principle that misleading claims etc could not be qualified by footnotes.

A doctor complained about an advertisement for Sporanox liquid (ref 0481 C(i)) issued by Janssen-Cilag Limited which had appeared in the April 1999 issue of the British Journal of Haematology.

COMPLAINT

The complainant noted that the double page advertisement had a very large caption stating that 'When Sporanox pours fungi cannot reign*'. This statement implied that Sporanox (itraconazole liquid formulation) was capable of preventing all fungal infections. This was not so.

The complainant stated that elsewhere in the advertisement in very small print it could be read that what the statement really meant was that itraconazole might be effective 'As prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy is considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplantation' and that 'At present there are insufficient clinical efficacy data in the prevention of aspergillosis'. This did not mean that fungi could not reign where Sporanox had poured.

The complainant stated that printing a miniprint rider to qualify a highly misleading headline statement left the casual reader turning the pages of the journal open to notice the headline claim and not the rider. This was clearly why the advertisement was formulated with such a disparity in print sizes.

The complainant stated that deliberate use of different print sizes to mislead medical readers was the sort of thing that brought the pharmaceutical industry into disrepute. To encourage doctors to use a treatment inappropriately in immunocompromised patients was very reprehensible indeed.

RESPONSE

Janssen-Cilag noted that essentially the complainant was of the opinion that differences in the print sizes for the headline caption and the qualifications to this might mislead the casual reader. The company considered, however, that since qualifying statements were in accordance with the summary of product characteristics for Sporanox, they were therefore intended to clarify the correct use of the product. Additionally, as these qualifying statements were of the same font size as the main body of the text, and were clearly marked in the headline caption and text by an asterisk and an obelus respectively, the company considered that they were readily visible and were not, therefore, misleading.

Consequently, Janssen-Cilag disagreed with the content of the complainant's letter and considered that the advertisement complied with Clauses 3.2 and 7.2 of the Code.

PANEL RULING

The Panel noted that Sporanox liquid was indicated for the treatment of oral and/or oesophageal candidosis in HIV-positive or other immuno-compromised patients. Also as prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy was considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplantation and who were expected to become neutropenic. At present there were insufficient clinical efficacy data in the prevention of aspergillosis.

The Panel noted that the prominent double-page headline 'When Sporanox pours fungi cannot reign*' was asterisked to a footnote near the bottom of the advertisement which stated 'As prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy is considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplantation'. Text just below the headline discussed the prophylactic use of Sporanox and fluconazole. It mentioned that comprehensive cover was of paramount importance and stated that Sporanox possessed a very broad spectrum of activity. It also stated 'So it eradicates many potential lethal mycopathogens that aren't susceptible to fluconazole'. This statement was referenced by way of an indistinct obelus to a second footnote near the bottom of the advertisement which stated 'At present there are insufficient clinical efficacy data in the prevention of aspergillosis'. The footnotes and the text beneath the headline were of a similar font size.

The Panel considered that the advertisement gave the impression Sporanox liquid could be used to prevent all fungal infections which was not so. The Panel

considered that the headline was therefore misleading. It was immaterial that additional data had been included in footnotes as it was an accepted principle under the Code that misleading claims etc could not be qualified by footnotes. A breach of Clause 7.2 was ruled.

Complaint received **26 April 1999**

Case completed **24 June 1999**

CODE OF PRACTICE REVIEW – AUGUST 1999

Cases in which a breach of the Code was ruled are indexed in **bold type**.

818/12/98	**Director/Media v Sanofi Winthrop**	**Epilepsy therapy cards**	**Breaches Clauses 9.9 and 20.2**	**Appeal by complainant**	**Page 3**
819/1/99	Bristol-Myers Squibb v Merck Sharp & Dohme	Promotion of Zocor	No breach	Appeal by complainant	Page 7
822/1/99	**Wyeth v Novo Nordisk**	**Promotion of Kliovance**	**One breach Clause 3.2 Three breaches Clause 7.2 Two breaches Clause 7.8**	**Appeal by respondent**	**Page 11**
831/1/99	**Allergan v Merck Sharp & Dohme**	**Cosopt detail aid**	**Breach Clause 7.3**	**Appeal by complainant**	**Page 15**
836/1/99	**Wyeth v Lilly**	**Promotion of Evista**	**Two breaches Clause 3.2 Three breaches Clause 7.2**	**No appeal**	**Page 21**
838/2/99	**Director/Media v Procter & Gamble**	**Letter in BMJ about Didronel PMO**	**Breach Clause 7.2**	**No appeal**	**Page 24**
839/2/99	**Rhône-Poulenc Rorer v Pierre Fabre**	**Promotion of Navelbine**	**Five breaches Clause 3.2**	**No appeal**	**Page 28**
842/2/99	**General Practitioner v Whitehall Laboratories**	**Traxam Gel journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 32**
843/2/99	**3M Health Care v Glaxo Wellcome**	**Conduct of representative**	**Breaches Clauses 2 and 8.1 Two breaches Clause 15.9**	**Appeals by complainant and respondent**	**Page 34**
845/2/99	Research Ethics Committee Chairman v Servier	Promotion of Natrilix SR	No breach	No appeal	Page 48
846/3/99	**General Practitioner v Glaxo Wellcome**	**Seretide news item on Radio 4**	**Breaches Clauses 20.1 and 20.2**	**No appeal**	**Page 50**
847/3/99	**Lilly v Wyeth**	**Premique journal advertisements**	**Breach Clause 4.1**	**No appeal**	**Page 52**
848/3/99	Bristol-Myers Squibb and Sankyo Pharma v Merck Sharp & Dohme	Zocor detail aid	No breach	No appeal	Page 54
857/3/99	**Zeneca Pharma v Glaxo Wellcome**	**Naramig journal advertisements**	**Breach Clause 7.8**	**No appeal**	**Page 56**
860/3/99	**NeXstar v The Liposome Company**	**Abelcet journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 59**
861/3/99 & 862/3/99	Medicines Control Agency v Searle and Pfizer	Advertisement for COX-2 technology	No breach	No appeal	Page 61
866/4/99	**Merck Sharp & Dohme v Glaxo Wellcome**	**Seretide leavepiece**	**Two breaches Clause 7.2 Breaches Clauses 7.3 and 7.6**	**No appeal**	**Page 62**
871/4/99	Local Medical Committee v Yamanouchi Pharma	Men's Health Matters – public awareness leaflet	No breach	No appeal	Page 64
872/4/99	**Doctor v Janssen-Cilag**	**Sporanox advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 66**

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, more than sixty 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 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 in connection therewith
- the provision of information to the general public either directly or indirectly
- 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 Philip Cox 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 0171-930 9677 facsimile 0171-930 4554).