PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 38 NOVEMBER 2002

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.

Gifts as inducements

Clause 18.1 of the Code states that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'.

Clause 18.2 states that 'Gifts in the form of promotional aids and prizes, whether related to a particular product or of general utility, may be distributed to members of the health professions and to appropriate administrative staff, provided that the gift or prize is inexpensive and relevant to the practice of their profession or employment'.

The Authority has been informed that some companies have been advised by a third party that as long as a gift is not given as an inducement to prescribe, supply, administer, recommend or buy any medicine, then Clauses 18.1 and 18.2 do not apply.

Companies are advised not to adopt this interpretation. Any gift provided to members of the health professions or appropriate administrative staff will be regarded as coming within the ambit of Clause 18 regardless of any finesse in describing the reason for its provision.

Further it should be borne in mind that Regulation 21(1) of The Medicines (Advertising) Regulations 1994 (SI 1994 No. 1932) states that '… where relevant medicinal products are being promoted to persons qualified to prescribe or supply relevant medicinal products, no person shall supply, offer or promise to such persons any gift, pecuniary advantage or benefit in kind, unless it is inexpensive and relevant to the practice of medicine or pharmacy'.

The only exception to Clauses 18.1 and 18.2 is that set out in the supplementary information to Clause 18.1 under the heading 'Provision of Medical and Educational Goods and Services' which relates to goods and services which will enhance patient care or benefit the National Health Service. Such goods or services must not be provided in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. They must be provided on an entirely non-promotional basis.

Gifts of stationery

Companies should be aware that any gifts of stationery must conform to the requirements of Clauses 18.1 and 18.2 of the Code. Appropriately styled stationery can be an acceptable gift in this regard but the cost of what is provided must not exceed £6 (excluding VAT).

It is not considered that the provision of stationery can be regarded as enhancing patient care or benefiting the National Health Service and the exception to the requirements of Clause 18.1 set out in the supplementary information to that clause under the heading 'Provision of Medical and Educational Goods and Services' would not apply.

Representatives missing appointments

From time to time the Authority is approached by doctors who are annoyed because of the failure of representatives to keep appointments with them.

Companies are asked to ensure that as much notice as possible is given if a representative is unable to keep an appointment. Similarly, where the representative in a particular territory moves on, any outstanding appointments should either be met by another representative or adequate notice given of cancellation.

It should be noted that the supplementary information to Clause 15.4 of the Code states that 'Representatives must always endeavour to treat doctors' time with respect and give them no cause to believe that their time might have been wasted. If for any unavoidable reasons, an appointment cannot be kept, the longest possible notice must be given'.

Notification of signatories

Companies are reminded that Clause 14.3 of the Code of Practice requires that the names of those nominated for the certification of promotional material, together with their qualifications, should be notified in advance to the Product Information and Advertising Unit of the Post Licensing Division of the Medicines Control Agency and to the Prescription Medicines Code of Practice Authority. The names and qualifications of designated alternative signatories must also be given and changes in the names of nominees must be promptly notified.

Although some companies do ensure proper notification in this way others do not and companies are reminded of their obligations in this respect.

CODE OF PRACTICE TRAINING

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

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

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

Tuesday, 18 March

Tuesday, 29 April

Friday, 23 May

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1250/11/01

PHARMACIA v ALCON LABORATORIES

Invitation to a scientific symposium

Pharmacia complained about an invitation to a scientific symposium sent by Alcon Laboratories on 28 September 2001. The symposium was to be about Alcon's prostaglandin analogue for glaucoma treatment which was currently undergoing approval; all aspects of development and phase III clinical trials would be discussed. The meeting would commence on Saturday, 1 December 2001, and hotel reservations would be made for the Friday and Saturday nights as there was a social function to follow the scientific programme. An accompanying partner programme was to take place whilst the scientific symposium was being held.

Pharmacia noted that Alcon's only prostaglandin analogue for glaucoma treatment was Travatan (travoprost) and so the company was clearly referring to this product in the invitation. As was stated in the invitation, the product was undergoing approval. Pharmacia alleged that the invitation thus promoted an unlicensed product. In addition, the hospitality offered appeared to be excessive. Partners were invited and a programme for them was offered. Because of the serious nature of these breaches, Pharmacia alleged a breach of Clause 2 of the Code.

The Panel considered that by referring to its prostaglandin analogue for glaucoma treatment in the invitation, Alcon in effect promoted Travatan prior to the grant of the marketing authorization and a breach of the Code was ruled. By the time of the meeting, the marketing authorization had been received.

The educational content of the meeting (9.00 to 12.30 on Saturday morning) was limited. Delegates were provided with two nights' accommodation. There was no scientific or medical content on the Sunday with delegates departing after breakfast. It was difficult to calculate the costs from the information provided by Alcon. It was estimated that the costs per delegate including travel, meals on Friday and Saturday, entertainment on Saturday afternoon, a gala dinner on Saturday evening and two nights' accommodation were between £693 and £765 per person. The cost for the accompanying partners would be between £347 and £414 per person.

The Panel considered that the arrangements for the meeting were unacceptable. Alcon had paid for the accompanying partners, although it had subsequently realised its mistake in that regard. A breach of the Code was ruled.

With regard to the delegates, a weekend meeting and associated hospitality had been arranged for a scientific programme which lasted 3½ hours. The Panel considered that the hospitality was not secondary to the main purpose of the meeting and exceeded that level which the recipients would pay if they were paying for themselves. The impression created by such arrangements should be borne in mind. The Panel ruled a further breach of the Code.

The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2 which was used as a sign of particular censure.

As with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was very concerned about the case and decided to report Alcon to the ABPI Board of Management. The ABPI Board was very concerned about the case. It noted the changes to procedures implemented by Alcon. The ABPI Board decided that Alcon should be required to undergo an audit of its procedures. On receipt of the audit report the ABPI Board noted that the company acknowledged that it had made an error and as a result had changed its procedures. The ABPI Board decided that on the basis that the audit recommendations were implemented no further action was necessary.

Pharmacia Limited complained about an invitation to a scientific symposium issued by Alcon Laboratories (UK) Limited. The letter of invitation, dated 28 September 2001, stated that the symposium was concerned with Alcon's prostaglandin analogue for glaucoma treatment. This was currently undergoing approval and all aspects of development and phase III clinical trials would be discussed at the meeting.

The invitation stated that the meeting would commence on Saturday, 1 December 2001, and hotel reservations would be made for the Friday and Saturday nights as there was a social function to follow the scientific programme. An accompanying partner programme was to take place whilst the scientific symposium was being held.

COMPLAINT

Pharmacia stated that, firstly, Alcon's only 'prostaglandin analogue for glaucoma treatment' was Travatan (travoprost). Thus it was clearly referring to this product in the invitation. As was stated in the invitation, the product was 'undergoing approval' as of 28 September. Therefore, Pharmacia considered that this invitation represented a breach of Clause 3.1 of the Code, by promoting a product that had not yet received its marketing authorization. In addition, the hospitality offered appeared to be excessive. An invitation was issued to an accompanying partner and a programme for said partner was offered. This was alleged to be clearly a breach of Clause 19.1 of the Code.

Pharmacia alleged that because of the serious nature of these breaches, the invitation itself constituted a breach of Clause 2, and should be withdrawn, with cancellation of the proposed meeting.

RESPONSE

Alcon Laboratories provided a copy of the agenda. The meeting commenced at 9am and finished at 12.30pm with lunch. There were six presentations and a twenty minute coffee break. All 87 participants

were consultant grade ophthalmologists from Ireland and Great Britain.

Alcon stated that the invitation made no mention of any product, either by brand name or generically, so the company would not consider this to be promotional in any way. The fact that the product was undergoing approval was information that had been in the public domain since August as it had been mentioned in Scrip on 1 August 2001 and on the CPMP website on 26 July. Subsequently, the product was approved on 27 November.

Clause 3 permitted the exchange of medical or scientific information during the development of a medicine. Even this was not done, as the letter was a notice to confirm a meeting that was to happen in the future, which Alcon firmly believed would be post-approval.

Alcon stated that there was no mention of hospitality in the letter, only that there would be a social function, secondary to the meeting, to follow the scientific programme. Therefore it was difficult to see how this could be construed to be excessive. As this meeting was to take place at the weekend, it was considered that accompanying partners should not be excluded and, in accordance with Clause 19.1, an alternative programme would be offered to them as they would be excluded from the scientific meeting.

The buffet on Friday evening and buffet lunch on the Saturday together cost around £100 per person. The cost of the accommodation and breakfast was £170 for a single room per night or £180 for a double room per night. The costs were provided for the spouses' programme on the Saturday morning and the social events for all attendees after the meeting. The activities on offer for the spouses were a tour of Portobello Market, a trip to Mossiman's Kitchen or at leisure at the hotel.

The social function after the meeting was either a trip on the London Eye or high tea at Fortnum and Mason followed by a gala dinner with partners at £160 per person, £60 of which related to the cost of the venue.

Alcon paid for the accompanying partners. Once the mistake had been realised the company did not consider that it could go back and request a contribution from the participants.

As the scientific agenda started first thing on Saturday morning, it was appropriate to provide accommodation on the Friday night, as attendees might have long distances to travel. Accommodation was offered for Saturday evening as there was a dinner arranged. Alcon certainly did not consider this to be hospitality at an excessive level. Travelling expenses were reimbursed at an average cost of £137 for those travelling by air and £70 for those travelling by other means.

Alcon stated that in answering Pharmacia's first two points, given that Alcon did not believe it was promoting the product before approval or that the degree of hospitality offered was excessive, it failed to see how it could be accused of bringing discredit upon the pharmaceutical industry or, indeed, reducing confidence in it.

PANEL RULING

The Panel considered that Alcon, by referring to its 'prostaglandin analogue for glaucoma treatment' in the invitation dated 28 September 2001, in effect promoted the medicine prior to the grant of the marketing authorization and a breach of Clause 3.1 of the Code was ruled. At the time of the meeting, 1 December, the marketing authorization for Travatan had been received.

The Panel noted that the supplementary information to Clause 3 of the Code permitted the legitimate exchange of medical and scientific information during the development of a medicine provided that any such information or activity did not constitute promotion prohibited under Clause 3 or any other clause. The Panel did not consider that, as submitted by Alcon, the invitation could be seen as the legitimate exchange of medical or scientific information during the development of a medicine as meant by the supplementary information to Clause 3.

The Panel noted that Clause 19.1 of the Code permitted companies to provide hospitality to members of health professions and appropriate administrative staff in association with scientific meetings, promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed that level which the recipients would normally adopt when paying for themselves.

The supplementary information stated that spouses and other accompanying persons, unless qualified as above, might not attend the actual meeting and might not receive any associated hospitality at the company's expense; the entire costs which their presence involved were the responsibility of those they accompanied. Meetings organised for groups of doctors, other health professionals and/or for administrative staff which were wholly or mainly of a social or sporting nature were unacceptable. In determining whether a meeting was acceptable or not, consideration must be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, hospitality provided and the like. It should be the programme that attracted delegates and not the associated hospitality or venue.

The Panel noted that the meeting was a half day meeting running from 9.00 to 12.30. The educational content was very limited. Delegates were provided with two nights' accommodation. There was no scientific or medical content on the Sunday with delegates departing after breakfast.

It was difficult to calculate the costs from the information provided by Alcon. It was estimated that the costs per delegate including travel, meals on Friday, Saturday, entertainment on Saturday and two nights' accommodation were between £693 and £765 per person. The cost for the accompanying partners would be between £347 and £414 per person; these costs had been paid by Alcon which was prohibited by the Code.

The Panel considered that the arrangements for the meeting were unacceptable. Alcon had paid for the accompanying partners, although it had subsequently realised its mistake in that regard. The supplementary information to Clause 19.1 required all meetings which were planned to be checked to see that they complied with the Code. A breach of Clause 19.1 was ruled.

With regard to the delegates, a weekend meeting and associated hospitality had been arranged for a scientific programme which lasted 3½ hours. The Panel considered that the hospitality was not secondary to the main purpose of the meeting and exceeded that level which the recipients would pay if they were paying for themselves. The impression created by such arrangements should be borne in mind. The Panel ruled a further breach of Clause 19.1 of the Code.

The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2 which was used as a sign of particular censure.

APPEAL BOARD CONSIDERATION

As with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board.

The Appeal Board was concerned about the meeting organised by Alcon noting that the company had been ruled in breach of Clauses 2, 3.1 and 19.1 of the Code. It decided in accordance with Paragraph 12.1 of the Constitution and Procedure to report the company to the ABPI Board of Management for it to consider whether further sanctions should be imposed under Paragraph 12.2.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board of Management was very concerned about the case. It noted the changes to procedures implemented by Alcon. The ABPI Board decided that Alcon should be required to undergo an audit of its procedures by the Authority. On receipt of the audit report the ABPI Board noted that the company acknowledged that it had made an error and as a result had changed its procedures. The ABPI Board decided that on the basis that the audit recommendations were implemented no further action was necessary.

Complaint received	**28 November 2001**
Case completed	**5 February 2002**
PMCPA proceedings completed	**28 February 2002**
ABPI Board proceedings completed	**10 September 2002**

CASE AUTH/1264/12/01

ASTRAZENECA v WYETH

Promotion of Zoton including breach of undertaking

AstraZeneca complained about the promotion of Zoton (lansoprazole) by Wyeth. The materials at issue were three journal advertisements, a leavepiece, a detail aid and a CD ROM. AstraZeneca supplied Losec (omeprazole) and Nexium (esomeprazole).

One journal advertisement featured a high jumper adjacent to the headline 'High Achiever'. The strapline 'Powerful PPI [proton pump inhibitor] Performance' appeared at the bottom. AstraZeneca alleged that the claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission' was exaggerated as it implied complete success in acid suppression and pain resolution.

AstraZeneca explained that the proportion of time over 24 hours that a medicine was able to maintain gastric pH above 4 was a standard method of evaluating acid suppressing capacity. Whilst there was data to show that lansoprazole 30mg effectively suppressed gastric acid production in that it maintained gastric pH above 4 for a mean of 16 hours, to state without qualification that it 'beats acid' was in AstraZeneca's view exaggerated.

AstraZeneca also considered the phrase 'conquer pain' implied absolute and maintained cessation of pain that could not be achieved and alleged that this was an exaggerated claim.

In the Panel's opinion neither the heading, 'High Achiever' nor the strapline 'Powerful PPI Performance' implied complete success. The Panel did not accept Wyeth's submission, however, that because of the context in which it appeared, the claim also did not imply complete success but only suggested the well established attributes of PPIs. The Panel considered that irrespective of the context in which it appeared the claim was a strong, unqualified claim for Zoton which was exaggerated as alleged. A breach of the Code was ruled.

AstraZeneca alleged that the question 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?' clearly implied that the majority of doctors prescribed Zoton in preference to other PPIs. However, the reference quoted only referred

to sales data. It was therefore unreasonable to make this claim. Furthermore the referenced data showed that rather than a majority, only 43.7% of all PPI counting units purchased by retail pharmacies and hospital doctors were for Zoton. AstraZeneca alleged that this claim misled and was unsubstantiable.

The Panel noted that the claim was referenced to data which related to the total amount of Zoton prescribed as number of capsules rather than the percentage of doctors who actually prescribed it. This was accepted by Wyeth which stated that as 43.7% of all PPI sales were for Zoton, which was a higher percentage than for any other PPI, this was a majority. The Panel noted that Wyeth had no data to show that the majority of doctors who prescribed any PPI, prescribed Zoton. The claim was misleading and not capable of substantiation and breaches of the Code were ruled.

AstraZeneca alleged that the claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission' with the question 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?' immediately underneath, suggested that, in comparison to other PPIs, Zoton was superior on the basis of pain relief, acid suppression, healing time etc. There was clear evidence that esomeprazole provided more prolonged acid suppression than lansoprazole and that it healed statistically significantly more patients with reflux oesophagitis than lansoprazole with more rapid onset of sustained heartburn relief. Therefore the implied comparative benefits of lansoprazole over other PPIs could not be substantiated and this claim was therefore potentially misleading.

The Panel noted its rulings above and considered that the juxtaposing of the two claims implied that Zoton was better than all other PPIs in relation to the parameters listed. A breach of the Code was ruled.

The second journal advertisement featured a picture of a pole vaulter adjacent to the heading 'Pole Position' which was followed by the claims at issue above. In AstraZeneca's view the term 'Pole Position' was well known from motor racing parlance and indicated one who was in the leading position. AstraZeneca alleged that the juxtaposing of this headline immediately above a clinical claim, followed by the message that the majority of doctors prescribed Zoton in preference to other PPIs, was highly misleading.

The Panel considered that the heading set the tone such that the juxtaposing of the two subsequent claims did imply that Zoton was better than all other PPIs in relation to acid control, pain relief and healing. A breach of the Code was ruled.

AstraZeneca reiterated its allegations that the claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission', the question 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?' and the juxtaposing of the two were in breach of the Code. The Panel considered that its rulings of breaches of the Code above applied here.

A third advertisement featured the heading 'Flying Start' above a picture of a javelin thrower. Adjacent text 'Reflux demands a rapid response. With Zoton, symptom relief and healing is fast from the start' was referenced to Castell *et al* (1996). The strapline at the bottom of the page beneath the Zoton 30mg logo, read 'Fast acting in reflux oesophagitis'. AstraZeneca considered that the claim 'fast from the start' implied that healing with lansoprazole began as soon as the patient started taking it. The Castell study, which compared lansoprazole and omeprazole in the treatment of erosive reflux oesophagitis, did not evaluate healing until week 2 and so in AstraZeneca's view it was incapable of showing that healing was fast from the start. AstraZeneca alleged that the advertisement was therefore unsubstantiable and misleading.

The Panel noted that Castell *et al* evaluated efficacy based on the percentage of patients healed after 2, 4, 6 and 8 weeks of treatment as determined from endoscopic evaluation. The Panel considered that the heading 'Flying Start', the visual of a javelin thrower aiming the javelin upwards and the strapline 'Fast acting in reflux oesophagitis' in association with the main body of text implied an immediate onset of action in relation to symptom relief and healing. The Panel queried whether 2 week data would be sufficient to support a claim for healing 'fast from the start' in this therapeutic field particularly given the overall impression of the advertisement. On balance the Panel considered the claim misleading and not capable of substantiation as alleged and ruled breaches of the Code.

A leavepiece featuring a runner on starting blocks headed 'Fast from the start' included two bar charts which depicted the results from Castell *et al* and appeared one above the other in a highlighted box beneath the main heading. The first bar chart headed '1 day' depicted the percentage of patients free of night heartburn after 1 day; Zoton 30mg as 62% and omeprazole 20mg as 52%, $p<0.05$. The second bar chart depicted the percentage nights free from heartburn after 1 week; Zoton 73% and omeprazole 67%.

AstraZeneca considered that the use of identical layouts, colours and type face to illustrate the different percentages led the reader to assume that percentages of patients were shown in both instances. This impression was further enhanced by stating the numbers of patients in each arm of the study on both sets of bars. In fact, the lower bar chart did not depict the percentage of patients at all. The overall impression given was that the symptom relief on day 1 was maintained in patients through until day 7.

The Panel considered that the design and layout of the page was such that the reader's eye was drawn to immediately compare the coloured bars depicting data from Castell *et al* under the main heading. It was not sufficiently clear that the data was not comparable. One bar chart related to patients the other to nights free from heartburn; enclosing both

bar charts within a single box compounded this impression. The page was misleading in this regard and a breach of the Code was ruled.

The claim 'Zoton has 91% initial bioavailability (in healthy volunteers)' appeared beneath the bar charts considered above and was referenced to Gerloff *et al* (1996). AstraZeneca stated that whilst the claim in itself was substantiable, its juxtaposition next to the bar charts ascribed clinical significance to the claim, when there was no reason why bioavailability *per se* was of any relevance to clinical efficacy or speed of onset of effect.

The Panel considered that although the claim would be read in the light of the clinical data presented, it had been made sufficiently clear that it related to healthy volunteers. The Panel did not consider that the presentation of the data was misleading; no breach of the Code was ruled.

A detail aid was entitled 'NICE guidance on the use of PPIs in the Treatment of Dyspepsia'. The page headed 'Competitive' and subheaded 'Consider Zoton on price and performance' featured a bar chart which depicted the cost of 4 weeks' treatment of 5 PPIs at various doses including Zoton 30mg and 15mg. At the bottom of the page beneath the product logo was the strapline 'Now more widely prescribed than any other PPI'. AstraZeneca stated that the subheading invited the reader to consider Zoton on grounds of 'price and performance', however the bar chart depicted solely a comparison of acquisition costs of different PPIs and no data on performance was presented. The reader was therefore not provided with any information upon which to base a judgement as to the relative performance of the product although the title of the page in conjunction with the bar chart would imply that Zoton was superior on both counts. As the PPIs were not equivalent in relation to performance this was an unfair and misleading comparison.

The Panel noted that the data shown in the bar chart related to the acquisition costs only of the various PPIs. The Panel considered that the heading 'Consider Zoton on price and performance' implied that the data related not only to cost but also took into account relative efficacy and that was not so; a breach of the Code was ruled.

A page headed 'Superior acid control' featured a chart in the form of a 24 hour clock face depicting the number of hours pH>4 for Zoton 15mg (12 hours), Zoton 30mg (16 hours) and omeprazole 20mg (12 hours). The claim 'Higher bioavailability than omeprazole' was followed, in small print, by 'absolute bioavailability following a single dose in volunteers (from different studies)' which introduced the two bar charts illustrating mean absolute bioavailability of single doses of omeprazole 20mg (35% (Cederberg *et al* 1989)) and lansoprazole 30mg (91% (Gerloff *et al* 1996)) each in a separate outline box. AstraZeneca alleged that it was misleading and inappropriate to juxtapose data from two separate studies in such a way as to invite the reader to directly compare them. It was, in AstraZeneca's view, far from clear that the bioavailability of PPIs had any direct relevance to either acid suppression or treatment of GORD and therefore this comparison was spurious.

The Panel noted its comments above with reference to Gerloff *et al* but noted the presentation of the bioavailability data in the detail aid now at issue was different. The Panel noted that the heading 'Higher bioavailability than omeprazole' invited the reader to directly compare the Zoton and omeprazole data from different studies and implied that it was valid to do so. That was not so and the impression created was misleading. A breach of the Code was ruled.

On a page headed 'Current prescribing in general practice', a sub-heading stated 'In the treatment of GORD, maintenance accounts for the majority of PPI prescriptions'. The descriptor 'PPI usage (licensed) in the maintenance of reflux' introduced two pie charts which depicted the results of an independent UK-wide audit. The pie charts showed the split between prescriptions for 10mg and 20mg omeprazole and 15mg and 30mg lansoprazole; the cost of treating 100 patients on this basis was calculated. AstraZeneca considered that such a comparison was extremely misleading in that the 'usage' was based on audit data of prescriptions – it took no account of whether or not the treatment was successful, or indeed of whether the patient took the dose correctly, for example doubling up a dose. Therefore it was not clear that like was being compared with like.

Above the two pie charts there was the statement 'PPI usage (licensed) in the maintenance of reflux'. AstraZeneca stated that unless Wyeth could show that the data used to support the representation by the pie-charts were truly for the licensed dose for maintenance of reflux, based on patients who actually met the definition of 'maintenance of reflux', then this was unsubstantiable.

The Panel noted that data on the page was referenced to prescribing usage data. There were no comparative efficacy or clinical claims on the page at issue. The cost comparison was clearly described as 'usage based cost of maintenance of 100 patients for 1 year', and in the Panel's view clearly related to acquisition cost of maintenance dosage. The Panel noted Wyeth's submission that patients outside licensed doses were excluded from the analysis. The Panel considered that the cost comparison was not misleading as alleged. No breach of the Code was ruled.

In relation to the claim 'PPI usage (licensed) in the maintenance of reflux', the Panel noted Wyeth's response with regard to the definition of reflux maintenance patients. In the context of the page at issue the Panel did not consider the claim unsubstantiable, as alleged. No breach of the Code was ruled.

On a page headed 'Low dose maintenance success in practice' a subheading read 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and was referenced to Cooper *et al* (2000). A highlighted box headed 'Outcome from 91 UK general practices (n=4843)' featured a pie chart above the descriptor '1,112 patients with long term

dyspeptic symptoms switched from omeprazole 20mg/day to Zoton 15mg/day at 21 weeks follow-up'.

AstraZeneca stated that this page referred to audit data on 4843 patients who switched medications, extracted from 91 practices. This data was used to support the claim that patients might be effectively switched from omeprazole 20mg to Zoton 15mg for 'maintenance'. AstraZeneca considered this page to be highly misleading. The audit actually encompassed 7121 patients, only a proportion of whom (1,112) were in fact switched from omeprazole 20mg to lansoprazole 15mg. The patients were selected on the basis that they were taking PPIs for unresolved dyspepsia and that a change in medication was 'appropriate'. AstraZeneca considered that the positioning of this page, following a page looking specifically at GORD, together with the title 'Low dose maintenance success in practice', was misleading since the indications under consideration were not the same. The reader was encouraged to believe however that lansoprazole 15mg and omeprazole 20mg were of equivalent efficacy in GORD maintenance.

The Panel considered that 'Outcome from 91 UK general practitioners (n=4843)' gave the impression that the audit encompassed 4843 patients; that was not so. The audit encompassed 7121 patients; 4843 related to the number of actual switches. The Panel noted the review authors' caveats that the 'results should be viewed in the context of the situation in which they were acquired. A large number of patients in the audit did not have a confirmed diagnosis. The *H.pylori* status and outcome of any eradication therapy was not as rigorously followed up as they would be in a formal clinical trial. Although this means that the outcome of the change in treatment is not necessarily known for every patient, it does reflect the clinical practice…'. The Panel considered that the pie chart depicted data in relation to a subgroup of patients; this had not been made sufficiently clear. It also gave the impression that the data was more robust than stated by the review authors. The Panel noted the subheading 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and considered that in conjunction with the page heading and the pie chart it was not clear that the data related to dyspepsia and not to GORD. The page implied that Zoton 15mg and omeprazole 20mg were of equivalent efficacy with regard to the treatment of GORD, this was not so. Overall the page was misleading as alleged; a breach of the Code was ruled. This ruling was appealed.

The Appeal Board considered the page misleading for the same reasons as expressed by the Panel. The Panel's ruling of a breach of the Code was upheld.

AstraZeneca noted that the statement 'Outcome from 91 UK general practices (n=4843)' appeared prominently above a box containing a pie-chart depiction of the study results. The claim '88% maintained on Zoton 15mg/day' was made in large lettering on the pie-chart. It was not until the reader looked to the bottom of the box that there was any indication that this claim referred to the smaller sub-set of 1112 patients. AstraZeneca believed this to be an attempt to mislead the audience that the claim was based on 4843 switches to lansoprazole. It was stated that the results were taken at 21 weeks follow-up. AstraZeneca believed this was also misleading. It implied that the patient was actually seen by someone involved in the study when in fact the results were based solely on a review of the patient notes. AstraZeneca did not believe that a review of the patient notes was adequately robust and systematic enough to support the above claim. AstraZeneca referred to evidence from Creed and Moran 1999 and Hatton *et al*.

The Panel considered that its comments above were relevant with regard to the review methodology, authors' caveats and presentation of the data. It did not accept Wyeth's submission that the inclusion of the n value minimised any chance of confusion that it was referring solely to the smaller subgroup; it referred to the number of switches. The long-term effect of therapy change and monitoring of compliance with amended treatment regimens was assessed by review of patient notes approximately six months after the initial stage of the audit was completed. This was not made clear. The Panel considered the claim 'Outcome from 91 UK general practices (n=4843)' and the implication that the patient was actually seen by a study investigator misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

AstraZeneca stated that although some patients could effectively be switched from omeprazole 20mg to Zoton 15mg, the claim 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' when placed together with the page heading and subsequent illustrations and claims suggested to the reader that patients in general could be switched as described. This would imply that 20mg of omeprazole might be considered to be clinically equivalent to 15mg of lansoprazole, a claim that had previously been ruled in breach of the Code (Case AUTH/964/12/99). In fact there was also a ruling of a breach of undertaking in this case because of two previous cases of breach relating to the same comparison (Cases AUTH/676/2/98 and AUTH/745/7/98). AstraZeneca supplied a recent literature search that did not show any new data supportive of comparable efficacy between the two medicines at this dose. AstraZeneca noted that this was the fourth instance that Wyeth had attempted to make this comparison.

The Panel noted that Case AUTH/964/12/99 concerned a complaint by AstraZeneca about comparisons between Losec and Zoton made by Wyeth in, *inter alia*, a cost calculation wheel and a detail aid. The Panel had considered that the cost calculator gave the impression that the doses of Zoton 15mg and omeprazole 20mg were therapeutically equivalent. Baldi *et al* (1996) had shown that omeprazole 20mg was significantly more effective than Zoton 15mg. The Panel considered that the cost calculator did not provide a fair comparison. A breach of the Code was ruled.

The Panel noted in its consideration of Case AUTH/964/12/99 that AstraZeneca had referred to previous rulings of breaches of the Code in Cases

AUTH/676/2/98 and AUTH/745/7/98. The Panel considered that the material was sufficiently similar such that it represented a failure to comply with the undertakings given in the previous cases. The Panel had therefore ruled a breach of the Code.

Turning to the present case, Case AUTH/1264/12/01, the Panel considered that although the material was different to that previously considered the impression of equivalence was such that it represented a failure to comply with the undertakings given in the previous cases. A breach of the Code was ruled. The Panel considered that Wyeth had not made sufficient effort to comply with the previous undertakings given. The company's conduct brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. These rulings were appealed.

The Appeal Board noted its acceptance above that the claim 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' implied therapeutic equivalence. The Appeal Board considered that Wyeth was thus in breach of its undertakings given in previous cases and upheld the Panel's ruling of a breach of the Code. The Appeal Board considered that Wyeth's conduct had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2.

The Appeal Board considered that Wyeth's failure to comply with previous undertakings was such that it decided to require an audit of Wyeth's procedures in relation to the Code to be carried out by the Authority in accordance with Paragraph 10.4 of the Constitution and Procedure.

On receipt of the audit report the Appeal Board decided that on the basis that Wyeth implemented the audit recommendations no further action was necessary.

AstraZeneca alleged that a cost calculator CD ROM was highly misleading and an unfair comparison as it suggested that omeprazole and Zoton were completely interchangeable. It was possible to assume that patients on 20mg of omeprazole could be switched wholesale to either 30mg or 15mg of Zoton. No constraint was provided to prevent the assumption that all patients on omeprazole 20mg could be switched to 15mg lansoprazole. The comparator was set up in such a way that hypothetical switching of patients was only from omeprazole to Zoton. There was no provision to allow for patients failing treatment and then being switched back to omeprazole. AstraZeneca again drew attention to previous rulings whereby the claim that these two medicines were clinically interchangeable had been ruled to be not substantiable. AstraZeneca therefore alleged that the cost calculator provided an unsubstantiable, unfair and unbalanced comparison. Again AstraZeneca also believed this type of comparison to be a breach of the undertakings referred to above.

The Panel noted its ruling above. The cost calculator part of the CD ROM consisted of the details of the use of omeprazole maintenance therapy being entered in the section 'Practice Data'. The next stage was a calculation of the current treatment costs, projected treatment costs and projected savings of switching patients from omeprazole to Zoton. The screen permitted the compliance rate to be set. The GP would decide the anticipated percentage split of patients changing to lansoprazole 15mg and 30mg from omeprazole. The Panel did not have before it any other audit materials or briefing instructions to the audit person. The Panel considered that the material was sufficiently different to that at issue in Case AUTH/964/12/99 such that it was not caught by the undertaking given in that case. No breach of the Code was ruled.

The Panel did not accept that the material was such that no constraint was provided to prevent the assumption that all patients on omeprazole 20mg would be switched to 15mg Zoton. The Panel noted Wyeth's submission that it was for the GP to decide according to their experience the anticipated percentage split of patients changing to Zoton 15 or 30mg from omeprazole. It was possible to set options to reflect the existing omeprazole usage and anticipated switch scenario. The Panel considered that the discretion given to the GP to decide switch options etc was such that there was no implication that the two medicines were interchangeable. No breach of the Code was ruled.

A screen was headed 'Bioavailability' followed by 'absolute bioavailability following a single dose in volunteers (from different studies)'. The screen was accessed under the heading 'Efficacy'. When choosing the Bioavailability Option, the bar chart for omeprazole came up immediately. The viewer had to click on a button to bring up the bar chart for Zoton. The two separate bar charts depicted 91% bioavailability for Zoton 30mg (n=12) and 35% bioavailability for omeprazole 20mg (n=81).

AstraZeneca referred to its complaint about bioavailability data above. On the CD ROM in the efficacy section the bar charts representing bioavailability of Zoton and omeprazole were depicted in the exact manner as in the leavepiece. In the same way as the leavepiece, AstraZeneca believed that it was misleading and inappropriate to juxtapose data from two separate studies in such a way as to invite the reader to directly compare them. The page was entitled 'Efficacy', suggesting to the user that bioavailability correlated with efficacy. It was in AstraZeneca's view far from clear that bioavailability of PPIs had any direct relevance to efficacy and therefore this comparison was spurious.

The Panel noted that there were minor differences between the bar charts at issue and those considered above; the Panel considered that its ruling above of a breach of the Code applied here. The design enhanced the impression that the data could be directly compared which was not so.

AstraZeneca noted the screen entitled 'Current prescribing in general practice' on the CD ROM was the same as on the page of the detail aid referred to above, except that the user could choose whether to see cost comparisons for 'Usage based cost of maintaining 1 patient for 28 days' or 'Usage based

cost of maintaining 100 patients for 1 year'. For the reasons stated above, AstraZeneca believed this screen was in breach of the Code.

The Panel noted that the screen at issue was different to the page of the detail aid discussed above. In addition to the 28 day cost calculation mentioned by AstraZeneca the percentage usage figures depicted by the pie charts were slightly different for each medicine and dosage; this was reflected in the cost calculation. The Panel considered that its ruling of no breach of the Code above nonetheless applied here.

AstraZeneca stated that it was its view that the misleading nature of the CD ROM was further compounded by a set of short video clips featuring an interview with a GP. The first clip was accessed by clicking on the statement 'What is your experience of switching patients on PPI maintenance therapy to Zoton?' The GP in the clip stated that 'now there is a better PPI that is more cost-effective'. This was a hanging comparison and one that implied that Zoton was superior in cost and efficacy to other PPIs. This was alleged to be unsubstantiable and misleading in breach of the Code.

The Panel considered that the statements constituted a hanging comparison even though the CD discussed switching patients from omeprazole to Zoton. The statements appeared as a separate video clip. The Panel considered the comparator was not sufficiently clear and a breach of the Code was ruled in this regard. The Panel did not accept Wyeth's submission that better should be interpreted as referring to cost effectiveness. The Panel considered that 'better' was a broad claim and within the context of the interview implied that Zoton was superior to all other PPIs. Wyeth had not submitted evidence to substantiate this broad claim which the Panel considered misleading and not capable of substantiation as alleged. Breaches of the Code were ruled on this point.

A second clip was accessed by clicking on the statement – 'What would be your advice to practices who want to undertake a switch?' The GP suggested that by switching patients to Zoton '… [the practice] will save money and improve patient care' and that '[the practice] will have no regrets'. AstraZeneca alleged this was unsubstantiable.

The Panel noted that whilst the claim was attributable to a GP, its use in such material nonetheless had to comply with the Code. To state or imply that all practices affecting a switch would have no regrets was a strong and all-encompassing claim. Wyeth had not submitted data to substantiate this. Nor had it submitted data to substantiate the cost savings or improvement in patient care. A breach of the Code was ruled.

AstraZeneca stated that there was no mention of the non-proprietary name in the CD ROM programme itself.

The Panel considered that the CD ROM and the CD case were separate items. The Panel accepted that the CD ROM case included both the brand name Zoton and its non-proprietary name. The CD itself included the brand name without the non-proprietary name. The CD programme included the product information. The Panel noted the company's submission that the CD ROM would be used by a Wyeth specialist audit person to discuss the programme for switching appropriate patients. The Panel considered that as the CD would be shown to health professionals then the CD programme should include the non-proprietary name next to the most prominent display of the brand name. Given the use of the CD it was in the Panel's view inadequate just to put the non-proprietary name on the CD case and not on the CD. The Panel therefore ruled a breach of the Code.

The Appeal Board required Wyeth to undergo an audit of its procedures in relation to the Code, as referred to above.

AstraZeneca UK Limited complained about the promotion of Zoton (lansoprazole) by Wyeth. The materials at issue were three journal advertisements (refs ZZOT2352/08/01, ZZOT2524/0801 and ZZOT2519/0801), a leavepiece (ref ZZOT2393/0101) a detail aid (ref ZZOT2468/08/01) and a CD ROM (ref ZZOT2397). AstraZeneca supplied Losec (omeprazole) and Nexium (esomeprazole).

1 Journal advertisement (ref ZZOT2352/08/01)

This double page advertisement featured a high jumper in action adjacent to the headline 'High Achiever' which preceded the claims at issue in points 1.1 and 1.2. The strapline 'Powerful PPI Performance' appeared at the bottom beneath the Zoton product logo.

1.1 Claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission'

COMPLAINT

AstraZeneca alleged that the claim at issue implied complete success in acid suppression and pain resolution that was exaggerated in relation to the available evidence.

Wyeth's own materials included data to demonstrate intra-gastric acid was maintained above pH 4 for a mean of 12 hours following ingestion of lansoprazole 15mg and for 16 hours after lansoprazole 30mg. The proportion of time over 24 hours that a medicine was able to maintain gastric pH above 4 was a standard method of evaluating acid suppressing capacity. Whilst such data clearly demonstrated lansoprazole was able to effectively suppress gastric acid production, to state without qualification that it 'beats acid' was in AstraZeneca's view exaggerated.

AstraZeneca also considered the phrase 'conquer pain' implied absolute and maintained cessation of pain that could not in practice be achieved. AstraZeneca alleged that this was an exaggerated claim in breach of Clause 7.10 of the Code.

RESPONSE

Wyeth stated that the claims were made in the context of the headline 'High Achiever', which did not imply complete success; rather it suggested the well established attributes of proton pump inhibitors (PPIs), namely that they were very effective in suppressing stomach acid and controlling symptoms, such as pain, in the vast majority of patients. It was therefore not an exaggerated claim.

PANEL RULING

Zoton was indicated for healing and long term management of gastro oesophageal reflux disease (GORD); healing and maintenance therapy for patients with duodenal ulcer, healing of benign gastric ulcer; treatment of NSAID-associated benign gastric ulcers and duodenal ulcers in patients requiring continued NSAID treatment; prophylaxis of NSAID-associated benign gastric and duodenal ulcers and relief of symptoms; treatment of Zollinger-Ellison syndrome; eradication of *H. pylori* from the upper gastro-intestinal tract in patients with peptic ulcer, in combination with antibiotics. Zoton was also effective in patients with benign peptic lesions unresponsive to H_2 receptor antagonists.

In the Panel's opinion neither the heading, 'High Achiever' nor the strapline 'Powerful PPI Performance' implied complete success. The Panel did not accept Wyeth's submission, however, that because of the context in which it appeared, the claim also did not imply complete success but only suggested the well established attributes of PPIs. The Panel considered that irrespective of the context in which it appeared the claim was a strong, unqualified claim for Zoton which was exaggerated as alleged. A breach of Clause 7.10 of the Code was ruled.

1.2 Question 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?'

COMPLAINT

AstraZeneca alleged that the question clearly implied that the majority of doctors prescribed Zoton in preference to other PPIs. The reference quoted did not however refer to prescription data at all, but to sales data (counting units, or in other words, number of tablets/capsules). Only the total amount of Zoton prescribed and not the proportion of doctors who prescribed Zoton versus other PPIs could be obtained from this data. It was therefore unreasonable to make this claim. Furthermore the referenced data (BPI, June 2001) showed that rather than a majority, only 43.7% of all PPI counting units purchased by retail pharmacies and hospital doctors were for Zoton. AstraZeneca alleged that this claim misled by implication and was unsubstantiable and therefore in breach of Clauses 7.2 and Clause 7.4 of the Code.

RESPONSE

Wyeth acknowledged that the reference reflected the total amount of Zoton prescribed. In this respect Wyeth's claim was not misleading as the 43.7% of Zoton prescribed was higher than that for any other PPI and was therefore a majority.

The claim in relation to prescription data could be substantiated with reference to DIN-Link Breadth and Depth of prescribing data. This showed that although the majority of doctors prescribed both lansoprazole and omeprazole (breadth approximately 95% for both), the depth of use (ie average number of prescriptions per prescribing doctor) was considerably higher for lansoprazole (approximately 54 prescriptions per prescribing doctor) compared with omeprazole (approximately 33 prescriptions per prescribing doctor). Wyeth stated that this was the most appropriate data currently available to substantiate the claim.

PANEL RULING

The Panel noted that the claim was referenced to BPI Maxims June 2001 which, according to AstraZeneca, related to the total amount of Zoton prescribed in terms of number of capsules rather than the percentage of doctors who actually prescribed Zoton. This was accepted by Wyeth which stated that as 43.7% of all PPI sales were for Zoton, which was a higher percentage than for any other PPI, this was a majority. The Panel also noted the DIN-Link Breadth and Depth of prescribing data in relation to Zoton and omeprazole. The Panel noted that Wyeth had no data to show that the majority of doctors who prescribed any PPI, prescribed Zoton. The claim was misleading and not capable of substantiation as alleged; breaches of Clauses 7.2 and 7.4 were ruled.

1.3 Juxtaposition of the above two statements

COMPLAINT

AstraZeneca alleged that the claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission' with the question 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?' immediately underneath, suggested to the reader that, in comparison to other PPIs, Zoton was superior on the basis of pain relief, acid suppression, healing time etc. There was clear evidence that AstraZeneca's product esomeprazole provided more prolonged acid suppression than lansoprazole and that it healed statistically significantly more patients with reflux oesophagitis than lansoprazole with more rapid onset of sustained heartburn relief. Therefore the implied comparative benefits of lansoprazole over other PPIs could not be substantiated and this claim was therefore potentially misleading and in breach of Clause 7.2.

RESPONSE

Wyeth stated that there was no implication that Zoton was clinically superior to other PPIs; rather Wyeth was listing some of the attributes pertaining to PPIs which a doctor would consider when making a PPI choice. Other factors would include cost, approved indications, range of presentations and published clinical audit/review data.

However, the current data showed that Zoton was now more widely prescribed than any other PPI, this

position arising from doctors having considered the all round attributes of Zoton as being more favourable compared with other PPIs.

PANEL RULING

The Panel noted its rulings at points 1.1 and 1.2 above. The Panel considered that the juxtaposing of the two claims implied that Zoton was better than all other PPIs in relation to the parameters listed as alleged. A breach of Clause 7.2 of the Code was ruled.

2 Journal advertisement (ref ZZOT2524/0801)

This double page advertisement featured a picture of a pole vaulter adjacent to the heading 'Pole Position' which was followed by the claims at issue in points 1.1 and 1.2 above.

2.1 Heading 'Pole Position'

COMPLAINT

In AstraZeneca's view the term 'Pole Position' was well known from motor racing parlance and indicated one who was in the leading position. AstraZeneca believed that the juxtaposing of this headline immediately above a clinical claim, that was then followed by the message that the majority of doctors prescribed Zoton in preference to other PPIs, was highly misleading in the same way as point 1.3 above and further compounded the implied comparison. This, in AstraZeneca's view, was misleading and in breach of Clause 7.2.

RESPONSE

Wyeth stated that it was fatuous to suggest that the advertisement related to motor racing as there was no depiction of a motor car; rather the headline was aligned with the image of a pole vaulter! As stated in Wyeth's response to point 1.3, similarly there was no implication that Zoton was clinically superior to other PPIs, rather that it was now the most widely prescribed PPI, with 'Pole Position' being based on doctors' beliefs in the all round attributes of Zoton compared with other PPIs.

PANEL RULING

The Panel considered its comments at point 1.3 above were relevant although the visual and heading in the present advertisement were different. The phrase 'Pole Position' was a play on words; it might be associated with the pole vaulter but in the opinion of the Panel it was more commonly associated with the vehicle in the leading position in a motor race as alleged by AstraZeneca. The Panel considered that the heading set the tone for the advertisement such that the juxtaposing of the two subsequent claims did imply that Zoton was better than all other PPIs in relation to acid control, pain relief and healing. A breach of Clause 7.2 was ruled.

2.2 Claim 'Proven to beat acid, conquer pain, heal fast and successfully maintain reflux patients in remission'

COMPLAINT

AstraZeneca alleged that this claim was in breach of Clause 7.10 as in point 1.1 above.

RESPONSE

Wyeth referred to its response in point 1.1 above.

PANEL RULING

The Panel considered its ruling at point 1.1 of a breach of Clause 7.10 applied here.

2.3 Question: 'Is this why the majority of doctors who prescribe a PPI prescribe Zoton?'

COMPLAINT

AstraZeneca alleged that this question was in breach of Clauses 7.2 and 7.4 as in point 1.2 above.

RESPONSE

Wyeth referred to its response in point 1.2 above.

PANEL RULING

The Panel considered that its ruling at point 1.2 of breaches of Clauses 7.2 and 7.4 applied here.

2.4 Juxtaposition of the above two statements

COMPLAINT

AstraZeneca alleged that this was in breach of Clause 7.2 as in point 1.3 above.

RESPONSE

Wyeth referred to its response in point 1.3 above.

PANEL RULING

The Panel considered that its ruling of a breach of Clause 7.2 at point 1.3 above applied here.

3 Journal advertisement (ref ZZOT2519/0801) featuring a javelin thrower and headline 'Flying Start'

This single page advertisement featured the heading 'Flying Start' above a picture of a javelin thrower. Adjacent text read 'Reflux demands a rapid response. With Zoton, symptom relief and healing is fast from the start' and was referenced to Castell *et al* (1996). The strapline at the bottom of the page beneath the Zoton 30mg logo, read 'Fast acting in reflux oesophagitis'.

COMPLAINT

AstraZeneca noted that the referenced study by Castell *et al* compared lansoprazole and omeprazole

in the treatment of erosive reflux oesophagitis. Healing was evaluated by endoscopy at weeks 2, 4, 6 and 8. AstraZeneca considered that the claim 'Fast from the start' implied that healing with lansoprazole began as soon as the patient started taking lansoprazole. As the Castell study did not evaluate healing until week 2 of the study, it was AstraZeneca's view that this study was incapable of showing that healing was fast from the start. AstraZeneca alleged that the advertisement was therefore unsubstantiable and misleading and thus in breach of Clauses 7.2 and 7.4.

RESPONSE

Wyeth stated that AstraZeneca had failed to point out that Castell *et al* also assessed patient diary based symptom relief – AstraZeneca was clearly aware of this as the day 1 data was depicted in the Zoton leavepiece referred to under point 4. The data showed evidence of significant symptom relief from day 1 using lansoprazole 30mg (62% relief of nocturnal heartburn), this correlated with significant day 1 acid suppression and bioavailability data.

Although Castell *et al* did not evaluate healing endoscopically at day 1 (most probably as it was not considered ethically justified or clinically relevant), current clinical practice dictated that symptom relief correlated well with healing of oesophagitis ie most gastroenterologists used symptom relief as a guide to evidence of healing rather than re-endoscoping. The claim was therefore substantiable.

PANEL RULING

The Panel noted that Castell *et al* (1996) was a randomized, double-blind, parallel group, multi centre study which compared the efficacy and safety of lansoprazole 30mg, 15mg, omeprazole 20mg and placebo in the treatment of erosive reflex oesophagitis. Efficacy was evaluated based on the percentage of patients healed after 2, 4, 6 and 8 weeks of treatment as determined from endoscopic evaluation. The results indicated that all active treatment groups had a higher healing rate than the placebo group at all time points in the study. At week 2 Zoton 30mg healed 65.3% of intention to treat patients; $p<0.001$ compared with placebo and $p<0.05$ compared with Zoton 15mg. Healing rate data of evaluable patients by baseline oesophagitis grades 2, 3 and 4 were not depicted for week 2. Primary symptom assessment included day or night heartburn, belching, gastro oesophageal regurgitation and painful swallowing as well as an evaluation of overall symptoms. Symptoms were rated as none, mild, moderate or severe and were assessed by investigation and by patient diary. Data for investigator-elicited symptom assessments were not depicted at 2, 4 and 6 weeks. Differences for all primary symptoms in evaluable patients between active and placebo groups were statistically significant at week 8. Diary data in evaluable patients showed that after the first day of therapy (mean) the first week and all eight weeks of therapy (median), the percentage with less day or night heartburn was statically significant compared with placebo. Patients receiving lansoprazole 30mg reported significantly less day and night heartburn during the first day and first week of treatment than did patients receiving omeprazole. Similar results were observed in the intention to treat population.

The Panel considered that the heading 'Flying Start' the visual of a javelin thrower aiming the javelin upwards and the strapline 'Fast acting in reflux oesophagitis' in association with the main body of text implied an immediate onset of action in relation to symptom relief and healing.

The Panel noted that Castell *et al* did not provide investigator assessed symptom data at the 2, 4 or 6 weeks time points or healing rate data prior to 2 weeks. The Panel queried whether 2 week data would be sufficient to support a claim for healing 'fast from the start' in this therapeutic field particularly given the overall impression of the advertisement. The Panel noted the data in relation to the patient diary data. On balance the Panel considered the claim misleading and not capable of substantiation as alleged and ruled breaches of Clauses 7.2 and 7.4 of the Code.

4 Leavepiece (ref ZZOT2393/0101) featuring a runner on starting blocks and headed 'Fast from the start'

4.1 Bar charts

Two bar charts depicting the results from Castell *et al* appeared one above the other in a highlighted box on page 2 beneath the main heading 'Fast relief from heartburn' and the subheading 'Symptom relief with Zoton 30mg vs omeprazole 20mg multicentre, double-blind, randomised, parallel group study'. The first bar chart headed '1 day' depicted the percentage of patients free of night heartburn after 1 day; Zoton 30mg as 62% and omeprazole 20mg as 52%, $p<0.05$. The second bar chart depicted the percentage nights free from heartburn after 1 week; Zoton 73% and omeprazole 67%.

COMPLAINT

AstraZeneca considered that the way in which the data was displayed was misleading. The use of identical layouts, colours and type face to illustrate the different percentages led the reader to assume that percentages of patients were shown in both instances. This impression was further enhanced by stating the numbers of patients in each arm of the study on both sets of bars. In fact, the lower bar chart did not depict the percentage of patients at all. The overall impression that could be given was that the symptom relief on day 1 was maintained in patients through until day 7. AstraZeneca alleged a breach of Clause 7.8.

RESPONSE

Wyeth stated that the depiction was an accurate reflection of the data tabulated in Castell's paper (Table 2: Diary Data from Evaluable Patients). The investigators chose to present percentage patient-based data after day 1 of therapy and percentage night-based data after 1 week. This was both

accurately and clearly portrayed in the depiction and could not be considered to be misleading in any way, and consequently it did not give the impression that the two were comparable – albeit they were both clinically relevant measures of onset of symptom relief, from which the authors concluded that lansoprazole 30mg provided superior symptom relief early in treatment compared with omeprazole 20mg.

PANEL RULING

The Panel noted its general comments on Castell *et al* above at point 3. The description of each bar chart; 'Percentage patients free of night heartburn after 1 day' and 'Percentage nights free from heartburn after 1 week' appeared in a small dark type face beneath each bar chart. The prominent heading 'Fast relief from heartburn' appeared in a bold yellow box; the same shade of yellow was used to depict each bar of Zoton data beneath. Omeprazole data was depicted in blue. The headings '1 day' and '1 week' were similarly prominent. The Panel considered that the design and layout of the page was such that the reader's eye was drawn to immediately compare the coloured bars depicting data from Castell *et al* under the main heading relating to relief from heartburn. It was not sufficiently clear that the data was not comparable, one bar chart related to patients the other to nights free from heartburn; enclosing both bar charts within a single box compounded this impression. The page was misleading in this regard and a breach of Clause 7.8 was ruled.

4.2 Claim 'Zoton has 91% initial bioavailability (in healthy volunteers)'

This claim appeared on page 2 beneath the bar charts considered in point 4.1 above and was referenced to Gerloff *et al* (1996).

COMPLAINT

AstraZeneca stated that whilst the claim in itself was substantiable, its juxtaposition next to the bar charts ascribed clinical significance to the claim, when there was no reason why bioavailability *per se* was of any relevance to clinical efficacy or speed of onset of effect. AstraZeneca therefore alleged a breach of Clause 7.2.

RESPONSE

Wyeth stated that it was well established that bioavailability (AUC) for PPIs correlated with acid suppression (mean 24 hour gastric pH) Tolman *et al* (1997), Lind T *et al* (1983) and Sandres *et al* (1992). Similarly there was evidence to suggest that early acid suppression correlated with early symptom relief. Consequently it was appropriate to position the Zoton day 1 high bioavailability data beneath a depiction of patients free from heartburn after day 1 of treatment, as the two parameters were indirectly related.

PANEL RULING

The Panel noted that the claim at issue was referenced to Gerloff *et al* (1996) a cross-over study in 12 healthy volunteers which investigated the pharmacokinetics and absolute bioavailability of Zoton and showed that absolute bioavailability was 91% for 30mg and 81% for 15mg.

The Panel noted that the claim at issue was a statement of fact; it related only to Zoton 30mg and in this regard the Panel noted that the subheading and other data presented on page 2 referred to Zoton 30mg. Although the claim would be read in light of the clinical data presented the Panel considered it had been made sufficiently clear that the data related to healthy volunteers and noted Wyeth's submission regarding early acid suppression and bioavailability in this regard. The Panel did not consider the presentation of the bioavailability data misleading as alleged and ruled no breach of Clause 7.2 of the Code.

5 Primary care detail aid (ref ZZOT2468/08/01)

The detail aid was entitled 'NICE guidance on the use of PPIs in the Treatment of Dyspepsia' and comprised 12 loose leaf pages printed on one side only.

5.1 Page headed 'Competitive' and subheaded 'Consider Zoton on price and performance'

The page at issue featured a bar chart which depicted the cost of 4 weeks' treatment of 5 PPIs at various doses including Zoton 30mg and 15mg. At the bottom of the page beneath the product logo was the strapline 'Now more widely prescribed than any other PPI'.

COMPLAINT

AstraZeneca stated that this page consisted solely of a comparison of acquisition costs of different PPIs at different dosages for 4 weeks' treatment.

The subheading invited the reader to consider Zoton on grounds of 'price and performance', however the comparison depicted by the bar chart was purely one of cost and no data on performance was presented. The reader was therefore not provided with any information upon which to base a judgement as to the relative performance of the product although the title of the page in conjunction with the bar chart would imply that Zoton was superior on both counts. As the PPIs were not equivalent in relation to performance this was an unfair and misleading comparison, AstraZeneca alleged a breach of Clause 7.2.

RESPONSE

Wyeth stated that the heading and subheading clearly suggested that Zoton should be considered in terms of its competitive price and competitive performance.

There was no implication that it was superior in performance, but safe to say that its all round competitive performance was reflected in the strapline that it was 'Now more widely prescribed than any other PPI'.

PANEL RULING

The data depicted in the barchart related to the acquisition costs only of the various PPIs and was

referenced to MIMS August 2001. The Panel considered that the heading 'Consider Zoton on price and performance' implied that the data depicted related not only to cost but also took into account relative efficacy and that was not so; a breach of Clause 7.2 was ruled.

During its consideration of the detail aid at issue the Panel noted that each loose-leaf page bore the statement 'Prescribing Information appears on the back page'. One loose-leaf page featured the prescribing information. The Panel considered that the loose-leaf format was such that prescribing information ought to have been printed on the reverse of each page to comply with the requirements of Clause 4.1 of the Code. The Panel requested that the company be advised of its views.

5.2 Page headed 'Superior acid control'

The top half of the page beneath a subheading 'Zoton 30mg keeps gastric pH>4 for longer than omeprazole 20mg', featured a chart in the form of a 24 hour clock face depicting the number of hours pH>4 for Zoton 15mg (12 hours), Zoton 30mg (16 hours) and omeprazole 20mg (12 hours). The claim 'Higher bioavailability than omeprazole' was followed, in small print, by 'absolute bioavailability following a single dose in volunteers (from different studies)' which introduced the two bar charts at issue, each in a separate outline box. The first bar chart depicted the percentage mean absolute bioavailability of Zoton 30mg as 91% and was referenced to Geloff *et al* (1996). The second bar-chart depicted similar data for omeprazole 20mg as 35% and was referenced to Cederberg *et al* (1989).

COMPLAINT

AstraZeneca stated that this page included two bar charts illustrating relative bioavailability of single doses of omeprazole 20mg and lansoprazole 30mg. AstraZeneca believed that it was misleading and inappropriate to juxtapose data from two separate studies in such a way as to invite the reader to directly compare them. The data were also taken from single dose studies and therefore were of questionable relevance in consideration of a disease where chronic therapy was the norm. It was, in AstraZeneca's view, far from clear that the bioavailability of PPIs had any direct relevance to either acid suppression or treatment of GORD and therefore this comparison was spurious, AstraZeneca alleged a breach of Clause 7.3.

RESPONSE

Wyeth stated that as there were no head-to-head bioavailability studies comparing lansoprazole with omeprazole, it considered it was appropriate to show single dose percentage mean absolute bioavailabilities for the two products in this context. As stated in point 4.2 above, there was evidence that bioavailability correlated with acid suppression. In this respect, the high day 1 bioavailability obtained with lansoprazole correlated with the fast onset of acid suppression, this being manifest as superior day 1 symptom relief for GORD patients taking lansoprazole compared with omeprazole. Also, it was well established that many patients on chronic PPI therapy actually used them on an intermittent/on demand basis.

Consequently, not only was it appropriate to show and juxtapose the data, but Wyeth considered that it was sufficiently clear that the data was from different studies and therefore not misleading.

PANEL RULING

The Panel noted its comments at point 4.2 above with reference to Gerloff *et al* but noted the presentation of the bioavailability data in the detail aid now at issue was different. The Panel noted that the heading 'Higher bioavailability than omeprazole' invited the reader to directly compare the Zoton and omeprazole data from different studies and implied that it was valid to do so. That was not so. The Panel noted that there was some data on clinical relevance but Panel considered that nonetheless the impression created was misleading. A breach of Clause 7.3 was ruled.

5.3 Page headed 'Current prescribing in general practice'

The subheading 'In the treatment of GORD, maintenance accounts for the majority of PPI prescriptions' was followed by the descriptor 'PPI usage (licensed) in the maintenance of reflux' which introduced two pie charts which depicted the results of an independent UK-wide audit. The Zoton pie chart depicted 36% at 30mg and 64% at 15mg, the omeprazole pie chart depicted 66% at 20mg and 34% at 10mg. The claim 'Usage cost of maintaining 100 patients for 1 year Zoton £21,914 omeprazole £32,863' appeared at the bottom of the page.

COMPLAINT

AstraZeneca stated that this page had two pie-charts showing the split between prescriptions for the 10mg and 20mg doses of omeprazole and the 15mg and 30mg doses of lansoprazole and went further to calculate the cost of treating 100 patients on this basis. However AstraZeneca considered that such a comparison was extremely misleading in that the 'usage' was based on audit data of prescriptions – it took no account of whether or not the treatment was successful, or indeed of whether the patient took the dose correctly, for example doubling up a dose. Therefore it was not clear that like was being compared with like. A breach of Clause 7.3 was alleged.

Above the two pie charts there was the statement 'PPI usage (licensed) in the maintenance of reflux'. Unless Wyeth could show that the DIN-Link data used to support the representation by the pie-charts were truly for the licensed dose for maintenance of reflux, based on patients who actually met the definition of 'maintenance of reflux', then this was unsubstantiable and in breach of Clause 7.4.

RESPONSE

Wyeth stated that the issue of the robustness of the referenced DIN-Link data had been the subject of minuted informal discussions between Wyeth and AstraZeneca. Wyeth provided AstraZeneca with a document from Compufile explaining how the DIN-Link data was derived. Wyeth stated that the DIN-Link data source best reflected PPI usage in GORD maintenance. However, although AstraZeneca undertook to provide Wyeth with alternative source data showing different percentages, no data was provided and the issue was dropped from the agenda.

A document from Compufile was provided which Wyeth stated clearly explained how the GP prescribing data for PPIs in relation to reflux maintenance therapy was derived using the DIN-Link system. The identification of reflux patients was based upon Read codes, with those who had remained on the same therapy continuously for 6 months out of the 12 month observation period being defined as reflux maintenance patients.

Patients outside licensed doses (as shown in the accompanying data print out) were excluded from the analysis. As stated above, the data adequately reflected long-term usage (ie 6 months continuous usage out of a 12 month observation period) and consequently appropriately reflected a satisfactory long-term response. Compufile had reassured Wyeth that patients taking twice daily doses, albeit they were a minimal number, could be identified and were appropriately represented.

Wyeth considered that the Compufile DIN-Link derived data was substantiable and also adequately compared like with like.

PANEL RULING

The Panel noted that data on the page was referenced to DIN-Link August 2001 and related to prescribing usage. There were no comparative efficacy or clinical claims on the page at issue. The cost comparison was clearly described as 'usage based cost of maintenance of 100 patients for 1 year', and in the Panel's view clearly related to acquisition cost of maintenance dosage. The Panel noted Wyeth's submission that patients outside licensed doses were excluded from the analysis. The Panel considered that the cost comparison was not misleading as alleged. No breach of Clause 7.3 was ruled.

In relation to the claim 'PPI usage (licensed) in the maintenance of reflux', the Panel noted Wyeth's response with regard to the definition of reflux maintenance patients. In the context of the page at issue Panel did not consider the claim unsubstantiable, as alleged. No breach of Clause 7.4 of the Code was ruled.

5.4 Page headed 'Low dose maintenance success in practice'

The subheading read 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and was referenced to Cooper *et al* (2000). A highlighted box, headed 'Outcome from 91 UK general practices (n=4843)' featured a pie chart above the descriptor '1,112 patients with long term dyspeptic symptoms switched from omeprazole 20mg/day to Zoton 15mg/day at 21 weeks follow-up'. The pie chart depicted 88% of patients maintained on Zoton 15mg/day; 4% changed to no treatment and 8% changed to other medication. 'The switch from omeprazole to Zoton was well tolerated by the vast majority of patients' appeared beneath the box.

5.4.1 Switching patients

COMPLAINT

AstraZeneca stated that this page referred to audit data on 4843 patients who switched medications, extracted from 91 practices. This data was used to support the claim that patients might be effectively switched from omeprazole 20mg to Zoton 15mg for 'maintenance'. AstraZeneca considered this page to be highly misleading. The audit actually encompassed 7121 patients, only a proportion of whom (1,112) were in fact switched from omeprazole 20mg to lansoprazole 15mg. The patients were selected on the basis that they were taking PPIs for unresolved dyspepsia and that a change in medication was 'appropriate'. AstraZeneca considered that the positioning of this page, following, as it did, from a page looking specifically at GORD, together with the title 'Low dose maintenance success in practice', was misleading since the indications under consideration were not the same. The reader was encouraged to believe however that lansoprazole 15mg and omeprazole 20mg were of equivalent efficacy in GORD maintenance. AstraZeneca believed this was therefore a breach of Clause 7.2.

RESPONSE

Wyeth stated that this issue had been extensively discussed at informal intercompany meetings, with Wyeth incorporating changes as considered appropriate in light of the discussions.

The page clearly only referred to the 'switch' element of the audit/prescribing review and hence it was considered more appropriate to cite the number of changes ('switches') rather than the total number of patients reviewed, as the latter would also have included non-switchers. Indeed in the context of 'switch', it would appear to be misleading to cite the total number of patients reviewed.

The patients had to have had a history of dyspepsia for at least the past 12 months, during which time they had to have been prescribed acid-lowering medicines more than 3 times. In this respect, it was perfectly correct to refer to the patients as having long-term dyspeptic symptoms.

There was no implication whatsoever that this page referred to GORD as AstraZeneca asserted. 'Low dose maintenance success in practice' clearly related to this stand-alone page. This referred to a 'switch' programme largely showing that long-term dyspeptic patients could effectively be changed from a higher and more expensive initial dose (omeprazole 20mg) to

a less expensive, lower dose (lansoprazole 15mg) as a long-term maintenance therapy. This was in keeping with NICE Guidance on the subject. Consequently there was no attempt to suggest that the comparison was between maintenance doses of lansoprazole and omeprazole.

PANEL RULING

Cooper *et al* (2000) was an audit in general practice to review the management of dyspepsia, improve care, rationalise therapy and reduce costs. Policy included identifying patients receiving PPI therapy and changing to low dose cost effect therapy. The audit was ongoing and the paper reported the results at the end of July 1999. The audit involved 7121 patients and a total of 4843 medicine changes including 1906 changes to Zoton 15mg of which 1112 were from omeprazole 20mg. An average of 21 weeks after initial review 88% of these patients remained on Zoton 15mg. The review authors warned that the 'results should be viewed in the context of the situation in which they were acquired. A large number of patients in the audit did not have a confirmed diagnosis. The *H.pylori* status and outcome of any eradication therapy was not as rigorously followed up as they would be in a formal clinical trial. Although this means that the outcome of the change in treatment is not necessarily known for every patient, it does reflect the clinical practice…'.

The Panel considered that 'Outcome from 91 UK general practitioners (n=4843)' gave the impression that the audit encompassed 4843 patients; that was not so. The audit encompassed 7121 patients; 4843 related to the number of actual switches. The Panel noted the review authors' caveats. The Panel considered that the pie chart depicted data in relation to a subgroup of patients; this had not been made sufficiently clear. It also gave the impression that the data was more robust than stated by the review authors. The Panel noted the subheading 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and considered that in conjunction with the page heading and the pie chart it was not clear that the data related to dyspepsia and not to GORD. The page implied that Zoton 15mg and omeprazole 20mg were of equivalent efficacy with regard to the treatment of GORD, this was not so. Overall the page was misleading as alleged; a breach of Clause 7.2 was ruled.

APPEAL BY WYETH

Wyeth noted that the Panel considered that 'Outcome from 91 UK general practitioners (n=4843)' gave the impression that the audit encompassed 4843 patients and that this was not so. Wyeth agreed; the study involved 7121 patients. The 4843 patients referred to were the number of medicine switches that were considered in the audit/prescribing review. The item in question clearly related to switches; in Wyeth's view it would have been misleading to cite the total number of patients, as this would have suggested a much larger patient population were involved in the review programme.

Wyeth noted that the Panel considered that the pie chart depicted data in relation to a subgroup of patients and that this had not been made sufficiently clear. The Panel also considered that the impression was given that the data was more robust than stated by the review authors.

As stated in the subheading – 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' – the purpose of this page was to inform GPs that the referenced study provided good practical evidence that patients could be effectively switched to Zoton 15mg from omeprazole 20mg.

The pie chart provided a graphic illustration of the study results that supported such a claim. The pie chart was contained in a highlighted box with all the relevant clarifying data. The data clearly identified the subgroup of patients ie: those with long term dyspeptic symptoms; that the results were based on 21 weeks follow up.

Wyeth did not accept that the pie chart depiction was not clear. Furthermore, Wyeth did not accept that the impression given was that the data was more robust than stated by the review authors. The page did not seek to do anything other than present data representing actual clinical practice, indeed Wyeth had not understood this to be an issue.

Wyeth noted that the Panel noted the subheading 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and considered that in conjunction with the page heading and the pie chart it was not clear that the data related to dyspepsia and not to GORD.

There was no mention of GORD at all on this page and so Wyeth found it difficult to comprehend how the Panel considered that a GP could gain the impression that this page related to GORD.

The patient group depicted in the chart was clearly stated as being 'patients with long term dyspeptic symptoms' – Wyeth made no further claim, nor implied more by the remaining content of the page. The statement gave a clear, unambiguous indication that the subject matter of the page was patients with long-term dyspeptic symptoms – and not GORD.

Wyeth could only assume that the Panel had accepted AstraZeneca's assertion that simply because the audit page followed on from a previous item relating to GORD, it implied that this item also related to GORD. In all respects, this item was a stand-alone page, Wyeth did not accept that it sought to rely on other items or pages for interpretation – as the page in question was from a detail aid accurate interpretation would be provided by the representative.

In such circumstances, Wyeth did not accept that the juxtaposition of the two pages could be used to read more into the page than was appropriate. Wyeth did not accept that the GP would read anything more into the page than was stated, and certainly not be misled into thinking that GORD was still being referred to.

Wyeth noted that the Panel stated that the page implied that 'Zoton 15mg and omeprazole 20mg were of equivalent efficacy with regard to the treatment of GORD' and that this was not so. There was no claim of equivalent efficacy. The item in question clearly stated that 'patients with long term dyspeptic

symptoms, can effectively be switched from omeprazole 20mg to Zoton 15mg' and this fact was substantiated by data taken from the clinical setting. The item did not state the two products were of equal efficacy in the treatment of GORD, the GP would well understand that equivalent efficacy was not a prerequisite for effective switching.

Wyeth noted that this item had been the subject of extensive informal discussions between Wyeth and AstraZeneca, and Wyeth had, prior to this complaint, incorporated changes considered necessary in the light of those discussions.

COMMENTS FROM ASTRAZENECA

AstraZeneca believed this page was misleading because the data related to maintenance treatment for patients with long-term dyspeptic symptoms, yet the impression likely to be given to readers was that the page referred to maintenance treatment for GORD. The reasons that led to this impression were:

a) *Flow of pages* The flow of the following four consecutive pages, which made the page in question misleading, was as follows: page discussing low dose maintenance of GORD; page discussing the prescribing trends in general practice in GORD maintenance; page in question; and page discussing healing of reflux oesophagitis (RO), which was the erosive form of GORD.

The very position of the page titled 'Low dose maintenance success in practice' within these four pages would lead the reader to consider the page in the context of GORD.

Indeed the page in question made no mention of the indication discussed – 'long term dyspeptic symptoms' – until three quarters down the page. AstraZeneca believed that Wyeth had failed to make this clear enough to the reader and this was further compounded due to the fact that it was in a small font, in an enclosed box and was the third statement made on the page.

b) *Title Structuring* The title structuring of the four pages referred to above was further likely to mislead. The pages were set up as a header in capital letters and sub-header underneath this, as follows:

page 1
EFFECTIVE LOW DOSE MAINTENANCE

Zoton 15mg maintains 69-87% of GORD patients in endoscopic remission for 12 months

page 2
CURRENT PRESCRIBING IN GENERAL PRACTICE

In the treatment of GORD, maintenance accounts for the majority of PPI prescriptions

page 3
LOW DOSE MAINTENANCE SUCCESS IN PRACTICE

Patients can effectively be switched from omeprazole 20mg to Zoton 15mg

page 4
HIGHLY EFFECTIVE HEALING

Zoton 30mg is as effective as omeprazole 40mg

AstraZeneca believed that Wyeth should have taken greater care to prevent the audience gaining the misleading impression that the switch audit related to GORD maintenance given that the sub-header of the previous two pages referred to GORD and the following page related to a claim in the treatment of reflux oesophagitis ie GORD.

c) *Use of 'maintenance'* The title of the page 'Low dose maintenance success in practice' was misleading. AstraZeneca believed that in this therapy area the word 'maintenance' was generally associated with the treatment of GORD or acid-related ulcer disease unless clearly defined.

This was backed-up by the NICE guidance on the use of proton pump inhibitors (PPIs) in the treatment of dyspepsia. In this document NICE described dyspepsia in its broadest sense as a catch all for a number of conditions. Specifically NICE did not recommend PPIs for the maintenance of non-ulcer dyspepsia (NUD) which made up 60% of the population with dyspepsia. NICE only recommended maintenance therapy with PPIs for some patients with GORD and ulcer disease. Practitioners who were familiar with the NICE guidance would not tend to associate the use of PPIs for maintenance of patients with general symptoms of dyspepsia but rather those of more specific diagnoses such as GORD.

There was already a high degree of confusion amongst GPs as to the definition of 'dyspepsia'. NICE used the term in its broadest sense but it went on to clearly define it in depth as being made up of GORD, gastric and duodenal ulcer disease, stomach cancer and NUD. Wyeth appeared to be trying to use dyspepsia in its broadest sense when referring to maintenance treatment when in fact 60% of patients, according to the NICE guidance, should not be treated with PPIs. The page in question was from a detail aid itself titled 'NICE Guidance on the use of PPIs in the Treatment of Dyspepsia'. This page therefore misled in the overall context of the piece as it clearly misrepresented the NICE guidance.

Further illustration that the word 'maintenance' was unlikely to be associated with the long-term maintenance treatment of dyspeptic symptoms came from the SPC for Zoton in which 'maintenance' treatment was only recommended in GORD and duodenal ulcer disease.

Crucially, Zoton was not licensed for acid-related dyspepsia other than for intermittent courses of 2-4 weeks and investigation was advised if there was no response after 4 weeks. It was for this reason that AstraZeneca not only believed the page to be misleading but that it could even be questioned whether it was promotion of a product outside its product licence, given that the page referred to maintenance treatment for patients with long-term dyspeptic symptoms not followed-up until 21 weeks after initiating treatment.

d) *Misuse of Data* AstraZeneca believed that the manner in which the data was used to demonstrate this 'maintenance success' was misleading. The audit encompassed 7121 patients and only a small proportion of these (1112) were actually switched specifically from omeprazole 20mg to lansoprazole

15mg. The page made no mention of the total number of patients in the audit but instead referred to the actual number of patients who switched medications (4843). The failure to cite the total number of patients left the reader to assume that 4843 patients in total made up the audit. The misleading impression was therefore given that the switch success figures were of a greater proportion of the total audit numbers than in actual fact. AstraZeneca therefore disagreed with Wyeth's view that to have stated the total number of patients in the study would have been misleading. In fact the converse to this clearly applied.

Analysis of the study results showed that of the 4843 patients who switched medications 2937 (61%) of patients were not switched to lansoprazole. The study report showed examples of how misleading the data presented in the detail aid was; for example 515 patients were actually switched from lansoprazole 15mg to a different medication and of these patients 214 were actually switched to omeprazole 20mg. This cast further doubt over the validity of using this data to support the claim of effective switching.

The page title suggested that the data reflected clinical 'practice'. AstraZeneca believed that to truly reflect clinical practice all of the patients making up the total audit should have been illustrated rather than selecting a much smaller subgroup. Furthermore, it was stated on the page that the patients who switched medications were followed up at 21 weeks. In actual fact there was no physical consultation with an investigator of any description and the results were only based on a follow-up of patient notes. This would appear unlikely to be in line with current best clinical practice and as the authors of the study suggested, the 'results should be viewed in the context of the situation in which they were acquired'.

Finally it was not even clear to the reader that the results came from an audit and could be mistakenly taken to be from a clinical trial.

For the reasons above AstraZeneca believed that the Panel ruling was correct and this page was misleading and therefore in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

At the appeal hearing the Wyeth representatives pointed out that AstraZeneca's comments about possible promotion outside Zoton's marketing authorization and the use of the word 'maintenance', being generally associated with the treatment of GORD or acid-related ulcer disease, had not been previously raised as part of the complaint.

Firstly the Appeal Board noted that the order of the loose leaf pages was different to that referred to by AstraZeneca. The page AstraZeneca referred to as following the page in question did not and in the detail aid supplied by Wyeth it appeared as the third page following the page in question. The page in question was followed by a page headed 'A rational choice' with a photograph of a pole vaulter. The Appeal Board noted that the subheadings to each of the two pages preceding that at issue referred to GORD. The first bullet point of the following page similarly referred to GORD in the claim 'Zoton 30mg is an optimal GORD healing dose'.

The Appeal Board considered that 'Outcome from 91 UK general practitioners (n=4843)' gave the impression that the audit encompassed 4843 patients; that was not so. The audit encompassed 7121 patients; 4843 related to the number of actual switches. The review authors' caveats were noted. The Appeal Board considered that the pie chart depicted data in relation to a subgroup of patients; this had not been made sufficiently clear. It also gave the impression that the data was more robust than stated by the review authors. The Appeal Board noted the subheading 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' and considered that in conjunction with the page heading and the pie chart it was not clear that the data related to dyspepsia and not to GORD. Nor did the Appeal Board accept that the claim merely implied that the referenced study provided good practical evidence that patients could be effectively switched to Zoton 15mg from omeprazole 20mg as submitted by Wyeth. The Appeal Board's view was that the page implied that Zoton 15mg and omeprazole 20mg were of equivalent efficacy with regard to the treatment of GORD, this was not so. Overall the Appeal Board considered the page misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

5.4.2 Claim '88% maintained on Zoton 15mg/day'

COMPLAINT

AstraZeneca noted that the statement 'Outcome from 91 UK general practices (n=4843)' appeared prominently above a box containing a pie-chart depiction of the study results. The claim at issue was made in large lettering on the pie-chart. It was not until the reader looked to the bottom of the box that there was any indication that this claim referred to the smaller sub-set of 1112 patients. AstraZeneca believed this to be an attempt to mislead the audience that the claim was based on 4843 switches to lansoprazole. It was stated that the results were taken at 21 weeks follow-up. AstraZeneca believed this was also misleading. It implied that the patient was actually seen by someone involved in the study when in fact the results were based solely on a review of the patient notes. AstraZeneca did not believe that a review of the patient notes was adequately robust and systematic enough for the review to support the above claim. AstraZeneca had evidence from a separate study of 82 GP practices in Devon that up to 42% of patients experienced significant problems when switching from omeprazole to lansoprazole (Creed and Moran 1999). Another study from the United States demonstrated a treatment failure rate of 57% in GORD patients switching from omeprazole 20mg to Zoton 15mg (Hatton *et al*). This latter study highlighted that the documentation of GP notes could be inadequate as the authors stated that it was not often possible to establish the nature of the problem from the GP notes.

AstraZeneca therefore alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

Wyeth stated that, once again, this issue of including the 'n' value was specifically discussed and resolved at informal intercompany meetings. Wyeth agreed to include an 'n' value at AstraZeneca's request so as to minimise any chance of confusion that Wyeth was referring solely to the smaller sub-group. Wyeth believed that this representation was conventional and appropriate and consequently was not misleading.

The method of follow-up by review of patient notes was clearly stated in the Cooper paper and was considered to be an adequately robust and systematic follow-up method by the journal's review board, as the study was published in a UK peer reviewed journal. The review of a patient's notes also included reviewing the repeat prescription card so as to get an accurate compliance rate. Wyeth believed that this method was robust within the NHS patient notes system and consequently could not be considered to be misleading. Indeed it was invidious and grossly misleading for AstraZeneca to cite a non-comparable US paper as a compliance comparison (Hatton *et al*). In addition, the authors did not state 'that it was often not possible to establish the nature of the problem from the GP notes' as stated by AstraZeneca, rather that 'Telephone interviews were conducted with all patients to ensure reliability and expand the information collected from the charts'.

The Creed and Moran study cited by AstraZeneca was the subject of an issue raised by Wyeth at informal intercompany meetings. The issues centred around this non peer reviewed abstract initially being used promotionally by AstraZeneca. Later it was cited by the company in a press release. On both occasions AstraZeneca agreed to cease further distribution of the respective items.

The study was an AstraZeneca sponsored postal questionnaire sent out to all 109 GPs in North Devon, to which 82 replied as AstraZeneca stated. However, what AstraZeneca misleadingly failed to say was that it quoted data from a selected subset of only 3 group practices, representing only 12 GPs (15%). This was not only highly misleading but also, as discussed and tacitly agreed at intercompany level, was an unacceptably biased population.

In support of this being a non-representative group, an independently published postal switch based study was also carried out in North Devon by a pharmacist and GPs in a community health centre. This showed that at least 80% of patients (40/50) who switched from omeprazole 20mg to lansoprazole 15mg were satisfactorily maintained at 6 month follow-up audit.

The study by Hatton *et al* from a veterans population in the US and cited by AstraZeneca was again a grossly misleading interpretation of the data. This study actually showed that 85% of patients were successfully switched from omeprazole to lansoprazole (ie only 15% [108/722] were unsuccessful). AstraZeneca would appear to have attempted to mislead the Authority by quoting data from the subgroup of 108 (15%) unsuccessful switches, which showed that 62 (57%) were true lansoprazole failures.

To further represent the balance of evidence, a similar study by Krinsky *et al* carried out in the US amongst a veterans population showed a 90% successful switch rate. This was in accord with the Hatton data when it was correctly represented.

There was a substantial published data base to support the audit scenario similar to that outlined in the Cooper *et al* paper. In addition there were two further papers, cited by AstraZeneca, which showed successful Zoton switches.

PANEL RULING

The Panel considered that its comments at point 5.4.1 above were relevant with regard to the review methodology, authors' caveats and presentation of the data. It did not accept Wyeth's submission that the inclusion of the n value minimised any chance of confusion that it was referring solely to the smaller subgroup; it referred to the number of switches. The long-term effect of therapy change and monitoring of compliance with amended treatment regimens was assessed by review of patient notes approximately six months after the initial stage of the audit was completed. This was not made clear.

The Panel considered the claim 'Outcome from 91 UK general practices (n=4843)' and the implication that the patient was actually seen by a study investigator misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

5.4.3 Claim 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg'

COMPLAINT

AstraZeneca stated that although some patients could effectively be switched from omeprazole 20mg to Zoton 15mg, the claim when placed together with the page heading and subsequent illustrations and claims suggested to the reader that patients in general could be switched as described. This would imply that 20mg of omeprazole might be considered to be clinically equivalent to 15mg of lansoprazole, a claim that had previously been ruled in breach of Clause 7.2 of the Code (Case AUTH/964/12/99). In fact there was also a ruling of a breach of undertaking in this case because of two previous cases of breach relating to the same comparison (Cases AUTH/676/2/98 and AUTH/745/7/98).

AstraZeneca believed that this was a breach of Clause 22 as a recent literature search it had conducted did not show any new data supportive of comparable efficacy between the two medicines at this dose. Since this was the fourth instance that Wyeth had attempted to make this comparison, and a repeated breach of Clause 22, AstraZeneca alleged this also to be a breach of Clause 2.

RESPONSE

Wyeth stated that it was only too apparent that this page related solely to the Cooper *et al* audit data, showing that 88% of switches from omeprazole 20mg to lansoprazole 15mg in patients with long-term

dyspeptic symptoms were successful at 21 week follow-up. It was clear that this applied only to the stated patient group.

This audit scenario clearly stood alone from the three previous rulings cited by AstraZeneca. The audit scenario was quite distinct from a randomized clinical trial setting in that it was more naturalistic in type (ie representing day-to-day clinical practice). Also, as outlined in Wyeth's response to point 5.4.2 above, the Cooper audit data was supported by a substantial published data base.

Consequently, it was incorrect for AstraZeneca to allege a breach of Clause 22 and therefore also totally inappropriate to allege a breach of Clause 2.

PANEL RULING

The Panel noted that Case AUTH/964/12/99 concerned a complaint by AstraZeneca about comparisons between Losec and Zoton made by Wyeth in, *inter alia*, a cost calculation wheel and a detail aid. The cost calculation wheel stated that it compared the differences in cost between the most commonly prescribed doses of Zoton (15mg; £14.21/28 days) and omeprazole (20mg; £28.56/28 days) in reflux maintenance and could be used to calculate the monthly and annual costs and savings associated with prescribing Zoton 15mg as opposed to omeprazole 20mg for 10, 50, 100, 200, 500, 750 or 1000 patients. The Panel noted that since that case the cost of Zoton 15mg had been reduced to £12.98/28 days.

In Case AUTH/964/12/99 the Panel had considered that, contrary to Wyeth's submission, the cost calculator gave the impression that the doses of Zoton 15mg and omeprazole 20mg were therapeutically equivalent. In the Panel's view it was not unreasonable for some readers to assume that in reflux maintenance it was a simple choice between prescribing Zoton 15mg or omeprazole 20mg. The Baldi *et al* (1996) data had shown that omeprazole 20mg was significantly more effective than Zoton 15mg. The Panel considered that the cost calculator did not provide a fair comparison. Zoton 15mg and omeprazole 20mg were not the only doses of each medicine which could be used in reflux maintenance, the impression given was that they were therapeutically equivalent and although they were the most commonly prescribed doses of each medicine, they accounted for different percentages of patients. A breach of Clause 7.2 was ruled.

The Panel noted in its consideration of Case AUTH/964/12/99 that AstraZeneca had referred to previous rulings of breaches of the Code in Cases AUTH/676/2/98 and AUTH/745/7/98. The Panel noted that the material at issue in this case was not the same as the material at issue in the previous two cases. The Panel considered that nonetheless the material was sufficiently similar such that it represented a failure to comply with the undertakings given in the previous cases. The Panel had therefore ruled a breach of Clause 21 of the Code (1998 edition).

Turning to the present case AUTH/1264/12/01 the Panel considered that the material was different to that previously considered which related to a cost calculation wheel and the impression of therapeutic equivalence of Zoton 15mg and omeprazole 20mg in reflux maintenance. The Panel did not accept Wyeth's submission that it was only too apparent that the page related solely to the Cooper *et al* audit data. The claim now at issue appeared before any reference to the audit data. The Panel noted its ruling at point 5.4.1 above and considered that the impression of equivalence was such that it represented a failure to comply with the undertakings given in the previous cases. A breach of Clause 22 was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was important for the reputation of the industry that companies complied with undertakings. The Panel considered that Wyeth had not made sufficient effort to comply with the previous undertakings given. The company's conduct brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled.

APPEAL BY WYETH

Wyeth noted that the Panel considered that the material was different to that previously considered which related to a cost calculation wheel, and the impression of therapeutic equivalence of Zoton 15mg and omeprazole 20mg in reflux maintenance. Wyeth agreed with this view and considered it to be material to the issue in question. More specifically, the previous scenarios ruled in breach were based on comparisons of Zoton 15mg and omeprazole 20mg in relation to the following: simple cost differences/savings (Case AUTH/676/2/98); randomised controlled trials in GORD maintenance (Case AUTH/745/7/98); cost savings, based on the most commonly prescribed doses in reflux maintenance (Case AUTH/964/12/99).

Wyeth noted that the Panel did not accept its submission that it was only too apparent that the page related solely to the Cooper *et al* audit data. Wyeth did not accept this – the subheading was clearly referenced and it was clear that the rest of the page was providing graphic illustration of the Cooper *et al* audit data.

Wyeth noted that the Panel stated that the claim now at issue appeared before any reference to the audit data. Wyeth did not accept this – the subheading was clearly referenced as being in relation to the Cooper *et al* audit data and there could be no doubt in this regard.

Wyeth noted that the Panel noted its ruling at point 5.4.1 and considered that the impression of equivalence was such that it represented a failure to comply with previous undertakings and ruled a breach of Clause 22. For the reasons stated at above, Wyeth did not accept that any impression of equivalence was given by the item. The company refuted any suggestion that this page could be misleading in referring to GORD. The GP audience would very well understand that effective switching did not require equivalence, and no such implication of equivalence was made or sought. In particular,

GPs would readily recognise and understand the NICE recommended process of reviewing patients 'in practice' on long-term treatment and 'switching' them, where appropriate, from a higher and more expensive initial dose to an effective but less expensive lower dose for long-term maintenance therapy. As such there could be no consequent misleading implication that Zoton 15mg and omeprazole 20mg were of equivalence in the treatment of GORD. It would be apparent to a GP that the page referred to audit data, with the patient group being stated as those with 'long-term dyspeptic symptoms'.

In the case of this item, neither the heading 'Low dose maintenance success in practice' nor the subheading 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' made any suggestion to GPs that Wyeth was comparing the products in any scenarios outlined in the previous cases, and subject to previous undertakings. In particular there was no suggestion of a randomised controlled trial setting relating to GORD maintenance therapy.

Wyeth did not accept that it had failed to comply with previous undertakings by publishing this item. Indeed, the company had, in response to previous undertakings, moved the claim away from therapeutic equivalence of the two products to simply a claim that patients could be effectively switched from one product to the other.

Accordingly, Wyeth appealed the ruling of a breach of Clause 22.

Wyeth noted that the Panel considered that the company had not made sufficient effort to comply with previous undertakings and to such an extent that Wyeth's conduct had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. For the reasons outlined above, Wyeth did not accept that it had failed to comply with previous undertakings and certainly did not accept that it had made insufficient effort to comply with previous undertakings. It was readily apparent that the audit scenario depicted was different to previous comparisons, and that a claim of effective switching was different to therapeutic equivalence.

Consequently, given the facts, it would appear both improper and without foundation to conclude that Wyeth had brought discredit upon and reduced confidence in the pharmaceutical industry. Such a finding was reserved for cases of particular censure and Wyeth did not accept that this was a case that deserved such a ruling, if any ruling in breach was deserved in relation to this item at all.

COMMENTS FROM ASTRAZENECA

AstraZeneca believed that the purpose of this page was to give the audience the impression that omeprazole 20mg and Zoton 15mg were of equivalent efficacy in the maintenance of GORD (reflux disease). AstraZeneca submitted that as it had demonstrated above, the page was misleading as readers could incorrectly assume that it applied to the maintenance treatment of GORD.

The impression of equivalent efficacy was given by the claims on the page:

'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg'

The term switched was generally used when describing the changing of a therapy to a therapy of equivalent efficacy for other reasons such as formulary or cost considerations; in other words, that the two therapies were interchangeable. To suggest that patients could effectively be switched from omeprazole 20mg to Zoton 15mg was clearly implying equivalent efficacy.

'Low dose maintenance success in practice'

This claim was used as the title of the page. As already described, the use of the word maintenance in this context implied that the effective switching of patients could be achieved in GORD maintenance. By using success in this context the overriding impression of effective switching of patients from omeprazole 20mg to Zoton 15mg/day and of equivalent efficacy at these doses was compounded.

AstraZeneca believed that this constituted a repeated breach of undertaking in light of the three previous rulings outlined below:

In Case AUTH/676/2/98 the Panel had ruled that a cost comparison in an advertisement ref: ZZOT840/0298 was in breach of Clause 7.2 of the Code as it referred only to Zoton 15mg and omeprazole 20mg and therefore readers would assume that that these were the only licensed doses. AstraZeneca believed this again implied a degree of equivalence in efficacy as the reader was led to believe that the only differentiating factor between the two was the price.

In Case AUTH/745/7/98 Astra alleged that by misrepresenting the Baldi *et al* data in promotional material Wyeth had attempted to imply that lansoprazole 15mg and omeprazole 20mg were equivalent in the maintenance of GORD. Wyeth had misrepresented the data in the following promotional materials using the claims outlined, which were ruled in breach:

Advertisement ref: ZZOT 861A/0498

Claim 'Zoton 15mg – comparable 12 month remission rates to omeprazole 20mg'.

Fact book ref: ZZOT 736/1297

Text 'In a comparison of Zoton 15mg and 30mg and omeprazole 20mg, the proportion of patients in whom compliance was >80% who were maintained in endoscopic remission was slightly greater than in the previous study, with 91% (15mg) and 96% (30mg) of patients in the Zoton groups successfully maintained over 12 months of treatment compared with 94% of patients treated with omeprazole. There was no significant difference between the treatments in the proportion of patients who remained in endoscopic remission'.

Text 'Zoton has never been beaten in any published comparative study. (In no published comparative study has a PPI demonstrated a statistically significant advantage over Zoton at recommended doses in licensed indications for Zoton)'.

Key Clinical References Summary document ref: ZZOT 740/079

Text 'The authors concluded that lansoprazole 15mg and lansoprazole 30mg is as safe and effective as omeprazole 20mg in the maintenance treatment of reflux oesophagitis'.

As the data did not substantiate this (in fact the Baldi data showed that omeprazole 20mg was significantly more effective than lansoprazole 15mg) the Panel had ruled a breach of Clause 7.2 of the Code and Clause 2. The Appeal Board had upheld these rulings.

In Case AUTH/964/12/99 the Panel had ruled that a cost comparator wheel that compared the differences in cost of Zoton 15mg and omeprazole 20mg in reflux maintenance gave the impression that the two doses were therapeutically equivalent. The Panel noted that the balance of evidence demonstrated that omeprazole 20mg was more effective than Zoton 15mg in GORD maintenance. A breach of Clause 7.2 of the Code was ruled.

In this case the Panel had also ruled a breach of undertaking as Wyeth was implying equivalence between Zoton 15mg and omeprazole 20mg and this had been ruled in breach of the Code in two previous cases (Cases AUTH/676/2/98 and AUTH/745/7/98, discussed above).

AstraZeneca had conducted a further literature search (16/04/02) using its own database. It had also conducted a Medline search. These searches demonstrated that since the above cases there had been no further evidence published contradicting the fact that omeprazole 20mg was superior in efficacy to lansoprazole 15mg.

For the reasons above AstraZeneca believed that Wyeth had once again attempted to imply equivalent efficacy between omeprazole 20mg and lansoprazole 15mg in GORD maintenance and that this page was therefore in breach of Clause 22 of the Code. AstraZeneca believed that the repeated presentation of misleading claims of this nature was sufficient to bring the industry into disrepute and that the Appeal Board should uphold the Panel's decision of a Clause 2 ruling in this instance.

APPEAL BOARD RULING

The Appeal Board noted its comments at point 5.4.1 above that the claim 'Patients can effectively be switched from omeprazole 20mg to Zoton 15mg' implied therapeutic equivalence. The Appeal Board considered that Wyeth was thus in breach of its undertakings given in previous cases. The Appeal Board upheld the Panel's ruling of a breach of Clause 22 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted that Clause 2 was used as a sign of particular censure and was reserved for such use and considered that Wyeth's conduct had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

The Appeal Board considered that Wyeth's failure to comply with previous undertakings was such that it decided to require an audit of Wyeth's procedures in relation to the Code to be carried out by the Authority in accordance with Paragraph 10.4 of the Constitution and Procedure. In this regard the Appeal Board was also concerned about the number of breaches in this case which it considered reinforced the apparent lack of control.

On receipt of the audit report the Appeal Board decided that on the basis that Wyeth implemented the audit recommendations no further action was necessary.

6 CD ROM (ref ZZOT2397)

6.1 Cost calculator – CD ROM

COMPLAINT

AstraZeneca noted that the cost calculator consisted of the following:

Practice data This screen allowed the practitioner to enter the number of patients in their practice who were on 'omeprazole maintenance therapy' and of those patients what proportion were on the 10mg, 20mg or 40mg strengths.

Therapeutic options This screen consisted of three slide rules. By moving the buttons from left to right the practitioner increased the number of patients switched from omeprazole to Zoton. By doing this for all three strengths of omeprazole, the user would then see through a cost calculation represented at the top of the screen by a bar chart, how much this equated in projected savings.

The options were switching omeprazole 10mg to Zoton 15mg, omeprazole 20mg to either Zoton 15mg or 30mg and omeprazole 40mg to Zoton 30mg.

AstraZeneca believed this to be highly misleading and an unfair comparison as it suggested that omeprazole and Zoton were completely interchangeable in that it was possible to assume that patients on 20mg of omeprazole could be switched wholesale to either 30mg or 15mg of Zoton. No constraint was provided within the system to prevent the assumption that all patients on omeprazole 20mg could be switched to 15mg lansoprazole. The comparator was set up in such a way that hypothetical switching of patients was one way only ie from omeprazole to Zoton.

There was no provision to allow for patients failing treatment and then being switched back to omeprazole.

AstraZeneca again drew attention to previous rulings whereby the claim that these two medicines were clinically interchangeable had been ruled to be not substantiable.

AstraZeneca therefore alleged that the cost calculator provided an unsubstantiable, unfair and unbalanced comparison in breach of Clauses 7.2 and 7.4.

Again AstraZeneca also believed this type of comparison to be a breach of undertaking as referred to in point 5.4.3 above and therefore in breach of Clause 22.

This should be taken into consideration when ruling on any breach of Clause 2 as referred to in point 5.4.3 above.

RESPONSE

Wyeth stated that it was important that this item should be put into its correct context. The CD ROM was entitled 'GI Review – interactive CD ROM' and as the title implied was only used in response to a specific request from a GP/practice for a Wyeth specialist audit person to discuss a programme for switching appropriate patients from omeprazole to lansoprazole. This was totally distinct from the sales/promotional scenario.

During the interactive session the GP/practice was able to set options to reflect their existing omeprazole usage and also their anticipated lansoprazole switch scenario, including a compliance rate setting. It enabled the GP/practice to decide, according to their experience, the anticipated percentage split of patients changing to lansoprazole 15mg or 30mg from omeprazole 20mg.

Consequently, Wyeth submitted that the programme was sufficiently flexible to allow the GP/practice to enter the data which was likely to reflect their own clinical scenario, in order to help them satisfy their own objectives. It was therefore not in breach of Clauses 7.2 and 7.4.

As stated under point 5.4.3 above, Wyeth considered that once again it was sufficiently clear that this was an audit scenario (practice experience based data input) rather than relating to randomized controlled trials and as such was not in breach of Clauses 2 and 22.

PANEL RULING

The Panel considered that the CD ROM was promotional for Zoton. It was used in response to a request from a GP/practice for a discussion about switching patients from omeprazole to Zoton. In the Panel's view it was not distinct from the sales/promotional role as submitted by Wyeth.

With regard to the allegation now at issue, the Panel noted its ruling at point 5.4.3 above. The process consisted of the details of the use of omeprazole maintenance therapy being entered in the section 'Practice Data'. The next stage was a calculation of the current treatment costs, projected treatment costs and projected savings of switching patients from omeprazole to Zoton. The screen permitted the compliance rate to be set. The GP would decide the anticipated percentage split of patients changing to lansoprazole 15mg and 30mg from omeprazole. The Panel did not have before it any other audit materials or briefing instructions to the audit person. The Panel considered that the material was sufficiently different to that at issue in Case AUTH/964/12/99 such that it was not caught by the undertaking given in that case. No breaches of Clauses 22 and 2 were ruled.

The Panel did not accept that the material was such that no constraint was provided within the system to prevent the assumption that all patients on omeprazole 20mg would be switched to 15mg Zoton. The Panel noted Wyeth's submission that it was for the GP to decide according to their experience the anticipated percentage split of patients changing to Zoton 15 or 30mg from omeprazole. It was possible to set options to reflect the existing omeprazole usage and anticipated switch scenario. The Panel considered that the discretion given to the GP to decide switch options etc was such that there was no implication that the two medicines were interchangeable. No breaches of Clauses 7.2 and 7.4 were ruled.

6.2 Bioavailability

The screen was headed 'Bioavailability' followed by 'absolute bioavailability following a single dose in volunteers (from different studies)'. The screen was accessed under the heading 'Efficacy'. When choosing the bioavailability option, the bar chart for omeprazole came up immediately. The viewer had to click on a button to bring up the bar chart for Zoton. The two separate bar charts depicted 91% bioavailability for Zoton 30mg (n=12) and 35% bioavailability for omeprazole 20mg (n=81).

COMPLAINT

AstraZeneca referred to point 5.2 above. On the CD ROM in the efficacy section the bar charts representing bioavailability of Zoton and omeprazole were depicted in the exact manner as in the leavepiece. In the same way as the leavepiece, AstraZeneca believed that it was misleading and inappropriate to juxtapose data from two separate studies in such a way as to invite the reader to directly compare them. The page was entitled 'Efficacy', suggesting to the user that bioavailability correlated with efficacy. It was in AstraZeneca's view far from clear that bioavailability of PPIs had any direct relevance to efficacy and therefore this comparison was spurious and, AstraZeneca believed, breached Clause 7.3.

RESPONSE

Wyeth referred to its response in point 5.2 above in relation to the first part of this allegation.

In response to the second point, in the context of the CD ROM and the limitations associated with them in general, it was perfectly reasonable that all the clinically associated data was listed under 'Efficacy'. In this particular case, the bioavailability data was appropriately placed after the clinical data, in the context of supporting data. In respect of its relevance to clinical efficacy, reference should be made to relevant parts of points 4.2 and 5.2 above.

PANEL RULING

The Panel noted that there were minor differences between the bar charts at issue and those considered at point 5.2; the patient numbers were provided and the subheading was in prominent yellow type face and efficacy data was on a separate page. Nonetheless the Panel considered that its ruling at point 5.2 of a breach of Clause 7.3 applied here. The design enhanced the impression that the data could be directly compared which was not so.

6.3 Screen entitled 'Current Prescribing in General Practice'

COMPLAINT

AstraZeneca referred to point 5.3 above. The screen entitled 'Current prescribing in general practice' on the CD ROM was the same as on the page of the detail aid referred to in 5.3, except that the user could choose whether to see cost comparisons for 'Usage based cost of maintaining 1 patient for 28 days' or 'Usage based cost of maintaining 100 patients for 1 year'. For the reasons stated in point 5.3 above, AstraZeneca alleged this screen was in breach of Clauses 7.3 and 7.4.

RESPONSE

Wyeth referred to its response in point 5.3 above.

PANEL RULING

The Panel noted that the screen at issue was different to the page of the detail aid at point 5.3. In addition to the 28 day cost calculation mentioned by AstraZeneca the percentage usage figures depicted by the pie charts were slightly different for each medicine and dosage; this was reflected in the cost calculation. The Panel considered that its ruling of no breach of Clauses 7.3 and 7.4 at point 5.3 above nonetheless applied here.

6.4 Video clips featuring an interview with a GP

AstraZeneca stated that it was its view that the misleading nature of the CD ROM was further compounded by a set of short video clips featuring an interview with a GP.

6.4.1 Clip 1

COMPLAINT

AstraZeneca stated that this clip was accessed by clicking on the statement – 'What is your experience of switching patients on PPI maintenance therapy to Zoton?' The GP in the clip stated that 'now there is a better PPI that is more cost-effective'. This was a hanging comparison and one that implied that Zoton was superior in cost and efficacy to other PPIs. This was clearly unsubstantiable and misleading in breach of Clauses 7.2 and 7.4.

RESPONSE

Wyeth stated that it was iniquitous for AstraZeneca to misquote the text in order to attempt, once again, to mislead the Authority. A full transcript of the actual text was provided which Wyeth stated also put the response into its proper context.

It actually initially stated 'that there was a better PPI around – a more cost effective PPI'. Later it stated (in light of the opening comment) 'we feel that this product is better and more cost effective'.

In the scenario of the GI Review interactive CD ROM, it was obvious from the start that only omeprazole and lansoprazole were under consideration. Consequently the text was qualified and therefore not a hanging comparison.

In the context of the full text, it was appropriate to interpret the word 'better' as referring to 'cost effective'. In the established setting of audit/switch, the general practitioner was obviously referring to his own experience of significant cost savings following switching (see text to clip 3), which he referred to as 'cost effective'. The claim in this situation was therefore appropriate and well substantiated.

PANEL RULING

The Panel considered that the statements constituted a hanging comparison even though the CD discussed switching patients from omeprazole to Zoton. The statements appeared as a separate video clip. The Panel considered the comparator was not sufficiently clear and a breach of Clause 7.2 was ruled in this regard.

The Panel did not accept Wyeth's submission that better should be interpreted as referring to cost effectiveness. The Panel considered that 'better' was a broad claim and within the context of the interview implied that Zoton was superior to all other PPIs. Wyeth had not submitted evidence to substantiate this broad claim which the Panel considered misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled on this point.

6.4.2 Clip 2

COMPLAINT

AstraZeneca stated that this clip was accessed by clicking on the statement – 'What would be your advice to practices who want to undertake a switch?' The GP suggested that by switching patients to Zoton '… [the practice] will save money and improve patient care' and that '[the practice] will have no regrets'. AstraZeneca alleged that this was not substantiable and was a breach of Clause 7.4.

RESPONSE

Wyeth stated that it was essential that the GP's response was read in its full context, rather than from the snippets quoted misleadingly by AstraZeneca. A full transcript was provided.

It was the GP's experience and evidence based opinion that a practice undertaking a switch programme would save significant amounts of money for the practice and the PCG. It would also improve patient care in terms of the practice being seen to take an active interest in the reviewed patients. It involved 'very little hassle'. All points were therefore fully substantiated.

PANEL RULING

The Panel noted that whilst the claim was attributable to a GP, its use in such material nonetheless had to comply with the Code. To state or imply that all practices affecting a switch would have no regrets was a strong and all-encompassing claim. Wyeth had not submitted data to substantiate this. Nor had it submitted data to substantiate the cost savings or

improvement in patient care. A breach of Clause 7.4 was ruled.

6.5 Non-proprietary name

COMPLAINT

AstraZeneca stated that there was no mention of the non-proprietary name in the CD ROM programme itself. This was a breach of Clause 4.3.

RESPONSE

Wyeth stated that AstraZeneca had only submitted to the Authority a 'burned' copy of Wyeth's original CD ROM. This was being returned to the Authority for comparison with originals which were provided.

The non-proprietary name was to be found adjacent to the most prominent display of the brand name ie on the inside cover of the CD ROM case. It therefore fully complied with Clause 4.3.

PANEL RULING

The Panel considered that the CD ROM and the CD case were separate items. The Panel accepted that the CD ROM case included both the brand name Zoton and its non-proprietary name. The CD itself included the brand name without the non-proprietary name. The CD programme included the product information. The Panel noted the company's submission that the CD ROM would be used by a Wyeth specialist audit person to discuss the programme for switching appropriate patients. The Panel considered that as the CD would be shown to health professionals then the CD programme should include the non-proprietary name next to the most prominent display of the brand name. Given the use of the CD it was in the Panel's view inadequate just to put the non-proprietary name on the CD case and not on the CD. The Panel therefore ruled a breach of Clause 4.3 of the Code.

During the consideration of this case the Panel considered that although the CD programme included the prescribing information as required by Clause 4.4 of the Code, it did not clearly display the instructions for accessing it as also required by that clause. The Panel requested that Wyeth be advised of its views on this point.

* * * * *

The Appeal Board required Wyeth to undergo an audit of its procedures in relation to the Code, as referred to in point 5.4.3 above.

Complaint received **12 December 2001**

Case completed **24 July 2002**

CASE AUTH/1290/3/02 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST PRESCRIBING ADVISER v NORGINE

Letter about Movicol

A prescribing adviser at a primary care trust complained that a letter from Norgine about Movicol (polyethylene glycol plus electrolytes) was misleading. The letter stated 'If you use Movicol instead of lactulose you will reduce the NHS cost of managing patients with chronic constipation by £11 per patient over a three month period'.

The complainant noted that the summary of product characteristics (SPC) stated that Movicol was licensed for chronic constipation at a dose of two-three sachets daily, or in the elderly initially one sachet daily, usually for up to two weeks, course repeated if required. Prolonged use was not recommended. The letter gave a comparison of Movicol with lactulose over three months which was a prolonged period.

The Panel noted that the SPC current at the time the letter was sent stated 'As for all laxatives, prolonged use is not recommended. A course of treatment for constipation with Movicol does not normally exceed two weeks, although this can be repeated if required'. The SPC did not limit the number of times treatment could be repeated. Nevertheless, the Panel considered that the comparison of Movicol with lactulose over three months was misleading and thus was not capable of substantiation. The Panel considered that the claim was inconsistent with the particulars in the SPC. Breaches of the Code were ruled. These rulings were appealed by Norgine.

The Appeal Board noted that most laxatives could be purchased for self-medication. The statement in the SPC 'Prolonged use is not recommended' was a class statement applying to all laxatives and, as submitted by Norgine, was applied to the medicines as a whole to discourage the majority of patients who took laxatives, ie those who bought them for self-medication of short-term constipation, from taking them for prolonged periods without medical advice.

The Appeal Board noted that Movicol was only promoted for prescription; it was not promoted to the general public for self-medication. The SPC anticipated that there might be circumstances when use for longer than two weeks might be necessary. Norgine submitted that these circumstances would include chronic constipation which would be treated

by a health professional and not by self-medication. The SPC did not limit the length of treatment other than a general statement that prolonged use was not recommended. Norgine did not consider, in terms of a doctor treating chronic constipation, that three months was prolonged use. The Appeal Board did not consider that, in the context of a letter to a health professional, the comparison of Movicol with lactulose over three months was inconsistent with the SPC as alleged and ruled no breach of the Code.

A prescribing adviser at a primary care trust complained about a letter (ref MO/01/0081-01/02) from Norgine Limited about Movicol (polyethylene glycol, sodium bicarbonate, sodium chloride and potassium chloride).

COMPLAINT

The complainant alleged that the letter which had been sent to the district nurse teams within the trust was misleading. The letter stated 'If you use Movicol instead of lactulose you will reduce the NHS cost of managing patients with chronic constipation by £11 per patient over a three month period'. The complainant pointed out that the summary of product characteristics (SPC) stated that Movicol was licensed for chronic constipation at a dose of two-three sachets daily, or in the elderly initially one sachet daily, usually for up to two weeks, course repeated if required. Prolonged use was not recommended. The letter gave a comparison of Movicol with lactulose over three months which was a prolonged period.

When writing to Norgine the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 7.4 of the Code.

RESPONSE

Norgine stated that the letter was sent out during the week commencing 11 February.

Norgine believed that the claim of reduced NHS cost if using Movicol rather than lactulose was accurate and capable of substantiation. The reference used for this statement was 'Data on file N110, Norgine Ltd' this was referred to as data on file at the time of production of the letter as the study had not then been published. It had now been published, Christie *et al* (2002). The authors concluded: 'This study indicated that managing idiopathic constipation in ambulant patients with [Movicol] instead of lactulose reduces the expected NHS cost by £11 per patient over 3 months'.

Norgine stated that the SPC in fact stated: 'As for all laxatives, prolonged use is not *usually* recommended' (Norgine's italics). Whilst prolonged use of laxatives was not usually recommended there were patients with severe chronic constipation in whom prolonged use of laxatives might be necessary for periods of time well in excess of three months. For example patients with chronic neurological disease or those being treated long-term with medicines that caused constipation (eg opioids, antimuscarinics) might require long-term laxative treatment.

Also, the SPC stated that a course of treatment with Movicol did not normally exceed 2 weeks although this could be repeated if required. Nowhere in the SPC was there any indication of a limit to the number of times a 'course' of treatment could be repeated.

Economic evaluation of medicines could give useful information to inform cost-effective prescribing, but it was important that the assumptions made in an economic evaluation were clinically appropriate.

The authors addressed this very point in their discussion; they stated: 'It usually takes 1 to 2 weeks to titrate the dose of [Movicol] or lactulose to provide optimum bowel movements for individual patients. Therefore we did not consider it appropriate to evaluate the economic impact of [Movicol] compared with lactulose after 1 month of treatment using the data from part A of the trial because this may have generated misrepresentative results, and would not have been clinically meaningful. Accordingly, the time frame for our economic analysis was 3 months'.

In order to formalise the situation with prolonged use of Movicol, Norgine made an application in July 2001 to vary the Movicol marketing authorization to include extended use in certain groups of patients. This application was approved by the Medicines Control Agency in March 2002.

The additional new wording in the SPC stated: 'Extended use may be necessary in the care of patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's disease or induced by regular constipating medication, in particular opioids and antimuscarinics'.

In summary therefore, Norgine believed that the economic evaluation of Movicol versus lactulose therapy over a three month period was both a clinically appropriate exercise and was consistent with the marketing authorization for the product, particularly in view of the fact that long-term use of Movicol and lactulose regularly occurred with both products.

Norgine had now formalised the situation with the use of Movicol for extended treatment of constipation and Movicol was now specifically licensed for the long-term treatment of certain groups of patients.

PANEL RULING

The Panel noted that the SPC current at the time the letter was sent stated 'As for all laxatives, prolonged use is not recommended. A course of treatment for constipation with Movicol does not normally exceed two weeks, although this can be repeated if required'. The dose was 2-3 sachets daily in divided doses for adults and adolescents, initially 1 sachet per day was recommended for the elderly.

The SPC dated March 2002 had similar statements but then referred to extended use in patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's disease, or induced by regular constipating medication, in particular opioids and antimuscarinics. The dose was 1-3 sachets daily in divided doses according to individual response. For extended use the dose could be adjusted down to 1 or 2 sachets daily.

At the time the letter in question was sent Movicol was not indicated for extended use in certain patients. The Panel noted that the SPC did not limit the

number of times treatment could be repeated. Nevertheless, the Panel considered that the comparison of Movicol with lactulose over 3 months was misleading and thus was not capable of substantiation. The relevant SPC stated that prolonged use was not usually recommended and that a course of treatment did not normally exceed two weeks. The Panel considered that the claim was inconsistent with the particulars in the SPC. Breaches of Clauses 3.2, 7.2 and 7.4 of the Code were ruled.

During its consideration of this case the Panel considered that the cost comparison was misleading. The authors stated that the study indicated that using Movicol instead of lactulose 'reduces the expected NHS cost by £11 per patient over 3 months'. This was more qualified than the claim in the letter. The Panel also queried whether there was sufficient data to substantiate the broad claim that Movicol was 'More cost effective than lactulose'. Such a claim implied that in all circumstances Movicol was more cost effective than lactulose. The SPC referred to a two week treatment period but the only data cited in support of the claim was from the three month study by Christie *et al*. The Panel requested that its concerns be drawn to Norgine's attention.

The Panel also noted that the study by Christie *et al* compared the use of Movicol and lactulose in the treatment of idiopathic constipation in ambulant patients. The revised SPC for Movicol referred to the extended use of the product in patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's disease, or induced by regular constipating medication, in particular opioids and antimuscarinics. The Panel noted that in its response Norgine had stated that Movicol was now specifically licensed for the long-term treatment of certain groups of patients. It appeared, therefore, that the extended use of Movicol was restricted to certain patient groups in whom there was a recognised cause of their constipation. In the Panel's view patients with idiopathic constipation would, by definition, not be included in these groups. The Panel requested that Norgine be advised of its concerns in this regard.

APPEAL BY NORGINE

Norgine noted that it was asked to respond to the complaint on the basis that the comparison might be misleading and/or incapable of substantiation and that a cost comparison over a 3-month period might be inconsistent with the SPC which was effective at the time the letter in question was sent.

Norgine restricted its appeal to consideration of consistency of claims made for Movicol with the SPC that was effective at the time the letter in question was sent. Norgine's response to the complaint might have confused the Panel by referring to a change to the SPC that took place after the letter in question was sent.

The areas at issue were: firstly was a claim made for Movicol that referred to its use over a 3-month period inconsistent with the wording of the SPC, bearing in mind that the SPC in force at the time stated that prolonged use was not recommended?; and secondly was a claim comparing Movicol with lactulose misleading and incapable of substantiation as it referred to a comparison over a 3 month period of treatment which would not be relevant in practice if the product was limited to shorter term use?

Inconsistency with the SPC

The relevant section of the Movicol SPC in force at the time the letter was sent stated 'As for all laxatives, prolonged use is not recommended. A course of treatment with Movicol does not normally exceed 2 weeks, although this can be repeated if required'.

Norgine interpreted the SPC to mean that for Movicol, as for all laxatives, in the usual circumstances prolonged use would not be recommended. Norgine also believed that the correct interpretation of an SPC must always reflect actual medical practice so that the interpretation of what was 'normal' in the context of the SPC should have been considered with reference to how constipation was normally treated.

Warning against prolonged use was appropriate as all laxatives were Pharmacy (P) or General Sales List (GSL) category medicines (with the exception of danthron-containing products). Movicol was a P medicine and could be purchased without a prescription. Therefore the normal circumstances for the majority of laxative users were that they bought the medicines for the self-medication of short-term constipation. It was therefore right that the patient information leaflet (PIL) (and SPC) should warn consumers who purchased laxatives from the pharmacist or supermarket that prolonged use in these circumstances was not recommended.

Nevertheless there were situations where patients whose constipation had become chronic presented to a GP or nurse and prolonged laxative use was needed to control constipation. Chronic constipation from whatever cause, be it poor diet, immobility or secondary to disease or medical treatment was seen in the primary care setting. All GPs would have a significant number of patients at any time who were receiving regular repeat prescriptions for laxatives and many of these patients took laxatives over a period of months or years, so in fact the routine situation in primary care was one of prolonged use of laxatives.

The symptom of constipation therefore covered a broad spectrum of severity from mild constipation through severe, chronic constipation up to faecal impaction. The use of laxatives covered this broad spectrum of severity and spanned both the over-the-counter (OTC) and prescription markets.

Norgine stated that 15 million packs of OTC laxatives were purchased in 2001. Whilst some purchasers might have been chronic users, most were likely to be occasional users. It was therefore reasonable to assume that in the order of 5-8 million people were buying OTC laxatives for themselves or their families each year in the UK.

In the prescription market a total of 20 million packs were prescribed in primary care in 2001. Data further showed that of these prescriptions, only around 5% were prescriptions for new patients. Movicol was consistent with other laxatives with 6% of prescriptions being for new patients. This meant that in the primary care setting, around 95% of laxative prescriptions were repeat prescriptions for existing

patients. As repeat prescriptions for chronic constipation were continued often for months or years for an individual patient, it would have been reasonable to assume that in any one year around 1.7-2.5 million patients were receiving laxatives prescribed by their GP.

Norgine exclusively promoted Movicol to prescribers in primary care and in hospitals, it did not promote Movicol to consumers as an OTC medicine.

The SPC stated 'A course of treatment with Movicol does not normally exceed 2 weeks….'. Norgine believed that the word 'normally' was critical in the interpretation of the SPC, as the SPC must cover the whole spectrum of constipation and use of a P category laxative.

Whilst normally a course should not exceed 2 weeks this referred to the situation in which the consumer would self-treat mild constipation. The converse of this was also allowed for in the wording of the SPC in that there must be circumstances in which a course might exceed 2 weeks. As noted above many of these were those patients seen in a primary care setting with long-term constipation for whom repeat prescriptions over the long-term were essential to control their constipation.

This wording regarding a 2 week course was qualified by the phrase '…although this can be repeated if required'. No limit was stated in the SPC as to how many times a course of treatment with Movicol could be repeated; this was left to the discretion of the prescriber according to the clinical needs of the patient.

The key issue was that in the context of the total spectrum of laxative usage (from mild to severe), whilst a 2 week course of Movicol in mild non-chronic constipation would have been sufficient, it was routine that the more difficult cases of chronic constipation seen in primary care would have frequently required repeat prescriptions for a prolonged period.

Norgine believed that the SPC current for Movicol at the time the letter in question was sent did not restrict its use to 2 weeks in all circumstances. Norgine believed the SPC allowed for longer term use in circumstances which might have been abnormal with regard to constipation as a whole, but which were clinically appropriate for that majority of patients in primary care who were often frail and elderly, suffering from chronic disease and who had chronic constipation needing treatment over a prolonged period.

Comparisons over 3 months were misleading and incapable of substantiation

Norgine submitted that the finding of the Panel that comparative claims over a 3-month period were misleading was critically dependent on the interpretation of the SPC as discussed above.

If the Appeal Board believed that there were circumstances in which prolonged use of Movicol was allowed by the SPC in force at the time, then the comparisons over a 3 month period were reasonable and valid, and were substantiated by Christie *et al*.

In summary therefore, Norgine believed that the SPC for Movicol in force at the time the letter in question was sent allowed for use beyond a two week course in a variety of circumstances. Norgine's promotion was therefore in accordance with the SPC. It was not therefore misleading to make comparative claims over a 3-month period and these claims were capable of being substantiated.

COMMENTS FROM THE COMPLAINANT

The complainant did not agree with Norgine's statement that the correct interpretation of an SPC must always reflect actual medical practice. It was essential that an SPC was followed strictly. The SPC for Movicol stated 'A course of treatment with Movicol does not normally exceed 2 weeks, although this can be repeated if required'. In the complainant's view this should be interpreted that Movicol should be given as a course of treatment, which could be repeated if required and not as a continuous treatment.

A course of Movicol might not even be required for as long as 2 weeks and several days' treatment might be sufficient.

APPEAL BOARD RULING

The Appeal Board noted that the relevant SPC was the one available at the time the letter in question was sent. The Appeal Board noted that most laxatives could be purchased for self-medication. The statement in the SPC 'Prolonged use is not recommended' was a class statement applying to all laxatives and, as submitted by Norgine, was applied to the medicines as a whole to discourage the majority of patients who took laxatives, ie those who bought them for self-medication of short-term constipation, from taking them for prolonged periods without medical advice. Norgine submitted that between 5 to 8 million patients per year purchased laxatives, whereas only 1.7 to 2.5 million patients per year were prescribed them. 95% of prescriptions were repeat prescriptions.

The Appeal Board noted that Movicol was only promoted for prescription; it was not promoted to the general public for self-medication. The SPC anticipated that there might be circumstances when use for longer than 2 weeks might be necessary. Norgine submitted that these circumstances would include chronic constipation which would be treated by a health professional and not by self-medication. The SPC did not limit the length of treatment other than a general statement that prolonged use was not recommended. Norgine did not consider, in terms of a doctor treating chronic constipation, that 3 months was prolonged use. The Appeal Board did not consider that, in the context of a letter to a health professional, the comparison of Movicol with lactulose over 3 months was inconsistent with the SPC as alleged and ruled no breach of Clauses 3.2, 7.2 and 7.4.

The appeal was successful.

Complaint received **25 March 2002**

Case completed **24 July 2002**

CASE AUTH/1298/4/02

ASTRAZENECA v GLAXOSMITHKLINE

Promotion of Seretide

AstraZeneca complained about the promotion of Seretide (salmeterol and fluticasone) by GlaxoSmithKline. A support card headed 'Seretide vs budesonide and formoterol' detailed the results of the EDICT study (Ringdal *et al* 2001, Chuchalin *et al* 2001), in which patients with moderate-severe asthma were treated either with Seretide or a combination of budesonide plus formoterol in separate inhalers. AstraZeneca marketed Symbicort, a combination of budesonide and formoterol. The support card presented two bar charts, one depicted mean rate of exacerbations and the other median nights of no awakening followed by a number of claims for Seretide based on the results of the EDICT study, one of which, 'Seretide 250 was significantly more effective at reducing asthma exacerbations', AstraZeneca alleged was incapable of substantiation and therefore misleading.

AstraZeneca was concerned about the way in which the EDICT study had been analysed. The primary analysis by Ringdal *et al* was a comparison of overall mean exacerbation rates between the two groups which showed an apparent statistically significant difference. Ringdal indicated no significant difference between groups in the number of patients experiencing each severity of exacerbation (mild, moderate or severe) although it was clear that the greatest difference between the groups was in the total number of mild exacerbations reported, however this parameter was not subjected to statistical appraisal in the study.

AstraZeneca noted that one of the definitions for a mild exacerbation was wakening at night due to asthma for ≥ 2 consecutive days. Therefore it would be important that baseline differences in night-time awakening between groups at randomisation had been adjusted for to avoid reporting bias for this result. AstraZeneca noted that the budesonide and formoterol group had 16.7% nights with no awakening compared to 28.6% nights with no waking in the Seretide group, a difference of 42% between groups which had not been included in the analysis. It would be logical to deduce that only a difference in waking at night due to asthma ≥ 2 consecutive days between groups would be responsible for a difference in mild exacerbations that would therefore affect the overall mean rate of exacerbations between groups. The patient population was reasonably severe in terms of its asthma severity at entry, therefore it was not surprising that the total number of mild exacerbations was high over the study period as indicated in the Ringdal *et al* poster.

The result for overall exacerbation rates in this study was therefore misleading in that the analyses did not adequately consider difference in baseline factors crucial for the determination of a mild exacerbation hence overall mean rate of exacerbations between the treatment groups. Treatment groups were not well matched at baseline, which consequently skewed the data, producing results that AstraZeneca considered could not substantiate the claim in question.

AstraZeneca considered that in common with other asthma studies examining effects on exacerbation rates, this study categorized exacerbations in terms of severity between mild, moderate and severe according to predefined criteria. The clinical significance of a moderate or severe exacerbation was far greater than that of a mild exacerbation. Therefore it was critical to define exactly what was meant by an asthma exacerbation in terms of severity when presenting exacerbation results, otherwise it could be misleading.

The Panel noted that the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations', was referenced to Ringdal *et al*. The Ringdal reference provided by AstraZeneca differed from that provided by GlaxoSmithKline. Ringdal (AstraZeneca) indicated the Seretide and budesonide plus formoterol groups experienced 142 and 222 mild exacerbations, 28 and 31 moderate exacerbations and 1 and 2 severe exacerbations respectively over the study period. The Panel noted that Ringdal *et al* listed defining criteria for asthma exacerbation severity and that the number of patients who experienced each severity of exacerbation during the study was not significantly different between treatment groups. The majority of the exacerbations were mild. The Panel noted AstraZeneca's submission that the clinical significance of a moderate or severe exacerbation was greater than a mild exacerbation and a trial involving Seretide 250 would be of interest to those treating asthma symptoms at the more severe end of the spectrum.

On balance the Panel considered that insufficient detail had been provided about the definition of asthma exacerbation. The clinical significance of the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations' was thus unclear and misleading in this regard as alleged. A breach of the Code was ruled.

The Panel noted that Ringdal *et al* stated that treatment groups were well matched at baseline. The majority of the exacerbations over the study period were mild in each treatment group. One of the defining criteria for a mild exacerbation was wakening at night due to asthma for ≥ 2 consecutive days. Chuchalin reported that at baseline the median % nights with no awakening was 28.6% in the Seretide group and 16.7% in the budesonide plus formoterol group. It was stated that night awakenings due to asthma were significantly lower in the Seretide group than the budesonide plus formoterol group. The p value at month 1 was 0.017, at month 2 was 0.024 and at month 3 there was no statistically significant difference. The median percentage of nights with no awakening over the three month period was greater in the Seretide group (80.3) than in the budesonide and formoterol group (60) (p=0.022). Night-time awakenings were

not included in the definitions of moderate or severe exacerbations in Ringdal. The statistical significance between groups in the number of patients experiencing each severity of exacerbations was not stated. The Panel noted AstraZeneca's submission regarding the difference in night-time awakening at baseline of 42%, and that the failure to consider this when determining the number of mild exacerbations in each group could lead to an overestimation in the budesonide plus formoterol group. GlaxoSmithKline stated that the analysis was re-run after unblinding using the baseline rather than the country as an adjustment to determine the sensitivity of the outcome to this parameter. The statistically significant effect on nights with no awakenings when stratified by country over the twelve-week study period overall (p=0.022) became, in fact, more significant when the data were corrected for baseline differences (p=0.013). The Panel noted that both studies stated that the treatment groups were well matched at baseline. It appeared that Chuchalin failed to take account of baseline differences between the groups.

The Panel noted the additional analysis provided by GlaxoSmithKline that the between group difference in median percentage of nights with no awakening became more significant when adjusted for baseline differences rather than the country. AstraZeneca's view was that both factors had to be taken into account when analysing the data. The protocol-defined analysis did not take baseline values into account as no difference was expected. GlaxoSmithKline had not submitted any material in relation to the effect, if any, the difference in nights with no awakening adjusted for baseline differences had upon the absolute numbers of mild exacerbations and hence the overall difference in the mean rate of asthma exacerbations for the products. In this regard the Panel noted that the numbers of patients who experienced each severity of exacerbation during the study was not significantly different between treatment groups. The Panel noted GlaxoSmithKline's submission that the significant differences in exacerbation rates between the groups were in the rate of exacerbations experienced by those patients who had exacerbations. Patients on Seretide who had exacerbations had a lower rate of exacerbations than those who exacerbated on budesonide plus formoterol.

On balance the Panel considered that given the data the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations' was misleading and unsubstantiated as alleged. A breach of the Code was ruled.

AstraZeneca UK Limited complained about the promotion of Seretide by GlaxoSmithKline UK Ltd. Seretide was a combination of a long-acting bronchodilator (salmeterol) and a corticosteroid (fluticasone). The item at issue was a support card (ref 20278669i-FP/September 2001), headed 'Seretide vs budesonide and formoterol' and reproduced at page 33 of an internal briefing document GP Campaign and Q&A Guidance (ref GEN 26955-FP/January 2002). The support card detailed the results of the EDICT study as published in poster format by Ringdal *et al* (2001) and Churchalin *et al* (2001). Patients in the EDICT study had moderate-severe asthma. Beneath the heading there were two bar charts, one depicting mean rate of exacerbations and the other median nights of no awakening. There then followed a number of promotional claims for Seretide based on the results of the EDICT study. AstraZeneca marketed Symbicort, a combination of a corticosteroid (budesonide) and a long-acting bronchodilator (formoterol).

Claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations'

This claim was referenced to Ringdal *et al*.

COMPLAINT

AstraZeneca stated that the support card was one of a series that was intended to be used by the salesforce with health professionals when discussing Seretide. The support card presented two graphs showing results from the EDICT study with reference to Ringdal *et al*. The card then listed a number of promotional claims based on these results, one of which was 'Seretide 250 was significantly more effective at reducing asthma exacerbations'.

AstraZeneca alleged that the claim was incapable of substantiation and therefore misleading for reasons described below. Breaches of Clauses 7.4 and 7.2 of the Code were alleged.

Additionally AstraZeneca believed that in the absence of asthma exacerbation being defined on the Seretide support card, the significance of the claim was open to interpretation and therefore misleading. AstraZeneca alleged a breach of Clause 7.2 for reasons described below.

AstraZeneca stated that the aim of the EDICT study was to compare the effect of Seretide 250 Accuhaler with budesonide 800mcg bd and formoterol 12mcg bd (both of which were given via the Turbohaler) on asthma exacerbations. In common with other asthma studies examining effects on exacerbation rates, this study categorized exacerbations in terms of severity between mild, moderate and severe according to predefined criteria.

A severe exacerbation according to the study definition was deterioration in asthma requiring emergency hospital treatment.

A moderate exacerbation was defined in the study as either: morning peak expiratory flow (PEF) ≥ 30% below baseline on ≥ 2 consecutive days; or deterioration in asthma requiring additional inhaled corticosteroids, and/or oral corticosteroids.

A mild exacerbation was defined in the study as: deterioration in asthma requiring an increase in relief medication use; or morning PEF ≥ 20% below baseline for ≥ 2 consecutive days; or ≥ 3 additional reliever inhalations in 24 hours compared to baseline for ≥ 2 consecutive days; or waking at night due to asthma for ≥ 2 consecutive days.

The clinical significance of a moderate or severe exacerbation was therefore far greater than that of a

mild exacerbation. This was especially true when considering the audience to which the results of a clinical trial involving Seretide 250 would be of interest, ie those treating asthma patients at the more severe end of the spectrum. Therefore it was critical to define exactly what was meant by an asthma exacerbation in terms of severity when presenting exacerbation results, otherwise it could be open to interpretation and therefore potentially misleading. It had been usual practice for AstraZeneca to define precisely exacerbation type(s) in presenting results from its asthma trials in promotional materials in order for the prescriber to appreciate the clinical implications of asthma treatment. AstraZeneca therefore alleged that not defining asthma exacerbations on the support card rendered the claim in question misleading in breach of Clause 7.2.

AstraZeneca had concerns as regards the methodology of the analysis of the study as presented in the two posters by Ringdal *et al* and Chuchalin *et al* that both detailed efficacy results from the EDICT study. The primary analysis in the Ringdal *et al* poster was a comparison of overall mean exacerbation rates between the two groups. An apparent statistically significant difference was found by looking at the mean rate of overall exacerbations between groups as indicated in Figure 4. The last point in the results section of the Ringdal poster indicated no significant difference between groups in the number of patients experiencing each severity of exacerbation (mild, moderate or severe). From Figure 2 which detailed the total number of exacerbations over the study period, it was clear that the greatest difference between the groups was in the total number of mild exacerbations reported, however this parameter was not subjected to statistical appraisal in the study.

One of the definitions for a mild exacerbation was wakening at night due to asthma for ≥ 2 consecutive days. Therefore it would be important that baseline differences in night-time awakening between groups at randomisation had been adjusted for to avoid reporting bias for this result. In fact, despite the Ringdal poster indicating that the treatment groups were well-matched at baseline, there was an apparent baseline difference in nights with no awakening at baseline between the groups as indicated in Figure 3 of the Chuchalin *et al* poster.

Whilst both groups had a high level of night-time awakening at baseline, the budesonide and formoterol groups had 16.7% nights with no awakening compared to 28.6% nights with no awakening in the Seretide groups. This difference of 42% between groups had not been taken into consideration in the statistical analysis comparing nights with no awakening between groups. GlaxoSmithKline indicated during inter-company discussions that a statistically significant effect over all months in nights with no awakening was still found when it stratified by baseline rather than by a country factor. However it would be necessary to balance for both country and baseline differences together in order to avoid overall bias of these factors.

The Chuchalin *et al* poster indicated that there were no significant differences between groups for mean morning or evening PEF, day-time symptom scores, or use of reliever medication as stated in the last claim of the support card. These parameters were used as the basis for two of the four definitions used for a mild exacerbation ie morning PEF ≥ 20% below baseline for ≥ 2 consecutive days, and ≥ 3 additional reliever inhalations in 24 hours compared to baseline for ≥ 2 consecutive days.

It would be logical therefore to deduce that only a difference in waking at night due to asthma ≥ 2 consecutive days between groups would be responsible for a difference in mild exacerbations that would therefore affect the overall mean rate of exacerbations between groups. One would have expected that a baseline difference of 42% in nights with no awakening between groups to have been considered when determining the number of mild exacerbations in each group.

As the patient population was reasonably severe in terms of its asthma severity at entry, there was already a high rate of night-time awakening at baseline in both groups. The criterion of waking at night due to asthma for ≥ 2 consecutive days was not compared to baseline values in contrast to the other criteria set for a mild exacerbation. Therefore it was not surprising that the total number of mild exacerbations was high over the study period as indicated in figure 2 of the Ringdal *et al* poster. A lack of correction for baseline night-time awakening would therefore lead to an overestimation of mild exacerbations in both groups.

The result for overall exacerbation rates in this study was therefore misleading in that the analyses employed did not adequately consider difference in baseline factors crucial for the determination of a mild exacerbation hence overall mean rate of exacerbations between the treatment groups. Treatment groups were not well matched at baseline, which consequently skewed the data, producing results that AstraZeneca considered could not substantiate the claim in question. The claim therefore, in AstraZeneca's opinion, constituted a breach of Clause 7.4 and owing to the misleading message the claim was likely to portray to the intended audience additionally represented a breach of Clause 7.2.

In summary, AstraZeneca believed that because the study analysis had failed to take into account baseline differences between the two treatment groups, the results could not substantiate the claim. This consequently delivered a misleading message and therefore breached Clauses 7.2 and 7.4 of the Code. AstraZeneca also considered the claim represented an additional breach of Clause 7.2 on the basis that asthma exacerbations had not been defined for the audience.

RESPONSE

GlaxoSmithKline stated that the support card was instructed to be for reactive use only.

1 Aim of EDICT Study

AstraZeneca stated that the aim of the EDICT study was to compare the effect of Seretide 250 Accuhaler with budesonide 800mcg bd and formoterol 12mcg bd on asthma exacerbations.

GlaxoSmithKline stated that the primary outcome measure for the EDICT study was to compare the effect of Seretide 250 with budesonide 800mcg plus formoterol 12mcg bd on mean morning peak flow values. The study was powered to show the non-inferiority of Seretide compared to budesonide plus formoterol for the effects on mean morning peak expiratory flow over the last week of treatment.

Among the secondary outcome measures was a measure of exacerbations. The strength of the evidence returned in this study for the difference in overall exacerbation rates between treatment groups ($p<0.001$) indicated that there was strong statistical evidence of a treatment benefit in favour of Seretide for this endpoint. The clinical relevance of this was discussed below.

2 Overall mean exacerbation rate

GlaxoSmithKline noted that AstraZeneca argued that the type of exacerbation (eg mild, moderate or severe) should be clearly defined and that the analysis and subsequent claim should take into consideration an examination of results by exacerbation type.

As stated above, the secondary outcome measures included exacerbations. Analysis by exacerbation type was not included in the statistical analysis template of the study protocol. Exacerbation type was defined within the study to guide physicians as to the categorisation of the exacerbations.

Had the numbers of patients experiencing each severity of exacerbation been greater, GlaxoSmithKline could have carried out a post hoc analysis on rates, with the results separated into severity subgroups. However the numbers in these subgroups were insufficient for robust statistical analysis.

The use of overall mean exacerbation rates was well recognised by clinicians as a clinical endpoint and well documented. Therefore physicians readily recognised this measure and would be able to assess the significance of the results in their clinical practice.

GlaxoSmithKline did not accept AstraZeneca's argument that the greater clinical significance of moderate or severe exacerbations meant that mild exacerbations were effectively not significant in clinical practice. The definition of a mild exacerbation included ≥ 3 additional reliever inhalations in 24 hours and waking at night due to asthma ≥ 2 consecutive nights. Such situations would require a change in therapy according to both the British Guidelines on Asthma Management and the Global Initiative for Asthma (GINA) guidelines. This was of obvious clinical significance to the clinicians managing these patients.

In summary, the overall mean exacerbation rate was a well recognised measure which was used frequently in clinical trials. In the EDICT study there was a highly significant difference between treatment groups for overall mean exacerbation rate ($p<0.001$). Making claims based on the apparent differences between exacerbation types could have been misleading, as this was not a pre-specified analysis within the statistical plan for the study. As a post hoc analysis the numbers were insufficient for sub-group analysis.

In the Ringdal *et al* poster there was no claim or statement relating to the differences between exacerbation subgroups, the conclusion related only to mean exacerbation rates.

GlaxoSmithKline did not therefore consider that presentation of the overall exacerbation rate was misleading, but accurately reflected the study results. It did not consider that there was any requirement on the support card to define the exacerbations. GlaxoSmithKline therefore did not consider that there was any breach of Clause 7.2 of the Code.

3 Methodology of the analysis

3.1 Analysis of night-time awakening data adjusted for baseline differences

GlaxoSmithKline noted that AstraZeneca argued that whilst both groups had a high level of night-time wakening at baseline, the budesonide plus formoterol group had a median 16.7% nights with no awakening compared to 28.6% nights with no awakening in the Seretide group. AstraZeneca suggested that this 'difference of 42%' between groups had not been taken into consideration in the statistical analysis comparing nights with no awakenings between groups.

AstraZeneca had suggested the need to stratify the night-time awakening analysis by both baseline and country together.

GlaxoSmithKline had already discussed this point on several occasions with AstraZeneca through inter-company discussions and correspondence. GlaxoSmithKline wrote to AstraZeneca explaining that when these analyses were adjusted for baseline differences and stratified by country, the differences between the Seretide and budesonide plus formoterol arms remained significant. Details were provided.

The statistically significant effect on nights with no awakenings when stratified by country over the twelve-week study period overall ($p=0.022$) became, in fact, more significant when the data were corrected for baseline differences ($p=0.013$) (baseline categories stratified into four equal groups).

As the data demonstrated the highly skewed distribution typical of such parameters, they could only be analysed using non-parametric methods. The numbers of countries relative to the numbers of patients allowed adjustments for country and baseline separately, but not both in the same analysis. Adjusting for either factor separately did not make the difference between study groups less significant.

3.2 Differences between outcomes measures and measures used to define exacerbations

GlaxoSmithKline noted that AstraZeneca argued that the Chuchalin *et al* poster indicated that there were no significant differences between treatment groups for mean morning or evening PEF, day-time symptom scores, or use of reliever medication and that these parameters were used as the basis for two of the four definitions for a mild exacerbation. AstraZeneca alleged that this suggested that only the difference in waking at night could be responsible for the observed

difference in mild exacerbations that would affect the overall mean rate of exacerbations.

GlaxoSmithKline stated that this assertion was incorrect. Lack of statistically significant differences in mean or median data did not preclude a numerical difference in the number of individuals that crossed a given threshold or the frequency and number of occasions on which they did so. It was therefore incorrect to state that the differences in mild exacerbations seen between the treatment groups could only have occurred as a result of differences in night-time waking.

To explain the difference between the outcome measures themselves and the aspect of the outcome measure used in the definitions of exacerbations, GlaxoSmithKline gave the example of the definition of a mild exacerbation: deterioration in asthma requiring an increase in relief medication use; or morning PEF ≥ 20% below baseline for ≥ 2 consecutive days; or >3 additional reliever inhalations in 24 hours compared to baseline for ≥ 2 consecutive days; or waking at night due to asthma for ≥ 2 consecutive days. GlaxoSmithKline had underlined parts of the definition to highlight that there was a difference between the measure used in analysis of individual efficacy parameters and the means by which patterns of change over time on treatment for these parameters led to identification of an exacerbation.

For example, there was clearly a difference between a measure of mean morning PEF over the last week of a 12 week study period and the measure of a change in morning PEF ≥ 20% below baseline for >2 consecutive days at any time during the study. Likewise a mean estimate of the number of times a patient woke during the 12 week study was not the same as a measure of night-time awakening for ≥ 2 consecutive days; and the use of >3 additional reliever inhalations in 24 hours compared to baseline for ≥ 2 consecutive days, was not the same as mean reliever medication use throughout the duration of the study.

GlaxoSmithKline noted that AstraZeneca had correctly stated that the Ringdal *et al* poster made the point that there were no significant differences between groups in the number of patients experiencing each severity of exacerbation. This highlighted the fact that the significant differences in exacerbation rates between the groups were in the rate of exacerbations experienced by those patients who had exacerbations. That was to say, patients on Seretide who had exacerbations had a lower rate of exacerbations than those who exacerbated on budesonide plus formoterol.

Group/median data (which were reported in all clinical trials for such endpoints) by their very nature, 'averaged out' variability in individual patient outcomes, and did not take into account the frequency or timing of such events. Therefore the factors contributing to an exacerbation within an individual could not be deduced from group mean/median data.

3.3 Exacerbation analysis adjusted for baseline differences

AstraZeneca stated that as the definition of a mild exacerbation included wakening at night it would be important that baseline differences between groups should be adjusted for.

Having carried out this analysis adjusting for baseline night-time awakening, GlaxoSmithKline still found an unchanged significant difference in exacerbation rates between the two treatment groups ($p<0.001$). The methodology for this statistical analysis used the Poisson model as presented in Ringdal *et al*.

GlaxoSmithKline therefore considered that the claim on the support card was not misleading and was not in breach of Clauses 7.2 and 7.4 of the Code.

In summary, GlaxoSmithKline believed that the study analysis was robust. When all baseline differences between the two groups had been taken into account the statistically significant difference between the two treatment groups on overall exacerbation rate and night-time awakenings was still present. In particular GlaxoSmithKline had explained the reasons for using a measure of overall exacerbation rate. It did not consider there was any obligation to present data which the study was not powered to analyse, and GlaxoSmithKline repeated that to do so could be considered to be misleading.

GlaxoSmithKline did not consider that this material was in breach of the Code.

PANEL RULING

The Panel noted that the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations', was referenced to Ringdal *et al* (2001). It immediately followed a bullet point 'Comparing Seretide 250 Accuhaler with budesonide and formoterol (given by turbo inhalers) using less than a third of the steroid dose:'. One of two bar charts at the top of the support card compared the mean rates of exacerbations. The mean rate for Seretide 250mcg was 0.576 and for budesonide 80mcg and formoterol 12mcg the mean rate was 0.836; $p<0.001$. A second bar chart compared the median nights of no awakening (%) of Seretide 80.3 (baseline 28.6) with budesonide and formoterol 12mcg, 60 (baseline 16.7); $p=0.022$.

The Panel noted that the Ringdal reference provided by AstraZeneca differed from that provided by GlaxoSmithKline. Ringdal *et al* (AstraZeneca) which presented the results of the EDICT study, was a randomised double-blind, double-dummy parallel group and multi-centre study on patients with moderate to severe asthma, symptomatic on inhaled corticosteroids which compared asthma exacerbations with Seretide 250mcg bid and budesonide 800mcg and formoterol 12mcg bid. Exacerbations were categorized by severity and analysed by a Poisson model, adjusted for age. The results stated that treatment groups were well matched at baseline. The total number of asthma exacerbations during the study period was higher in the budesonide plus formoterol group than in the Seretide group. Figure 2 of Ringdal (AstraZeneca) indicated the Seretide and budesonide plus formoterol groups experienced 142 and 222 mild exacerbations, 28 and 31 moderate exacerbations and 1 and 2 severe exacerbations respectively over the study period (12 weeks).

Figure 3 of Ringdal (AstraZeneca) depicted the percentage of patients experiencing each number of exacerbations by treatment group; 71.6% and 66.7% of Seretide and budesonide plus formoterol patients respectively experienced no exacerbations, 20.7% and 21.3% experienced 1-3 exacerbations and 7.7% and 12.0% experienced ≥ 4. Figure 4 depicted the mean rate of exacerbations over 12 weeks of treatment and was reproduced on the support card. The authors noted that the mean rate of exacerbations remained significantly different when patients with more than 6 exacerbations were omitted from the analysis at the sixth exacerbation. The number of patients who experienced each severity of exacerbation during the study was not significantly different between treatment groups. The authors concluded that Seretide 250 controlled asthma exacerbations significantly more effectively than budesonide plus formoterol, using less than one third of the steroid.

Additional data was provided in Ringdal (GlaxoSmithKline) such as a section headed 'abstract' which included a summary of the results of the numbers of exacerbations. These were given in Table 1. (There was no Table 1 in Ringdal (AstraZeneca)). The results showed that the overall exacerbation rate on Seretide was reduced by 31%. Chuchalin *et al* (2001), a poster, depicted the EDICT results for nocturnal asthma symptoms.

The Panel noted that Table 2 of Ringdal *et al* listed defining criteria for asthma exacerbation severity and that the number of patients who experienced each severity of exacerbation during the study was not significantly different between treatment groups. The majority of the exacerbations were mild. The Panel noted AstraZeneca's submission that the clinical significance of a moderate or severe exacerbation was greater than a mild exacerbation and a trial involving Seretide 250 would be of interest to those treating asthma symptoms at the more severe end of the spectrum. The Panel also noted GlaxoSmithKline's submission that the mean overall exacerbation rate was a well recognized measure. The claim at issue referred to exacerbations and not exacerbation rate. No details were provided as to how the rates were calculated.

On balance the Panel considered that insufficient detail had been provided about the definition of asthma exacerbation. The clinical significance of the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations' was thus unclear and misleading in this regard as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that Ringdal *et al* stated that treatment groups were well matched at baseline. The majority of the exacerbations over the study period were mild in each treatment group. One of the defining criteria for a mild exacerbation was wakening at night due to asthma for ≥ 2 consecutive days. Chuchalin reported on night-time symptoms. At baseline the median % nights with no awakening was 28.6% in the Seretide group and 16.7% in the budesonide plus formoterol group. It was stated that night awakenings due to asthma were significantly lower in the Seretide group than the budesonide plus formoterol group. The p value at month 1 was 0.017, at month 2 was 0.024 and at month 3 there was no statistically significant difference. The median percentage of nights with no awakening over the three month period was greater in the Seretide group (80.3) than in the budesonide and formoterol group (60) (p=0.022). Night-time awakenings were not included in the definitions of moderate or severe exacerbations in Ringdal. The statistical significance between groups in the number of patients experiencing each severity of exacerbations was not stated. The Panel noted AstraZeneca's submission regarding the difference in night-time awakening at baseline of 42% and that the failure to consider this when determining the number of mild exacerbations in each group could lead to an overestimation in the budesonide plus formoterol group. GlaxoSmithKline stated that the analysis was re-run after unblinding using the baseline rather than the country as an adjustment to determine the sensitivity of the outcome to this parameter. The statistically significant effect on nights with no awakenings when stratified by country over the twelve-week study period overall (p=0.022) became, in fact, more significant when the data were corrected for baseline differences (p=0.013). The Panel noted that both studies stated that the treatment groups were well matched at baseline. It appeared that Chuchalin failed to take account of baseline differences between the groups.

The Panel noted the additional analysis provided by GlaxoSmithKline that the between group difference in median percentage of nights with no awakening became more significant when adjusted for baseline differences rather than the country. AstraZeneca's view was that both factors had to be taken into account when analysing the data. The protocol-defined analysis did not take baseline values into account as no difference was expected. GlaxoSmithKline had not submitted any material in relation to the effect, if any, the difference in nights with no awakening adjusted for baseline differences had upon the absolute numbers of mild exacerbations and hence the overall difference in the mean rate of asthma exacerbations for the products. In this regard the Panel noted that the numbers of patients who experienced each severity of exacerbation during the study were not significantly different between treatment groups. The Panel noted GlaxoSmithKline's submission that the significant differences in exacerbation rates between the groups were in the rate of exacerbations experienced by those patients who had exacerbations. Patients on Seretide who had exacerbations had a lower rate of exacerbations than those who exacerbated on budesonide plus formoterol.

On balance the Panel considered that given the data the claim 'Seretide 250 was significantly more effective at reducing asthma exacerbations' was misleading and unsubstantiated as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **9 April 2002**

Case completed **6 August 2002**

CONSULTANT MANAGER OF INTENSIVE CARE UNIT v INO THERAPEUTICS

Promotion of nitric oxide

The consultant manager of an intensive care unit complained about the promotion of INOmax (nitric oxide) by a representative of INO Therapeutics. The representative had requested an appointment to see the complainant to promote the use of nitric oxide using the company's gas and delivery system for adult patients. The representative informed the complainant that nitric oxide now had a European licence for use in neonates. However, despite reiterating that he only treated adults and her admitting that she was promoting in an area outside the product licence, she continued to persuade him to use her company's product.

The Panel noted that prior to INOmax receiving a marketing authorization, unlicensed nitric oxide had been supplied by BOC (British Oxygen Company). A letter sent by BOC advised hospital consultants that a marketing authorization for INOmax had been granted to INO Therapeutics. The INO Therapeutics team would visit each hospital to agree arrangements. BOC was unable to supply INO Therapeutics with the recipient's personal details but would supply it with a list of hospitals. The letter stated that it would be very helpful if the reader would establish contact with INO Therapeutics as soon as possible. A reply paid card was provided.

The Panel noted the representative stated that the purpose of the call was to 'explain the changes that were going to take place with nitric oxide …'. She explained about INOmax and its licence and indications. In the Panel's view the BOC letter and reply paid card meant that in effect the visit was solicited.

The Panel considered that the circumstances which gave rise to this case were unusual. Prior to INOmax receiving a marketing authorization, unlicensed nitric oxide, supplied by BOC, appeared to have been used in neonates and adults. Following the grant of the INOmax marketing authorization INO Therapeutics could only promote use in neonates. In the Panel's view it appeared that if clinicians wished to use nitric oxide outside the licensed indications the INO Therapeutics product might be used and that other sources of the unlicensed product were available.

The Panel considered that INO Therapeutics and the representative failed to clearly establish the purpose of the meeting with the complainant and this was not helped by the unlicensed use of nitric oxide. In this regard the Panel noted that representatives were instructed to redirect questions about off-label use to other personnel. It was difficult to determine precisely what had been said; the parties' accounts differed in some respects. Given the complexity of the situation, the Panel considered that on balance the medicine had not been promoted for an unlicensed indication. No breach of the Code was ruled.

COMPLAINT

The consultant manager of an intensive care unit complained about the promotion of INOmax (nitric oxide) by a representative of INO Therapeutics.

The complainant stated that he had always up until now found the way members of the pharmaceutical industry promoted their medicines to be highly professional and ethical. However, a meeting he had had with a representative of INO Therapeutics had alarmed him greatly.

The representative, specifically on her request, made an appointment to see the complainant to promote the use of nitric oxide using the company's gas and delivery system for adult patients.

The representative informed the complainant that nitric oxide now had a European licence for use in neonates. However, as the complainant was a consultant on an adult only unit she was clearly promoting its use in an area in which she admitted the company did not have a product licence. The complainant did not believe that this was an isolated error or misunderstanding because despite reiterating that he only treated adults, she continued to persuade him to use her company's product for his group of patients.

In contacting colleagues around the country whom were also adult intensivists they too had had similar experiences from representatives of this company.

The complainant was not sure whether medical gases were covered by the Code but clearly from the nature of the conversation and the promotional material that was left with him, the company intended to promote its product as a pharmaceutical medicine.

When writing to INO Therapeutics the Authority asked it to respond in relation to the requirements of Clause 3 of the Code.

RESPONSE

INO Therapeutics stated that nitric oxide for medical use had been manufactured and supplied to UK hospitals by British Oxygen Company (BOC) in the past as an unlicensed medicinal product. In November 2001 BOC wrote to hospitals in the UK advising of the change in registration status of nitric oxide. INOmax 400ppm nitric oxide inhalation gas was approved via the European centralised procedure in August 2001. This application to the European Medicines Evaluation Agency was initiated in January 2001, and the rapporteur for the procedure was the UK Medicines Control Agency.

It was concluded by INO Therapeutics that the complainant was one of the recipients of the letter from BOC, and pursuant to the BOC communication, that he willingly solicited contact from INO Therapeutics via BOC. Clearly there remained a

difference of opinion between the INO Therapeutics representative and the complainant with regard to initiation of contact between the two parties, although the document signed by the complainant appeared to substantiate his wish to discuss INO Therapeutic's product.

The INO Therapeutics representative attended the appointment with the complainant, understanding that he was already familiar with the therapeutic potential of nitric oxide as a selective pulmonary vasodilator and that as a non-neonatologist he likely exclusively treated adults with nitric oxide as an unapproved medicine. INO Therapeutics confirmed that the visit by the INO Therapeutics representative was completed with the expectation that the complainant was interested in the change in registration status of nitric oxide, and the practical issues to his hospital relating to a transition from an unapproved medicine to the approved medicine.

The representative provided the complainant with a copy of the INOvent brochure. INOvent was a CE-marked delivery device designed for administration of nitric oxide inhalation gas. INO Therapeutics supported the administration of INOmax by providing support and training on the INOvent in those hospitals who planned to use INOmax. An important consideration for all hospitals using nitric oxide was the concentration of nitric oxide in the cylinder and from unapproved sources of this medicinal product. Calibration of the delivery device to accommodate the cylinder concentration was a very important consideration, and INO Therapeutics was mindful of the possibility of error in administration when different concentration sources co-existed. Moreover, INO Therapeutics took a responsible position with regard to training in delivery of its medicinal product.

Assuring a safe transition from the unapproved formulations of nitric oxide in nitrogen, to the approved medicinal product, was an important consideration for INO Therapeutics prior to the launch of INOmax in UK. For this reason, the INO Therapeutics representative specifically responded to the contact request by the complainant, even knowing that he was likely not to be treating term and near-term infants.

With specific regard to the complainant's issue with INOmax as a pharmaceutical medicine, the Committee for Proprietary Medicinal Products reviewed and approved the product as an innovative medicine. The summary of product characteristics (SPC) for INOmax addressed the following key elements relevant to patient safety: maximum recommended doses; weaning strategy; minimal specifications for an approved (CE marked) nitric oxide delivery system; training requirements for hospital personnel responsible for delivery of INOmax; monitoring of methaemoglobin formation; monitoring of nitrogen dioxide formation.

INO Therapeutics submitted that continued co-existence of unapproved formulations of nitric oxide with the approved and adequately studied product, INOmax, might undermine patient safety and examples were given.

In conclusion, prior to launch of INOmax in UK, it was important to tell the medical community about the changes associated with provision of the approved product. The visit to the complainant was not intended to persuade him of the therapeutic potential of nitric oxide as a selective pulmonary vasodilator, for which he was clearly already convinced, based on his prior use. Rather, the visit was made in response to his written consent and was a genuine attempt to tell him about the practical changes he might realise as the unapproved, multiple concentrations of nitric oxide became unavailable from BOC.

INO Therapeutics would provide the approved product, INOmax, supported with the standards expected of an innovative medicine: pharmacovigilance, medical information, training to hospital personnel in safe delivery, access to a delivery device meeting the minimal specifications mandated by CPMP, and full service support for this delivery device, the INOvent.

INO Therapeutics looked forward to promoting the administration of INOmax, in conjunction with ventilatory support and other appropriate agents in newborns ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

Furthermore, INO Therapeutics was vigilant in the review of all promotional practices, training of all field representatives, and had a high regard for the role of medical information, particularly with regard to unapproved uses of INOmax, for which it was committed to good clinical research. INO Therapeutics could not promote off-label use for which rigorous clinical trials had not yet proven nitric oxide to be effective.

The allegation that colleagues of the complainant around the country had had similar experiences with INO representatives was unsubstantiated, and should be withdrawn.

INO Therapeutics provided a copy of the circular letter sent to consultants by BOC Medical advising that once INO Therapeutics was ready to supply INOmax and had agreed supply arrangements and trained staff in its use, BOC would no longer be in a position to supply inhaled nitric oxide to the hospital. Recipients were provided with a reply paid card to permit BOC Medical to pass on their details to INO Therapeutics.

INO Therapeutics also provided a copy of such a card completed by the complainant. It stated 'I give my consent for BOC Medical to pass on my name, title and phone number to INO Therapeutics. I understand that they will contact me shortly'.

In response to a request for further information INO Therapeutics stated that whilst recognizing the limitations associated with recounting a hearsay conversation, it provided a statement of the encounter between the complainant and its representative. INO Therapeutics took this situation very seriously and had instructed the representative as to the importance

of accuracy and full disclosure of the events in her statement.

The representative stated that at a team meeting with her country manager there was a discussion about contacts on the list of current BOC customers who had positively replied to BOC when informed that BOC was withdrawing from the nitric oxide market and asking whether they would like their details passed on to INO Therapeutics for a representative to make contact. A name on the list identified as yet to be contacted was the complainant.

The representative contacted the complainant's secretary. She explained that BOC was withdrawing from the nitric oxide market and that INO Therapeutics had been asked to contact the complainant at his request in order to explain the changes. When she saw the complainant by appointment she introduced herself and began to inquire about what he knew of the changes. She explained about INOmax and its licence and indications. It was at this point that the complainant remarked that he was not within those indications, and was unhappy with her trying to promote something off label. She explained to the complainant that at the moment all INO Therapeutics was doing was responding to BOC's customers who had asked for their details to be passed on to a representative, and explaining about the changes that were going to take place with nitric oxide, that INO Therapeutics had not yet launched and that the intention of the meeting at this point was to explain the changes that were going to take place. The complainant did not say whether he had contacted BOC but she was left feeling he had not. The representative asked at this point if he wanted her to continue and he motioned that she was to do so. The representative began explaining about the INOvent and the complainant asked if she had any literature. She said that she had one INOvent brochure but that it was prelaunch material. At this point the complainant said that he was uncomfortable with this appointment, at which point the representative rose and said that it would probably be best if she left. Leaving the complainant with her business card, and the invitation to call if she could answer any questions or queries he had regarding INO Therapeutics, she left. The representative had no further contact with the complainant.

INO Therapeutics had seen the letter sent by BOC and specifically its representative had seen it. The representative was also provided with the contact information the complainant had sent to BOC in response to its letter.

In response to a question whether the only source of inhaled nitric oxide, for whatever purpose, was INOmax, which was only licensed for use in newborns, INO Therapeutics stated that there was no agreement between BOC and INO Therapeutics that BOC must withdraw its product. INO Therapeutics did have an explicit licensing agreement with BOC under the terms of the applicable patent for INOmax. Moreover, there was no agreement between INO Therapeutics and any other supplier of nitric oxide regarding withdrawal of competitive products. However, it should be emphasized that AGA AB was the only company that held a marketing authorization for nitric oxide. INOmax was the proprietary drug of AGA AB, and was only approved for treatment of newborns ≥ 34 weeks gestation with hypoxic respiratory failure. The marketing authorization would be transferred to INO Therapeutics AB, which was a wholly owned subsidiary of AGA AB.

In response to a request for instructions provided to representatives, INO Therapeutics provided a record of sales training as well as copies of training materials. INO Therapeutics stated that in accordance with Clause 15.9 it would be noted that these briefing materials consisted of sections relevant to off-label promotion. All INO Therapeutics employees were specifically advised against promoting for off-label sales. As a result of this most unfortunate incident and the types of questions and materials the Authority had requested, policies were being implemented that would provide additional legal caveats for investigation and for-cause dismissal. At the time of this incident, INO Therapeutics had not launched the product in the UK. The representative was only following up on the contact under the BOC arrangement described previously. In that context, she intended only to describe the transition of the registration status of this medicinal product, and the practical issues relating to a transition from an unapproved medicine to the approved medicine. Consistent with Clause 3.2, the representative did not promote the use of the product for any unauthorized indications. INO Therapeutics contended that it was the complainant's presumption that because he was not a neonatologist any conversation by the representative implied a sanction of off-label use. It was INO Therapeutics' position that its representative was responding to his inquiry to BOC and required information on the transition in status from an unapproved medicine to the approved medicine, which was in fact consistent with the type of planning information described in Clause 3.1. INO Therapeutics stated that Clause 3 was not applicable. Moreover in regard to the broader sharing of medical information for nitric oxide literature, INO Therapeutics had an organizationally discreet and separate group, the clinical specialists, who were able to discuss medical data on INOmax without any promotional intent should the complainant have asked for such discussion between health professionals.

PANEL RULING

The Panel noted that nitric oxide had been supplied as an unlicensed medicine. This was to change. The Panel noted that according to its SPC INOmax was indicated, in conjunction with ventilatory support and other appropriate agents, for the treatment of newborns ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiograph evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. INOmax was the only nitric oxide with a marketing authorization.

A letter sent by BOC (which had previously supplied unlicensed nitric oxide) advised hospital consultants

that a marketing authorization for INOmax had been granted to INO Therapeutics Inc and consequently BOC would no longer supply inhaled nitric oxide. The INO Therapeutics team would visit each hospital on a rolling programme to agree detailed arrangements. Reference was made to transitional arrangements. The letter stated that the company was unable to supply INO Therapeutics with the reader's personal details due to the provisions of the Data Protection Act 1998, but would supply a list of hospitals. The letter stated that it would be very helpful if the reader would establish contact with INO Therapeutics as soon as possible. A telephone number and reply paid card were supplied for this purpose.

The reply paid card completed by the complainant read 'I give my consent for BOC Medical to pass on my name, title and phone number to INO Therapeutics. I understand they will contact me shortly'.

The representative stated that the purpose of the call was to 'explain the changes that were going to take place with nitric oxide …'. On arrival she, *inter alia*, explained about INOmax and its licence and indications. The Panel noted that the company could not take advantage of the provision in Clause 1.2 of the Code which exempted from the definition of promotion the response of pharmaceutical companies to specific communications from individual healthcare professionals whether of enquiry or comment, but only if they related solely to the subject matter of the letter or enquiry were accurate, did not mislead and were not promotional in nature. Such enquiries, however, had to be unsolicited. In the Panel's view the BOC letter and reply paid card meant that in effect the visit was solicited. The exemption did not apply. The Panel did not accept INO Therapeutics' submission that the information was the type of planning information described in Clause 3. The supplementary information to Clause 3.1 referred to the introduction of products or indications that had significant budgetary implications. This did not apply to the situation at issue.

The Panel considered that the circumstances which gave rise to this case were unusual. Prior to INOmax receiving a marketing authorization, unlicensed nitric oxide had been supplied by BOC and it appeared that it had been used in neonates and adults. Following the grant of the INOmax marketing authorization INO Therapeutics could only promote use in neonates. In the Panel's view it appeared that if clinicians wished to use nitric oxide outside the licensed indications the INO Therapeutics product might be used and that other sources of the unlicensed product were available.

The Panel noted INO Therapeutics' submission that the complainant was familiar with nitric oxide and that as a non-neonatologist he likely used nitric oxide in adult patients as an unapproved medicine. Given the circumstances the product's licensed indication should have been made very clear. It would have been helpful if the letter sent by BOC had stated the licensed indication. There was nothing in the letter regarding clinical issues which might need to be considered as a result of the grant of the marketing authorization. The general impression from the letter was that practical administrative issues might need to be discussed with INO Therapeutics. It would have been helpful if a further communication had been sent by INO Therapeutics acknowledging that a visit had been requested so that the basis of the meeting was clear. It appeared that the complainant was expecting the representative to promote the product whereas the representative's understanding was that the meeting was to explain the changes regarding the supply of nitric oxide. It was important in these circumstances to ensure that healthcare professionals were clear about what the representative was going to discuss and that unlicensed indications were not promoted.

The Panel considered that INO Therapeutics and the representative failed to clearly establish the purpose of the meeting with the complainant and this was not helped by the unlicensed use of nitric oxide. In this regard the Panel noted that representatives were instructed to redirect questions about off-label use to other personnel. It was difficult to determine precisely what had been said; the parties' accounts differed in some respects. The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he/she was moved to submit a complaint. Given the complexity of the situation the Panel considered that on balance, taking all the factors into account, the medicine had not been promoted for an unlicensed indication. No breach of Clause 3.2 of the Code was ruled.

Complaint received **12 April 2002**

Case completed **15 July 2002**

CASE AUTH/1304/4/02

SCHWARZ PHARMA/DIRECTOR v SCHERING-PLOUGH

Promotion of NeoClarityn including breach of undertaking

Schwarz Pharma complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough. The items at issue were a 'Dear Nurse' letter and an accompanying mailer. Schwarz supplied Mizollen (mizolastine).

Two of the matters of complaint involved alleged breaches of the undertaking and assurance given in Case AUTH/1172/3/01 and these were taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

Schwarz stated that the Medicine Control Agency recommendations were that black triangle medicines should not be included in the Nurse Prescribers' Extended Formulary but the letter did not indicate that NeoClarityn would still require prescribing by a doctor. Attention was drawn to the claim 'When the first patient with hayfever presents at your surgery, we hope you will remember NeoClarityn'. The material was alleged to be misleading in that it was not tailored to the nurse audience.

The Panel considered that the letter was not sufficiently clear about whether the recipients, nurses, were permitted to prescribe NeoClarityn. It was not sufficient to assume that the inclusion of the black triangle made it clear that the product was not suitable for nurse prescribers. The letter had not been sufficiently tailored for the audience. The Panel ruled a breach of the Code.

Schwarz alleged that the statement 'Patients need effective relief from hayfever, so when Clarityn (loratadine) was discontinued last year we recommended NeoClarityn, a purified form of loratadine in its place' was misleading as it implied direct comparative data was available for the efficacy and tolerability of NeoClarityn against Clarityn which could not be substantiated.

The Panel did not accept that the statement implied that direct comparative data was available for efficacy and tolerability as alleged. There was no express or implied comparison of the products. The Panel ruled no breach of the Code.

Schwarz alleged that the claim 'It is a suitable first-choice for patients over the age of 12, regardless of their previous medication' was all-encompassing and misleading as it suggested that even patients with hypersensitivity to loratadine could take NeoClarityn, despite this being listed as a contraindication to its use. Furthermore the claim suggested that NeoClarityn could be prescribed for an indication for which it had no licence; Clarityn was licensed for perennial allergic rhinitis – NeoClarityn was not.

The Panel considered that NeoClarityn would be a suitable first choice for patients over the age of 12 but considered that it was misleading to state that this would be regardless of their previous medication. Patients who were hypersensitive to loratadine should not be prescribed NeoClarityn. The claim was all-embracing and a breach of the Code was ruled. The Panel did not accept that the claim implied that NeoClarityn could be prescribed for perennial allergic rhinitis which was not one of its licensed indications although it was one of Clarityn's licensed indications. The letter was clearly headed 'for hayfever and chronic idiopathic urticaria' and stated 'NeoClarityn relieves the symptoms of hayfever'. No breach of the Code was ruled in this regard.

Schwarz alleged that the claim 'NeoClarityn has demonstrated improved total symptom scores including nasal congestion. It has also demonstrated improved quality of life scores in hayfever' was a hanging comparison, as there was no indication as to the comparator. The Panel did not consider that the claim was a hanging comparison as alleged. It noted that the comparison was with the untreated disease state and considered that it would be read as such. No breach of the Code was ruled.

Schwarz noted that the claim 'Without impairing performance' was similar to the claim 'No impairment of performance' which had been ruled in breach of the Code in Case AUTH/1172/3/01. This, therefore, represented a failure to comply with the undertaking.

The Panel noted that in Case AUTH/1172/3/01 it had considered that the claim that NeoClarityn caused no impairment of performance was misleading and exaggerated and breaches of the Code were ruled. In the case now before it the Panel noted that new data suggesting that NeoClarityn might be suitable for those involved in skilled activity had to be presented in the context of the statement in the summary of product characteristics (SPC) which referred to no or negligible influence on the ability to drive and use machinery. The Panel considered that the claim 'without impairing performance' was sufficiently similar to the previous claim at issue 'no sedation or impairment of performance' for it to be covered by the undertaking given in the previous case. A breach of the Code was ruled.

Schwarz stated that one of the references did not correlate with the publication cited in the list of references. The Panel noted that the cited references referred to 'Poster 4'. The actual poster provided by Schering-Plough did not refer to Poster 4. The authors were as cited in the 'Dear Nurse' letter. The claim was not one that required a reference and the Panel therefore ruled no breach of the Code.

The statement 'Prescribing information may be found on reverse' appeared on the front page of the mailer. Schwarz noted that the prescribing information was not available on the reverse. Only on fully opening out the mailing was prescribing information available. As such, the reference for location of prescribing information was not clear. The Panel noted that the front page of the mailer stated that prescribing information was available on

the reverse and when turning it over the prescribing information could be found by opening up the mailing to the third page. It was not necessary to fully open the mailer. Given the layout of the material the Panel considered that on balance the mailer was not unreasonable in this regard. A reference to the location of the prescribing information had been given. The Panel ruled no breach of the Code.

The claim 'A prescription that's evolved' appeared as a heading to one of the folded pages. It was followed by a claim that 'NeoClarityn contains desloratadine – a purified development of loratadine' and data relating to *in vitro* and *in vivo* activity. Schwarz alleged that this claim, taken with subsequent information, implied that NeoClarityn possessed advantages, either in efficacy or side effect profile, over Clarityn. There had been no direct comparative studies of NeoClarityn and Clarityn to draw further conclusions relating to either efficacy or side effect profiles. As such, this claim was not substantiated.

The Panel did not accept that either the claim or the subsequent information on the page implied that NeoClarityn had advantages over Clarityn with regard to either efficacy or side effect profile. In the Panel's view the claim would be read in conjunction with the claim that followed it 'NeoClarityn contains desloratadine – a purified development of loratadine'. The rest of this section referred to *in vitro* and *in vivo* material and stated that the data were preclinical: the clinical relevance of these observations remained to be confirmed. The Panel did not consider that the claim was unsubstantiated as alleged. No breach of the Code was ruled.

The claim 'Lack of performance impairment' was followed by three bullet points. Firstly a statement that patients might be unaware that they were affected by drowsiness and might continue to engage in activities such as driving. Secondly 'NeoClarityn has no effect on psychomotor performance' and thirdly a reference to two studies which had 'confirmed that NeoClarityn could be suitable for those involved in skilled activity and transportation, in particular flying'. Schwarz stated that this claim suggested there was no impairment of performance. A subsequent point stated 'NeoClarityn had no effect on psychomotor performance'. The SPC for NeoClarityn stated that 'NeoClarityn has no or negligible influence on the ability to drive and use machines'. As such, the claim was exaggerated and could not be substantiated. In Case AUTH/1172/3/01, the claim 'No sedation or impairment of performance' was found to be in breach of the Code in relation to the 'impairment of performance'. As such, this represented a failure to comply with the undertaking given in the previous case. The Panel considered that this was similar to a point above and its ruling above applied here.

A cost comparison headed 'And just look at the price' listed the monthly cost of NeoClarityn (£7.57), loratadine (£7.57), Zirtek (£8.73) and Telfast (180mg (£9.63) and 120mg (£7.40)). Schwarz stated that the cost comparison table was based on the 'leading four branded antihistamines by cash sales, January 2002', but the mailer did not provide a reference. Additionally, including mizolastine in the relative potency chart and not in the cost comparison unfairly identified NeoClarityn as the cheapest antihistamine. This was misleading as current pricing of Mizollen would place it at the top of the table. As the table was comparing antihistamine tablets and included Clarityn which the 'Dear Nurse' letter stated was to be 'discontinued' yet was still available at pharmacies, this was not a balanced comparison.

The Panel did not accept that the inclusion of mizolastine in a chart comparing relative *in vitro* potency meant that it should necessarily be included in the cost comparison chart. NeoClarityn was not the cheapest medicine listed. The Panel noted Schering-Plough's submission that Clarityn was included in the chart because although the promotion and supply of Clarityn had been discontinued its availability was still such that it had a place as a leading antihistamine in terms of cash sales. The Panel did not accept that the omission of mizolastine and the inclusion of Clarityn meant that the cost comparison was misleading as alleged. No breach of the Code was ruled. (The Panel was concerned that the selection of products on the basis of cash sales might not be fair. There was no complaint in this regard.)

Schwarz alleged that the continued failure to comply with the Code in the promotion of NeoClarityn reduced confidence in the pharmaceutical industry. The promotional material continued to use claims that were sufficiently similar to past rulings of breaches.

The Panel considered that the failure of Schering-Plough to comply with the undertaking brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel decided that the circumstances warranted reporting Schering-Plough to the Appeal Board.

The Appeal Board was concerned that this was yet another case involving the promotion of NeoClarityn by Schering-Plough. The company had been ruled in breach for failing to comply with an undertaking. This was a serious matter. The Appeal Board noted that Schering-Plough had been required to undergo two audits (Case AUTH/1210/7/01) and had been reported to the ABPI Board of Management (Case AUTH/1234/10/01). The ABPI Board had decided to publicly reprimand the company.

The Appeal Board was extremely concerned about the conduct of Schering-Plough. It noted the sanctions imposed as a result of previous cases and that there was now a new Managing Director who had taken some action. The Appeal Board decided on balance not to report Schering-Plough to the ABPI Board of Management.

Schwarz Pharma Limited complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough Ltd. The items at issue were a 'Dear

Nurse' letter (ref NCL/02-219) and an accompanying mailer (ref NCL/02-213). Schwarz supplied Mizollen (mizolastine).

Two of the allegations involved alleged breaches of the undertaking and assurance given in Case AUTH/1172/3/01 and these were taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

A 'Dear Nurse' letter

1 Alleged misleading promotion for nurse prescribing

COMPLAINT

Schwarz Pharma stated that the 'Dear Nurse' letter promoted NeoClarityn to a health professional recommending its use. Following Medicine Control Agency (MCA) recommendations that black triangle medicines should not be included in the Nurse Prescriber's Extended Formulary, the letter did not indicate that NeoClarityn would still require prescribing by a doctor. The impression was that NeoClarityn should be considered for treating patients with hayfever, who would present to nurses able to prescribe other antihistamines. In this regard attention was drawn to a claim 'When the first patient with hayfever presents at your surgery, we hope you will remember NeoClarityn'. The material, without clarification about prescribing NeoClarityn, addressed to a nurse was alleged to be misleading in that it was not tailored to the audience which was currently unable to prescribe NeoClarityn, in breach of Clause 12.1 of the Code.

RESPONSE

Schering-Plough stated that the mailing was designed to inform nurses of the availability and characteristics of NeoClarityn. The black triangle that this product carried was prominently displayed and this made it clear that it was not suitable for nurse prescribers.

Clearly nurse practitioners had a role in educating their patients on the products physicians prescribed for them, and it was appropriate for these practitioners to be educated on the products, especially in areas such as allergy where their input was likely to be significant.

Schering-Plough could not agree with the assertion that mailing information to a health professional was, of itself, a breach of Clause 12.1.

PANEL RULING

The Panel noted that the mailing had been sent to nurses. NeoClarityn was a prescription only medicine. It was not on the Nurse Prescriber's Extended Formulary as set out in the recent legislation (The Prescription Only Medicines (Human Use) Amendment Order 2002, No 549).

The Code permitted advertising to health professionals and the supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that the 'Dear Nurse' letter did not refer to prescribing NeoClarityn as such. Nevertheless the Panel considered that the letter was not sufficiently clear about whether the recipients, nurses, were permitted to prescribe NeoClarityn. It was not sufficient to state that the inclusion of the black triangle made it clear that the product was not suitable for nurse prescribers. The letter had not been sufficiently tailored for the audience. The Panel ruled a breach of Clause 12.1 of the Code.

2 Statement 'Patients need effective relief from hayfever, so when Clarityn (loratadine) was discontinued* last year we recommended NeoClarityn, a purified form of loratadine in its place'.

The asterisk referred to a footnote at the bottom of the letter which read 'Clarityn Allergy Tablets and Syrup are still available at pharmacies and Clarityn Syrup is still available on prescription'

COMPLAINT

Schwarz alleged that this statement was misleading in recommending NeoClarityn in place of Clarityn, as it implied direct comparative data was available for the efficacy and tolerability of NeoClarityn against Clarityn. Such an implication could not be substantiated by currently available evidence. A breach of Clause 7.4 of the Code was alleged.

RESPONSE

Schering-Plough submitted that the statement was simply a reiteration of the fact that, for patients with seasonal allergic rhinitis and chronic idiopathic urticaria, indications that were prominently featured on the heading of the letter, Schering-Plough believed that NeoClarityn was an effective treatment, and one which, with the discontinuation of Clarityn, it was happy to recommend. These were the licensed indications for this product. A recommendation that NeoClarityn was a suitable remedy for patients with these conditions did not imply a comparison with Clarityn, only that it was an accepted and established therapy for these conditions.

Schering-Plough did not agree that recommending a suitable medicine was in breach of Clause 7.4.

PANEL RULING

The Panel did not accept that the statement implied that direct comparative data was available for efficacy and tolerability as alleged. There was no express or implied comparison of the products; it was merely stated that certain presentations of Clarityn had been withdrawn and NeoClarityn was recommended. The Panel ruled no breach of Clause 7.4 of the Code.

3 Claim 'It is a suitable first-choice for patients over the age of 12, regardless of their previous medication'

COMPLAINT

Schwarz stated that the use of 'regardless' was an all-encompassing claim that was misleading as it would even suggest that individuals with hypersensitivity to loratadine could take NeoClarityn, despite this being listed as a contraindication for the use of NeoClarityn. A breach of Clause 7.10 of the Code was alleged.

Furthermore, the claim opened the possibility of NeoClarityn being prescribed for an indication for which it currently did not hold a marketing authorization eg NeoClarityn's indications were seasonal allergic rhinitis and chronic idiopathic urticaria; Clarityn's indications were seasonal allergic rhinitis, perennial allergic rhinitis and idiopathic chronic urticaria. As such, the claim was alleged to be in breach of Clause 3.2.

RESPONSE

Schering-Plough believed it was very unlikely that a doctor, given the similarities between the two products and the labelling in the prescribing information in the letter, would make this error. However Schering-Plough was happy to further reduce the possibility of this error happening and would not be repeating the claim.

Schering-Plough disagreed that the claim opened up the possibility of NeoClarityn being prescribed for an indication for which it currently did not hold marketing authorization. The indications for NeoClarityn were made clear. The letter stated, in bold capitals, at the top 'FOR HAYFEVER AND CHRONIC URTICARIA' in a font size much bigger than that of the claim at issue.

Schering-Plough considered that the piece made it very clear that it was only supporting the use of NeoClarityn within its licensed indications.

PANEL RULING

The Panel noted that the letter was aimed at nurses not at doctors. The Panel considered that NeoClarityn would be a suitable first choice for patients over the age of 12 but considered that it was misleading to state that this would be regardless of their previous medication. Patients who were hypersensitive to loratadine should not be prescribed NeoClarityn. The claim was all-embracing and a breach of Clause 7.10 was ruled.

The Panel did not accept that the claim implied that NeoClarityn could be prescribed for perennial allergic rhinitis which was not a licensed indication for NeoClarityn although it was one of Clarityn's licensed indications. The letter was clearly headed 'for hayfever and chronic idiopathic urticaria'. The sentence prior to the one at issue read 'NeoClarityn relieves the symptoms of hayfever'. No breach of Clause 3.2 was ruled in this regard.

4 Claim 'NeoClarityn has demonstrated improved total symptom scores including nasal congestion. It has also demonstrated improved quality of life scores in hayfever'

COMPLAINT

Schwarz alleged that the claim represented a hanging comparison, as there was no indication as to the comparator from which NeoClarityn had improved these scores. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Schering-Plough disagreed. The claim simply reflected the fact that in hayfever NeoClarityn improved the symptoms of hayfever. This was in line with the prescribing information which stated 'NeoClarityn is indicated … for the relief of symptoms associated with seasonal allergic rhinitis …'.

Any comparison, real or implied, was with the untreated disease state. Schering-Plough believed health professionals would understand this. There was no breach of Clause 7.2.

PANEL RULING

The Panel did not consider that the claim was a hanging comparison as alleged. It noted that the comparison was with the untreated disease state and considered that it would be read as such. No breach of Clause 7.2 of the Code was ruled.

5 Claim 'Without impairing performance'

This claim appeared as an emboldened subheading in the letter.

COMPLAINT

Schwarz stated that this was an all-encompassing claim that suggested NeoClarityn did not impair performance. According to the summary of product characteristics (SPC) for NeoClarityn, 'NeoClarityn has no or negligible influence on the ability to drive and use machines'. In Case AUTH/1172/3/01 a similar claim, 'no impairment of performance', was ruled in breach. This, therefore, represented a failure to comply with the undertaking. A breach of Clause 22 of the Code was alleged.

RESPONSE

Schering-Plough stated that the references to lack of performance inhibition were linked to the specific areas where data confirmed the lack of performance impairment of desloratadine: driving and flying. The discussion in the letter singly focused on the flying data, and the pictures, as well as the text of the leavepiece, reflected the driving and flying data referenced.

The statement represented the current body of evolving medical opinion. Three recent publications reinforced this message.

Scharf *et al* 2000 concluded that even at a dose level that exceeded the recommended daily dose by 50%, desloratadine did not alter daytime somnolence or impair psychomotor performance. The authors further noted that no significant differences were noted

between desloratadine and placebo in any of the performance measures evaluated.

Valk *et al* 2000 concluded that no significant differences were found between desloratadine daily and placebo in performance of flying ability or in sleepiness. The authors suggested that the tests demonstrated that desloratadine was non-sedating and would not be expected to impair pilot vigilance or ability to perform complex tasks during aircraft operation.

Similarly Nicholson *et al* 2001 concluded that 'Desloratadine appears to be free of adverse effects on psychomotor performance, daytime sleep latencies and subjective sleepiness'.

Schering-Plough was not aware of a single publication that suggested that NeoClarityn had been shown to have a deleterious effect on performance, even under similarly rigid environments to those used above.

This work, and these publications, were subsequent to the Panel's ruling on a similar claim last year. Schering-Plough strongly contended that this statement reflected the body of current medical evidence and was capable of substantiation.

PANEL RULING

The Panel noted that in a previous case, Case AUTH/1172/3/01, the Panel had noted that Section 4.7 of the SPC stated 'NeoClarityn has no or negligible influence on the ability to drive or use machines'. The Panel considered, therefore, that the claim that NeoClarityn caused no impairment of performance was misleading and exaggerated. The claim could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

Turning to the case now before it, Case AUTH/1304/4/02, the Panel noted that Section 4.7 of the SPC had not changed. It noted the data referred to by Schering-Plough; this had not been considered in the previous case. Some of the data related to sedation. The Panel had decided in the previous case that it was not misleading to claim that NeoClarityn caused no sedation given that Section 5.1 of the SPC stated that desloratadine was non-sedating. The material currently before the Panel made no mention of sedation.

The new data, suggesting that NeoClarityn might be suitable for those involved in skilled activity, had to be presented in the context of the statement in the SPC which referred to no or negligible influence on the ability to drive and use machinery. Claims made for a product must not be inconsistent with the particulars listed in its SPC. The Panel considered that the claim 'without impairing performance' was sufficiently similar to the previous claim at issue 'no sedation or impairment of performance' for it to be covered by the undertaking given in the previous case. The SPC still referred to the possibility of impairment of performance. The Panel therefore ruled a breach of Clause 22 of the Code.

6 Inaccurate references

COMPLAINT

Schwarz stated that reference number 2 to the letter did not correlate with 'Poster 4' from the EAACI 2001 Congress. As such, this reference was in breach of Clause 7.6.

RESPONSE

Schering-Plough stated that the reference was correctly linked to the poster by Lorber and Danzing presented at the EAACI meeting in Berlin in May 2001. A copy of the poster was provided.

PANEL RULING

The Panel noted that the cited references referred to 'Poster 4'. The actual poster provided by Schering-Plough did not refer to Poster 4. The authors were as cited in the 'Dear Nurse' letter. The claim was not one that required a reference as set out in Clause 7.6 of the Code. The Panel therefore ruled no breach of that clause.

B Mailer (ref NCL/02-213)

The mailer that accompanied the 'Dear Nurse' letter was two pages printed on both sides and folded concertina fashion into ten pages.

1 Statement 'Prescribing information may be found on reverse'

COMPLAINT

The above statement appeared on the front page of the mailer. Schwarz noted however, on turning to the immediate reverse, that the prescribing information was not available. Only on fully opening out the material was prescribing information available. As such, the reference for location of prescribing information was not clear. A breach of Clause 4.8 of the Code was alleged.

RESPONSE

Schering-Plough noted that Schwarz agreed that on fully opening out the mailer, the prescribing information was available on the reverse.

Schering-Plough believed that health professionals would similarly open up the mailer and find the prescribing information available on the reverse of the statement.

While it was possible to enter the discussion on which 'reverse' was meant by the statement, Schering-Plough did not believe that, in practice, health professionals would have difficulty in identifying the material from the directions given.

PANEL RULING

The Panel noted that the front page of the mailer stated that prescribing information was available on the reverse and when turning it over the prescribing information could be found by opening up the mailing to the third page. It was not necessary to

fully open the mailer. Given the layout of the material the Panel considered that on balance the mailer was not unreasonable in this regard. It was arguable whether the mailer was two pages or ten pages; nonetheless a reference to the location of the prescribing information had been given. The Panel ruled no breach of Clause 4.8 of the Code.

2 Claim 'A prescription that's evolved'

The claim appeared as a heading to one of the folded pages. It was followed by a claim that 'NeoClarityn contains desloratadine – a purified development of loratadine' and data relating to *in vitro* and *in vivo* activity.

COMPLAINT

Schwarz alleged that this claim, taken with subsequent information, implied that NeoClarityn possessed advantages, either in efficacy or side effect profile, over Clarityn. The NeoClarityn European Public Assessment Report concluded that '…the clinical efficacy of 5mg desloratadine is probably not superior to 10mg loratadine'. There had been no direct comparative studies of NeoClarityn and Clarityn to draw further conclusions relating to either efficacy or side effect profiles. The supporting bulleted statements did not substantiate the evolution of a prescription, as issuing a prescription implied that '*in vitro* and *in vivo* animal studies show NeoClarityn to be more potent than loratadine' had clinical relevance. This suggestion might be seen to be refuted by a subsequent statement beneath the relative potency chart, 'Pre-clinical data: the clinical relevance of these observations remains to be confirmed'. As such, this claim was not substantiated. A breach of Clause 7.4 was alleged.

RESPONSE

Schering-Plough submitted that examining the 'subsequent information' made it clear that Schwarz's interpretation was incorrect. The page with this heading made it very clear that no clinical implications were made. The footer at the bottom of the page highlighted, in capitals, 'PRE-CLINICAL DATA: THE CLINICAL RELEVANCE OF THESE OBSERVATIONS REMAINS TO BE CONFIRMED'.

Similarly the only point which mentioned a comparison of the two products stated '*in vitro* and *in vivo* animal studies show NeoClarityn to be more potent than loratadine', and the graph that followed it referred specifically to the relative potency in 'the cloned human H1-receptor *in vitro* in CHO cells'.

It was significant that Schwarz itself stated that the suggestion that a clinical comparison was made might be seen to be refuted by a subsequent statement beneath the relative potency chart. As this was the case, Schering-Plough was unsure why Schwarz chose to interpret the heading to imply a clinical advantage.

PANEL RULING

The Panel did not accept that either the claim or the subsequent information on the page implied that NeoClarityn had advantages over Clarityn with regard to either efficacy or side effect profile.

In the Panel's view the claim would be read in conjunction with the claim that followed it 'NeoClarityn contains desloratadine – a purified development of loratadine'. The rest of this section referred to *in vitro* and *in vivo* material and stated that the data were preclinical: the clinical relevance of these observation remained to be confirmed.

The Panel did not consider that the claim was unsubstantiated as alleged. No breach of Clause 7.4 was ruled.

3 Claim 'Lack of performance impairment'

The claim appeared as a heading to one of the folded pages. It was followed by three bullet points. Firstly a statement that patients might be unaware that they were affected by drowsiness and might continue to engage in activities such as driving. Secondly 'NeoClarityn has no effect on psychomotor performance' and thirdly a reference to two studies which had 'confirmed that NeoClarityn could be suitable for those involved in skilled activity and transportation, in particular flying'.

COMPLAINT

Schwarz stated that this claim suggested there was no impairment of performance. A subsequent point stated 'NeoClarityn had no effect on psychomotor performance'. Section 4.7 of the SPC for NeoClarityn stated that 'NeoClarityn has no or negligible influence on the ability to drive and use machines'. As such, the claim was exaggerated and could not be substantiated. In Case AUTH/1172/3/01, the claim 'No sedation or impairment of performance' was found to be in breach of the Code in relation to the 'impairment of performance'. As such, this represented a failure of compliance with an undertaking. A breach of Clause 22 of the Code was alleged.

RESPONSE

Schering-Plough stated that this issue had been dealt with in point A5 above.

PANEL RULING

The Panel considered that this was similar to point A5 above. The Panel considered that its ruling in point A5 above applied here.

4 Misleading omission in cost comparison table

The cost comparison headed 'And just look at the price' listed the monthly cost of NeoClarityn (£7.57), loratadine (£7.57), Zirtek (£8.73) and Telfast (180mg (£9.63) and 120mg (£7.40)) and was based on the leading four branded antihistamines by cash sales, January 2002.

COMPLAINT

Schwarz stated that in compiling the cost comparison

table, the medicines quoted were based on the 'leading four branded antihistamines by cash sales, January 2002', but the mailer did not reference the source or locality this data referred to. Additionally, in including mizolastine in the relative potency chart, the failure to include it in the cost comparison unfairly identified NeoClarityn as the cheapest antihistamine. This was a misleading omission, the current pricing of Mizollen would place it at the top of the table, even though the table was compiled from the four leaders in terms of cash sales. As the table was comparing antihistamine tablets, included Clarityn which the 'Dear Nurse' letter stated to be 'discontinued' yet was still available at pharmacies, this was not a balanced comparison. A breach of Clause 7.2 of the Code was alleged as the table did not provide a fair, balanced presentation of the information.

RESPONSE

Schering-Plough stated that the cost comparison table clearly stated the frame of reference which was the 'Leading four branded antihistamines by cash sales, January 2002'.

It did not unfairly identify NeoClarityn as the cheapest antihistamine, only as one of the cheapest among the four highest selling antihistamines, which between them accounted for the vast majority of prescriptions.

While Schering-Plough had discontinued the promotion and supply of Clarityn tablets their availability from previous stock as well as parallel importation, meant that they still had a position in the leading antihistamines in terms of market sales.

Mizollen, with a current market share of around 1%, was currently excluded from the highest selling antihistamines. Schering-Plough believed that the most valid comparison for GPs to examine was with the antihistamines that they were most likely to prescribe. The sales figures were an accurate surrogate for the most prescribed antihistamines.

PANEL RULING

The Panel noted that the cost comparison was based on the cash sales of the leading four branded antihistamines. The Panel did not accept Schering-Plough's submission that cash sales figures were an accurate surrogate for the most prescribed antihistamine. Such a figure was influenced by the cost of a pack, not just the number of packs sold.

The Panel did not accept that the inclusion of mizolastine in a chart comparing relative *in vitro* potency meant that the product should necessarily be included in the cost comparison chart. NeoClarityn was not the cheapest medicine listed. The Panel noted Schering-Plough's submission that loratadine was included in the chart because although the promotion and supply of Clarityn had been discontinued, its availability was still such that it had a place as a leading antihistamine in terms of cash sales. The Code did not require a reference to the source of the cost comparison, only that it must be capable of substantiation as required by Clause 7.4 of the Code. There was no allegation in this regard.

The Panel did not accept that the omission of mizolastine and the inclusion of Clarityn meant that the cost comparison was misleading as alleged. No breach of Clause 7.2 of the Code was ruled.

The Panel was concerned that the selection of the products on the basis of cash sales might not be fair as this would depend on the cost as well as the volume. There was no complaint in this regard. The Panel requested that Schering-Plough be advised of its concerns. The Panel also queried the reference in Schering-Plough's submission to GPs. The Panel's understanding was that the mailer had been sent only to nurses.

C Damaging the image of the pharmaceutical industry

COMPLAINT

Schwarz stated that in view of the continued failure to comply with the Code in the promotion of NeoClarityn, reducing confidence in the pharmaceutical industry, it alleged that Schering-Plough was in breach of Clause 2 of the Code. The promotional material continued to use claims that were sufficiently similar to past rulings of breaches, in addition to two breaches of Clause 22, by failing to comply with previous undertakings. Additionally, Schwarz was concerned that such promotional pieces would be directed at a health professional unable to prescribe the product, yet implying that NeoClarityn should be prescribed by this individual when alternatives were available as part of the Nurse Prescribers' Extended Formulary. Schwarz was concerned that these mailings had been sent out, Schwarz suspected, also to GPs, and as such, could not feasibly be withdrawn despite the continued use of claims previously found in breach of the Code.

RESPONSE

Schering-Plough did not respond specifically to this allegation. The points raised were covered in A1, A5 and B3.

PANEL RULING

The Panel considered that the failure of Schering-Plough to comply with the undertaking, points A5 and B3, brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel did not consider that the mailing of the material to nurses, considered at point A1 above, was a factor in its ruling of a breach of Clause 2.

The Panel noted that the Constitution and Procedure required it to report a company to the Code of Practice Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2) in relation to additional sanctions as set out in Paragraphs 10.3, 10.4 and 12.1. Failure to comply with an undertaking was a serious matter. The Panel decided that the circumstances warranted reporting Schering-Plough to the Appeal Board.

APPEAL BOARD CONSIDERATION

The Appeal Board was concerned that this was yet another case involving the promotion of NeoClarityn by Schering-Plough. Amongst other things, the company had been ruled in breach for failing to comply with an undertaking given in an earlier case. This was a serious matter. The Appeal Board noted that Schering-Plough had been required to undergo two audits (Case AUTH/1210/7/01) and had been reported to the ABPI Board of Management in accordance with Paragraph 12 of the Constitution and Procedure (Case AUTH/1234/10/01). The ABPI Board had decided to publicly reprimand the company; details of this were to be published in the August edition of the Code of Practice Review.

The Appeal Board noted that Schering-Plough's new Managing Director had been in that post since 1 June 2002. The Managing Director stated that the company accepted the rulings and had made tremendous steps to improve its procedures and activities in relation to the Code. The Managing Director now had final sign off for all materials and had stated that there should not be repeat violations. He also stated that compliance was a very important issue for the UK company and the Head Office.

The Appeal Board was extremely concerned about the conduct of Schering-Plough. It noted the sanctions imposed as a result of previous cases and that there was now a new Managing Director who had taken some action. The Appeal Board decided on balance not to report Schering-Plough to the ABPI Board of Management.

Complaint received **22 April 2002**

Case completed **24 July 2002**

CASE AUTH/1305/4/02

VOLUNTARY ADMISSION BY WYETH

Breach of undertaking

Wyeth voluntarily advised the Authority that a journal advertisement ruled in breach in Case AUTH/1264/12/01 had appeared in the BMJ. A letter from the BMJ Publishing Group accepted responsibility and apologised for the error.

The Authority had previously asked the Code of Practice Appeal Board for guidance about the voluntary admission of potentially serious breaches. The Appeal Board advised that companies should be cautioned that, if they were going to admit to a serious breach of the Code, then this information might be used as the basis for a formal complaint against them.

The Director decided in this instance that, as the matter related to a possible breach of undertaking, it had to be taken up and dealt with as a formal complaint.

The Panel noted that in Case AUTH/1264/12/01 Wyeth accepted the Panel's rulings of breaches of the Code in relation to, *inter alia*, Zoton advertisement ZZOT2524/0801 and provided the requisite form of undertaking and assurance.

The Panel noted that prior to the provision of the undertaking in Case AUTH/1264/2/01 Wyeth had taken steps to ensure that its advertising agency knew that the advertisement at issue was no longer to be used. The advertising agency was originally notified by telephone and it sent out faxed revised copy instructions to publishers requesting a written confirmation of receipt. The revised copy instructions read: 'The pole position/flying start and high achiever adverts are being pulled from the schedule until further notice, the maintaining control advert is to replace these'. Wyeth stated that a follow-up meeting had been held with the agency pursuant to which the agency made follow-up calls with all publishers to check compliance with the revised copy instructions. Wyeth's investigations revealed that the original advertisement had been used due to the failure to communicate the revised copy instructions internally within the publishing house. As a consequence the company had failed to comply with its undertaking. A breach of the Code was ruled. This ruling was accepted.

There appeared to be no written instruction from Wyeth to the advertising agency regarding the withdrawal process; Wyeth had, however, held a meeting with the advertising agency to discuss the process. The Panel queried whether the written instructions from the advertising agency to the publishing house were sufficient. The impression from the revised copy instructions was that the advertisements in question might be used again sometime in the future. Although the letter had been sent out by the advertising agency it was incumbent upon the pharmaceutical company to ensure that such letters gave adequate instruction. The Panel noted that the company had made efforts to comply with the undertaking but nonetheless the Panel considered that despite Wyeth voluntarily bringing the matter to the attention of the Authority, Wyeth's effort was, on balance, insufficient such that it brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

The Appeal Board considered that although the instructions from the advertising agency to the publishers might have been better worded, adequate attempts had been made by Wyeth to comply with the undertaking. The company had been let down by a third party. Wyeth had been ruled in breach of the Code for failing to comply with its undertaking.

This ruling had been accepted. The company had acted quickly to withdraw the advertisement and had voluntarily admitted that it had reappeared as a result of an error by the BMJ. The Appeal Board did not consider that in the circumstances Wyeth's actions had brought discredit upon or reduced confidence in the pharmaceutical industry. The Appeal Board ruled no breach of Clause 2. The appeal was successful.

Wyeth voluntarily advised the Authority that a journal advertisement (ref ZZOT2502/0801) ruled in breach in Case AUTH/1264/12/01 had appeared in the BMJ General Practice issued on 13 April.

Wyeth subsequently provided a copy of a letter from the BMJ Publishing Group accepting responsibility and apologising for the error.

The Authority had previously asked the Code of Practice Appeal Board for guidance about the voluntary admission of potentially serious breaches. The Appeal Board advised that companies should be cautioned that, if they were going to admit to a serious breach of the Code, then this information might be used as the basis for a formal complaint against them. Companies should be asked to provide details of the action taken to correct the admitted breach. The Director of the Authority should decide whether or not to initiate a formal complaint about the matter. The Appeal Board had considered that it would be helpful to draw this to the attention of companies and details were published in the August 1997 edition of the Code of Practice Review. Wyeth was advised about the Appeal Board's guidance and provided with a copy of the article published in the Code of Practice Review.

The Director decided in this instance that, as the matter related to a possible breach of undertaking, it had to be taken up and dealt with as a formal complaint. Wyeth was asked to comment in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Wyeth confirmed that the erroneous publication of the Zoton advertisement which had been ruled in breach of the Code and which was the subject of an undertaking given by Wyeth, took place in the BMJ General Practice issue dated 13 April 2002.

Wyeth received notification from the Authority on 6 March that the Zoton advertisement in question had been ruled in breach of the Code. Wyeth gave an undertaking on 22 March that the advertisement, if not already discontinued or no longer in use, would cease forthwith. An assurance was also given that Wyeth would take all possible steps to avoid a similar breach of the Code occurring in future.

Further to the notification of the ruling and in anticipation of the provision of the undertaking, Wyeth telephoned its agency to ascertain all publications affected by the ruling and to agree necessary actions. It was agreed that the agency would refer to its media schedule of all such publications and contact the publishers involved directly to notify them of revised copy instructions in relation to, amongst others, the Zoton advertisement in question.

The agency then contacted all relevant publishers, sending out faxed revised copy instructions to each publisher involved with a request for written confirmation that the revised copy instruction had been received. A copy of the written confirmation of receipt by the BMJ Publishing Group was provided.

A follow-up meeting was then held between Wyeth and the agency to go through the agency's media schedule and confirm that all publications had been considered and all appropriate publishers had been provided with revised copy instructions. It was agreed at that meeting that the agency would make follow-up calls to double check that all publishers had taken note of and complied with the revised copy instructions. Such a call was made to the BMJ Publishing Group that afternoon.

On Friday, 12 April the BMJ Publishing Group became aware that it had re-run the Zoton advertisement in question in error and, via the agency, alerted Wyeth to this. Wyeth then made an immediate voluntary admission of this incident to the Authority which was, of course, the subject of the current complaint.

Wyeth had investigated with both the agency and the BMJ Publishing Group why it was that this advertisement had been published notwithstanding the actions it had taken and the instruction for withdrawal of the advertisement it had given. It would appear that, historically, the agency had dealt with only one administrative contact at the BMJ despite copy being submitted for more than one publication. Any individual contacted had previously communicated any copy instructions provided to the BMJ Publishing Group internally within the group as necessary.

The agency had no reason to believe that the revised copy instruction given to the BMJ Publishing Group on this occasion would not have been communicated in the same way. Again, the agency reasonably believed that the reaffirmation it had given would be communicated internally as had always previously been the case. Wyeth was now aware that the internal communication within the BMJ did not take place.

Given the actions of Wyeth and its agency as stated above, Wyeth considered that it took all possible, reasonable and necessary steps to comply with its undertaking. Wyeth considered that its instructions to its agency were more than adequate and that its agency acted reasonably in the circumstances following such instructions. The erroneous publication of the advertisement in question was due to a breakdown in communication within the BMJ Publishing Group and such breakdown was beyond the reasonable control of Wyeth and/or its agency.

Wyeth therefore believed that in the circumstances there was no breach by it of its undertaking and therefore of Clause 22. Wyeth also believed that it had operated both directly and through its agency to a sufficiently high standard in order to comply with the undertaking and had not compromised the status of the pharmaceutical industry, and therefore that there had been no breach of either Clause 9.1 or Clause 2.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

Case AUTH/1264/12/01 concerned the promotion of Zoton by Wyeth; several promotional items were at issue. Wyeth accepted the Panel's rulings of breaches of the Code in relation to, *inter alia*, Zoton advertisement ZZOT2524/0801 and provided the requisite form of undertaking and assurance stating that the advertisement had last appeared on 21 March 2002. Other rulings were the subject of appeal to the Code of Practice Appeal Board.

Turning to the case now before it, Case AUTH/1305/4/02, the Panel noted that Wyeth had contacted the Authority to advise it that the advertisement at issue had appeared, due to human error in the BMJ Publishing Group, in the general practice edition of the BMJ, 13 April.

The Panel noted that prior to the provision of the undertaking in Case AUTH/1264/2/01 Wyeth had taken steps to ensure that its advertising agency knew that the advertisement at issue was no longer to be used. The advertising agency was originally notified by telephone and it sent out faxed revised copy instructions to publishers requesting a written confirmation of receipt. The revised copy instructions read: 'The pole position/flying start and high achiever adverts are being pulled from the schedule until further notice, the maintaining control advert is to replace these'. Wyeth stated that a follow-up meeting had been held with the agency pursuant to which the agency made follow-up calls with all publishers to check compliance with the revised copy instructions. Wyeth's investigations revealed that the original advertisement had been used due to the failure to communicate the revised copy instructions internally within the publishing house. As a consequence the company had failed to comply with its undertaking. A breach of Clause 22 was ruled. This ruling was accepted.

There appeared to be no written instruction from Wyeth to the advertising agency regarding the withdrawal process although Wyeth had however held a meeting with the advertising agency to discuss the process. The Panel queried whether the written instructions from the advertising agency to the publishing house were sufficient; the importance of the withdrawal process had not been made sufficiently clear and there was no mention of the consequences should there be inadvertent use of old printing plates nor was there any recommendation regarding their destruction. The impression from the revised copy instructions was that the advertisements in question might be used again sometime in the future. Although the letter had been sent out by the advertising agency it was incumbent upon the pharmaceutical company to ensure that such letters gave adequate instruction. The Panel noted that the company had made efforts to comply with the undertaking but nonetheless the Panel considered that despite Wyeth voluntarily bringing the matter to the attention of the Authority, Wyeth's effort was, on balance, insufficient such that it brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY WYETH

Wyeth stated that in March 2002 it gave an undertaking that use of journal advertisement ZZOT2524/0801 would cease 'forthwith' (subject to the exceptions set out in the undertaking). The company subsequently learnt that a similar advertisement (ZZOT2502/0801) was published in BMJ General Practice, 13 April 2002, and immediately advised the Authority of this fact. Wyeth accepted that, as a matter of fact, this publication breached the undertaking it had given and it accepted the ruling of a breach of Clause 22.

Wyeth agreed that an undertaking was a very important document and that it was vital for the reputation of the industry that companies complied with such undertakings. Wyeth noted that it was never, and would never be, its intention to breach, either deliberately or otherwise, any undertaking it had given to the Authority. Wyeth considered that it did not, by its actions, bring discredit upon or reduce confidence in the pharmaceutical industry, but that, on balance, it made sufficient effort avoiding the publication of the advertisement and to comply with its undertaking. Wyeth believed its efforts were very significant and should have been sufficient for the purpose of withdrawing the advertisement in question and preventing its re-use. Further, the company voluntarily brought the matter to the attention of the Authority.

Wyeth honestly believed that use of the advertisement in question had ceased and was shocked to learn that it had been used again. Until it learnt of the 13 April publication, the company believed that the steps it had taken had ensured compliance with the undertaking it had given. The confirmations it had sought, and resought, had confirmed that its instructions to cease publication had been received and no further publications would take place. Wyeth was of the view that the steps that it took should have been adequate to ensure compliance with the undertaking and would have been adequate were it not for an error by a third party that was beyond Wyeth's control – the BMJ Publishing Group had accepted that the publication took place due to an error in its production department.

The Panel commented that there was no written instruction from Wyeth to the advertising agency during and relating to the withdrawal process and queried whether the written instructions from the advertising agency to the publisher were sufficient.

Wyeth had taken heed of these comments and was in the process of reviewing its internal procedures in order to improve them wherever possible in order that they were in line with current Authority opinion. Wyeth had also commissioned an independent audit of third party activity as a follow up action from this.

However, in respect of the current case Wyeth reiterated the steps it took to ensure compliance with

the undertaking and identified why it believed these steps were adequate in the circumstances.

The steps taken in relation to this advertisement were as follows (Wyeth pointed out that other steps were taken in relation to compliance with the undertaking as a whole which related to a further 19 items of various different natures):-

1 on 12 March (10 days before the undertaking was given), Wyeth had a one-to-one telephone conversation with personnel at its advertising agency and discussed the issue and ascertained all publications affected to allow the agency to put together the media schedule for those publications;

2 during that telephone conversation, Wyeth gave verbal instructions to the agency to contact each publisher to notify them that the advertisement in question was not now to be used and to instruct them not to use it, to confirm this instruction in writing and to seek from the publisher written confirmation of receipt of the instruction;

3 the advertising agency carried out this instruction as requested and a copy of the relevant written communication received from the BMJ Publishing Group on the 18 March confirming receipt of the agency's instructions was provided;

4 Wyeth then held a follow-up meeting with the advertising agency on the 19 March (3 days before the undertaking was given) to check that all relevant publishers had been contacted;

5 at the follow-up meeting, Wyeth instructed the agency to make follow-up calls to the publishers to double-check that the revised copy instructions had been received and understood;

6 the advertising agency made such a call to the BMJ Publishing Group that same afternoon and again received confirmation that the instructions had been received and were understood.

In this case, there was no doubt that the agency received Wyeth's instructions to stop further use of the advertisement in question and it was Wyeth's view that the fact that the instructions were not in writing did not affect their adequacy in practice.

In respect of point 2 above, the written communication from the advertising agency to the publishers might not have been as detailed as it could have been, but it instructed the publisher that the relevant advertisement was being pulled from the advertising schedule which was the main purpose of the communication. The words 'until further notice' did not detract from the instruction to cease use of the advertisement and made it clear that the advertisement should not be re-used unless and until the publisher was notified to do so – which would not happen. The instruction to withdraw was adequate, the follow-up actions relating to destruction and disposal might not have been given in full detail but that did not affect the purpose and efficacy of the original instruction.

Wyeth noted that the advertising agency had confirmed that historically it had always dealt with one point of contact at the BMJ Publishing Group and that contact had previously always communicated information internally as necessary. The agency had no reason to believe that the revised copy instruction received and acknowledged by the BMJ Publishing Group had not been treated in the same way as all previous instructions. The BMJ Publishing Group had also confirmed in writing that it was a lack of internal communication that led to the erroneous re-use of the advertisement.

In conclusion, Wyeth noted from previous cases that the Panel and the Appeal Board had an element of discretion in relation to Clause 2 rulings raised in connection with rulings of a breach of undertaking. Accordingly, Wyeth appealed to the Appeal Board to exercise its discretion in this case as it considered its own actions warranted such discretion being exercised. Wyeth's actions in this case were not deliberate, were not in disregard of the original ruling by the Panel and the offensive action was taken by a third party over which Wyeth had no direct control. Wyeth had in fact made very substantial efforts to comply with its undertaking. These steps were sufficient in respect of all other materials ruled in breach in the original case, sufficient in respect of all other publishers involved in respect of the advertisement in question and should, given previous practice, have been sufficient in the case of the BMJ Publishing Group.

At the appeal hearing the company representatives stated that of 37 advertisements due to appear in 20 publications only the advertisement at issue had been published in error.

APPEAL BOARD RULING

The Appeal Board noted the efforts made by Wyeth to comply with its undertaking given in Case AUTH/1264/12/01. The company had acted to withdraw the advertisement in question even before it had signed its undertaking. The Appeal Board considered that the message from the advertising agency to the publishers that certain advertisements were '… being pulled from the schedule until further notice, the maintaining control advert is to replace these' might have been better worded by stating that they must not be used but nonetheless the communication had been effective with all but one of the twenty publications notified. The Appeal Board noted the representatives' submission in that regard.

The Appeal Board considered that adequate attempts had been made by Wyeth to comply with the undertaking. The company had been let down by a third party. Wyeth had been ruled in breach of Clause 22 for failing to comply with its undertaking. This ruling had been accepted. The company had acted quickly to withdraw the advertisement and had voluntarily admitted that it had reappeared as a result of an error by the BMJ. The Appeal Board did not consider that in the circumstances Wyeth's actions had brought discredit upon or reduced confidence in the pharmaceutical industry. The Appeal Board ruled no breach of Clause 2. The appeal was successful.

Proceedings commenced 23 April 2002

Case completed 24 July 2002

CASE AUTH/1314/5/02

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Cozaar (losartan) press information

A general practitioner complained about the advertising of losartan to the public. Losartan (Cozaar) was a prescription only medicine marketed by Merck Sharp & Dohme.

The general practitioner complained about the recent heavy public advertising campaign for losartan which had included advertisements on television and in several national newspapers. Several of his patients had demanded this medicine and the advertising campaign was clearly interfering with his patients' treatment. Armed with advertisement clippings patients claimed it was totally free of side effects, and would not believe him when he tried to put them straight on this point. They had outrageously high expectations, based on excessively optimistic claims in the media regarding the efficacy of this medicine and its superiority over their current treatment.

Merck Sharp & Dohme submitted that it had not advertised Cozaar directly to the public. It had, however, issued press packs detailing the results of the Losartan Intervention For Endpoint reduction (LIFE) study. The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company or its agent and not on what had appeared in the press.

The Panel noted that the LIFE study (Dahlöf *et al* 2002) had compared the long-term effects of losartan with atenolol in patients with hypertension and left ventricular hypertrophy. The phrase 'LIFE … is for living' in logo format appeared on the top of most of the press materials. Some of the documentation included the British Cardiac Patients Association (BCPA) logo. The role of Merck Sharp & Dohme had not been made clear. Some of the documents included a statement in small type 'Sponsored by Merck Sharp & Dohme Limited' while others made no reference to the company.

The Panel noted that the press pack for the lay media comprised, *inter alia*, three documents headed 'LIFE … is for living'. Background information comprised factual leaflets from the BCPA and a fact sheet from the Stroke Association (SA). Also included were a four page leaflet about Cozaar and the RENAAL study and a company sponsored booklet entitled 'Hypertension – Key Facts File'.

The document subheaded 'Cozaar (losartan)' discussed Cozaar in relation to its class, dosage and worldwide use. Reference was made to its excellent tolerability which was described as a major advantage. The document subheaded 'The LIFE Study' discussed the study design and methodology. The third document was subheaded 'The Landmark Study LIFE Heralds a Mandate for Change in GP prescribing' followed by 'COZAAR (losartan) assumes the gold medal position, in reducing death, stroke and heart attack associated with high blood pressure'. This document referred to the superiority of Cozaar as the only blood pressure medicine ever to demonstrate significant benefits over the established medicine atenolol, in the reduction of hospitalisation and death from heart attack and stroke.

The agenda for the press conference featured presentations and questions on hypertension management lasting a total of an hour. The presentations were given by BCPA, SA and LIFE investigators, a consultant in cardiothoracic surgery and a former professional footballer.

The website made available to journalists referred to the 'supremacy of losartan over the best established beta-blocker atenolol'. Losartan's tolerability was described as 'the most striking feature' and 'the most stunning finding of this trial is that not only did both drugs prevent heart attacks and stroke, but losartan was associated with a low instance of cardiovascular events'. Similar information appeared on a CD Rom.

A media transcript of interviews was provided; an interview with a consultant physician similarly referred to the tolerability of losartan as a striking feature and to the 'stunning finding' of the trial in relation to outcome data. The interview concluded that 'there's no doubt at all that losartan … has a mandate to be considered as a first line drug for hypertension …'.

A video included an interview with a patient who described the effect of the medication on his lifestyle. The Panel noted that whilst it was not unacceptable to feature such patient interviews in press materials any statements by the patient nonetheless had to comply with the Code. The patient made positive statements about the effect the medicine had upon his well being and referred to patients in the study benefiting terrifically. The patient stated that he felt like a 'new man, marvellous', that it would be 'wonderful for everybody to be on them' and encouraged viewers to see their doctor. The video included similar information to that in other materials.

In the Panel's view the tone and nature of the material meant that it was not factual or presented in a balanced way. Statements in the press video and phrases in the press pack such as 'most stunning finding', 'supremacy' and 'gold medal position' were inappropriate. The materials would encourage the public to ask their doctors to prescribe Cozaar. The Panel therefore ruled a breach of the Code. The Panel considered that the promotional nature of the materials meant that they constituted an advertisement to the public for a prescription only medicine. Breaches of the Code were ruled.

Given the nature of the materials, the Panel considered that Merck Sharp & Dohme had failed to maintain a high standard. The Panel ruled a breach of the Code.

A general practitioner complained to the Medicines Control Agency (MCA) about the advertising of losartan (Merck Sharp & Dohme Limited's prescription only medicine Cozaar) to the public. The

MCA's Information Centre forwarded the complaint to the Authority and also copied it to the MCA's Advertising Unit.

COMPLAINT

The general practitioner complained about the recent heavy public advertising campaign for losartan, a prescription only medicine, which had included advertisements on television and in several national newspapers.

He had had several patients come in over the last few weeks demanding this medicine and the advertising campaign was clearly interfering with his patients' treatment. Patients were coming along with advertisement clippings claiming it was totally free of side effects, and would not believe him when he tried to put them straight on this point. Patients were coming with outrageously high expectations, based on excessively optimistic claims in the media regarding the efficacy of this medicine and its superiority over their current treatment.

This was clearly a breach of ethical agreements in this country, where medical practitioners should be free to recommend medications they believed were best suited to their patients, rather than being forced to accede to the influence of pharmaceutical companies with the most persuasive lay advertising coverage. It was a totally unacceptable attempt to break down the nation's system of health care in favour of big profits for pharmaceutical companies, and, if allowed to pass unchallenged, would be severely detrimental to the health of the majority of Britons.

When writing to Merck Sharp & Dohme, the Authority had limited information and drew attention to Clauses 7.2, 7.9, 9.1, 20.1 and 20.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it was confused by this complaint and the alleged breaches of the Code, as it had not placed any advertisements about Cozaar in the consumer press and nor had any such advertisements appeared on television – to do so would have been a clear breach of the Code. Merck Sharp & Dohme had also not conducted a disease awareness or public health campaign aimed at the general public in this therapeutic field. For the purposes of its response, it had assumed, therefore, that the complainant was referring to any recent publicity which might have been generated in the consumer press in response to the results of the landmark Losartan Intervention For Endpoint Reduction (LIFE) study.

The results of the LIFE study were announced at the American College of Cardiology Meeting in Atlanta in March and were subsequently published in The Lancet in March. The complainant did not appear to be complaining about any material appearing in the medical media. However, he did seem to be concerned that he and his patients had been alerted to the importance of these study results and Cozaar's role within the study by the consumer media.

Clause 20.2 of the Code allowed the provision of non-promotional information about prescription only medicines to the general public. Information of this kind might be disseminated to the media in the form of a press pack and related activities. It had always been Merck Sharp & Dohme's understanding that, assuming the contents of any such press pack complied with the Code, a company was judged not by what was actually published but on the contents of the information provided to the media. Merck Sharp & Dohme believed that the information about the ground-breaking results of this landmark study released by it to the consumer media was genuinely newsworthy and in the public interest. Merck Sharp & Dohme also believed that the information was provided in a manner which satisfied the requirements of Clause 20.2 of the Code.

To enable the Authority to assess whether the requirements of Clause 20.2 had been fulfilled, Merck Sharp & Dohme provided full details of the press material and associated documentation including: the press pack provided to the consumer media on 20 March. This comprised the LIFE press release, details of the LIFE study, details about Cozaar, information about the British Cardiac Patients Association and the Stroke Association and a hypertension booklet (which also included a copy of the press release previously issued in relation to the RENAAL study); invitation details for the consumer media for the launch event on 20 March including the invitation, programme and speaker biographies; information which was made available on a specially devised website for journalists from 20-30 March; and a copy of the B-roll (LIFE study broadcast material) which was provided to any television company on request from Merck Sharp & Dohme's PR agency. Also provided was the reprint from The Lancet and the summary of product characteristics (SPC).

* * * * *

In view of the confusion expressed by Merck Sharp & Dohme the Authority sought further information from the complainant. The complainant advised that so far three patients had specifically requested losartan, two referring to TV coverage and three to press coverage. One brought a press clipping but the complainant did not note where from. It was claimed by the patients that losartan had no side effects whatsoever. He had only these 'second-hand' accounts. Although he might have dismissed one, three seemed too many to have misinterpreted the information given.

FURTHER RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that it was grateful for the opportunity to comment further but unfortunately found the further information to be as confusing as the original complaint. The complaint was based upon a GP's experiences with three patients who specifically requested losartan. No further details of the actual coverage were provided to substantiate the complaint, even though these patients drew their GP's attention to the coverage and he was specifically referred to a press cutting.

Whilst Merck Sharp & Dohme fully supported the GP's right to complain, it was disappointed by the absence of any details of the actual press coverage which prompted the patients' discussions with him. The LIFE study results received world-wide coverage on the Internet and in the medical press, as 800 clinical centres in the UK, Scandinavia and the USA took part in this study. Consequently, Merck Sharp & Dohme was unable to comment further as to whether this second-hand account of the coverage in the consumer media resulted directly from the supply of the press materials enclosed with its last letter. Even if Merck Sharp & Dohme was to assume that it did, the lack of specificity in this complaint meant that it could not ascertain whether or not the journalist's interpretation of such materials was accurate. On this basis Merck Sharp & Dohme did not feel that it would assist to supply copies of the press articles resulting from the press conference and distribution of the press pack. All that this could possibly demonstrate was that press reports did in fact result from these items but not which, if any, of these reports were seen by these three patients.

Merck Sharp & Dohme provided a list of those invited to the press conference, together with a list of attendees. Whilst Merck Sharp & Dohme had not placed any advertisements in the media as previously alleged, it did anticipate media interest in the LIFE study results. Merck Sharp & Dohme provided journalists with a number of background items about the study, losartan and the problems associated with hypertension and stroke. Merck Sharp & Dohme did so in the belief that the results of this landmark study were genuinely newsworthy and in the public interest in accordance with Clause 20.2. Merck Sharp & Dohme had no editorial control over any of the coverage. It was aware that a number of UK hypertension experts and UK LIFE study participants had been interviewed by the media, but again it had had no input into the content of these interviews. Any responses made in these interviews represented their personal opinions and not those of Merck Sharp & Dohme.

Indeed it was clear from the complaint in question that the claim by the three patients that the product had no side effects whatsoever did not accurately reflect the information which was supplied to the lay media. The press pack and the closed access website for journalists did not state this at all, although losartan's tolerability and low side effect profile was the subject of comment in these items.

In conclusion, there had been no advertising of Cozaar to the public. Whilst Merck Sharp & Dohme accepted that there had been media coverage following the announcement of the LIFE study results, this was as a result of a genuine interest on the part of the media into a major advance in the treatment of cardiovascular disease. Merck Sharp & Dohme believed that the information supplied to the media regarding the LIFE study results was provided in a factual and balanced manner in accordance with Clause 20.2 of the Code and not for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

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 and not on what had appeared in the press.

Clause 20.1 prohibited the advertising of prescription only medicines to the general public and medicines which, although not prescription only, might not legally be advertised 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 press materials concerned the results of the LIFE study (Dahlöf *et al* 2002) which compared the long-term effects of losartan with atenolol in patients with hypertension and left ventricular hypertrophy; the primary endpoint was cardiovascular morbidity and death, a composite endpoint of cardiovascular death, myocardial infarction and stroke. It was not unacceptable to issue press materials *per se*; such material had to comply with the Code.

The Panel noted that the phase 'LIFE … is for living' appeared on the top of most of the documentation. The word 'LIFE' appeared cradled in two hands in logo format in that the 'I' appeared as II. Cozaar was an angiotension II antagonist. Some of the documentation included the British Cardiac Patients Association (BCPA) logo. The role of Merck Sharp & Dohme had not been made clear. Some of the documents included a statement in small type 'Sponsored by Merck Sharp & Dohme Limited'. Other documents made no reference to Merck Sharp & Dohme.

The Panel noted that the press pack for lay media comprised three documents headed 'LIFE … is for living', one about Cozaar, one about the LIFE study and the third headed 'The Landmark Study LIFE Heralds a Mandate for Change in GP prescribing'. Background information comprised factual leaflets from the BCPA and a fact sheet from the Stroke Association (SA). Also included were a four page leaflet about Cozaar and the RENAAL study and a company sponsored booklet entitled 'Hypertension – Key Facts File'.

The document subheaded 'Cozaar (losartan)' discussed Cozaar in relation to its class, dosage and worldwide use. Reference was made to its excellent tolerability which was described as a major advantage. LIFE and OPTIMAAL studies were mentioned. The RENAAL study (the renal protection study for losartan) was discussed in greater detail. The Panel queried whether the discussion of these studies had been sufficiently placed within the context of the licensed indication for Cozaar, the treatment of hypertension.

The document subheaded 'The LIFE Study' discussed the study design and methodology. The third

document was subheaded 'The Landmark Study LIFE Heralds a Mandate for Change in GP prescribing' followed by 'COZAAR (losartan) assumes the gold medal position, in reducing death, stroke and heart attack associated with high blood pressure'. This document referred to the superiority of Cozaar as the only blood pressure medicine ever to demonstrate significant benefits over the established medicine atenolol, in the reduction of hospitalisation and death from heart attack and stroke and featured quotations from the BCPA, referring to LIFE data dramatically and positively affecting the way high blood pressure was treated in the UK. A quotation from a GP trial investigator referred to 'minimal side effects of losartan compared to older medicines'.

The agenda for the press conference featured presentations and questions on hypertension management lasting a total of an hour. The presentations were given by BCPA, SA, LIFE investigators, a consultant in cardiothoracic surgery and a former professional footballer.

The website made available to journalists referred to the 'supremacy of losartan over the best established beta-blocker atenolol'. Losartan's tolerability was described as 'the most striking feature' and 'the most stunning finding of this trial is that not only did both drugs prevent heart attacks and stroke, but losartan was associated with a low instance of cardiovascular events'. Other descriptions were 'great news for patients with hypertension' 'going to make a huge difference to patient's and their families lives'. Similar information appeared on the CD Rom entitled 'Life E-Flyer'.

A media transcript of interviews was provided; an interview with a consultant physician similarly referred to the tolerability of losartan as a striking feature and to the 'stunning finding' of the trial in relation to outcome data. The interview concluded that 'there's no doubt at all that losartan … has a mandate to be considered as a first line drug for hypertension …'.

The video featured among other interviews an interview with a patient who described the effect of the medication on his lifestyle. The Panel noted that whilst it was not unacceptable to feature such patient interviews in press materials any statements by the patient nonetheless had to comply with the Code. The patient made positive statements about the effect the medicine had upon his well being and referred to patients in the study benefiting terrifically. The patient stated that he felt like a 'new man, marvellous', that it would be 'wonderful for everybody to be on them' and encouraged viewers to see their doctor. The video included similar information to that in other materials.

In the Panel's view the tone and nature of the material meant that it was not factual or presented in a balanced way. Statements in the press video and phrases in the press pack such as 'most stunning finding', 'supremacy' and 'gold medal position' were inappropriate. The materials would encourage the public to ask their doctors to prescribe Cozaar. The Panel therefore ruled a breach of Clause 20.2 of the Code. The Panel considered that the promotional nature of the materials meant that they constituted an advertisement to the public for a prescription only medicine. A breach of Clause 20.1 was ruled.

Given the nature of the materials, the Panel considered that Merck Sharp & Dohme had failed to maintain a high standard. The Panel ruled a breach of Clause 9.1 of the Code.

During its consideration of this case the Panel queried whether the documentation made Merck Sharp & Dohme's role sufficiently clear. The cover of the press pack folder featured the prominent heading 'LIFE … is for living'. A prominent heart logo above 'BCPA British Cardiac Patients Association' appeared in red in the bottom left-hand corner. Small black print at the bottom read 'sponsored by Merck Sharp & Dohme Ltd'. Reference in small print to Merck Sharp & Dohme providing sponsorship appeared on some of the other material alongside the BCPA logo and LIFE heading. The material might give the impression that it had been produced by BCPA, the company's involvement limited to financial sponsorship and that was not so. The role of the company was not sufficiently clear. The Panel requested that the company be advised of its views in this regard.

Complaint received **10 May 2002**

Case completed **30 July 2002**

ANONYMOUS v ASTRAZENECA

Corporate journal advertisement to health professionals

An anonymous complaint was received about an AstraZeneca corporate advertisement which had appeared in Hospital Doctor. The advertisement was headlined 'Successful research over decades; whatever will we think of next?' Decades from the 1960s onwards were presented such that various medicines marketed by AstraZeneca took the place of some of the numbers. For example '1960s' was shown with an upright capsule of propranolol in place of the figure one; beneath the image of the capsule was 'propranolol'. Atenolol, lisinopril and felodipine similarly appeared in the '1970s', '1980s' and '1990s' respectively. The final decade to be shown was '200?s' in which no number had been replaced by a medicine.

The advertisement referred to AstraZeneca being 'dedicated to reducing the risks associated with cardiovascular disease', and stated that through its investment in global research and development it intended to be the world leader in cardiovascular medicine by 2010 and that it was confident that its next contributions to the area of cardiovascular risk reduction would prove to be further breakthroughs in cardiovascular research.

The complainant noted that there was no prescribing information and that AstraZeneca's product names were displayed next to the claim '… reducing the risks associated with cardiovascular disease …'. The complainant was also concerned by this teaser advertisement and noted that AstraZeneca claimed that '… we are confident that our next contribution to the area of cardiovascular risk reduction will prove to be further breakthrough in cardiovascular research …'.

The Panel noted that prescribing information did not need to be provided in abbreviated advertisements. The advertisement in question was not an abbreviated advertisement. AstraZeneca had placed an advertisement which referred to products in which it had a commercial interest; the use of the product names in the advertisement to health professionals triggered the requirement for prescribing information. The Panel accordingly ruled a breach of the Code. This ruling was appealed.

The Panel did not consider that a reader would assume that the next breakthroughs in cardiovascular research would relate to disease management or such like as submitted by AstraZeneca. The Panel considered that the prominence given to the specific medicines and succession of decades was such that readers were likely to assume that a cardiovascular medicine would be launched in the next decade. The advertisement stated that AstraZeneca had a pipeline of innovative new products and intended to be the world leader in cardiovascular medicine by 2010. However, the Panel did not consider that the advertisement promoted a particular product prior to the grant of its marketing authorization. No breach of the Code was ruled.

Corporate advertising *per se* was not unacceptable. The Panel did not consider that the advertisement was likely to cause offence in this regard. No breach of the Code was ruled. In the Panel's view, some information had been given and the advertisement had not teased. No breach of the Code was ruled.

The Panel did not consider that the advertisement was such as to bring discredit upon or reduce confidence in the pharmaceutical industry and no breach of Clause 2 of the Code was ruled.

The Appeal Board noted that the text of the advertisement referred to cardiovascular medicine in broad terms. Although cardiovascular risk reduction was mentioned none of the medicines featured were so licensed. The Appeal Board considered that the advertisement promoted AstraZeneca's heritage in the cardiovascular therapy area. The Appeal Board did not consider that the advertisement promoted propranolol, atenolol, lisinopril or felodipine and therefore prescribing information was not required. No breach of the Code was ruled.

An anonymous complaint was received about a two page AstraZeneca corporate advertisement (ref 10227c) which had appeared in Hospital Doctor 2 May 2002. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

The advertisement was headlined 'Successful research over decades; whatever will we think of next?' Decades from the 1960s onwards were presented such that various medicines marketed by AstraZeneca took the place of some of the numbers. For instance '1960s' was shown with an upright capsule of propranolol in place of the figure one; beneath the image of the capsule was 'propranolol'. Similarly in '1970s' a tablet took the place of the zero with 'atenolol' beneath, in '1980s' two tablets appeared instead of an eight with 'lisinopril' beneath and the zero in '1990s' was replaced by a tablet with 'felodipine' beneath. The final decade to be shown was '200?s' in which no number had been replaced by a medicine.

The text of the advertisement referred to AstraZeneca being 'dedicated to reducing the risks associated with cardiovascular disease'. The company stated that through its investment in global research and development it intended to be the world leader in cardiovascular medicine by 2010 and that it was confident that its next contributions to the area of cardiovascular risk reduction would prove to be further breakthroughs in cardiovascular research.

In the bottom right-hand corner of the advertisement was the AstraZeneca cardiovascular company logo together with the strapline 'Bringing research to life'.

COMPLAINT

The complainant noted that with prescribing information absent, AstraZeneca's product names were displayed juxtaposed to the claim '… reducing the risks associated with cardiovascular disease …'.

The complainant was also concerned by this teaser advertisement and noted that AstraZeneca claimed

that '… we are confident that our next contribution to the area of cardiovascular risk reduction will prove to be further breakthrough in cardiovascular research …'.

The complainant thought that the Medicines Control Agency, the Committee on Safety of Medicines and the National Institute of Clinical Excellence might have some role in this matter.

At a time with NHS concerns about medicine costs and the proposition of new and potentially expensive medicines, the complainant disliked the arrogance and certainly this did nothing to enhance the reputation of the pharmaceutical industry.

The Authority asked AstraZeneca to respond in relation to the requirements of Clauses 3.1, 4.1, 9.1 and 2 of the Code.

RESPONSE

With regard to the requirement for prescribing information, AstraZeneca noted that products mentioned in the advertisement were presented as generic names only. There was neither branding nor claim associated with any of them. Contrary to what the complainant had stated, the generic product names were not juxtaposed to a specific claim in relation to any of them.

AstraZeneca noted that the complainant referred to '… reducing the risks associated with cardiovascular disease …'. This statement in full read 'AstraZeneca is one of the world's major suppliers of cardiovascular medicines. With over 40 years' experience in this field, we are dedicated to reducing the risks associated with cardiovascular disease'. The statement, therefore, referred specifically to AstraZeneca as a pharmaceutical company with a commitment to cardiovascular research and risk reduction. In AstraZeneca's view the statement did not constitute a claim for any one product and did not make reference to any particular aspect of cardiovascular disease such as hypertension or angina. The company did not consider that the advertisement necessitated prescribing information and therefore refuted the suggestion of a breach of Clause 4.1 of the Code.

AstraZeneca noted that Clause 3.1 of the Code stated 'A medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply'. The complainant had quoted as follows from the advertisement '… we are confident that our next contribution to the area of cardiovascular risk reduction will prove to be further breakthrough in cardiovascular research …'. AstraZeneca noted that the advertisement actually stated '… we are confident that our next contributions to the area of cardiovascular risk reduction will prove to be further breakthroughs in cardiovascular research'. These contributions could include areas such as disease management, risk management and understanding mechanisms of disease in addition to provision and supply of medicines. Since there was no reference to a particular medicine AstraZeneca did not consider that wording in the advertisement could be perceived as being promotion outside a licence. The company did not consider that the statement was a breach of Clause 3.1.

AstraZeneca noted that teaser advertising was defined in Clause 9.1 of the Code as 'promotional material intended to 'tease' the recipient by eliciting an interest in something which will be following or will be available at a later date without providing any actual information about it'. As stated above, it was quite clear from the advertisement that AstraZeneca was involved in ongoing research in the area of cardiovascular medicine. The advertisement reflected quite clearly that there had been decades of research invested in the area of cardiovascular risk reduction. Since the decade portrayed as '200?s' had a question mark, AstraZeneca considered the implication was such that the contributions to the area of cardiovascular risk reduction would take place during this decade. There was no indication that a specific product was going to be available at a later date. Given this and the broad nature of the advertisement the company did not consider that this was in breach of Clause 9.1 of the Code.

AstraZeneca stated that cardiovascular disease was one of the main causes of death in the UK and guidelines to reduce its impact on the nation's health were given high priority by government. The pharmaceutical industry played a key role in the development of strategies to counter cardiovascular disease. In this context AstraZeneca was proud of its cardiovascular heritage and considered it was important to inform health professionals that it was continuing to invest heavily in research. It was unfortunate that the complainant considered that corporate advertising of research into a therapy area was arrogant. AstraZeneca considered that this was very much a minority view and that most health professionals would understand and appreciate the impact pharmaceutical companies had had on the management of cardiovascular disease. There were currently a number of corporate advertisements in differing therapeutic areas including psychiatry and respiratory disease. Such advertising was therefore commonplace across the industry and a useful tool in reminding clinicians of the considerable investment of time, people and money necessary to develop new medicines for them to use.

AstraZeneca stated that in light of the points raised above it did not consider it had in any way reduced confidence in the pharmaceutical industry and therefore was not in breach of Clause 2 of the Code.

In summary AstraZeneca considered that the corporate advertisement was within the boundaries set by the Code. In particular it did not accept that such promotion in any way tarnished the reputation of the pharmaceutical industry.

AstraZeneca stated that it was not due to receive a UK marketing authorization in the area of cardiovascular risk reduction in the near future.

PANEL RULING

Clause 4.1 of the Code stated, *inter alia*, that the prescribing information listed in Clause 4.2 must be provided in a clear and legible manner in all

promotional material for a medicine except for abbreviated advertisements. The advertisement in question was not an abbreviated advertisement. AstraZeneca had placed an advertisement which referred to products in which it had a commercial interest; it was immaterial that the company had only used generic names. In the Panel's view the use of the product names in the advertisement to health professionals triggered the requirement for prescribing information for the named products. The Panel accordingly ruled a breach of Clause 4.1 of the Code. This ruling was appealed.

The Panel noted that the complainant had misquoted the claim '… we are confident that our next contributions to the area of cardiovascular risk reduction will prove to be further breakthroughs in cardiovascular research …'. The complainant had used the singular whereas the claim in the advertisement used the plural. The Panel did not consider that a reader would assume that the next breakthroughs in cardiovascular research would relate to disease management or such like as submitted by AstraZeneca. The design and content of the advertisement was such that a specific medicine was associated with each decade above the term '200?s'. Beneath this appeared the subheading 'successful research over decades; whatever will we think of next?' In the Panel's view a reader was likely to assume that a cardiovascular medicine in the AstraZeneca pipeline would be launched in this decade and the advertisement was designed to elicit interest in this and in AstraZeneca's history of cardiovascular research. The Panel considered that the prominence given to the specific medicines and succession of decades was such that the text, in any event, did not negate the overall impression given. The advertisement stated that AstraZeneca had a pipeline of innovative new products and intended to be the world leader in cardiovascular medicine by 2010. However, the Panel did not consider that the advertisement promoted a particular product prior to the grant of its marketing authorization. No breach of Clause 3.1 was ruled.

Corporate advertising *per se* was not unacceptable. The Panel did not consider that the advertisement was likely to cause offence in this regard. No breach of Clause 9.1 was ruled. A 'teaser' advertisement as referred to in the supplementary information to Clause 9.1 related to a situation where promotional material teased the recipient by eliciting an interest in something which would be following or would be available at a later date without providing any further information about it. In the Panel's view, some information had been given and the advertisement had not teased. No breach of Clause 9.1 was ruled.

Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the advertisement was such as to bring discredit upon or reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

APPEAL BY ASTRAZENECA

AstraZeneca appealed the Panel's ruling of a breach of Clause 4.1 of the Code for not providing prescribing information, as it believed this set a precedent which restricted the legitimate practice of corporate advertising without improving the quality of information to the doctor or protecting patients.

AstraZeneca submitted that the advertisement in question was clearly intended as corporate promotion and this seemed to have been accepted by the Panel in the wording of its ruling. The positioning of the names of the medicines mentioned and the use of generic names with no claims made it clear that this promotion was not for particular medicines.

The use of product names in corporate promotion was not unique to AstraZeneca.

Clause 4.1 of the Code stated that prescribing information was required 'in all promotional material for a medicine'. As this promotion was clearly corporate in execution and intent AstraZeneca did not believe prescribing information was required – indeed the addition of it would have changed the overall impression towards the advertisement being about individual medicines.

AstraZeneca maintained that it was the intention of the promotion which should govern the requirement for the prescribing information and that in this instance the intention was clear.

APPEAL BOARD RULING

The Appeal Board did not accept AstraZeneca's submission that the intention of the promotion should govern whether or not prescribing information was needed. The content of the advertisement was the relevant factor not the intent.

The Appeal Board noted that the text of the advertisement referred to cardiovascular medicine in broad terms. Although cardiovascular risk reduction was mentioned none of the medicines featured were so licensed.

The Appeal Board considered that the advertisement promoted AstraZeneca's heritage in the cardiovascular therapy area.

The Appeal Board did not consider that the advertisement promoted propranolol, atenolol, lisinopril or felodipine. The Appeal Board did not consider that prescribing information was required. No breach of Clause 4.1 was ruled.

The appeal on this point was successful.

Complaint received **10 May 2002**

Case completed **24 July 2002**

CASE AUTH/1316/5/02

NOVARTIS v FUJISAWA

Article in Kidney Life magazine

Novartis complained about the activities of Fujisawa in relation to an article entitled 'Life after transplant – recipients demand more information' which appeared in Kidney Life, the magazine of the patient support group the National Kidney Federation (NKF). The article detailed the results of a questionnaire and discussed issues relevant to transplant procedure and the effect of a transplant. Fujisawa marketed the immunosuppressant Prograf (tacrolimus) while Novartis marketed Neoral and Sandimmun (both forms of cyclosporin) also for immunosuppression.

Novartis noted that the article did not state that the survey was funded by Fujisawa, that the questionnaires were analysed by it or that the publication in question had had significant input from Fujisawa. The absence of a declaration of sponsorship was misleading as it disguised a vested interest by the company in communicating positive messages about its products. Novartis stated that it was clear that Fujisawa had used this vehicle to communicate information directly to transplant patients and their carers.

The emphasis of the article in relation to immunosuppressant therapy was that a large number of patients in the survey were switched from cyclosporin to tacrolimus and that these switches were mostly because of side effects, implying a safety benefit for tacrolimus. The article failed to point out that 59 per cent of patients were on cyclosporin in the first instance, or that side effects were a common issue with all immunosuppressants, not least with tacrolimus, and was thus not balanced in relation to cyclosporin and could give unfounded confidence in the safety of tacrolimus.

The Panel noted that the article mentioned side effects as the most common reason for a patient to switch anti-rejection medication and that switching was common amongst all anti-rejection medication, the largest number of patients were switched from cyclosporin to tacrolimus.

The Panel considered that, as acknowledged by Fujisawa, the NKF article should have contained a declaration that it had been sponsored by Fujisawa as required by the Code; a breach was ruled.

The Panel noted that Fujisawa's role in the generation of the article had extended beyond the provision of financial sponsorship. The initial draft had been written by Fujisawa's public relations agency. Fujisawa had been afforded an opportunity to comment on the draft article. The Panel did not however consider that the article constituted the promotion of a prescription medicine to the general public and no breach of the Code was ruled. On the evidence before it the Panel did not consider that the article was unbalanced in relation to cyclosporin nor did it give unfounded confidence in the safety of tacrolimus as alleged. No breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about the activities of Fujisawa Limited in relation to the transplantation patient support group, the National Kidney Federation, and an article entitled 'Life after transplant – recipients demand more information' which appeared in the summer 2002 edition of Kidney Life, the magazine of the National Kidney Federation (NKF). The article detailed the results of a questionnaire included in the winter 2001 edition and discussed issues relevant to transplant procedure and the effect of a transplant.

Fujisawa marketed the immunosuppressant Prograf (tacrolimus) while Novartis marketed Neoral and Sandimmun (both forms of cyclosporin) also for immunosuppression.

COMPLAINT

Novartis noted that the article at issue, a summary of a questionnaire involving 2,500 transplant patients, did not state that the survey was funded by Fujisawa, that the questionnaires were analysed by it or that the publication in question had had significant input from Fujisawa. The absence of a declaration of sponsorship on such an item was in itself misleading to the reader disguising as it did a vested interest by the company in communicating positive messages about its products in breach of Clause 9.9.

Novartis stated that it was clear that Fujisawa had used this vehicle to communicate information directly to an audience of transplant patients and their carers. As such this item should conform to the requirements of the Code in relation to communications with the public. Clause 20.2 of the Code clearly stated that any information made available to the general public must be factual and presented in a balanced way, must not be misleading with respect to the safety of a medicine and must not encourage patients to ask their doctor to prescribe a specific medicine.

The emphasis of this article in relation to immunosuppressant therapy was that a large number of patients in the survey were switched from cyclosporin to tacrolimus and that these switches were mostly because of side effects, implying a safety benefit for tacrolimus. The article failed to point out that the reason for the majority of switches being from cyclosporin was that 59 per cent of patients were on cyclosporin in the first instance, or that side effects were a common issue with all immunosuppressants, not least with tacrolimus. The information presented was clearly not balanced in relation to cyclosporin and could give unfounded confidence in the safety of tacrolimus.

Promoting tacrolimus directly to members of the general public in this way was clearly a breach of both Clause 20.1 of the Code and of the Advertising Regulations. Novartis stated that its major concern however in relation to the presentation of this data, was that it could potentially alarm patients into seeking to alter their immunosuppressant protocol which would have been carefully selected for them by their medical team. Patients and their carers did not have the expert knowledge of health professionals to place this information in context and would not be in

a position to make a fully informed judgement on their therapy regimen. Compliance with immunosuppressant therapy was vital for the wellbeing of transplant patients and any activity targeted at patients which directly or indirectly undermined their confidence in their therapy could only compromise patient safety.

RESPONSE

Fujisawa stated that Kidney Life was sent out to 18,000 members of the NKF. The article entitled 'Recipients demand more information' reported on the findings of a study carried out by questionnaire of 2500 renal transplant recipients contacted by the NKF.

Fujisawa stated that during the initial discussions regarding the provision of financial support to assist with this major undertaking planned by the patients' charity, NKF, it was made clear to Fujisawa by the NKF that it preferred that the questionnaire should be sent out with no mention of the financial support that Fujisawa would provide. The wording 'The NKF will share the conclusions of the survey with one or more industry partners involved in renal care' was included in the introductory letter that formed page 1 of the questionnaire.

Regarding the article published/produced by the NKF, an assumption was made that the same conditions would apply and that Fujisawa would not be mentioned in the feature. The study itself and the report contained in Kidney Life were of such a quality that Fujisawa would have been proud to have had its support acknowledged. In retrospect it should have insisted that its financial support be acknowledged but felt that it would be inappropriate to do so in view of the previous discussions with the NKF.

The article that appeared in Kidney Life was actually written by a collaboration between the NKF and a public relations agency with Fujisawa providing some financial support. Fujisawa played no part in the analysis of the data. Following its enquiries it now understood that at a planning meeting between the agency and the NKF it was agreed that the agency would construct a first draft and then the NKF would make changes and return the document to the agency. It was agreed that the NKF would have editorial control and would produce the final draft for submission to the publishers. Indeed, some final adjustments were made to the article by the editor of Kidney Life prior to insertion in the magazine and these were referred to in an email, a copy of which was provided.

Fujisawa submitted that as this article had been produced and published by the NKF any additional criticism of its contents concerning the balance and factual veracity would be a matter between Novartis and the NKF and as the NKF was a charity organisation this discussion should therefore not be a matter for the Code. Likewise, the suggestion that this was an attempt by Fujisawa to promote tacrolimus directly to members of the general public (Clause 20.1) was not supported by the facts described above.

In response to a request for further information, Fujisawa stated that the initial idea for carrying out a survey of the experiences of renal transplant patients actually came from the Renal Transplant Nurses Association (RTNA) which had designed a questionnaire to be completed by patients during a face-to-face interview with renal transplant nurses. However, it became clear that there would be logistic difficulties in performing this exercise in terms of the nurses' time involved. An examination of the RTNA questionnaire itself should make it obvious that the questions contained therein originated from the nursing members of the RTNA and not Fujisawa. For instance, in the section on 'Medication and Rejection' the terms 'MMF' and 'Cellcept' (the proprietary name for a Roche product) appeared and Prograf was referred to as 'FK506/Prograf/tacrolimus' (a format that Fujisawa would not wish to use). The important question 'Have you changed your anti-rejection medication' appeared on page 8 of the questionnaire. Fujisawa had earlier been involved in discussions with the RTNA and had been asked to provide support for the printing of the questionnaire. In a later meeting between the NKF and industry members it became clear that the NKF were also interested in asking some important questions of its members. A copy of the RTNA questionnaire was then given to the NKF and this was considered together with some questions drawn up by the NKF. An email from the NKF to Fujisawa dated 13 March 2001 (with the NKF questions attached) used the phase 'I would like to see the type of questions that Fujisawa were thinking of to see how they might fit together'. This area of confusion was dealt within a subsequent email dated 27 April 2001 where it was made clear that the questionnaire sent earlier had been the creation of the RTNA. The use of the expression 'we' in this email of course referred to the NKF together with Fujisawa's support.

The questions contained in the final questionnaire were designed to meet the interests of the NKF whilst the questions originally suggested by the RTNA on immunosuppression were designed to provide information of interest to the RTNA (and also subsequently the NKF and Fujisawa).

The data analysis was performed independently by a research company which had been instructed by the public relations agency to whom the questionnaires were initially delivered. Fujisawa had no influence over the way the data was analysed.

The article was initially drafted by the agency based on the report from the research company. Subsequent draft versions were exchanged between the agency and the NKF. The final version was written by the NKF. Fujisawa did see an early draft version of the article and suggested some minor changes in relation to some points that were loosely phrased and could be more clearly stated. These points related to discussions on live-donor expenses and graft survival. In particular, the NKF suggested and drafted the table highlighting all recorded switches that appeared in the published version.

The public relations agency had been instructed by Fujisawa in agreement with the wishes of the NKF.

Regarding the costs of printing the results of the survey in Kidney Life, this was identified within the

overall cost calculation performed by the NKF and was one of the costs covered by the grant from Fujisawa.

Fujisawa would again make the point that it regarded the help provided to the NKF as a praiseworthy example of a member of the UK pharmaceutical industry assisting a medical charity to complete some work which otherwise would have been impossible to perform. Fujisawa stated that as an ethical company its relationships with such organisations were important and something of which it was justifiably proud.

Although a small subgroup of the information obtained from the study was of direct interest to Fujisawa in terms of market research regarding the use of immunosuppression in this patient group, this was not the primary reason for Fujisawa's involvement in the study.

The Kidney Life article remained the responsibility of the NKF and any additional criticism of its content was a matter between Novartis and the NKF.

PANEL RULING

The Panel noted that the article mentioned side effects as the most common reason for a patient to switch anti-rejection medication and that switching was common amongst all anti-rejection medication, the largest number of patients were switched from cyclosporin to tacrolimus (173). A table highlighting all recorded switches indicated that the greatest number of recorded switches was from any cyclosporin to tacrolimus.

Readers were told that the most commonly used anti-rejection medicines were prednisolone, cyclosporin and azathioprine with nearly a quarter of patients taking a combination of all three.

The Panel noted that the front page of the questionnaire comprised a letter signed by the Chairman of the NKF which referred to the results being analysed for future publication and stated that 'The NKF will share the conclusions of the survey with one or more industry partners involved in renal care'.

Fujisawa stated that the idea for the survey came from the RTNA with whom it had earlier been in discussions and had been asked to provide financial support for printing costs. The NKF subsequently became involved. A copy email discussing the extent of Fujisawa's financial sponsorship of the questionnaire was provided; the NKF proposed the statement 'The NKF will share the results of the survey with one or more industry partners' be included in the covering letter. One email from the NKF to Fujisawa headed Potential Survey stated 'I would like to see the type of questions that Fujisawa are thinking of …'. A further email discussed the questionnaire proposed by the RTNA and referred to a second joint NKF/Fujisawa document which might be combined with it. The outcome of these discussions was not before the Panel; the Panel nonetheless considered that Fujisawa's involvement in the questionnaire was not limited to financial sponsorship.

Fujisawa had instructed a public relations agency which had instructed a research company to analyse the data with the agreement of the NKF. The initial draft of the article at issue was written by the public relations agency and subsequent draft versions exchanged between it and the NKF. Fujisawa stated that the final version was written by the NKF. Fujisawa did have an opportunity to comment and amend a draft version.

The Panel considered that, as acknowledged by Fujisawa, the NKF article should have contained a declaration that it had been sponsored by Fujisawa as required by Clause 9.9 of the Code; a breach of that clause was ruled. In the Panel's view the questionnaire should also have included a declaration that it was sponsored by Fujisawa. There was no complaint in this regard.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that Fujisawa's role in the generation of the article had extended beyond the provision of financial sponsorship. The initial draft had been written by Fujisawa's public relations agency. Fujisawa had been afforded an opportunity to comment on the draft article. The Panel considered that given the role of Fujisawa and its agents the article had to comply with the requirements of Clause 20 of the Code. The Panel did not however consider that the article constituted the promotion of a prescription medicine to the general public contrary to the provisions of Clause 20.1 of the Code; no breach of that clause was ruled. On the evidence before it the Panel did not consider that the article was unbalanced in relation to cyclosporin nor did it give unfounded confidence in the safety of tacrolimus as alleged. No breach of Clause 20.2 of the Code was ruled.

Complaint received	**10 May 2002**
Case completed	**2 August 2002**

BOEHRINGER INGELHEIM v GLAXOSMITHKLINE

Promotion of Serevent

Boehringer Ingelheim complained about a mailing sent by GlaxoSmithKline to promote Serevent (salmeterol), a long-acting bronchodilator, in chronic obstructive pulmonary disease (COPD). The mailing consisted of a four page leaflet and a letter headed 'Which regular bronchodilator do you choose after salbutamol prn in COPD?'. Boehringer Ingelheim marketed the anticholinergic bronchodilator ipratropium on its own (Atrovent) or in combination with salbutamol (Combivent).

The front cover of the leaflet stated 'Do more for your COPD patients', the second page continued 'and they can do more with their lives'. The claim at issue 'Rx Serevent 50 mcg b.d. for your COPD patients after salbutamol prn before anticholinergics' appeared in bold as a summary on the third page beneath a section headed 'Do something different in COPD, starting today'.

Boehringer Ingelheim did not know of any substantial evidence to support the use of Serevent (a long-acting beta-agonist) in preference to an anticholinergic. Barnes (2000) stated 'COPD appears to be more effectively treated by anticholinergic drugs than by ß-agonists'; whilst Halpin (2001) stated 'Anticholinergic bronchodilators should be tried in patients who remain symptomatic despite using short-acting beta-agonists'. Wedzicha *et al* (2001) stated that 'Anticholinergic drugs are at least as effective as, if not more so than $ß_2$ agonists in improving lung function and symptoms in COPD'.

Boehringer Ingelheim considered that the paper by Mahler *et al* (1999) referred to by GlaxoSmithKline found that both salmeterol and ipratropium produced significant improvements in patients' health status compared to placebo, however GlaxoSmithKline had used this paper to support the duration of action of salmeterol (which was not in question), and had used a paper that compared salmeterol to placebo alone to support claims for improved health status. This was clearly misleading as GlaxoSmithKline had failed to provide an evaluation of all the clinical evidence, and was heavily reliant on clinical data from one paper.

Boehringer Ingelheim also alleged that the claim was not supported by international guidelines on COPD. At no point did these guidelines advocate the use of one class of bronchodilator (beta agonist or anticholinergic) in preference to another, nor did they advocate in what particular order different classes of bronchodilator should be used.

Boehringer Ingelheim considered that the entire tenet of the mailing implied that treatment with ipratropium was inferior and that doctors were failing in their duties to their patients if they considered using an anticholinergic before Serevent. Boehringer Ingelheim alleged that GlaxoSmithKline had failed to support the claim 'Rx Serevent 50 mcg b.d. for your COPD patients after salbutamol prn before anticholinergics' which was not an accurate, balanced or fair evaluation of all the available data, and which made selective reference to clinical data in a way which was misleading.

The Panel noted that there were two studies comparing salmeterol and ipratropium bromide in COPD. Mahler *et al* compared salmeterol twice daily with ipratropium and placebo. With regard to night-time shortness of breath salmeterol was statistically superior to ipratropium (p=0.043) over the 12 week period. Analysis of the time to first COPD exacerbation demonstrated salmeterol to have a delayed onset of exacerbations compared with ipratropium (p=0.0411). Both salmeterol and ipratropium provided significant increases in lung function, improved dyspnoea ratings, reduced the use of supplemental albuterol [salbutamol] and enhanced disease specific quality of life compared with placebo. The study concluded that the collective data supported the use of salmeterol as first-line bronchodilator therapy for the long-term treatment of airflow obstruction in patients with COPD.

The Panel considered that there was some data to show some advantages for Serevent compared to ipratropium. It was not unreasonable to advocate prescribing Serevent after prn salbutamol before anticholinergics. It was immaterial that this was not in line with international prescribing guidelines; Serevent was licensed for use in COPD patients who required long-term regular bronchodilator-therapy and so could be promoted for such use. The Panel did not consider the leaflet was unreasonable in this regard. The letter stated that many doctors prescribed an anticholinergic when COPD patients required more than a short-acting $ß_2$ agonist and the purpose of the mailing was to explain how Serevent in COPD could offer a different treatment option in early disease. The Panel did not consider that the claim was misleading as alleged and no breach of the Code was ruled.

Boehringer Ingelheim Limited complained about a mailing sent by GlaxoSmithKline UK Ltd to promote Serevent (salmeterol xinafoate) in chronic obstructive pulmonary disease (COPD). Salmeterol was a long-acting bronchodilator. The mailing consisted of a four page leaflet (Ref HM5974-FP/December 2001) and a letter headed 'Which regular bronchodilator do you choose after salbutamol prn in COPD?' (Ref HM5996-FP/Jan 2002).

Boehringer Ingelheim marketed the anticholinergic bronchodilator ipratropium bromide on its own (Atrovent) or in combination with salbutamol (Combivent).

The front cover of the leaflet stated 'Do more for your COPD patients', the second page continued 'and they can do more with their lives'. The third page was divided into three sections, one headed 'COPD involves more than bronchoconstriction. The second section was headed 'Serevent in COPD may provide more than bronchodilation'. The claim at issue 'Rx Serevent 50 mcg b.d. for your COPD patients after salbutamol prn before anticholinergics' appeared in bold as a summary beneath the third section headed

'Do something different in COPD, starting today'. The second and third pages were designed to be read as a double page spread.

COMPLAINT

As far as Boehringer Ingelheim was aware, there was no substantial evidence to support the use of Serevent (a long-acting beta-agonist) in preference to an anticholinergic. Barnes (2000) stated 'COPD appears to be more effectively treated by anticholinergic drugs than by ß-agonists'; whilst Halpin (2001) stated, 'Anticholinergic bronchodilators should be tried in patients who remain symptomatic despite using short-acting beta-agonists'. Wedzicha *et al* (2001) stated that 'Anticholinergic drugs are at least as effective as, if not more so than $ß_2$ agonists in improving lung function and symptoms in COPD'.

Boehringer Ingelheim believed GlaxoSmithKline had failed to support the claim, 'Rx Serevent 50 mcg b.d. for your COPD patients after salbutamol prn before anticholinergics' which was not an accurate, balanced or fair evaluation of all the available data, and which made selective reference to clinical data in a way which was misleading.

Boehringer Ingelheim considered that the paper by Mahler *et al* (1999) referred to by GlaxoSmithKline found that both salmeterol and ipratropium bromide produced significant improvements in patients' health status compared to placebo, however GlaxoSmithKline had used this paper to support the duration of action of salmeterol (which was not in question), and had used a paper that compared salmeterol to placebo alone, to support claims for improved health status. This was clearly misleading. Boehringer Ingelheim believed that the conclusions drawn from the references provided by GlaxoSmithKline were misleading as it had failed to provide an evaluation of all the clinical evidence, and was heavily reliant on clinical data from one paper.

Boehringer Ingelheim also alleged that the claim was not supported by the international guidelines on COPD produced in 2001 by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). These guidelines provided the most comprehensive evaluation of all the available data on COPD to date. They stated 'The choice between $ß_2$ agonist, anticholinergics, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects' and in the section on Therapy at Each Stage of COPD they advocated: a short-acting bronchodilator (which would include an anticholinergic such as ipratropium) when needed for mild COPD; regular treatment with one or more bronchodilators for moderate and severe COPD.

At no point did the GOLD guidelines advocate the use of one class of bronchodilator (beta agonist or anticholinergic) in preference to another, nor did they advocate in what particular order different classes of bronchodilator should be used.

The entire tenet of the mailing, starting with the front cover and the second page which together stated 'Do more for your COPD patients … and they can do more with their lives' implied that treatment with ipratropium was inferior and that doctors were failing in their duties to their patients if they considered using an anticholinergic before Serevent.

In conclusion, Boehringer Ingelheim believed the promotional materials were misleading. They had failed to provide an up-to-date evaluation of all the evidence, and had failed to adequately support the claim. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline stated that the quotations in the complaint as to the relative efficacy of $ß_2$ agonists and anticholinergics (all from reviews and books rather than primary sources) were based on references which compared short-acting $ß_2$ agonists with anticholinergics rather than long-acting $ß_2$ agonists. For example, under the heading 'Anticholinergics versus short-acting $ß_2$ agonists', Marin *et al* (2001) stated that: 'Anticholinergic drugs are at least as effective as, if not more so than $ß_2$ agonists in improving lung function and symptoms in COPD'. However, on the same page, under the heading 'Anticholinergics versus long-acting $ß_2$ agonists', the same authors stated that: 'Although anticholinergic agents may be more effective than short-acting $ß_2$ agonists, trials comparing ipratropium with long-acting agents such as salmeterol have found the reverse'.

GlaxoSmithKline believed that while there was some evidence to suggest anticholinergics such as ipratropium (the most widely used anticholinergic medicine in the UK) might be more effective than short-acting $ß_2$ agonists, there was no evidence of a greater effect compared with long-acting $ß_2$ agonists. GlaxoSmithKline believed, on the contrary, the balance of evidence was in favour of the long-acting $ß_2$ agonist salmeterol compared with ipratropium bromide.

GlaxoSmithKline believed the Mahler *et al* paper to be representative of the balance of evidence between Serevent and ipratropium bromide and did not consider that it had made 'selective reference' to clinical data in a way which was misleading. GlaxoSmithKline believed the claim was based on an up-to-date evaluation of the balance of evidence for salmeterol and ipratropium bromide.

There had been two randomised, double-blind, double-dummy, placebo-controlled 12-week studies comparing salmeterol and ipratropium bromide, involving over 800 patients, Mahler *et al* and Rennard *et al* (2001). These studies both showed the effectiveness of salmeterol and ipratropium bromide in the treatment of patients with COPD. However, there were differences significantly in favour of salmeterol.

In the Mahler *et al* study (n=411) salmeterol 50mcg bd significantly improved morning pre-dose forced expiratory volume in one second (FEV_1) compared with ipratropium. After 12 weeks' treatment, salmeterol was significantly more effective than ipratropium bromide at hours 0, 4 and 6 ($p<0.001$)

showing a longer duration of action and therefore better sustained bronchodilation over 12 hours. Similar improvements over ipratropium bromide were seen for forced vital capacity (FVC) (hours 0 and 6 at week 12). For night-time shortness of breath, there were significantly greater improvements in the salmeterol group than in the placebo or ipratropium groups and over the 12-week treatment period, salmeterol was superior to ipratropium bromide (p=0.043).

The Rennard *et al* study (n=405) confirmed the efficacy of salmeterol and ipratropium in the treatment of COPD, although fewer significant differences between salmeterol and ipratropium bromide were seen. This was not unexpected since it would be unusual to exactly replicate the findings of another study. However there were similar trends in terms of baseline lung function, and night-time breathlessness, this time reflected in night-time prn Ventolin use. For example, over the 12-week study period patients receiving salmeterol required significantly fewer mean puffs of Ventolin compared to placebo (p=0.016) and compared to ipratropium bromide for weeks 9-12 of the study (p=0.041). Furthermore, data on file showed that over the 12 weeks of the study there was a significantly greater improvement in mean percentage nights without prn Ventolin among those receiving salmeterol compared with ipratropium (p<0.001) and placebo (p<0.001).

Because these two studies were identical in design, it was also of relevance to consider their combined results to inform GlaxoSmithKline's understanding of the balance of evidence.

Anderson *et al* (1997) and data on file in terms of 12 hour serial pulmonary function (FEV_1) at week 12, salmeterol was significantly more effective than ipratropium at hours 0, 4, 6 and 12 ($p \leq 0.041$). These data were supported by a significantly greater effect on mean morning PEF (p<0.001) from week 1, and maintained throughout the 12 weeks of the study (data on file).

GlaxoSmithKline referred to Cox *et al* (2000) where the two studies had been analysed together to look at the percentage of patients showing a clinically relevant improvement in quality of life. In this analysis, a significantly higher proportion of patients receiving salmeterol achieved a clinically meaningful improvement in health status compared with placebo (p<0.05). However, for this measure, ipratropium was not significantly different to placebo. Therefore, while the statement in the mailing referred to data compared with placebo, the balance of evidence for health status data was still in favour of salmeterol.

A similar result was seen when the time to first exacerbation data were combined from the two studies. Patients receiving salmeterol showed a significantly longer time to first exacerbation compared with placebo (p=0.0127), while ipratropium was not significantly different to placebo for this endpoint (data on file).

Taken together, GlaxoSmithKline believed there was more consistent evidence of the efficacy of salmeterol, across a range of endpoints in the treatment of COPD compared with ipratropium, and that where significant differences, and trends towards differences, between salmeterol and ipratropium were demonstrated, they were almost always in favour of salmeterol. Mahler *et al* was representative of these data. However in order to try to address some of Boehringer Ingelheim's concerns, GlaxoSmithKline had already agreed to ensure that in future a more comprehensive list of references was given.

Under Clause 7.3, a comparison was permitted if one or more material, relevant, substantiable and representative features were compared. The mailing complied with this clause and gave the rationale for why health professionals should have considered using salmeterol in patients for whom salbutamol was no longer enough to control their symptoms.

GlaxoSmithKline agreed with Boehringer Ingelheim's interpretation of the GOLD guidelines, which positioned anticholinergics and long-acting $ß_2$ agonists as maintenance bronchodilators. GlaxoSmithKline was aiming to address the decision that a prescriber faced when confronted with patients who were not controlled on salbutamol alone. The doctor needed to decide whether to prescribe an anticholinergic or a long-acting $ß_2$ agonist, (based on COPD guidelines and licensed medications), and the claim reflected what GlaxoSmithKline believed to be the balance of evidence comparing salmeterol with ipratropium bromide. As such, it was a positioning statement and GlaxoSmithKline was unaware of any requirement within the Code that positioning statements must follow published treatment guidelines. Having chosen to prescribe salmeterol there was no reason why the prescriber should not add ipratropium bromide at a later date.

The fact that both ipratropium bromide and salmeterol were effective medicines was not in question. 'Do more for your patients' related to those patients for whom salbutamol was no longer enough. GlaxoSmithKline intended 'Do more for your patients and they can do more with their lives' to be read within the context of the whole mailing which set out representative evidence and, based on this evidence made a recommendation for the prescription of Serevent 50mcg bd in these patients. The data presented were not disparaging to ipratropium and there was no attempt to suggest that a doctor was failing in his or her duty by prescribing ipratropium – the doctor may have added in an anticholinergic at a subsequent point in the treatment pathway. Furthermore there was no suggestion that patients should be switched from ipratropium to Serevent, as this would be inappropriate.

Although GlaxoSmithKline intended the statements to be read within the context of the whole mailing, it had already agreed that the positioning of the phrase 'Do more for your patients' on the front page without accompanying text meant it could have been misinterpreted and GlaxoSmithKline undertook not to use the phrase again without clarifying the context.

In conclusion, GlaxoSmithKline did not consider that the items were in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim at issue appeared

beneath two claims 'Serevent in COPD has been shown to provide significant improvements in health status when compared to placebo' referenced to Jones *et al* (1997) and 'Serevent in COPD provides better sustained 24 hour relief of shortness of breath than ipratropium bromide' referenced to Mahler *et al* (1999).

The Panel noted that there were two studies comparing salmeterol and ipratropium bromide in COPD. Mahler *et al* compared salmeterol twice daily with ipratropium and placebo in the treatment of COPD. FEV_1 and dyspnea ratings were considered as primary outcome measures. After 12 weeks' treatment change in FEV_1 from baseline for salmeterol was statistically significantly superior compared to ipratropium at 0, 4 and 6 hours. Significant differences in FVC between patients treated with salmeterol and with ipratropium were noted at hour 6 at all serial assessments and at hour 0 for the serial assessments at week 4 and week 12. With regard to night-time shortness of breath salmeterol was statistically superior to ipratropium (p=0.043) over the 12 week period. Analysis of the time to first COPD exacerbation demonstrated salmeterol to have a delayed onset of exacerbations compared with ipratropium (p=0.0411). Both salmeterol and ipratropium provided significant increases in lung function, improved dyspnoea ratings, reduced the use of supplemental albuterol and enhanced disease specific quality of life compared with placebo. The study concluded that the collective data supported the use of salmeterol as first-line bronchodilator therapy for the long-term treatment of airflow obstruction in patients with COPD.

Rennard *et al* was not designed to demonstrate equivalence of salmeterol and ipratropium but rather to show comparability. Some differences were observed.

GlaxoSmithKline had some data to show some advantages for Serevent compared to ipratropium. It was not unreasonable to advocate prescribing Serevent after prn salbutamol before anticholinergics. It was immaterial that this was not in line with international prescribing guidelines; Serevent was licensed for use in COPD patients who required long-term regular bronchodilator-therapy and so could be promoted for such use. The Panel considered that there was data to show advantages for Serevent compared to ipratropium. The Panel did not consider the leaflet was unreasonable in this regard. The letter stated that many doctors prescribed an anticholinergic when COPD patients required more than a short-acting $ß_2$ agonist and the purpose of the mailing was to explain how Serevent in COPD could offer a different treatment option in early disease. The Panel did not consider that the claim was misleading as alleged and no breach of Clause 7.2 was ruled.

The Panel was concerned that the statement 'Do more for your COPD patients … and they can do more with their lives' was a broad statement which in the Panel's view was not sufficiently qualified and was thus misleading. The Panel noted that GlaxoSmithKline had agreed to amend the statement. Nevertheless, the Panel requested that GlaxoSmithKline be advised of its concerns.

Complaint received **15 May 2002**

Case completed **25 July 2002**

CASE AUTH/1324/5/02

CONSULTANT PSYCHIATRIST v JANSSEN-CILAG

Risperdal Consta advisory board meeting

A consultant psychiatrist complained about a letter from Janssen-Cilag inviting him to participate in an advisory board meeting on Risperdal Consta (risperidone). The objective of the evening meeting was to review the Risperdal Consta data with the intention of eliciting the views of the participants, as experts in the field of schizophrenia, and to ask for feedback on some of the proposed promotional materials for the product. Travel expenses would be covered and accommodation provided if required. An honorarium of £250 was offered. The complainant stated that the letter appeared to be offering a financial inducement to attend a promotional event.

The Panel noted that the letter referred to the product launch but did not mention that the medicine was unlicensed. The meeting started at 6.30pm with a meal afterwards, according to the letter provided by the complainant. The pro forma letter provided by Janssen-Cilag stated that the evening would begin with a hot buffet and would take a specified length of time. Spaces were left for the details to be added. No information had been given by Janssen-Cilag about the timings in the letter received by the complainant. Janssen-Cilag had advised the Panel that the meetings were to last approximately three hours. The agenda listed the objectives of the meeting in bullet point format; no details regarding specific feedback sessions or timings were mentioned. A PowerPoint presentation on Risperdal Consta clearly stated that the product was not yet licensed. Risperdal Consta was referred to in brand name logo format and the risperidone product logo appeared in the bottom right hand corner of each of the slides discussing the product's pharmaceutical development and clinical profile.

The meeting in question had not taken place. It was one in a series of five planned, each with eight attendees/invitees. Four meetings had taken place.

The Panel decided that the overall arrangements for the meeting, particularly the invitations and agenda, were such that they were not sufficiently clear about the role and amount of work to be undertaken by participants. The payment of an honorarium in such circumstances was thus inappropriate and amounted to a payment to attend a promotional meeting contrary to the Code; a breach was ruled. A high standard had not been maintained and a further breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and no breach of that clause was ruled.

On appeal by Janssen-Cilag of the Panel's ruling with regard to payment to attend a promotional meeting, the Appeal Board was very concerned that the company's initial response stated that it had provided a complete list of invitees for all of the advisory board meetings when that was not so. Upon questioning at the appeal hearing it was revealed that a number of potential invitees could have been informally approached by Janssen-Cilag's medical liaison officers.

The Appeal Board noted that Risperdal Consta was the first atypical antipsychotic to be formulated into a long-acting preparation and noted the company's submission about the input sought and received from health professionals at the meetings. The Appeal Board considered that there were legitimate reasons for the meetings to take place but was concerned about the presence of the product logo on the slides. It further considered that the letter of invitation and agenda could have made the role and amount of work to be undertaken by the recipients clearer. Nonetheless, on balance, the Appeal Board considered that the arrangements as a whole were not unacceptable and thus the payment of an honorarium was not unreasonable in such circumstances. No breach of the Code was ruled.

A consultant psychiatrist complained about a letter which he had received from Janssen-Cilag Ltd.

The letter invited the complainant to participate in an advisory board meeting focussing on Risperdal Consta, Janssen-Cilag's new long-acting injectable formulation of risperidone (Risperdal), in preparation for the product launch in the United Kingdom. The objective of the evening meeting was stated to be to seek counsel on two issues. Firstly, to review the data on Risperdal Consta with the intention of eliciting the views of the participants, as experts in the field of schizophrenia, as to how it might potentially change the pattern of care as well as how the patient flow might evolve. Secondly, to ask for feedback from the participants on some of the proposed promotional materials for the product. The meeting would begin at 6.30pm with a meal afterwards. Travel expenses would be covered and accommodation would be provided if required. An honorarium of £250 was offered in recognition of the addressee's valuable contribution to this very important meeting.

COMPLAINT

The complainant stated that behind the window dressing the letter appeared to be offering a financial inducement to attend a promotional event.

When writing to Janssen-Cilag, the Authority asked it to bear in mind the requirements of Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

Janssen-Cilag stated that Risperdal Consta did not currently have a licence (although approval from the MCA was imminent). Risperdal Consta was a new product – a unique formulation of an atypical antipsychotic using a novel delivery system. It was the first in its class. In such circumstances it was usual to gain feedback from prescribers, nursing staff, pharmacists and other health professionals about the data the company had available on the product. Such feedback would include: how and where they saw it being used, in which patient groups, and reactions to the planned sales and marketing strategy and

advertising materials for the product. This was an iterative process and at each advisory board new/changed materials and information were presented based on the feedback from the previous advisory board.

Janssen-Cilag planned a maximum of five advisory boards, with a maximum of eight invitees/attendees, with the following proposed locations: Scotland – there were significant differences in the way products were handled north of the border; London, Bristol and Manchester – as city areas – in the event the Bristol meeting was not held; and Cambridge – rural area.

The product was for use in patients with schizophrenia as part of a complete care package. However delivery of this package was influenced strongly by geography. Four advisory boards had been held to date, in Scotland, Cambridge, London and Manchester. The advisory board meeting in Bristol was cancelled as the company could not get more than two attendees for the specific date. Each meeting lasted approximately three hours.

Delegates were selected by the medical relations manager and the senior medical advisor, and consisted of a mix of local key opinion leaders and Risperdal Consta trialists, pharmacists and budgetholders. A complete list was provided of the people (and their titles) invited and who participated at each advisory board, as well as dates when the letters were sent out and when the advisory boards were actually held.

At the advisory board, participants would be asked, from a regional perspective, to comment on the relevance and usefulness of the clinical data presented; feedback on patterns of care and potential patient flow changes; and feedback on draft promotional materials.

The meeting started with an agenda, followed by a PowerPoint presentation on Risperdal Consta research data – during which time comments and questions were received. This was followed by an active discussion around patterns of care, patient flow, as well as participants' perceptions around the draft promotional materials (in terms of relevance, credibility etc). Participants were told that Janssen-Cilag did not have a licence for the product and that it was looking for honest and open feedback on the data presented and where and how they saw the product being used. They were told that their input at this stage would help Janssen-Cilag ensure it brought the product to market in a credible and cohesive way, providing relevant and useful support to prescribers and other health professionals who might come into contact with the product. The participants involved themselves in the meetings very much as intended and provided lively, constructive feedback that had helped Janssen-Cilag considerably in achieving its stated objectives. No materials were provided to delegates to take away. Planned sales materials changed progressively in the process as a result of the helpful feedback received.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. The selection of attendees had to stand up to independent scrutiny and the arrangements had to comply with the Code.

The Panel noted the company's submission that the purpose of the meeting was to comment on the relevance and usefulness of the clinical data presented, feedback on patterns of care and potential patient flow changes and feedback on draft promotional materials. The letter referred to the product launch but did not mention that the medicine did not yet have a product licence. The letter referred to the product's brand name in upper case logo format on three occasions. The meeting started at 6.30pm with a meal afterwards according to the letter provided by the complainant. The pro forma letter provided by Janssen-Cilag stated that the evening would begin with a hot buffet and would take a specified length of time. Spaces were left for the details to be added. No information had been given by Janssen-Cilag about the timings in the letter received by the complainant. Janssen-Cilag had advised the Panel that the meetings were to last approximately three hours. The agenda merely listed the objectives of the meeting in bullet point format; no details regarding specific feedback sessions or timings were mentioned. The PowerPoint presentation clearly stated that the product was not yet licensed. Risperdal Consta was referred to in brand name logo format and the risperidone product logo appeared in the bottom right hand corner of each slide discussing the product's pharmaceutical development and clinical profile (36 slides). Two slides discussed depot conventional antipsychotics and a further two discussed patient pathways.

The meeting in question had not taken place. It was one in a series of five planned each with eight attendees/invitees. Four meetings had taken place. These being Scotland, 9 attendees; Cambridge, 5 attendees; London, 7 attendees; and Manchester, 7 attendees.

The Panel was concerned that by not including sufficient details the invitation gave the impression that the meeting was a promotional meeting. The Panel considered that although the invitation mentioned the interactive nature of the meeting in general terms, it was not sufficiently clear about the precise role of the invitees and how much work would be involved. Given the limited information and absence of information on the agenda about timings or feedback sessions, it was unclear whether the meeting was designed to achieve the stated objectives.

The Panel considered that it was difficult in such cases to determine precisely where the boundary lay. On balance the Panel decided that the overall arrangements for the meeting, particularly the invitations and agenda were such that they were not sufficiently clear about the role and amount of work to be undertaken by participants. The payment of an honorarium in such circumstances was thus inappropriate and amounted to a payment to attend a

promotional meeting contrary to Clause 18.1 of the Code; a breach of that clause was ruled. A high standard had not been maintained and a breach of Clause 9.1 of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

During its consideration of this case, the Panel was concerned that as the meeting had been deemed to be promotional then the company had in effect promoted Risperdal Consta prior to the grant of its marketing authorization which was not in accordance with Clause 3.1. The Panel requested that its concerns be drawn to Janssen-Cilag's attention.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag did not accept the ruling that the meetings themselves were promotional and that an inappropriate payment was made. The ruling implied that the Bristol meeting was promotional which Janssen-Cilag found surprising given that it did not actually proceed for logistical reasons. Accordingly Janssen-Cilag wished to appeal the ruling of a breach of Clause 18.1.

The meetings were held to gain input from physicians and other members of mental health care teams on the likely impact of Risperdal Consta on patient care and the translation of the available data into effective promotional materials. Management of patients with mental health problems required a multidisciplinary approach and an integrated package of treatment options of which medicine therapy formed only a part.

Janssen-Cilag stated that Risperdal Consta was the first long-acting form of an atypical antipsychotic that differed significantly in its pharmacokinetics, its delivery system and in its reconstitution. In order to maximize the potential patient benefit of this significant advance in the treatment of schizophrenia, Janssen-Cilag had needed insight from professionals to elucidate the role of the product within the existing and any future treatment paradigms and the strategies and messages required to effectively communicate this.

The meetings were scheduled to run for two hours (excluding the time allowed for refreshments) and on at least two occasions ran over by an additional 30-45 minutes in order to capture the outcome of the highly interactive discussion with the participants.

Following a presentation of the data on Risperdal Consta during which the clinical data was presented and discussed with participants they were asked to give their feedback on the product and how they saw it impacting on their particular area of care. These discussions were lively and provided much useful feedback on the different care settings in the UK, the varied roles of the health professionals involved and the need for differing levels of education on the product and its correct usage. A number of ways of achieving effective communication to the different healthcare groups were discussed and led to generation of new materials to achieve this aim.

Promotional materials which were in their early draft stages were reviewed at the meeting and discussed in a frank and open way with considerable changes being made from one meeting to the next to reflect the input received.

Janssen-Cilag therefore felt strongly that these meetings were not promotional but were held with professional colleagues to help the company determine the place of Risperdal Consta and appropriate communication thereof to health professionals. The honorarium paid for such input was not excessive and within industry norms.

The Panel's ruling of a breach of Clause 9.1 was not appealed.

COMMENTS FROM THE COMPLAINANT

There were no comments.

APPEAL BOARD RULING

The Appeal Board noted that the advisory board meeting at issue did not take place. Four other meetings went ahead as planned; they were held across the UK and attended by a total of twenty-eight delegates.

The Appeal Board was very concerned that Janssen-Cilag's initial response stated that it had provided a complete list of invitees for all of the advisory board meetings when that was not so. Upon questioning at the appeal hearing it was revealed that a number of potential invitees could have been informally approached by Janssen-Cilag's medical liaison officers.

The Appeal Board noted that the first slide of the presentation on the Risperdal Consta research data was sub-titled 'Advisory Board'; the second slide clearly stated that the product was not yet licensed. The Appeal Board noted that Risperdal Consta was the first atypical antipsychotic to be formulated into a long-acting preparation and noted the company's submission about the input sought and received from health professionals at the meetings. The Appeal Board considered that there were legitimate reasons for the meetings to take place but was concerned about the presence of the product logo on the slides. It further considered that the letter of invitation and agenda could have made the role and amount of work to be undertaken by the recipients clearer. Nonetheless, on balance, the Appeal Board considered that the arrangements as a whole were not unacceptable and thus the payment of an honorarium was not unreasonable in such circumstances. No breach of Clause 18.1 of the Code was ruled.

During its consideration of this case the Appeal Board noted the company representatives' submission that the company's procedures had not been followed in relation to the issue and distribution of the letter of invitation for the Bristol meeting. The Appeal Board was concerned that health professionals had been informally invited to attend the meeting. There was no complete record of who had been invited. Given the nature of the meeting the Appeal Board expressed concern over the relative lack of control exercised in

relation to the arrangements and requested that the company be advised of its concerns.

Complaint received **24 May 2002**

Case completed **12 September 2002**

CASE AUTH/1325/5/02

JANSSEN-CILAG/DIRECTOR v LILLY

Promotion and medical information relating to Zyprexa

Janssen-Cilag complained about three Zyprexa (olanzapine) leavepieces and a medical information letter issued by Lilly stating that the claims at issue were of a type which applied to the whole campaign. Janssen-Cilag's allegation of a breach of undertaking was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

Janssen-Cilag supplied Risperdal (risperidone). Both Zyprexa and Risperdal were atypical antipsychotics.

Janssen-Cilag alleged that the claim 'Superior efficacy to risperidone' was misleading and not based on an up-to-date evaluation of all the evidence. The claim was not substantiated by its reference (Tran *et al*, 1997) in which the primary endpoint, 'mean change in Positive and Negative Symptom Scale (PANSS) total score', demonstrated no statistically significant difference between olanzapine and risperidone. The claim failed to acknowledge more recently published results (Conley and Mahmoud, 2001) and present the totality of data in a balanced way. Conley and Mahmoud was the first randomised, controlled, double-blind trial of Risperdal and olanzapine using clinically relevant doses (in accordance with the current summaries of product characteristics (SPCs)) for the products. Patients were randomised to receive flexible doses of Risperdal (2-6mg/day) or olanzapine (5-20mg/day) for 8 weeks; the mean modal doses were 4.8mg/day for Risperdal and 12.4mg/day for olanzapine. Based on comparisons of the total PANSS (the same primary efficacy variable used in the Tran study), risperidone and olanzapine were equally efficacious.

The Panel noted that Lilly had cited a number of trials which compared the efficacy of olanzapine and risperidone. Two of these, however, involved small numbers of patients and two others had been open label. In the Panel's view the balance of the data lay in the results of Tran *et al* and Conley and Mahmoud, both of which were large, randomized, double-blind studies.

When the study by Tran *et al* was published, the data sheet for Risperdal stated that the usual optimal dose was 4-8mg/day. The current SPC stated that most patients would benefit from daily doses of 4-6mg although in some an optimal response might be obtained at lower doses. Doses above 10mg/day should only be used if the benefit was considered to outweigh the risk. Doses above 16mg/day should not be used.

Tran *et al* had used risperidone in the dose range of 4-12mg; the mean modal dose was 7.2mg/day. The Panel noted that in a previous case, Case AUTH/1022/5/00, the Appeal Board had considered that Tran *et al* was a well designed study and that the mean modal dose for the risperidone group was within the recommendations in the Risperdal SPC. Conley and Mahmoud had used doses of risperidone in the range of 2-6mg and the mean modal dose of 4.8mg daily. The Panel did not consider that the doses used in either study were inconsistent with the current Risperdal SPC dosage recommendations.

Tran *et al* stated that the study indicated that both olanzapine and risperidone were safe and effective in reducing overall psychopathology in patients with chronic schizophrenia and related psychotic disorders. With regard to the primary efficacy measure (PANSS total score) there was no significant difference between the products. The olanzapine treatment group showed significantly greater improvement in the SANS (Scale for Assessment of Negative Symptoms) summary score than risperidone (p=0.020). Thus although some efficacy advantages were demonstrated for olanzapine, it was not superior to risperidone in every aspect.

The Conley and Mahmoud study was of a shorter duration than the Tran *et al* study – 8 weeks as compared to 28 weeks. Conley and Mahmoud reported that both olanzapine and risperidone were well tolerated and efficacious. PANSS scores on two factors – positive symptoms and anxiety/depression – were better with risperidone than with olanzapine (p=0.05 and 0.02 respectively). In other aspects there was no difference between the products.

The Panel noted that the efficacy of antipsychotics was measured according to a number of factors. The claim at issue 'Superior efficacy to risperidone' implied that in all aspects of efficacy olanzapine was superior to risperidone. This was not so. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

Janssen-Cilag alleged that the claim 'Zyprexa reduces the burden of extrapyramidal side effects [EPS] when compared to risperidone' was misleading as the Tran *et al* study upon which it was based used a dosage regimen which was not consistent with the current SPC or relevant to current clinical practice. The study in isolation did not reflect the totality of the available data.

In Tran *et al*, patients received risperidone 1mg twice daily on day 1, 2mg twice daily on day 2 and then 3mg twice daily on days 3 through to 7. The daily dose could then be adjusted. Doses ranged

from 10-20mg for olanzapine and 2-12mg for risperidone. The mean modal doses were 17.2mg for olanzapine and 7.2mg for risperidone. This dose regimen was inconsistent with the current Risperdal SPC, which stated 'patients should start on 2mg/day, increase to 4mg on the second day, and from then on the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4-6mg/day although in some, an optimal response may be obtained at a lower dose'. The mean modal dose used for risperidone was therefore higher than that recommended by the current SPC. Indeed, an inevitable result of the dose regimen used by Tran *et al* (which was consistent with the data sheet current at the trial's inception) would be that a larger number of patients remained on 6mg than would happen if the current SPC was followed. This conclusion was supported by current clinical practice whereby the current average daily dose of Risperdal for the treatment of schizophrenia was 4.4 - 4.8mg/day and by the available contemporary published literature (Kasper, 1998; Taylor, 2001; Csernansky *et al*, 2002; Maudsley Guidelines, 2002; Conley and Mahmoud, 2001). Furthermore, the high doses of risperidone used by Tran *et al* 'might have led to more extrapyramidal side effects and worse compliance in the Risperdal group' (Glick and Berg 2002).

The Panel noted its comments above with regard to the trials which had compared olanzapine and risperidone and again considered that the balance of the data lay in the results of Tran *et al* and Conley and Mahmoud. The Panel noted that in the above it had not considered that the doses used in the studies were inconsistent with the current Risperdal SPC.

The claim at issue related to extrapyramidal symptoms. The Risperdal SPC advised prescribers that doses above 10mg/day might increase the risk of EPS. The claim was referenced to Tran *et al* which had used risperidone in the dose range of 4-12mg. It was not possible to determine from the published paper how many patients, if any, had received more than 10mg risperidone daily. The mean modal dose was 7.2mg ± 2.7mg. Tran *et al* reported that significantly fewer olanzapine-treated patients experienced treatment-emergent EPS than risperidone-treated patients.

Conley and Mahmoud had used risperidone in daily doses of 2-6mg; according to the study design no patient could have received a dose of risperidone in excess of 10mg/daily. The mean modal dose was 4.8mg. Conley and Mahmoud reported that similar proportions of the risperidone and olanzapine groups reported EPS (24% and 20% respectively p=0.44).

The Panel considered that an up-to-date evaluation of all the evidence regarding EPS had to take into account the results of Conley and Mahmoud. Although in an earlier Zyprexa case (Case AUTH/1022/5/00) a claim for 'significantly lower EPS than risperidone' based on the Tran *et al* data had been ruled not to be in breach of the Code this was before the publication of Conley and Mahmoud. The Panel considered that the claim now before it no longer reflected all of the available evidence and so was misleading in that regard. A breach of the Code was ruled.

The claim 'Significant reduction in relapse rates compared to risperidone' appeared above a graph, referenced to Tran *et al*, which compared the cumulative percentage of patients maintaining a response with Zyprexa and risperidone. The starting doses for Zyprexa in Tran *et al* and the Zyprexa SPC were stated. Janssen-Cilag stated that as previously stated the mean modal dose used for risperidone in Tran *et al* was higher than that recommended by the SPC. The graph acknowledged that the doses used were not consistent with those recommended by the olanzapine SPC, but failed to acknowledge the same for Risperdal.

The surrogate measure of relapse used in the claim at issue was an estimate of the percentage of patients who had a response at week 8 and who maintained that response. The more recent publication by Glick and Berg concluded that 'Using the measures of study discontinuation, relapse and non-compliance, in one trial the atypical antipsychotic olanzapine was superior to haloperidol, while in a second trial (Tran *et al*) there were no differences between olanzapine and risperidone'.

Geddes 2002 concluded that there was now unique evidence to support the role of Risperdal in the prevention of relapse and that such support was not available for other atypical antipsychotics. It was stated 'There is little reliable evidence of long-term efficacy of other atypical drugs. Studies of the use of the other atypical drugs for the prevention of relapse are therefore required. Direct comparisons of atypical drugs are also needed'.

Janssen-Cilag alleged that the claim was misleading and unrepresentative of the totality of the currently available data.

The Panel noted that the graph immediately following the claim 'Significant reduction in relapse rates compared to risperidone' was also from Tran *et al* and depicted the cumulative percentage of patients maintaining a response for up to 200 days of treatment. The study by Tran *et al* did not refer to relapse rates and had not been designed to measure relapse rates; maintenance of response as defined by two parameters was not the same as prevention of relapse. The Panel considered that the claim did not accurately represent the findings of Tran *et al* and was misleading in that regard. A breach of the Code was ruled.

The claims 'Helping to avoid distressing prolactin effects' and 'Switching to Zyprexa from risperidone can normalize prolactin levels in patients suffering from hyperprolactinaemia' appeared above a bar chart which depicted the mean prolactin level in patients entering on risperidone at baseline and then switched to Zyprexa for up to 3 weeks; the data was referenced to Kinon *et al*. Janssen-Cilag stated that the claims were clearly intended to imply that olanzapine had a significantly better prolactin

mediated side effect profile than Risperdal. It was therefore alleged that the confusing representation of biochemical events as side effects was not fair or balanced. This was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels, and was not reflective of the SPCs. The Zyprexa SPC stated that elevated plasma prolactin levels were very common, but associated clinical manifestations (eg gynaecomastia, galactorrhoea and breast enlargement) were rare. The Risperdal SPC did not quantify the clinical manifestations of increased prolactin levels.

Janssen-Cilag noted that essentially the same claim in a previous mailing to psychiatrists had been ruled in breach of the Code (Case AUTH/1022/5/00), and therefore alleged a breach of the undertaking. Given that these claims were made in full knowledge of a previous ruling it also believed a breach of Clause 2 should be considered.

The claim 'Switching to Zyprexa from risperidone can normalize prolactin levels …' was referenced to a poster derived from a published study (Kinon *et al* 2000) which was designed to determine optimal methods for switching to olanzapine. It investigated 4 different algorithms – 2 of which consisted of one week of placebo, one week of olanzapine therapy (5mg/day) and one week of olanzapine therapy (10mg/day). This regimen was not in line with the SPC for Zyprexa. The prolactin data was collapsed across all 4 switching groups. It was therefore not a fair comparison as half the patients had only been on the recommended dose of olanzapine for 1 week. The graph implied the majority of patients had received 3 weeks of olanzapine treatment, which evidently was not the case. Janssen-Cilag also noted there was no mention of the dose of Risperdal. This was of particular relevance given that the Risperdal SPC acknowledged increases in prolactin were dose dependent. Janssen-Cilag alleged that the data presented from Kinon *et al* on prolactin levels was misleading and did not represent the data in a fair and balanced manner.

The Panel noted that the decreased propensity to be associated with serum prolactin increases might have important clinical consequences. Trials on prolactin levels showed that olanzapine treatment caused only mild elevations in serum prolactin levels compared to haloperidol thus establishing olanzapine as an atypical antipsychotic (Crawford *et al*, Esel *et al*). David *et al* examined the comparative effects on plasma prolactin levels of olanzapine, risperidone and haloperidol using data from three separate trials. The results suggested that olanzapine treatment resulted in smaller elevations in plasma prolactin (mean change 1-4ng/ml) than risperidone treatment (mean change 45-80ng/ml). The Panel considered that the balance of the evidence was that olanzapine did not raise serum prolactin as much as risperidone.

Tran *et al* demonstrated that the evidence of hyperprolactinaemia was statistically significantly lower in olanzapine-treated than risperidone-treated patients. Conley and Mahmoud reported that risk ratios for change were worse for risperidone than for olanzapine in relation to plasma prolactin levels.

The Panel noted that Kinon *et al* had evaluated the effect on serum prolactin levels of switching patients from conventional antipsychotics or risperidone (n=45) to olanzapine. The authors demonstrated that after 3 weeks prolactin levels in risperidone treated patients fell from 48.8ng/ml to 16.54ng/ml on switching to olanzapine ($p<0.001$). The abstract did not state what dose of risperidone patients had been taking before they were switched. In this regard the Panel noted the Risperdal SPC referred to a dose dependent increase in plasma prolactin. Patients had been switched to olanzapine in different ways such that some of the patients had been on olanzapine 10mg daily for the whole of the 3 weeks whereas others had had one week of placebo, one week of olanzapine 5mg and one week of olanzapine 10mg. The Panel noted that the Zyprexa SPC stated that the starting dose should be 10mg/daily. The dose could be subsequently adjusted on the basis of individual need to 5-20mg/daily; the routine therapeutic dose was 10mg/day. The Panel noted that whilst the heading to the bar chart referred to patients being 'switched to Zyprexa for up to 3 weeks' the claims at issue in combination with the immediate visual impression of the bar chart gave the overall impression that all patients who had been switched to Zyprexa had been on the medicine for three weeks which was not so. Those patients who had been changed over to olanzapine slowly had only been taking the medicine for the last two weeks of the study and for the first of those two weeks they took a lower than recommended starting dose. This information had not been made sufficiently clear in the bar chart. The Panel questioned the effect that this stepwise dosing would have on the plasma prolactin levels as measured after 3 weeks. Crawford *et al* had reported a dose-related increase in serum prolactin with olanzapine although David *et al* had shown no consistent dose response relationship. Nonetheless the Panel considered that the amount of information given in the bar chart with regard to dosing of olanzapine was not sufficient such as to allow the reader to understand how the switching of risperidone to olanzapine had happened. The bar chart was misleading in this regard. A breach of the Code was ruled.

The Panel considered that the heading 'Helping to avoid distressing prolactin effects' together with the claim which referred to 'prolactin levels in patients suffering from hyperprolactinaemia' inferred that prolactin-mediated adverse events would be seen less often in Zyprexa-treated patients than in those taking risperidone. Conley and Mahmoud however had actively solicited reports of side-effects potentially related to prolactin; symptoms were common, but differences between olanzapine treated patients and those receiving risperidone were not statistically significant. The Panel considered that the page was misleading with respect to the differential clinical advantage of olanzapine versus risperidone with regard to their propensity to cause prolactin-mediated side effects. Prolactin-mediated side effects were included in the Zyprexa SPC. There was no data to show that Zyprexa caused these side effects less often than risperidone. The page was misleading in this regard. A breach of the Code was ruled.

The Panel noted that in Case AUTH/1022/5/00 it had considered that most readers would assume that a claim for 'significantly fewer elevations of prolactin than risperidone (p<0.001)' meant that olanzapine had a significantly better prolactin-mediated side effect profile than risperidone. The Panel had considered that this was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels. A breach of the Code was ruled.

The Panel noted that the claims now before it in Case AUTH/1325/5/02 were not the same as that considered in Case AUTH/1022/5/00; the overall message to prescribers was not sufficiently similar and thus the Panel did not consider that the claims at issue in Case AUTH/1325/5/02 were caught by the undertaking given in Case AUTH/1022/5/00 and so ruled no breach of the Code in that regard. The Panel also ruled no breach of Clause 2 of the Code.

The claim 'Poor compliance can contribute to relapse' appeared in one of the leavepieces. Janssen-Cilag stated that the first two pages of the leavepiece under the banner 'Zyprexa helping you build a lasting therapeutic relationship', were clearly designed to link symptom control, relapse and side effects. These sections were clearly separated on the piece from the page referred to above with the banner headline 'Helping to avoid distressing prolactin effects'.

Janssen-Cilag accepted that the statements 'Poor compliance can contribute to relapse' and 'Side effects may cause patients to discontinue treatment' were general and related to the totality of side effects. However to focus specifically on sexual side effects without mention of other side effects, such as weight gain, which undoubtedly would have an impact on compliance and relapse was a totally selective and unbalanced presentation of the information. Indeed, in the National Schizophrenia Fellowship survey, referenced in the leavepiece, almost two thirds of responders referred to weight gain whilst only one-third experienced sexual side effects while on antipsychotic therapy. By misrepresenting the results of this survey Janssen-Cilag believed the reader would be deliberately misled into thinking that sexual side effects, rather than weight gain, were the major concern for patients and the main driver of non-compliance and relapse.

The Panel noted that the page in question had linked general statements regarding poor compliance, side effects and discontinuation of treatment specifically to prolactin-mediated side effects and not to the side effects profile in general. In the Panel's view there were some side effects which because of their nature or because they occurred much more frequently than sexual dysfunction, might cause a greater number of patients to discontinue treatment. The Panel considered that the page was misleading and ruled a breach of the Code.

Janssen-Cilag alleged that a medical information letter 'Zyprexa-Diabetes and Hyperglycaemia', which had been sent in response to queries from health professionals about the effect of olanzapine on glucose and diabetes, did not adequately reflect, in a fair, balanced and up-to-date manner the ongoing debate in the medical literature regarding the association of atypical antipsychotics on glucose metabolism and diabetes.

Janssen-Cilag strongly disputed the remark '… the accruing evidence [regarding the incidence of hyperglycaemia and/or the exacerbation of existing diabetes referred to in the Zyprexa SPC] is relevant to all antipsychotics' which it believed to be disparaging to Risperdal.

There was no mention of glucose abnormalities or diabetes on the Risperdal SPC. However, Janssen-Cilag was aware the Zyprexa SPC had been updated in this regard and stated: 'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus'. This statement had recently been amplified in a Current Updates in Pharmacovigilance newsletter, issued by the Medicines Control Agency, which concluded 'The product information for olanzapine recommends that in diabetics and patients with risk factors for diabetes mellitus, appropriate clinical and blood glucose monitoring is conducted'.

Janssen-Cilag believed the letter was misleading, biased, and by implication disparaged Risperdal. A breach of Clause 2 was also alleged.

The Panel noted that Lilly had not submitted any data to show that the statement which now appeared in the Zyprexa SPC was wholly applicable to all other antipsychotics. The Panel considered that in this regard the letter was inaccurate and thus subject to the Code. The Panel considered that the letter was disparaging as alleged. A breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 was regarded as a sign of particular censure and reserved for such use. The Panel did not consider that the medical information letter brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of the Code was ruled.

Janssen-Cilag Ltd complained about three Zyprexa (olanzapine) leavepieces (refs ZY916, ZY1099 and ZY877) issued by Eli Lilly and Company Limited and also about a Zyprexa letter from Lilly's medical information department. Janssen-Cilag supplied Risperdal (risperidone). Both Zyprexa and Risperdal were atypical antipsychotics.

The complaint involved an allegation of a breach of undertaking. That part of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

1 Claim 'Superior efficacy to risperidone'

This claim appeared in the leavepiece ref ZY877.

COMPLAINT

Janssen-Cilag alleged that the unqualified use of this claim was misleading, was not based on an up-to-date evaluation of all the evidence and was in breach of Clause 7.2 of the Code.

The claim was not substantiated by its reference. It relied on a single study (Tran *et al*, 1997) in which the primary endpoint, 'mean change in Positive and Negative Symptom Scale (PANSS) total score', demonstrated no statistically significant difference between olanzapine and risperidone. Neither was a difference seen for any of the subscales of PANSS (other than the depression subscale), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), or response defined as a more than 20% reduction in PANSS total score.

Olanzapine demonstrated significantly greater improvements in the Scale for Assessment of Negative Symptoms Summary Score (SANS); however, values of SANS were significantly different at baseline; baseline scores were always higher in the olanzapine group, therefore increasing the chance for a larger percentage change from baseline.

Any claim must be capable of substantiation and differences that did not reach statistical significance must not be presented in such a way as to mislead. Clearly Tran *et al* did not support such a broad claim of superior efficacy which was alleged to be misleading.

There was a failure to acknowledge results from more recently published comparative trials and present the totality of data in a balanced way. Since the Tran paper was published, a major head-to-head comparative trial had been completed and published (Conley and Mahmoud, 2001). This was the first randomised, controlled, double-blind, head-to-head trial of Risperdal and olanzapine using clinically relevant doses (in accordance with the current summaries of product characteristics (SPCs) for both products). In this study patients were randomised to receive flexible doses of Risperdal (2-6mg/day) or olanzapine (5-20mg/day) for 8 weeks. Analysis of the data on 377 patients from 39 sites showed the mean modal doses employed were 4.8mg/day for Risperdal and 12.4mg/day for olanzapine. With respect to efficacy, based on comparisons of the total PANSS (the same primary efficacy variable used in the Tran study), risperidone and olanzapine were equally efficacious. It was important to note that this was a large, controlled, head-to-head study that had been published in the prestigious American Journal of Psychiatry. It had been exposed to rigorous peer review and therefore must be considered as valid as Tran *et al*.

RESPONSE

Lilly did not agree that the claim was misleading and not capable of substantiation. Under the Code a claim must be capable of substantiation, any references cited must be bibliographically correct, and any study referenced must have results which were compatible with the claim. Lilly believed that these conditions had been met.

Lilly noted that Janssen-Cilag agreed that Tran *et al* showed a statistically significantly greater improvement in SANS [for olanzapine compared with risperidone] and a greater improvement for olanzapine compared to risperidone in a number of efficacy and safety endpoints. Lilly provided a table summarizing the significant findings in the study. Lilly stated that the study provided comprehensive evidence of superior efficacy of olanzapine over risperidone.

In addition Lilly considered that the claim was capable of substantiation on the basis of the results reported in the following clinical trials:

a) Thomas *et al* (1998) compared the efficacy of olanzapine and risperidone in the treatment of patients who met the DSM IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. After previous antipsychotic therapy was discontinued for up to nine days, sixty-two patients were randomised to receive either olanzapine, 10 to 20mg/day (n=32) or risperidone 4 to 8mg/day (n=30) for thirty weeks. Olanzapine-treated patients showed a significantly greater improvement in BPRS, total score (p=0.042) and PANSS general psychopathology score (p=0.049) at thirty weeks compared to the risperidone-treated patients. The proportion of patients exhibiting an improvement at thirty weeks of at least 20% over their baseline PANSS total score was statistically significantly higher in the olanzapine-treated group than in the risperidone-treated group (75% vs. 40% respectively, p=0.01). Olanzapine-treated patients showed statistically significant changes from baseline to endpoint in total score and three of the four subscales of the Quality of Life in Schizophrenia Scale.

b) Purdon *et al* (2000), in a multi-centre, double-blind trial compared the efficacy of olanzapine, risperidone and haloperidol on cognitive function in early phase schizophrenia. The fifty-four week trial included sixty-five stable outpatients diagnosed with schizophrenia or schizophreniform disorder who were within the first five years of first neuroleptic exposure, and had PANSS scores less than 90. Patients were randomised to receive olanzapine 5 to 20mg/day, risperidone 4 to 10mg/day, or haloperidol 5 to 20mg/day. A comprehensive neuropsychological test battery was used to assess cognition. In addition, the following measures were also made during the study: PANSS, Extrapyramidal Symptom Rating Scale (ESRS), Barnes Akathisia, and health economics. The mean modal doses of olanzapine (11.7mg/day), risperidone (6.1mg/day), and haloperidol (10.2mg/day) matched the current SPC doses very closely. The PANSS showed no statistically significant differences between groups. The general cognitive index revealed a significantly greater benefit of olanzapine relative to haloperidol and risperidone, but no significant difference between risperidone and haloperidol. Improvement with olanzapine was apparent after six weeks and sustained after thirty and fifty-four weeks of treatment. Secondary analysis of each cognitive domain revealed a significant improvement in attention with haloperidol, significant improvement in verbal skills and new learning with risperidone, and significant improvement in motor,

attention, nonverbal, executive, and new learning skills with olanzapine.

c) Ho *et al* (1999) was a naturalistic trial which compared olanzapine and risperidone on schizophrenia symptoms, global functioning, and extrapyramidal side effects before and after acute treatment (discharge from the hospital) and again at a six month follow-up visit. The trial was not blinded and thus open to significant bias. Both agents were found to be equally effective as acute treatments. Six months' follow-up information could only be obtained from twenty-six patients (thirteen in each treatment group).

d) Gómez *et al* (2000) was a prospective, observational, naturalistic study which assessed the safety and efficacy of olanzapine compared with other antipsychotics in the treatment of outpatients with schizophrenia. The six month study included 2,967 outpatients diagnosed with schizophrenia according to ICD-10. The only patients excluded were those in whom antipsychotic therapy was contraindicated or those with treatment resistant schizophrenia. Patients entered the study when they received a new prescription of an antipsychotic and were followed for six months. Treatment assignment was based on clinical criteria and did not include any experimental intervention. Treatment response was defined as at least a 2 point decrease in the Clinical Global Impressions-Severity (CGI-S) scale plus a maximum endpoint score of 4 or less in the CGI-S score. Principal analyses compared olanzapine (n=2128) versus the control group as a whole (n=821). Secondary analyses compared the olanzapine group versus drug-specific subgroups of patients of greater than n=100, including risperidone (n=417) and haloperidol (n=112). Both treatment groups (olanzapine and control group as a whole) were comparable at baseline. The initial and overall mean (± SD) daily doses used in the trial were: olanzapine 12.23 ± 4.85mg (overall 13.01 ± 4.97mg), risperidone 5.18 ± 2.32mg (overall 5.39 ± 2.5mg), and haloperidol 13.92 ± 9.26mg (overall 13.64 + 8.72mg). Data analysis showed that the percentage of responders at 6 months was significantly greater ($p<0.05$) in the olanzapine group (37.3%) than in the risperidone group (31.5%). Improvement in quality of life (QOL), as measured by the mean change in the Euroqol was significantly greater for olanzapine compared with the control group (mean change 20.45 vs. 13.83, $p<0.001$). Patient attitude with regard to their therapy was also improved for patients treated with olanzapine as measured by the mean score on the DAI-10 which was significantly higher in the olanzapine treatment group compared to the control group ($p<0.001$). Although methodologically weak this study also provided some evidence supporting the claim of superior efficacy of risperidone over olanzapine.

e) Conley and Mahmoud (2001) was a randomised double-blind trial which compared the safety and efficacy of olanzapine and risperidone over a period of only 8 weeks. Although few of the endpoints showed any difference between the treatments, Janssen-Cilag had acknowledged that olanzapine did demonstrate significantly greater improvements in SANS.

In conclusion, Lilly believed it had provided a significant body of published evidence to substantiate the claim of superior efficacy of olanzapine over risperidone and the claim at issue was not in breach of the Code.

Lilly noted the allegation that it had failed to acknowledge results from more recently published comparative trials and present the totality of the data in a balanced way. Lilly pointed out that the Code did not state that all of the literature on a topic must be cited in promotional material, indeed the Code did not require any company *per se* to acknowledge in print the existence of particular publications which their competitors favoured. Lilly stated that in its view the recent publication of a short term study showing no difference between olanzapine and risperidone did not invalidate *per se* the citing of an earlier longer term study showing superiority of olanzapine over risperidone and nor did it necessitate *per se* the citing of the more recent paper in promotional material. What the Code did require was that claims made must be capable of substantiation and must be based on an up-to-date evaluation of the literature.

Lilly accepted that Conley and Mahmoud must be taken into account and it had done so in its up-to-date evaluation of the literature. Since Conley and Mahmoud had been published in a peer review journal its results were certainly valid; however the weight given to them depended upon factors other than the journal in which they were published. Important factors included the quality of the study design, execution, analysis and reporting as well as the relevance of the length of time patients were treated to the situation in which the medicines studied were generally used. In the study the change at endpoint (ITT analysis) was greater for olanzapine than for risperidone but the difference between treatments did not reach statistical significance. Lack of a statistically significant difference did not prove equivalence: only a study designed to show equivalence could demonstrate equivalence. Equivalence study designs included setting up a pre-defined equivalence interval at the outset against which the size of any difference was measured. No such equivalence interval was defined in Conley and Mahmoud. Furthermore, Lilly noted that, for risperidone, the week 8 population was 134 compared to 183 at baseline (ITT), 175 endpoint and 188 enrolled and for olanzapine, the 8 week population was 144 compared with 186 at baseline (ITT), 181 at endpoint and 189 enrolled for olanzapine. Thus more patients remained on treatment with olanzapine at 8 weeks than on risperidone. This might have reflected either better efficacy or better tolerability of olanzapine compared to risperidone. Clearly the generalisability of a short term study such as Conley and Mahmoud to decision making about treatment for a chronic condition such as schizophrenia was questionable. The treatment duration in Tran *et al* was 6 months, a much more relevant treatment duration in the context of schizophrenia. Furthermore, the doses used were appropriate when the study was done, remained compatible with the SPCs for both medicines and resulted in both medicines being dosed at similar points in their current recommended dose ranges.

There were no questions about the quality of Tran *et al*: no centres were excluded from the analysis. Janssen-Cilag acknowledged that the doses used in Tran *et al* did reflect the SPCs at the time the study was designed, thus Conley and Mahmoud was not the first randomised, controlled, double-blind, head-to-head trial of Risperdal and olanzapine using clinically relevant doses in accordance with the current SPCs for both products as alleged by Janssen-Cilag.

There could therefore be little doubt that Tran *et al* provided a more appropriate guide to choice of antipsychotic than Conley and Mahmoud and thus the claim did indeed represent an up-to-date evaluation of the literature. Thus Lilly rejected the allegation that there had been a breach of the Code.

PANEL RULING

The Panel noted that Lilly had cited a number of trials in which the comparative efficacy of olanzapine and risperidone had been studied. Two of these trials, however, involved small numbers of patients (Thomas *et al* (n=32), Purdon *et al* (n=65)) and two others had been open label (Ho *et al*, Gómez *et al*). In the Panel's view the balance of the data thus lay in the results of Tran *et al* and Conley and Mahmoud, both of which were large randomized double-blind studies. The Panel noted the difference in the duration of each trial – 28 weeks for Tran *et al* and 8 weeks for Conley and Mahmoud.

In 1997, the year in which Tran *et al* was published, the data sheet for Risperdal (risperidone) stated that the usual optimal dose was 4-8mg/day. The usual daily dosage recommendations had since been revised and the current SPC now stated that most patients would benefit from daily doses of 4-6mg although in some an optimal response might be obtained at lower doses. In both the 1997 data sheet and the current SPC prescribers had been advised that doses in excess of 10mg/daily generally had not been shown to have additional efficacy to lower doses and might increase the risk of extrapyramidal symptoms. Doses above 10mg/day should only be used if the benefit was considered to outweigh the risk. Doses above 16mg/day should not be used.

Tran *et al* had used risperidone in the dose range of 4-12mg; the mean modal dose was 7.2mg. Over 50% of patients treated with risperidone had a modal dose of 6mg/day or less. The Panel noted that in a previous case, Case AUTH/1022/5/00, the Appeal Board had considered that Tran *et al* was a well designed study and that the mean modal dose for the risperidone group, 7.2 ± 2.7mg/day, was within the recommendations in the Risperdal SPC. Conley and Mahmoud had used doses of risperidone in the range of 2-6mg and the mean modal dose of 4 or 6mg daily. The Panel did not consider that the doses used in either study were inconsistent with the current Risperdal SPC dosage recommendations.

Tran *et al* stated that the study indicated that both olanzapine and risperidone were safe and effective in reducing overall psychopathology in patients with chronic schizophrenia and related psychotic disorders. With regard to the primary efficacy measure (PANSS total score) there was no significant difference between the products. The olanzapine treatment group showed significantly greater improvement in the SANS summary score than risperidone (p=0.020). Thus although some efficacy advantages were demonstrated for olanzapine, it was not superior to risperidone in every aspect. The study concluded with the statement that 'Additional studies across more heterogeneous populations that use various dosing strategies will be of interest to confirm the differential clinical effectiveness of olanzapine observed in this trial'.

Conley and Mahmoud was a more recent comparative study of olanzapine and risperidone than Tran *et al* although it was of a shorter duration – 8 weeks as compared to 28 weeks. Conley and Mahmoud reported that both treatments were well tolerated and efficacious. PANSS scores on two factors – positive symptoms and anxiety/depression – were better with risperidone than with olanzapine (p=0.05 and =0.02 respectively). In other aspects there was no difference between the products.

The Panel noted that the efficacy of antipsychotics was measured according to a number of factors. The claim at issue 'Superior efficacy to risperidone' implied that in all aspects of efficacy olanzapine was superior to risperidone. This was not so. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

2 Claim 'Zyprexa reduces the burden of extrapyramidal side effects when compared to risperidone'

This claim appeared in the leavepiece ref ZY916.

COMPLAINT

Janssen-Cilag alleged that this claim was misleading and in breach of the Code as the single comparative trial upon which it was based (Tran *et al*, 1997) was flawed in that the dosage regimen was not consistent with the current SPC or relevant to current clinical practice. The study when used in isolation did not reflect the totality of the available data.

In Tran *et al*, patients received risperidone at a dosage of 1mg twice daily on day 1, 2mg twice daily on day 2 and then 3mg twice daily on days 3 through to 7. The daily dose could then be adjusted. Dose ranges used in this trial were 10-20mg for olanzapine and 2-12mg for risperidone. The mean modal doses were 17.2mg for olanzapine and 7.2mg for risperidone.

The dose regimen was inconsistent with the current Risperdal SPC, which stated 'patients should start on 2mg/day, increase to 4mg on the second day, and from then on the dosage can be maintained unchanged, or further individualized, if needed. Most patients will benefit from daily doses between 4-6mg/day although in some, an optimal response may be obtained at a lower dose'. The mean modal dose used for risperidone was therefore higher than that recommended by the current SPC.

Indeed, an inevitable result of the fixed dose titration design used by Tran *et al* (which was consistent with

the data sheet current at the trial's inception) would be that a larger number of patients remained on 6mg than would happen if the current SPC was followed.

This conclusion was supported by current clinical practice whereby the current average daily dose of Risperdal for the treatment of schizophrenia was 4.4 – 4.8mg/day (repeat prescription data from HMSL – Nov 2001 to April 2002) and by the available contemporary published literature (Kasper, 1998; Taylor, 2001; Csernansky *et al*, 2002; Maudsley Guidelines, 2002; Conley and Mahmoud, 2001).

Furthermore, this limitation of Tran *et al* was acknowledged in Glick and Berg (2002), which stated '… risperidone was used in high doses up to 12mg/day, with a mean modal dose of 7.2mg (which is almost twice the recommended dose). This might have led to more extrapyramidal EPS side effects and worse compliance in the Risperdal group'. Janssen-Cilag noted that Berg gave his affiliation as Lilly Research Laboratories.

Janssen-Cilag stated that there was a failure to acknowledge results from more recently published comparative trials and present the totality of data in a balanced way. Since the Tran *et al* was published, a major head-to-head comparative trial had been completed and published (Conley and Mahmoud). This was the first randomised, controlled, double-blind, head-to-head trial of Risperdal and olanzapine using clinically relevant doses (in accordance with the current SPCs for both products). In this study patients were randomised to receive flexible doses of Risperdal (2-6mg/day) or olanzapine (5-20mg/day) for 8 weeks. Analysis of the data on 377 patients from 39 sites showed the mean modal doses employed were 4.8mg/day for Risperdal and 12.4mg/day for olanzapine. With respect to efficacy based on comparisons of the total PANSS, (the same primary efficacy variable used in Tran *et al* study) risperidone and olanzapine were equally efficacious. In addition to efficacy, the severity of EPS was reduced over the course of the study with no significant differences between the two treatment groups. It was important to note that this was a large, controlled, head-to-head study that had been published in the prestigious American Journal of Psychiatry. It had been exposed to rigorous peer review and therefore must be considered as valid as Tran *et al*. Similar results were seen in an additional smaller study (Ho *et al*, 1999).

The results of Conley and Mahmoud and of Ho *et al*, particularly with regard to comparative efficacy and EPS effects, must be considered when making any comparative claims between Risperdal and olanzapine.

Janssen-Cilag also noted that Glick and Berg stated within its discussion 'Our findings are consistent with current thinking that the drugs in this new generation of antipsychotics are equal, or superior, to conventional antipsychotics and are similar in efficacy to each other'. Glick and Berg also stated '… that although one atypical has some advantages over the other, no clear findings have emerged'. The limitations of Tran *et al* were discussed in some detail (as described above). Given the fact that one of the authors stated an affiliation to Lilly Research Laboratories, USA, this paper and its conclusions must have been known to Eli Lilly & Company even in advance of its publication.

According to the Code, information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication. The evidence as presented above indicated that Lilly had made claims and comparisons based on information which was not balanced, fair or up-to-date and did not reflect accurately the totality of the evidence. Janssen-Cilag therefore alleged a breach of Clause 7.2.

Janssen-Cilag acknowledged that in an earlier case (Case AUTH/1022/5/00) a claim of a superior EPS profile of olanzapine over risperidone by Lilly was ruled not to be in breach of the Code. However, Janssen-Cilag now believed that the current balance of data represented by, amongst other things, the publication of a second comparative double-blind controlled trial (Conley and Mahmoud), dosage audit data, the current SPC and the study published by Glick and Berg, that the Lilly position on this matter was no longer tenable.

RESPONSE

Lilly stated that it was widely accepted that the atypical antipsychotics differed from each other in their side effect profiles. In this respect Janssen-Cilag had acknowledged that in a previous case a claim of a superior EPS profile for olanzapine over risperidone made by Lilly was not ruled in breach of the Code.

Lilly contended that, although the claim was referenced to Tran *et al*, it was readily substantiated by numerous other data and was thus not in breach of the Code. The publication of the short term study, Conley and Mahmoud, had not altered the balance of the available literature and the claim was thus supported by an up-to-date evaluation of all the literature. Lilly also contended that the doses used in Tran *et al* were compatible with the SPCs for both products and thus there had been no breach of the Code in this respect either.

Lilly contended that data from pharmacovigilance sources demonstrated quite clearly that EPS was a much more prominent component of the side effect profile of risperidone than of olanzapine.

Data from the PEM studies conducted on risperidone (Mckay *et al* 1998) and olanzapine (Biswas *et al* 2001) showed that the rate of EPS observed with risperidone was higher than that observed with olanzapine. Lilly provided a table giving a comparison of ID1 values ≥ 2/1000 patient months in the PEM studies of risperidone and olanzapine with ≥ 10% excess of larger over smaller (Mckay *et al*, Biswas *et al*).

Data from the Medicines Control Agency's (MCA) AEGIs system showed that the rate of EPS observed with risperidone was higher than that observed with olanzapine. Lilly provided a table giving extracts from the drug analysis print (DAP) for risperidone and DAP for olanzapine. Lilly stated that these data

showed that spontaneous reports of EPS comprised almost twice as much of the risperidone side effect profile as they did for olanzapine.

Lilly contended that data from clinical trials demonstrated quite clearly that EPS was a more prominent component of the side effect profile of risperidone than of olanzapine. This was clearly the case in Tran *et al* and even the short term study by Conley and Mahmoud showed larger differences in EPS rating scale scores for olanzapine than for risperidone. More striking differences were observed in the naturalistic study by Gómez *et al*. The statistically significant safety findings were summarised in a table provided by Lilly.

Finally, Lilly pointed out that the argument about the relative merits of Tran *et al* and Conley and Mahmoud had been discussed above. The doses used by Tran *et al* remained compatible with the SPCs for both medicines but the duration of treatment in the study by Conley and Mahmoud was too short to allow its findings to be generalisable to a population with such a chronic disorder as schizophrenia.

In summary Lilly considered that it had shown that the claim was readily substantiated by numerous data and was thus not in breach of the Code. The publication of Conley and Mahmoud had not altered the balance of the available literature and the claim was thus supported by an up-to-date evaluation of all the literature as required by the Code. Lilly considered that it had shown that the doses used by Tran *et al* were compatible with the SPCs for both products as outlined above and thus there had been no breach of the Code in this respect either.

In relation to the allegation that the dosage regimen was not consistent with the current SPC or relevant to current clinical practice, Lilly stated that it should be noted that the argument about the relative merits of Tran *et al* and Conley and Mahmoud had been discussed above.

Lilly noted that the objection raised by Janssen-Cilag related to the compatibility of the dose regimens used in Tran *et al* over 6 months with the text of the current SPCs for both olanzapine and risperidone. In fact, the mean doses used were not incompatible with the SPCs for either of the products (mean dose of risperidone used in Tran *et al* was 7.2mg: SPC for risperidone : Adults 'The usual effective dose is 4 to 8mg/day', and mean dose of Zyprexa used in Tran *et al* was 17.2mg : SPC for Zyprexa : Adults 'Daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg daily'). Furthermore, for both medicines the titration process resulted in doses towards the top of the recommended range indicating that the dose titration process was fair to both products. Clause 7 of the Code did not say that doses of medicines used in clinical trials should exactly prefigure the doses eventually used in routine clinical practice, but Clause 3 of the Code did say that claims (in this case doses) should be compatible with the SPC, which both doses were. Thus Lilly contended that there had been no breach of the Code in relation to doses.

In relation to the allegation that there had been a failure to acknowledge results from more recently published comparative trials and present the totality of the data in a balanced way, Lilly stated that it had already addressed this issue above in relation to totality of the data and substantiation of the EPS claim. Conley and Mahmoud did not alter the balance of the data. Lilly was of the opinion that the claim was adequately substantiated by the data presented in this response and thus no breach of the Code had occurred.

Lilly noted that Janssen-Cilag had re-stated its general claims about Conley and Mahmoud, pointing out that it was another major head-to-head comparative trial which had been completed and published since Tran *et al*. Janssen-Cilag wrongly alleged that Conley and Mahmoud was the first randomised, controlled, double-blind, head-to-head trial of Risperdal and olanzapine using clinically relevant doses (in accordance with the current SPCs for both products) but elsewhere in its allegations it accepted that Tran *et al* used doses which were compatible with the data sheets in force at the time the study was designed. Janssen-Cilag re-stated its assertion that in Conley and Mahmoud patients were randomised to receive flexible doses of Risperdal (2-6mg/day) or olanzapine (5-20mg/day) for 8 weeks. Analysis of the data on 377 patients from 39 sites (two sites were withdrawn from the analysis) showed the mean modal doses used were 4.8mg/day for Risperdal and 12.4mg/day for olanzapine. Janssen-Cilag asserted irrelevantly that with respect to efficacy based on comparisons of the total PANSS, (the same primary efficacy variable used in Tran *et al*) risperidone and olanzapine were equally efficacious and more relevantly, that in addition to efficacy, the severity of EPS was reduced over the course of the study with no significant differences between the two treatment groups.

In response Lilly noted that Conley and Mahmoud had been subjected to peer review and was a valid piece of research; however Lilly contended that it was not true to say that the two treatments were shown to be equally effective or equally well tolerated.

Lilly noted that in Conley and Mahmoud, for risperidone, the week 8 population was 134 compared to 183 at baseline (ITT), 175 endpoint and 188 enrolled and for olanzapine, the 8 week population was 144 compared to 186 at baseline (ITT), 181 at endpoint and 189 enrolled for olanzapine. Thus more patients remained on treatment with olanzapine at 8 weeks than on risperidone. This might have reflected either better efficacy or better tolerability of olanzapine compared to risperidone. Reduction in EPS was greater on olanzapine than on risperidone at endpoint for total EPS and all sub-scale EPS measures, and more patients on risperidone than olanzapine required anti-Parkinsonian treatment. Thus, although not statistically significant in this study, the data consistently showed differences in favour of olanzapine over risperidone regarding EPS even though the study only lasted for 8 weeks and used low doses of risperidone.

Lilly noted that Ho *et al* was statistically flawed. The study was too small to show statistically significant differences in the side effect profiles of the medicines and the study design was inadequate because the study was not double-blind.

In addition to Tran *et al* which showed a significant difference between olanzapine and risperidone in EPS, Lilly also drew attention to the results of the PEM studies carried out on risperidone and olanzapine (Biswas *et al*, Mckay *et al*). A comparison of the ID1 values (rate of events per 1000 patient treatment months in the first month on treatment) highlighted EPS as an issue with risperidone. Furthermore the rate of EPS remained higher with risperidone in subsequent months (ID2 values).

Lilly provided a table giving a comparison of ID1 values ≥ 2/1000 patient months in the PEM studies of risperidone and olanzapine with ≥ 10% excess of larger over smaller (Mckay *et al*, Biswas *et al*).

Lilly contended that the balance of the data supported the claim and thus it did not breach Clause 7.2 of the Code.

PANEL RULING

The Panel noted its comments in point 1 above with regard to the trials which had compared olanzapine and risperidone and again considered that the balance of the data lay in the results of Tran *et al* and Conley and Mahmoud. The Panel noted that in point 1 above it had not considered that the doses used in the studies were inconsistent with the current Risperdal SPC.

The claim at issue related to extrapyramidal symptoms. The Risperdal SPC advised prescribers that doses above 10mg/day might increase the risk of EPS. The claim was referenced to Tran *et al* which had used risperidone in the dose range of 4-12mg. It was not possible to determine from the published paper how many patients, if any, had received more than 10mg risperidone daily. The mean modal dose was 7.2mg ± 2.7mg. Tran *et al* reported that significantly fewer olanzapine-treated patients experienced treatment-emergent EPS than risperidone-treated patients.

Conley and Mahmoud had used risperidone in daily doses of 2-6mg which reflected the downward revision in the dosage recommendations for Risperdal which had come into effect since the publication of Tran *et al*. According to the study design no patient in the Conley and Mahmoud study could have received a dose of risperidone in excess of 10mg/daily. The mean modal dose was 4.8mg. Conley and Mahmoud reported that similar proportions of the risperidone and olanzapine groups reported EPS (24% and 20% respectively, p=0.44).

The Panel considered that an up-to-date evaluation of all the evidence regarding EPS had to take into account the results of Conley and Mahmoud. Although in an earlier Zyprexa case (Case AUTH/1022/5/00) a claim for 'significantly lower EPS than risperidone' based on the Tran *et al* data had been ruled not to be in breach of the Code this was before the publication of Conley and Mahmoud. The Panel considered that the claim now at issue no longer reflected all of the available evidence and so was misleading in that regard. A breach of Clause 7.2 was ruled.

3 Claim 'Significant reduction in relapse rates compared to risperidone'

This claim appeared in the leavepiece ref ZY1099 above a graph referenced to Tran *et al* which compared the cumulative percentage of patients maintaining a response with Zyprexa and risperidone. The starting doses for Zyprexa in Tran *et al* and the Zyprexa SPC were stated.

COMPLAINT

Janssen-Cilag stated that the graph, and the statement 'Significant reduction in relapse rates compared to risperidone' purported to show superiority of olanzapine over risperidone. This was referenced to Tran *et al*. As previously stated the dose ranges used in this trial were 10-20mg for olanzapine and 2-12mg for risperidone. The mean modal doses were 17.2mg for olanzapine and 7.2mg for risperidone. The Risperdal SPC clearly stated, 'Most patients will benefit from daily doses between 4-6mg/day although in some, an optimal response may be obtained at a lower dose'. The mean modal dose used for risperidone in this study was therefore higher than that recommended by the SPC. The graph acknowledged that the doses used were not consistent with those recommended by the olanzapine SPC, but failed to acknowledge the same for Risperdal. Such doses were important to study interpretation as, in addition to reducing tolerability, excessive doses might actually reduce efficacy.

The surrogate measure of relapse used in the claim at issue, referenced to Tran *et al*, was an estimate of the percentage of patients who had a response at week 8 and who maintained that response. It was interesting to note that the more recent publication by Glick and Berg concluded that 'Using the measures of study discontinuation, relapse and non-compliance, in one trial the atypical antipsychotic olanzapine was superior to haloperidol, while in a second trial (Tran *et al*) there were no differences between olanzapine and risperidone'.

A recent editorial concluded that there was now unique evidence to support the role of Risperdal in the prevention of relapse and that such support was not available for other atypical antipsychotics. It was stated 'There is little reliable evidence of long-term efficacy of other atypical drugs. Studies of the use of the other atypical drugs for the prevention of relapse are therefore required. Direct comparisons of atypical drugs are also needed' (Geddes 2002).

Janssen-Cilag therefore alleged that the claim was misleading and unrepresentative of the totality of the currently available data and in breach of Clause 7.2 of the Code.

RESPONSE

Lilly noted that Janssen-Cilag believed that its claim that use of olanzapine resulted in 'significant reduction in relapse rates compared to risperidone' was misleading and unrepresentative of the totality of the currently available data resulting in a breach of Clause 7.2 of the Code; however no evidence had been produced to support this assertion other than second-hand opinion from the review literature.

Lilly noted that Janssen-Cilag took issue with the dose regimens used in Tran *et al* but Lilly had addressed this point elsewhere in its response.

Lilly noted that the published data on relapse rates provided the following results:

Olanzapine versus risperidone. The relapse rate in Tran *et al* which compared olanzapine with risperidone was estimated using Kaplan-Meier survival statistics. The results showed a highly statistically significant difference in favour of olanzapine (p=0.001). The results were illustrated in a figure taken from the paper which was provided by Lilly.

Olanzapine and risperidone versus placebo or haloperidol. There were published reports giving relapse rates for olanzapine and risperidone compared to haloperidol or placebo. Csernansky *et al* compared risperidone to haloperidol giving both medicines at SPC compatible doses. The main results were: discontinued treatment (non-relapse): risperidone 44.1% versus haloperidol 52.7%; relapsed: risperidone 25.4% versus haloperidol 39.9%; not relapsed and still on treatment: risperidone 30.5% versus haloperidol 7.5%; risk of relapse (Kaplan-Meier estimate): risperidone 34% versus haloperidol 60%; median duration of treatment on risperidone was 12 months. Dellva *et al* (1997) compared olanzapine to placebo and an ineffective dose of olanzapine in the prevention of relapse. The one year relapse rates on olanzapine (Kaplan-Meier estimates) for the two comparisons were 22% for the comparison versus placebo (North American Study) and 13% for olanzapine versus an ineffective dose of olanzapine (international study). In addition Tran *et al* (1998) reported relapse data derived from studies in which olanzapine had been compared to haloperidol. In this study the estimated one year relapse rate on olanzapine (Kaplan-Meier estimate) was 19.7%. Thus the one year Kaplan-Meier estimate for relapse on risperidone was 34% but for relapse on olanzapine was variously 13%, 19.7% and 22%. These data supported the suggestion that patients with schizophrenia were less likely to relapse on olanzapine treatment than on risperidone treatment.

Olanzapine and risperidone continuation rates in PEM studies. The continuation rates in the published PEM studies were 80% at six months on olanzapine and 76% at six months on risperidone (Biswas *et al*, Mckay *et al*).

Rate calculated for use in health economic assessments. The relapse rates and dropout rates used in health economic evaluations of antipsychotic drugs were set out in a table provided by Lilly (Almond *et al* 2000).

In summary, Lilly considered that the opinions cited by Janssen-Cilag from the review literature did not represent the results of the published studies correctly and that the published results did support its claim of a lower relapse rate on olanzapine than on risperidone. As a result no breach of the Code had occurred.

PANEL RULING

The Panel noted that the claim 'Significant reduction in relapse rates compared to risperidone ' was referenced to Tran *et al*. The graph which immediately followed the claim, to illustrate the point, was also from Tran *et al* and depicted the cumulative percentage of patients maintaining a response for up to 200 days of treatment. The Panel noted that the Tran paper had not referred to relapse rates. The primary objective of the study was to evaluate the effectiveness and safety of olanzapine versus risperidone during double blind therapy. The maintenance of response as measured by Tran *et al* had only taken into account PANSS total score and CGI score. In this regard, the Panel noted that in a study which had specifically examined relapse rates in patients with schizophrenia, relapse was defined by any one of 5 parameters (Csernansky *et al*). In the Panel's view the study by Tran *et al* had not been designed to measure relapse rates; maintenance of response as defined by two parameters was not the same as prevention of relapse. The Panel considered that the claim did not accurately represent the findings of Tran *et al* and was misleading in that regard. A breach of Clause 7.2 was ruled.

4 Claims 'Helping to avoid distressing prolactin effects' and 'Switching to Zyprexa from risperidone can normalize prolactin levels in patients suffering from hyperprolactinaemia'

These claims appeared in leavepiece ref ZY1099 above a bar chart which depicted the mean prolactin level in patients entering on risperidone at baseline and then switched to Zyprexa for up to 3 weeks. The data was referenced to Kinon *et al*.

COMPLAINT

Janssen-Cilag stated that the two claims taken together as laid out in the leavepiece were clearly intended to imply that olanzapine had a significantly better prolactin mediated side effect profile than Risperdal. It was therefore alleged that the confusing representation of biochemical events as side effects was not fair or balanced.

Janssen-Cilag believed that given the layout of the piece most recipients, ie general practitioners who might not be as familiar with the effect of antipsychotics on prolactin levels, would assume that 'normalizing prolactin levels', as Lilly claimed olanzapine was capable of, meant that olanzapine had a significantly better prolactin-mediated side effect profile than risperidone. This was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels, which generally showed a poor correlation between raised plasma prolactin and clinical symptoms (Kleinberg *et al* 1999) and more importantly it was not reflective of the SPCs. The Zyprexa SPC stated that elevated plasma prolactin levels were very common, but associated clinical manifestations (eg gynaecomastia, galactorrhoea and breast enlargement) were rare. The Risperdal SPC did not quantify the clinical manifestations of increased prolactin levels.

Janssen-Cilag noted that essentially the same claim in a previous mailing to psychiatrists had been ruled in breach of Clause 7.2 (Case AUTH/1022/5/00), and therefore alleged a breach of Clause 22. Given that these claims were made in full knowledge of a

previous ruling it also believed a breach of Clause 2 should be considered.

Furthermore, the reference cited (Kinon *et al* 2000) was a poster derived from a published study, which stated in its discussion that it was neither designed to determine whether patients should be switched nor to determine the outcome of olanzapine versus prior antipsychotic. The poster specifically focused on the prolactin levels; however Janssen-Cilag noted that the original study was designed to determine optimal methods for switching to olanzapine. It investigated 4 different algorithms – 2 of which consisted of one week of placebo, one week of olanzapine therapy (5mg/day) and one week of olanzapine therapy (10mg/day). This regimen was not in line with the SPC for Zyprexa. The prolactin data was collapsed across all 4 switching groups. It was therefore not a fair comparison as half the patients had only been on the recommended dose of olanzapine for 1 week. The graph implied the majority of patients had received 3 weeks of olanzapine treatment, which evidently was not the case. Janssen-Cilag also noted there was no mention of the dose of Risperdal. This was of particular relevance given that the Risperdal SPC acknowledged increases in prolactin were dose dependent.

Janssen-Cilag alleged that the data presented from Kinon *et al* on prolactin levels was misleading and did not represent the data in a fair and balanced manner, in breach of Clause 7.2 of the Code.

RESPONSE

Lilly noted that biochemical results derived from clinical trials provided relevant information about the safety profile of medicines: it was for this reason that blood testing was done in clinical trials. Abnormalities in blood test results pointed to organ systems in which symptomatic side effects could be observed: thus, far from being misleading, reporting prolactin data was highly responsible. Furthermore, a recent leading article in the BMJ (Wieck 2002) argued that prolactin was an important neglected issue in medicine safety.

Lilly accepted that the design of Kinon *et al* included data on patients treated with olanzapine in a number of different ways; however this had no impact on the plasma prolactin levels present during the previous time when patients were receiving risperidone. Since all patients were switched from SPC compatible doses of risperidone and ended up on SPC compatible doses of olanzapine, the pooling of the biochemical data at baseline (risperidone value) and endpoint (olanzapine value) was reasonable and not misleading. The prolactin results reported by Kinon *et al* were based on measurements made during a multi-centre study designed to evaluate the efficacy and safety of switching patients from previous antipsychotic therapy to olanzapine. Data regarding serum prolactin was collected at baseline and at three weeks. Patients were switched from conventional antipsychotic therapy or risperidone to olanzapine and received from 1 to 3 weeks of olanzapine therapy. Baseline and endpoint serum prolactin levels were obtained in 176 out of 209 patients. The prevalence of hyperprolactinaemia (prolactin 18.66ng/ml [0.81 nmol/L], males; >24.19ng/ml [1.05nmol/L], females) among patients previously taking conventional antipsychotics (n=131) dropped from 36% to 13% after three weeks of study ($p<0.001$). For those previously on risperidone (n=45), the prevalence dropped from 76% to 22% after three weeks of the study ($p<0.001$). In those patients switched from risperidone to olanzapine, mean serum levels decreased from 48.8 ±38.14ng/ml [2.12 + 1.65 nmol/L] to 16.54 ± 17.51ng/ml [0.72 + 0.76nmol/L] ($p<0.001$) (Kinon 2000a). Lilly submitted that the conclusion of Kinon *et al* was entirely consistent with other data on the relative frequency of prolactin related side effects with olanzapine and risperidone. Conley and Mahmoud showed that abnormal prolactin levels were significantly more of an issue with risperidone than olanzapine ($p=0.001$).

Lilly also noted that several other studies supported the claim. Crawford *et al* reported the effects of olanzapine, haloperidol and placebo on serum prolactin concentrations from a clinical trial involving 335 patients with schizophrenia (Beasley *et al* 1996). Prolactin levels were measured at baseline and at weeks 2, 4 and 6 during the acute phase of the study. Patients were randomised to one of five treatment groups: a fixed dose range of olanzapine (olanzapine-low: 5 ±2.5mg daily, olanzapine-mid: 10 ±2.5mg daily, or olanzapine high 15 ±2.5mg daily), placebo, or haloperidol (15 ±5.0mg daily). Over 75% of patients in each group were male. Of the three hundred and thirty patients with measurements at baseline, 91% had a baseline prolactin level at or below the upper limit of normal (0.6nmol/L for males, 0.8nmol/L for females) and were therefore included in the prolactin analysis. At week two, 72% of haloperidol patients had prolactin elevations above the upper limit of normal (ULN) compared to 8% of patients taking placebo ($p<0.001$). In contrast, prolactin elevations (above ULN) with olanzapine were lower in magnitude and transient. At week two, 38% of the olanzapine high dose, 24% of the olanzapine mid dose, and 13% of the olanzapine low dose treatment groups exhibited a treatment emergent prolactin elevation, with a mean increase of 0.35, 0.52 and 0.61nmol/L respectively (for haloperidol the mean increase was 1.23nmol/L). Only at week two did the incidence of prolactin elevations with olanzapine-mid and high differ significantly from placebo. By treatment week six, all three olanzapine groups exhibited incidences of prolactin elevation that were comparable to placebo and were significantly less than observed with haloperidol. Thus the short time on olanzapine in Kinon *et al* would not have had any impact on the prolactin levels measured.

Similar results had also been reported by Esel *et al* (2001) in a six week study of twenty-nine male inpatients with schizophrenia which compared the effects of olanzapine and haloperidol on prolactin levels. After a two-week washout period, fifteen patients received a fixed dose of olanzapine (10mg/day) and fourteen patients received a fixed dose of haloperidol (10mg/day). A control group of fifteen age-matched healthy controls was also evaluated. Prolactin levels were measured in both patient groups at baseline and after the six week treatment period. Baseline prolactin levels were

comparable among all three groups. The haloperidol group showed a statistically significant increase in prolactin at endpoint compared to the olanzapine and control groups (haloperidol 30.3ng/ml [1.31nmol/L], olanzapine 15.3ng/ml [0.66nmol/L], and controls 13.9ng/ml [0.60nmol/L], p<0.001).

David *et al* (2000) reported the comparative effects of olanzapine, haloperidol and risperidone on prolactin levels in patients with schizophrenia or related psychoses participating in three double-blind, randomised clinical trials: study 1 was a six week acute trial comparing olanzapine 5-20mg/day (n=1336) and haloperidol 5-20mg/day (n=660), with a one year, open-label olanzapine extension for responders (Tollefson *et al* 1997); study 2 was a fifty-four week study comparing olanzapine 5-20mg/day (n=21), risperidone 4-10mg/day (n=21), and haloperidol 5-20mg/day (n=23) in early illness (Purdon *et al*); study 3 was a twenty-eight week study comparing olanzapine 10-20mg/day (n=172) and risperidone 4-12mg/day (n=167) (Tran *et al*). The mean baseline to endpoint elevations in prolactin were significantly greater with risperidone than with either olanzapine or haloperidol in study 2 and significantly greater than with olanzapine in study 3.

In addition, the results of the PEM studies carried out on olanzapine and risperidone (Biswas *et al* 2001, Mckay *et al*) showed that in routine clinical practice using routine clinical doses prolactin related side effects were a more prominent feature of the risperidone side effect profile that the olanzapine side effect profile.

A comparison of ID1 values ≥ 2/1000 patient months in the PEM studies of risperidone and olanzapine with ≥ 10% excess of larger over smaller (Mckay *et al*, Biswas *et al*) was provided. Lilly stated that thus the PEM study data confirmed that the presence of prolactin related side effects was only an issue with risperidone and was not seen at all frequently with olanzapine. This finding supported the claim made by Lilly about the prolactin related side effect profile of risperidone. Perhaps the SPC for risperidone should list galactorrhoea, menstrual disorders, impotence and ejaculation failure in relation to hyperprolacinaemia.

In addition the MCA's AEGIS system, DAPs for olanzapine and risperidone showed that in routine clinical practice using routine clinical doses prolactin related side effects were a more prominent feature of the risperidone side effect profile than the olanzapine side effect profile as collected by the yellow card system. Lilly provided extracts from DAP for risperidone (13/6/02) and DAP for olanzapine (11/6/02).

Lilly stated that it would be noted that sexual side effects and hyperprolactinaemia were less than half as common amongst MCA yellow card reports for olanzapine as for risperidone.

Thus Lilly believed that the claim was not unrepresentative of the published data, was based on an up-to-date evaluation of the available evidence and was not misleading. Thus there had been no breach of Clauses 2, 7.2 or 22 of the Code.

PANEL RULING

The Panel noted that the decreased propensity to be associated with serum prolactin increases might have important clinical consequences. Prolactin elevations might be associated with acute effects, such as galactorrhea, amenorrhea and decreased libido, and chronic effects such as pre-disposition to osteoporosis. In males, prolactin elevations had been linked specifically to diminished libido, impotence and sterility. One of the defining criteria for an atypical antipsychotic was the relative lack of persistent prolactinaemia (Crawford *et al*).

Trials comparing the effect of haloperidol, a typical antipsychotic, and olanzapine on prolactin levels showed that olanzapine treatment caused only mild elevations in serum prolactin levels compared to haloperidol thus establishing olanzapine as an atypical antipsychotic (Crawford *et al*, Esel *et al*). David *et al* examined the comparative effects on plasma prolactin levels of olanzapine, risperidone and haloperidol using data from three separate trials. The results suggested that olanzapine treatment resulted in smaller elevations in plasma prolactin (mean change 1-4ng/ml) than risperidone treatment (mean change 45-80ng/ml). The Panel considered that the balance of the evidence was that olanzapine did not raise serum prolactin as much as risperidone.

Tran *et al* demonstrated that the evidence of hyperprolactinaemia was statistically significantly lower in olanzapine-treated than risperidone-treated patients. Conley and Mahmoud reported that risk ratios for change were worse for risperidone than for olanzapine in relation to plasma prolactin levels.

The Panel noted that Kinon *et al* had evaluated the effect on serum prolactin levels of switching patients from conventional antipsychotics or risperidone (n=45) to olanzapine. The authors demonstrated that after 3 weeks prolactin levels in risperidone treated patients fell from 48.8ng/ml to 16.54ng/ml on switching to olanzapine (p<0.001). The abstract did not state what dose of risperidone patients had been taking before they were switched. In this regard the Panel noted the Risperdal SPC referred to a dose dependent increase in plasma prolactin. The results from Kinon *et al* had been depicted in the bar chart featured in the leavepiece. Patients had been switched to olanzapine in different ways such that some of the patients had been on olanzapine 10mg daily for the whole of the 3 weeks whereas others had had one week of placebo, one week of olanzapine 5mg and one week of olanzapine 10mg. The Panel noted that the Zyprexa SPC stated that the starting dose should be 10mg/daily. The dose could be subsequently adjusted on the basis of individual need to 5-20mg/daily; the routine therapeutic dose was 10mg/day. The Panel noted that whilst the heading to the bar chart referred to patients being 'switched to Zyprexa for up to 3 weeks' the claims at issue in combination with the immediate visual impression of the bar chart gave the overall impression that all patients who had been switched to Zyprexa had been on the medicine for three weeks which was not so. Those patients who had been changed over to olanzapine slowly had only been taking the medicine for the last two weeks of the study and for the first of

those two weeks they took a lower than recommended starting dose.

This information had not been made sufficiently clear in the bar chart. The Panel questioned the effect that this stepwise dosing would have on the plasma prolactin levels as measured after 3 weeks. Crawford *et al* had reported a dose-related increase in serum prolactin with olanzapine although David *et al* had shown no consistent dose response relationship. Nonetheless the Panel considered that the amount of information given in the bar chart with regard to dosing of olanzapine was not sufficient such as to allow the reader to understand how the switching of risperidone to olanzapine had happened. The bar chart was misleading in this regard. A breach of Clause 7.2 was ruled.

The Zyprexa SPC stated that although elevated prolactin levels were very common (>10%), associated clinical manifestations were rare. The Risperdal SPC stated that the product could induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations were listed but their incidence was not stated.

The Panel considered that the heading 'Helping to avoid distressing prolactin effects' together with the claim which referred to 'prolactin levels in patients suffering from hyperprolactinaemia' inferred that prolactin-mediated adverse events would be seen less often in Zyprexa-treated patients than in those taking risperidone. Conley and Mahmoud however had actively solicited reports of side effects potentially related to prolactin; symptoms were common, but differences between olanzapine treated patients and those receiving risperidone were not statistically significant.

The Panel considered that the page was misleading with respect to the differential clinical advantage of olanzapine versus risperidone with regard to their propensity to cause prolactin-mediated side effects. Prolactin-mediated side effects were included in the Zyprexa SPC. There was no data to show that Zyprexa caused these side effects less often than risperidone. The page was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that in Case AUTH/1022/5/00 it had considered that most readers would assume that a claim in a Zyprexa leavepiece for 'significantly fewer elevations of prolactin than risperidone ($p<0.001$)' meant that olanzapine had a significantly better prolactin-mediated side effect profile than risperidone. The Panel had considered that this was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the claims now before it in Case AUTH/1325/5/02 were not the same as that considered in Case AUTH/1022/5/00. The Panel considered that the overall message to prescribers was not sufficiently similar and thus the Panel did not consider that the claims at issue in Case AUTH/1325/5/02 were caught by the undertaking given in Case AUTH/1022/5/00 and so ruled no breach of Clauses 22 and 2.

5 Claim 'Poor compliance can contribute to relapse'

This claim appeared in the leavepiece ref ZY1099.

COMPLAINT

Janssen-Cilag stated that the first two pages of the leavepiece under the banner 'Zyprexa helping you build a lasting therapeutic relationship', were clearly designed to link symptom control, relapse and side effects. These sections were clearly separated on the piece from the page referred to above with the banner headline 'Helping to avoid distressing prolactin effects'.

Janssen-Cilag accepted that the statements 'Poor compliance can contribute to relapse' and 'Side effects may cause patients to discontinue treatment' were general and related to the totality of side effects. However, Janssen-Cilag considered that to focus specifically on sexual side effects without mention of other side effects, which undoubtedly would have an impact on compliance and relapse, was a selective and unbalanced presentation of the information.

Indeed, in the National Schizophrenia Fellowship (NSF) survey, referenced in the leavepiece, weight gain was rated more frequently (almost two in every three responders) whilst only one-third of patients experienced sexual side effects while on antipsychotic therapy. The survey stated that there was no significant difference between the type of medicine being taken and the reported severity of sexual side effects. Moreover, it stated that the side effect most likely to be rated 'very bad' by people in receipt of atypical antipsychotics was weight gain.

By misrepresenting the results of this survey Janssen-Cilag believed the reader would be deliberately misled into thinking that sexual side effects, rather than weight gain, were the major concern for patients and the main driver of non-compliance and relapse. Janssen-Cilag alleged a breach of Clause 7.2 of the Code.

RESPONSE

Lilly was surprised by the suggestion that it had misrepresented the NSF survey and was thus in breach of Clause 7.2 of the Code. Lilly had certainly used the survey to support a point about a particular type of side effect being relatively common, potentially distressing to patients, and a possible reason for poor compliance, but this was not a misrepresentation of the survey. Janssen-Cilag argued that any discussion of the side effects must encompass the whole spectrum of side effects but the Code did not require all side effects to be reported in any mention of side effects. The Code required any comparison to be fair and any claim made to be capable of substantiation. It was obviously absurd to suggest that all comparative pieces about side effects should discuss the whole side effect profile or that failure to do so might be a breach of Clause 7.2.

PANEL RULING

The Panel noted that the page now at issue preceded that considered in point 4 above. The page at issue

had a sub-heading of 'Poor compliance can contribute to relapse' followed by the first of four bullet points 'Side effects may cause patients to discontinue treatment'. The third bullet point stated that 'Over 1/3 of patients responding to a mental health survey experienced sexual side effects while on antipsychotic therapy' and the final bullet point stated 'Raised prolactin levels may be the cause of sexual dysfunction and other complications'. The Panel noted its discussion of the preceding page in point 4 above and considered that the two pages together implied that prolactin-medicated side effects were more common with risperidone which would in turn lead to more patients discontinuing therapy. The survey from the NSF, however, reported that loss of energy and weight gain were experienced by 63% and 62% of responders respectively compared to only 39% reporting sexual side effects.

The Panel noted that the page in question had linked general statements regarding poor compliance, side-effects and discontinuation of treatment specifically to prolactin-mediated side effects and not to the side effects profile in general. In the Panel's view there were some side effects which because of their nature or because they occurred much more frequently than sexual dysfunction, might cause a greater number of patients to discontinue treatment. The Panel considered that the page was misleading and ruled a breach of Clause 7.2 of the Code.

6 Medical information letter 'Zyprexa-Diabetes and Hyperglycaemia'

COMPLAINT

Janssen-Cilag alleged that a medical information letter, which had been sent in response to queries from health professionals about the effect of olanzapine on glucose and diabetes, did not adequately reflect, in a fair, balanced and up-to-date manner the ongoing debate in the medical literature regarding the association of atypical antipsychotics on glucose metabolism and diabetes.

Janssen-Cilag had alerted Lilly of its concerns and had been assured that the letter had been amended. However, despite the amendments, the same general conclusion remained that '… the accruing evidence is relevant to all antipsychotics'. Janssen-Cilag strongly disputed this remark, which it believed to be disparaging to Risperdal and accordingly alleged a breach of Clause 8.1.

There was no mention of glucose abnormalities or diabetes on the Risperdal SPC. However, Janssen-Cilag was aware that Lilly had been required to update its prescribing information to reflect its data. The Zyprexa SPC on this subject stated:

'Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.'

This statement had recently been amplified to prescribers by the MCA which circulated information as part of the Current Updates in Pharmacovigilance newsletter and concluded 'The product information for olanzapine recommends that in diabetics and patients with risk factors for diabetes mellitus, appropriate clinical and blood glucose monitoring is conducted'.

It was a requirement of medical information departments to provide accurate, balanced and scientifically valid non-promotional information. It was clear that this letter although apparently comprehensive to the casual observer did not meet these requirements. Janssen-Cilag believed the letter to be misleading, biased, and by implication deliberately disparaging to Risperdal. The Procrustean approach adopted by Lilly to the totality of the information in this area, and its continued minimization of serious, labelled adverse events through its medical information department, was a cause of great concern. Health professionals expected to receive unbiased, scientifically robust and objective information, particularly from a scientific department of a reputable pharmaceutical company. Failure to do so represented a clear breach of the Code and brought the industry into disrepute. Janssen-Cilag therefore alleged a breach of Clause 2.

RESPONSE

Lilly noted that the Code applied to medical information letters only in specific circumstances. The Code stated i) that they were not considered to be promotional: Clause 1.2 of the Code in defining promotion stated that it did not include: replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, including letters published in professional journals (but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature), ii) that replies intended for use in response to enquiries which were received on a regular basis might be drafted in advance provided that they were used only when they directly and solely related to the particular enquiry, and that such documents must not have the appearance of promotional material, iii) that companies must have a scientific service responsible for information and iv) the Code listed 'Guidelines on Standards for Medical Information Departments (Association of Information Officers in the Pharmaceutical Industry)' in its list of legislation, other codes and guidelines. For these reasons the medical information service at Lilly was organised quite separately from the marketing department and had its own procedures for reviewing and updating its materials on a regular basis in co-operation with Lilly's corporate medical information service based in the USA.

Lilly noted that Janssen-Cilag alleged that its medical information letter was disparaging to risperidone by implication. Lilly noted that Janssen-Cilag found the medical information letter apparently comprehensive and noted that Janssen-Cilag had not pointed out any way in which the letter was not comprehensive in its discussion of the extensive scientific literature

regarding diabetes, schizophrenia and antipsychotic medicines including olanzapine. Indeed in its current form, the letter included several new references to material which was supplied by Janssen-Cilag in its initial letter of complaint. It followed that Janssen-Cilag's allegation of a breach of Clause 8.1 of the Code (and thus Clause 2) rested only on the alleged slur on its product Risperdal implied by the phrase '… the accruing evidence is relevant to all antipsychotics'.

Lilly considered that the question of diabetes and schizophrenia was relevant to all antipsychotics. Just as some side effects (such as EPS or prolactin related events) were more of an issue with one medicine than with another, so diabetes might be more of an issue with one medicine than with another, but the accruing evidence was relevant to all, whether in a positive or a negative way. In this context Lilly noted the results of simple literature searches carried out on MedLine (PubMed) using the same format of '___ AND diabetes'. Schizophrenia AND diabetes 222 citations, Clozapine AND diabetes 51 citations, Chlorpromazine AND diabetes 47 citations, Olanzapine AND diabetes 47 citations, Haloperidol AND diabetes 38 citations, Risperidone AND diabetes 23 citations and Quetiapine AND diabetes 16 citations.

The results of these searches showed that there were publications in which diabetes was linked to all important antipsychotic drugs and that there was a substantial literature on schizophrenia and diabetes in general. Furthermore, a recent peer reviewed paper reporting on the prevalence of co-morbid diabetes in patients on various antipsychotic drugs (Sernyak *et al*, 2002) gave the results of logistic regression analysis of association between prescription of atypical and typical neuroleptic medication and presence of a diagnosis of co-morbid diabetes mellitus in patients with schizophrenia, by age.

Lilly stated that these results clearly showed that the odds ratio (or risk) of having co-morbid diabetes was of a similar magnitude for most atypical antipsychotic drugs in most age bands compared to the rate on typical antipsychotic drugs. Thus the issue of diabetes was as relevant for risperidone as it was for olanzapine.

In this context it was not disparaging to risperidone *per se* to state, in a thoroughly researched, lengthy scientific communication from a medical information department, that '… the accruing evidence is relevant to all antipsychotics'.

Lilly therefore rejected the suggestion that its medical information letter was in breach of Clause 8.1 of the Code or that its behaviour in issuing the letter was in breach of Clause 2.

PANEL RULING

The Panel noted that the letter had been supplied to it in the form of a document headed 'Zyprexa – Diabetes and Hyperglycaemia'. The letter would be sent from Medical Information. Clause 1.2 of the Code stated that the term promotion did not include replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Panel had first to decide whether or not the letter was subject to the Code. In terms of its content the letter related solely to the subject of the heading. The letter examined data from the olanzapine clinical trial database, post-marketing experience with olanzapine and gave a summary of the literature. In order to be exempt from the Code under Clause 1.2 the letter had to be accurate, not misleading and not promotional.

The Panel noted that the copies of the medical information letter provided by both Janssen-Cilag and Lilly stated:

'The following statement is included in the Zyprexa Summary of Product Characteristics.

Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

In view of the body of evidence presented above, this advice may be relevant for all patients receiving antipsychotics.'

Following a request for further information Janssen-Cilag confirmed that the final statement above had replaced the statement originally referred to in its complaint ie '…. the accruing evidence is relevant to all antipsychotics'. Although the letter supplied by Lilly had contained the final statement as above, the company responded citing '… the accruing evidence is relevant to all antipsychotics'. The Panel considered that its ruling must be made on the basis of the statement originally complained of and not on the basis of the revised statement. The Panel considered that the original statement, '… the accruing evidence is relevant to all antipsychotics', suggested that the statement which had been added to the Zyprexa SPC should be similarly added to the SPCs of all antipsychotics. This was disparaging of the other antipsychotics. Although the Panel accepted that the data had some relevance to other antipsychotics it was its view that the degree to which it applied might vary. Lilly had not submitted any data to show that the statement which now appeared in the Zyprexa SPC was wholly applicable to all other antipsychotics. The Panel considered that in this regard the letter was inaccurate and thus subject to the Code. The Panel considered that the letter was disparaging as alleged. A breach of Clause 8.1 of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 was regarded as a sign of particular censure and reserved for such use. The Panel did not consider that the medical information letter brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **27 May 2002**

Case completed **14 August 2002**

CASE AUTH/1327/5/02

SCHWARZ PHARMA v AVENTIS PHARMA

Telfast 120 leavepiece

Schwarz Pharma complained about a Telfast 120 (fexofenadine) leavepiece issued by Aventis Pharma. Schwarz considered that by implication, the claim 'The least expensive antihistamine – Telfast 120 compared to NeoClarityn, Clarityn, Xyzal or Zirtek', was a cost comparison of all once-daily non-sedating antihistamines. As such, this claim was not balanced as it omitted Schwarz's product Mizollen (mizolastin) which was the least expensive of this group. The omission meant that the claim was inaccurate, unfair and did not reflect the current pricing status of once-daily non-sedating antihistamines. Schwarz alleged that the claim was misleading and in breach of the Code.

The Panel considered that although the comparators were listed, the basis of selecting the products had not been made clear. According to Aventis' submission the basis was related to market share. A reader might assume that it was a cost comparison of all once-daily non-sedating antihistamines. The Panel considered that the claim was misleading. A breach of the Code was ruled.

Schwarz Pharma Limited complained about a Telfast 120 (fexofenadine) leavepiece (ref TEL 1221201) issued by Aventis Pharma Ltd.

COMPLAINT

Schwarz Pharma drew attention to a claim 'The least expensive antihistamine – Telfast 120 compared to NeoClarityn, Clarityn, Xyzal or Zirtek'. It stated that the implication of the included comparators was a cost comparison of once-daily non-sedating antihistamines. As such, this claim was not balanced as it omitted Schwarz's product Mizollen (mizolastin), a once-daily non-sedating antihistamine, which was the least expensive of this group, priced at £6.20. Schwarz alleged that the claim was inaccurate and not a fair or balanced representation of this group of antihistamines, despite listing the comparators.

In intercompany correspondence, Aventis stated that the five medicines compared represented 83% cash market share of all antihistamines, referenced to IMS Dataview CRCPU, MAT11/01. At this point in time, Xyzal had MAT sales of only £42,100 compared to Mizollen's cash sales of £912,200. Additional comparison extended to include all antihistamines demonstrated cash sales for Piriton (less expensive than Telfast 120) of £5,477,700 and for Semprex of £530,600. It therefore, seemed to be reasonable that the antihistamines being compared were of the once-daily non-sedating group.

Schwarz alleged that the omission of Mizollen in the cost comparison meant that it was inaccurate, unfair and did not reflect the current pricing status of once-daily non-sedating antihistamines; it was misleading and in breach of Clause 7.2 of the Code.

This issue concerned Schwarz as the market was of a seasonal nature. Claims related to cost had a significant influence on the development of primary care formularies. Schwarz had had feedback that potential prescribers were under the impression that Telfast 120 was the 'least expensive' antihistamine. It was with these factors in mind that it requested Aventis' co-operation in withdrawing this claim from promotional material and activities as a matter of urgency.

Schwarz stated that in intercompany correspondence Aventis had acknowledged the price change of Mizollen since its material was produced, and the need to reflect this in forthcoming pieces. Schwarz stated that as there had been such a change, the claim currently made by Aventis was inaccurate, even to its own acknowledgement. With all these points in mind, Schwarz considered that a formal complaint was now justified as this misleading claim continued, without it possessing an assurance that it would be withdrawn immediately to ensure balanced material was available for the seasonal market.

RESPONSE

Aventis Pharma stated that the comparators for the five drugs represented 83% cash market share of all antihistamines prescribed (Source: IMS Dataview CRCPU, MAT 11/01) and constituted a suitable comparative group.

The cash market share for the once-daily antihistamines up to the end of the calendar year 2001 (Source IMS Dataview CRCPU R6A Cash Cal year 12/01) was as follows: Clarityn – 38%; Zirtek – 31%; Telfast – 8%; NeoClarityn – 5.9% and Mizollen – 1.1%. However these figures were annual, and Aventis noted that Xyzal was launched in October 2001 in anticipation of the patent expiry of Zirtek in February 2002. If Aventis reviewed the cash market share data for year to date in 2002 (Source IMS Dataview CRCPU R6A Cash year to date 2002), this was as follows: Clarityn – 16.4%; generic cetirizine – 16.3%; NeoClarityn – 16.1%; Zirtek – 15.4%; Telfast – 8.6%; Xyzal – 1.5% and Mizollen – 0.8%.

Aventis therefore re-iterated that the comparators defined in the promotional piece constituted a suitable comparator group.

Aventis stated that Schwarz referred to its letter dated 22 May 2002, where it made reference to the need to reflect changes in price in forthcoming items. Aventis clarified that this related to the difference in price between Clarityn tablets (which had been discontinued) and Clarityn syrup (still in production, and more expensive per month than the tablet form). Both formulations of Clarityn were more expensive than Telfast, and the promotional item therefore remained accurate.

PANEL RULING

The claim at issue, referenced to MIMS, November

2001, appeared beneath a claim 'If cost is important, Telfast deals with it fast'.

The Panel noted that whilst it was not necessarily unreasonable to compare the costs of a selection of products, an important factor was the basis of the comparison. This should be fair, unambiguous and should be made clear to readers. Another factor was the number of available products. Such cost comparisons had to be accurate not only when the item was produced but also whilst the item was used.

At the time the leavepiece was produced Mizollen cost £8.55 for 30 tablets which was more expensive than Telfast 120 at £7.40. The lower price of £6.20 was given in MIMS, January 2002. Clarityn tablets were not listed in MIMS, November 2001. Clarityn syrup cost £7.57 for 100ml (to be given at 10ml per day).

The Panel considered that the basis of selecting the products had not been made clear. According to Aventis' submission the basis was related to market share. Although the leavepiece listed the comparators, the basis of the comparison was unclear and the claim was thus misleading. A reader might assume that it was a cost comparison of all once-daily non-sedating antihistamines. The Panel ruled a breach of Clause 7.2 of the Code.

The claim at issue was followed by a comparison of the savings when changing patients from Telfast 120 to NeoClarityn/Clarityn, Zirtek and Xyzal. The Panel noted the difference in the cost of Clarityn tablets and the cost of Clarityn syrup. The comparison with the cost of Telfast was not entirely accurate as the leavepiece did not specify the Clarityn presentation. The savings would be larger with Clarityn syrup than with Clarityn tablets. It requested its views be drawn to Aventis' attention.

Complaint received **29 May 2002**

Case completed **15 July 2002**

CASE AUTH/1329/6/02

GLAXOSMITHKLINE CONSUMER HEALTHCARE v PHARMACIA

Nicorette Patch journal advertisement

GlaxoSmithKline Consumer Healthcare complained about a journal advertisement for Nicorette Patch (transdermal nicotine) issued by Pharmacia. The advertisement featured the claim 'For patients who want to give up smoking, not their sleep' above a photograph of a woman sleeping in a bed beneath which was a figure representing a cigarette. Text read '… It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers don't smoke while they sleep. In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance. So help them beat cigarettes all day – and then look forward to a comfortable night's sleep – prescribe Nicorette 16 hour Patch'. Nicorette pack shots for 5, 10 and 15mg patches appeared in the left-hand corner and the Nicorette logo and the claim '15mg patch for 16 hr use' appeared in the bottom right-hand corner.

GlaxoSmithKline Consumer Healthcare stated that the licensed name for the product being advertised, Nicorette Patch 15mg, should appear unambiguously on the advertisement. It was important that it was clear which of the various Nicorette formulations was being promoted. The current brand name logo gave the impression that 'Nicorette' was the brand name. Further below was the claim '15mg patch for 16hr use'. This was not an acceptable format for displaying the latter half of the brand name as it was being used as part of a promotional claim. GlaxoSmithKline Consumer Healthcare alleged that the reference to '– prescribe Nicorette 16 hour Patch' was misleading as the correct brand name had a number in it (5, 10 or 15) relating to the mg strength of the product, not to duration of use.

The Panel did not accept that reference to 'Nicorette', 'Nicorette 16 hour patch' or 'prescribe Nicorette 16 hour patch' was misleading about the brand name as alleged. It was clear as to which formulation of Nicorette was being promoted. No breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare considered that the claims 'For patients who want to give up smoking, not their sleep' and '… by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – …' would lead the reader to believe that 24 hour patches would disturb patients' sleep, whereas the use of a 16 hour patch would parallel smoking habit by not being used at night and therefore would mean that the patient slept well. Sleep disturbance, due to nicotine withdrawal, was, however, part and parcel of quitting smoking; a patch which continued to supply nicotine during sleep might be more likely to alleviate this withdrawal symptom than one which did not. There was evidence showing the beneficial effect of a 24 hour patch on sleep disturbance. (Wetter *et al* 1995, Gourley, *et al* 1999). GlaxoSmithKline Consumer Healthcare alleged that the claims and comparisons were misleading.

The Panel considered that most readers would gain the impression that patients using the Nicorette patch would not suffer sleep disturbance at all.

Although Nicorette would not result in night-time nicotine dosing which in itself was associated with sleep disturbance, it would not avoid the sleep disturbance caused by lack of nicotine. The Panel considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better, while using Nicorette as opposed to other nicotine patches. Breaches of the Code were ruled.

GlaxoSmithKline Consumer Healthcare alleged that, contrary to the claim 'It's the only patch designed to mimic your patient's regular smoking pattern …', the patch did not mimic smoking pattern; it was not 'as required' as cigarettes were, it did not pulse nicotine intake as smoking did nor did it deliver nicotine levels anywhere near those of a cigarette. It was not the only daytime-only patch; NiQuitin CQ patches could also be removed at night.

The Panel considered that the claim 'It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers do not smoke while they sleep' was sufficiently clear; the Nicorette patch was designed to be worn for 16 hours within a 24 hour period. The claim was not misleading as alleged; no breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare alleged that 'useful' in the claim '… useful as smokers don't smoke while they sleep' implied a clinical benefit of taking the patch off at night, which was not supportable. On the contrary, there was good justification for using a 24-hour patch to minimise morning craving resulting from prolonged overnight abstinence.

The Panel considered that its ruling above was relevant here and that the claim was sufficiently clear; useful had been explained in the preceding part of the sentence. The Panel did not consider the term 'useful' misleading as alleged. No breaches of the Code were ruled.

GlaxoSmithKline Consumer Healthcare alleged that the claim 'In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance' was misleading as it was based on a presumption that nicotine withdrawal (including placebo patch) did not cause sleep disturbance, whereas it was a well recognised symptom. In this situation, being equivalent to placebo was likely to mean that sleep was disturbed and this was not made clear. The references cited in support of this claim did not support the contention that Nicorette Patches used at UK licensed dosages did not cause sleep disturbance.

The Panel noted that the claim, within the context of the advertisement as a whole, gave the impression that a patient on the Nicorette patch would not experience sleep disturbance and that was not necessarily so. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare noted the claim '… and then look forward to a comfortable night's sleep –' and stated that it was not aware of data showing no sleep disturbance on Nicorette Patch. As discussed above 'the same as placebo' did not necessarily equate to a comfortable night's sleep. If a patient awoke three times in the night from nicotine withdrawal, being equivalent to this did not constitute a comfortable night's sleep.

The Panel considered that its ruling above was relevant; the claim was misleading and not capable of substantiation as alleged. Breaches of the Code were ruled.

GlaxoSmithKline Consumer Healthcare complained about an advertisement for Nicorette Patch (transdermal nicotine) issued by Pharmacia Limited which appeared in the BMJ, 9 March 2002. The advertisement featured the claim 'For patients who want to give up smoking, not their sleep' above a photograph of a woman sleeping in a bed beneath which was a figure representing a cigarette. Text read '… It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers don't smoke while they sleep. In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance. So help them beat cigarettes all day – and then look forward to a comfortable night's sleep – prescribe Nicorette 16 hour Patch'. Nicorette pack shots for 5, 10 and 15mg patches appeared in the left-hand corner and the Nicorette logo and the claim '15mg patch for 16 hr use' appeared in the bottom right-hand corner.

GlaxoSmithKline Consumer Healthcare marketed 24 hour nicotine transdermal patches – NiQuitin CQ.

1 Brand name

COMPLAINT

GlaxoSmithKline Consumer Healthcare stated that according to the summary of product characteristics (SPC) the licensed name for the product being advertised was Nicorette Patch 15mg. This was what should appear unambiguously on the promotional material. The Nicorette range had various formulations, each with their own efficacy and safety profiles. It was important that it was clear to the reader which formulation was being promoted. The current brand name logo gave the impression that 'Nicorette' was the brand name; 'Nicorette' was a large bold logo, with the generic name below. Further below this was the claim '15mg patch for 16hr use'. This was not an acceptable format for displaying the latter half of the brand name as it was being used as part of a promotional claim.

In the body of the text there was reference to Nicorette 16 hour Patch, the capitalisation of the P confusingly making it look like it was the brand name. The prescribing information was entitled Nicorette Patch, but to be correct should be Nicorette Patch 5mg, 10mg and 15mg.

The reference to '– prescribe Nicorette 16 hour Patch' was not the brand name and was potentially confusing for prescribers and dispensers as the correct brand name had a number in it (5, 10 or 15) relating to

the mg strength of the product, not to duration of use. This was alleged to be misleading in breach of Clause 7.2.

RESPONSE

Pharmacia did not believe that the use of the brand name and strength as 'Nicorette 15mg patch for 16 hr use' or 'Nicorette Patch' was misleading and therefore there was no breach of Clause 7.2 of the Code. There would be no confusion as to which formulation of Nicorette was being promoted as the word patch was placed adjacent or next to each use of 'Nicorette' throughout this piece. In addition, the statement 'Nicorette 15mg patch for 16 hr use' appeared in the right-hand corner in large, prominent bold letters.

The Nicorette 15mg 16 hour patch, in common with all nicotine transdermal patches, was part of a treatment regimen that included a weaning phase when progressively lower strength patches were used (10mg and 5mg patches). All three strengths of the Nicorette 16 hour patch, not just the 15mg strength, could be prescribed by doctors. The prescribing information clearly stated the starting dose and treatment schedule. Therefore, this was not misleading and no breach of Clause 7.2 of the Code had occurred.

PANEL RULING

The Panel noted that there was no obligatory requirement in the Code to mention a product's brand name in an advertisement. Clause 4.2 of the Code required prescribing information to consist, *inter alia*, of the name of the medicine (which may be either a brand name or generic). Pack shots of Nicorette patch 5, 10 and 15mg patches appeared adjacent to the text. The daily dose was one patch delivering 15, 10 or 5mg Nicotine with application limited to 16 hours in a 24 hour period. The recommended treatment programme should occupy 3 months with 15mg patches for 8 weeks, 10mg patches for 2 weeks followed by 5mg patches for 2 weeks. It was clear that Nicorette Patch was being promoted. The Panel did not accept that reference to 'Nicorette', 'Nicorette 16 hour patch' or 'prescribe Nicorette 16 hour patch' was misleading about the brand name as alleged. It was clear as to which formulation of Nicorette was being promoted. No breach of Clause 7.2 was ruled.

2 Claims 'For patients who want to give up smoking, not their sleep'

'… by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – …'

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the advertisement led the reader to believe that 24 hour patches would disturb patients' sleep, whereas the use of a 16 hour patch would parallel smoking habit by not being used at night and therefore would mean that the patient slept well. This was not an up-to-date evaluation or reflective of the body of evidence and patently ignored the well recognised effect of tobacco withdrawal on sleeping pattern. Night-time wakenings were listed as a major sign of cigarette withdrawal in the report of the Tobacco Advisory Group of the Royal College of Physicians. Insomnia was included as a nicotine withdrawal sign in the Diagnostic and Statistical Manual of Mental Disorders. Therefore sleep disturbance was part and parcel of quitting smoking because it was due to lack of nicotine. A patch which continued to supply nicotine during sleep might be more likely to alleviate this withdrawal symptom than one which did not. There was evidence showing the beneficial effect of 24 hour patch on sleep disturbance. Wetter *et al* (1995) demonstrated objectively assessed sleep disturbance was increased by tobacco withdrawal and that 24 hour nicotine patch resulted in improvements. Gourley *et al* (1999) looking at adverse experiences on 24 hour transdermal nicotine supported this. The authors concluded that 'Sleep disturbance during therapy appeared to be primarily associated with tobacco withdrawal rather than with nicotine excess from treatment with transdermal nicotine'. GlaxoSmithKline alleged that the claims and comparisons were misleading in breach of Clauses 7.2 and 7.3.

RESPONSE

Pharmacia submitted that the claim reflected the available body of evidence and therefore was not in breach of Clause 7.2 of the Code nor was it a misleading comparison in breach of Clause 7.3 of the Code.

Withdrawal effects versus adverse side effects of nicotine replacement therapy

The advertisement clearly focused on a clinically relevant benefit of using Nicorette 16 hour Patch; the avoidance of sleep disturbance associated with nocturnal nicotine delivery. The text went on to explain that when compared to placebo, Nicorette 16 hour Patch had not been shown to cause sleep disturbance, and could be used to avoid nocturnal dosing of nicotine. It was the effect of nocturnal dosing of nicotine that was the subject of the advertisement which also could be associated with sleep disturbance and not the lack of nicotine.

The advertisement was not claiming that a patient would sleep well but that a more comfortable night's sleep was achievable with the Nicorette 16 hour Patch as there was no nocturnal nicotine dosing which could cause sleep disturbances.

Safety data from placebo-controlled studies on Nicorette 16 hour Patch

The effect of nicotine withdrawal on sleeping patterns could be captured in a placebo-controlled study of nicotine replacement therapy (NRT) since those subjects receiving the placebo did not receive nicotine. However, measurement of withdrawal effects would not always capture sleep disturbances unless specifically examined. Sleep disturbances (whether caused by nicotine withdrawal or a side effect of nocturnal nicotine) were likely to be recorded as side effects as all adverse events would be captured.

It had been shown that relative to placebo, Nicorette 16 hour Patch did not increase the rate of sleep disturbance. Sleep disturbance was not recorded as an undesirable effect in the Nicorette 16 hour Patch SPC. This had been demonstrated in 4 large placebo-controlled trials, Sachs *et al* (1993), Tønnesen *et al* (1991 and 1999) and Stapleton *et al* (1995). These trials showed that sleep disturbances were not reported more frequently in patients using an active 16 hour patch compared to placebo.

Safety data from placebo-controlled studies on 24 hour patches

In contrast, there was evidence that 24 hour nicotine transdermal patches were associated with an increased rate of sleep disturbance relative to placebo, an effect that was recognized as being due to nocturnal delivery.

Abnormal dreams and insomnia appeared in the NiQuitin CQ Clear SPC, as systemic effects found in clinical studies to occur at the rate of 17.3% (placebo 3.8%) and 12.3% (placebo 8.3%) respectively. A table summarizing the safety data of the key 24 hour patch studies regarding sleep disturbances was provided. All these studies showed a significant increase of sleep disturbances for patients on active 24 hour patch versus placebo.

Investigator observations from patch studies

Pharmacia did not accept the inference in the complaint that the difference between withdrawal effects resulting from a lack of nicotine and the side effects associated with nocturnal nicotine no longer existed and that only withdrawal effects were recognized. The two were different and would be understood by doctors as being different. The authors of some of the clinical studies referenced in this response, separately commented on withdrawal effects and side effects in their respective publications. For example, as noted in a review article on patches 'Much more common during smoking cessation are general systemic complaints, or continued tobacco withdrawal symptoms, unrelated to transdermal nicotine. It is important to differentiate these from true adverse effects, as patients are apt to blame the therapeutic intervention, rather than the withdrawal of tobacco, for their problems. Sleep disturbance, however, may be attributable to 24-hour nicotine therapy, as it is more common than during placebo therapy (20.4% v 7.5%).

'Use of transdermal nicotine therapy during waking hours only does not appear to cause this problem' (Gourlay 1994).

Furthermore, Stapleton (1995), used by GlaxoSmithKline Consumer Healthcare to support its complaint, stated 'Sleep disturbance is a recognized tobacco withdrawal symptom but may also occur as a systemic side effect of 24-hour transdermal nicotine dosage'.

Other studies

Wetter *et al* (1995) examined the effects on sleep of the Prostep (Lederle) nicotine 24 hour replacement patch and was quoted by GlaxoSmithKline Consumer Healthcare as demonstrating that the 24 hour patch might have a beneficial effect on sleep disturbance. This publication lacked essential information on basic sleep parameters and did not include a 16 hour patch. It appeared to have been published in isolation and the results had not been replicated to date.

In Gourlay *et al* (1999), quoted by GlaxoSmithKline Consumer Healthcare, subjects in a 24 hour transdermal nicotine replacement patch (Novartis patch) study (without a placebo arm) were allowed to remove their transdermal nicotine patch before sleep if they experienced sleep disturbance. This advice to subjects contradicted the study conclusion quoted that 'sleep disturbance during therapy appeared to be primarily associated with tobacco withdrawal rather than nicotine excess from treatment with transdermal nicotine'.

Other investigator comments

GlaxoSmithKline Consumer Healthcare's argument about the benefits of 24-hour nicotine delivery on sleep disturbance was contradicted by its own admission in that the NiQuitin CQ patches could also be removed at night but this was NOT the routine intended way to use 24-hour patches. Nor was it the way 24-hour patches were used in clinical studies of efficacy. The NiQuitin SPC was consistent with recommendations made in published literature, such as: stated by Mendelsohn and Richmond 1994 in their study of the NiQuitin 24 hour patch 'The most common systemic side effects with 24-hour patches are disturbed sleep (up to 30% of patients) and vivid dreams (up to 26% of patients). These do not appear to occur with the 16-hour patch. If they persist, the 24-hour patch may be removed at bedtime, or a lower strength patch can be used'.

Gourley (1994), on the pros and cons of transdermal nicotine therapy. 'Both 24-hour and 16-hour (taken off before bed) transdermal treatment regimens were effective in clinical trials. Sixteen-hour therapy avoids sleep disturbance caused by nocturnal nicotine absorption'.

'The different brands of transdermal nicotine planned for marketing in Australia all deliver nicotine at approximately the same rate. Therefore, smokers who complain of sleep disturbance during 24-hour therapy can simply be advised to remove their current brand of patch before sleep to see if the symptom resolves'.

Approved labelling

The labelling for NiQuitin CQ (and Nicoderm, the US brand name) advised that the patch might be removed before going to bed if desired. The reason for the removal of 24-hour patches at bedtime was to avoid nocturnal dosing of nicotine because of the adverse effect of sleep disturbances with these types of patches. This was confirmed by the United States Pack Labelling Information for Nicoderm (NiQuitin CQ) which stated: 'If you begin to have vivid dreams or other disruptions of your sleep while wearing the patch 24 hours, try taking the patch off at bedtime (after about 16 hours) and putting on a new one when you get up the next day'.

It was therefore evident that GlaxoSmithKline Consumer Healthcare accepted that its 24 hour patch

could cause vivid dreams and/or other sleep disturbances as a result of delivering nicotine during sleep.

Pharmacia stated that based on these sources of data presented it affirmed that Nicorette 16 hour patch avoided nocturnal nicotine dosing which was commonly associated with sleep disturbances.

PANEL RULING

The Panel noted that for patients giving up smoking sleep disturbance was a likely consequence of nicotine withdrawal. Several studies had shown that sleep disturbances were not reported more frequently in patients using an active 16 hour patch compared to placebo. It appeared therefore that although a 16 hour patch did not cause sleep disturbance *per se* it did not prevent the sleep disturbance which resulted from total nicotine withdrawal.

Sleep disturbance during smoking cessation could also be caused by night-time nicotine dosing if a patient used a 24-hour patch. The Panel noted Pharmacia's submission that it was this effect on sleep which was the subject of the advertisement and not the sleep disturbance caused by the lack of nicotine. In the Panel's view this had not been made sufficiently clear.

The Panel considered that most readers would gain the impression from the advertisement that patients using the Nicorette patch would not suffer sleep disturbance at all. One of the claims at issue 'For patients who want to give up smoking, not their sleep' was the headline to the advertisement and the picture was of a woman fast asleep in bed. Although Nicorette would not result in night-time nicotine dosing which in itself was associated with sleep disturbance, it would not avoid the sleep disturbance caused by lack of nicotine. The Panel considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better while using Nicorette as opposed to other nicotine patches. Breaches of Clauses 7.2 and 7.3 were ruled.

3 Claim 'It's the only patch designed to mimic your patient's regular smoking pattern …'

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the patch did not mimic smoking pattern; it was not 'as required' as cigarettes were, it did not pulse nicotine intake as smoking did nor did it deliver nicotine levels anywhere near those of a cigarette. It was not the only daytime-only patch; as stated in its SPC, NiQuitin CQ patches could also be removed at night.

Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Pharmacia stated that it was clear from the context of this advertisement that 'regular smoking pattern' was referring to the pattern of smoking during the day and not smoking while asleep. This was evident by the statement that followed the claim in question, 'useful as smokers don't smoke while they sleep'.

Nicorette 16 hour Patch was the only transdermal patch designed to be worn solely during the daytime and therefore not to deliver nicotine whilst the patient was asleep. The fact that the NiQuitin patch could also be removed at night was not relevant as it was designed to be worn for 24 hours and therefore to deliver nocturnal nicotine. This was recognised by The Tobacco Advisory Group of the Royal College of Physicians (2000) which noted: 'Some patches are designed to be worn for only 16 hours to avoid sleep-time nicotine dosing …'.

PANEL RULING

The Panel considered that the claim 'It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers do not smoke while they sleep' was sufficiently clear; the Nicorette patch was designed to be worn for 16 hours within a 24 hour period. Whilst the NiQuitin patch could be removed at night it was designed to be worn for 24 hours. The Panel noted GlaxoSmithKline Consumer Healthcare's submission regarding pulse nicotine intake and nicotine levels but on balance considered that it was sufficiently clear that the claim referred to when a patient would normally smoke; the pattern of daytime smoking. The claim was not misleading as alleged; no breach of Clauses 7.2 and 7.4 was ruled.

4 Claim '… useful as smokers don't smoke while they sleep.'

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that 'useful' implied a clinical benefit of taking the patch off at night, which was not supportable. On the contrary, there was good justification for using 24-hour patch to minimise morning craving resulting from prolonged overnight abstinence. Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Pharmacia did not believe this claim to be either misleading in breach of Clause 7.2 of the Code or incapable of substantiation in breach of Clause 7.4 of the Code. The word 'useful', in this context, was not intended to imply clinical benefit but to reflect the fact that smokers simply did not smoke whilst they were asleep.

PANEL RULING

The Panel considered that its ruling at point 3 above was relevant here. The Panel noted that the preceding part of the sentence specifically referred to 'avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance …'. The Panel considered that the claim was thus sufficiently clear; useful had been explained in the preceding part of the sentence. The Panel noted its ruling at point 2 above regarding the overall impression of the advertisement about nocturnal nicotine dosing and nicotine withdrawal. Nonetheless on this discrete point the Panel did not

consider the term 'useful' misleading as alleged. No breach of Clauses 7.2 and 7.4 were ruled.

5 Claim 'In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance'

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that this was misleading. The claim was based on a presumption that nicotine withdrawal (including placebo patch) did not cause sleep disturbance, whereas it was a well recognised symptom (see above). In this situation, being equivalent to placebo was likely to mean that sleep was disturbed and this was not made clear to the reader. Not being shown to make something worse was not the same as having been positively shown to make something better.

The papers cited by Pharmacia as references for this claim did not support the contention that Nicorette Patches used at UK licensed dosages did not cause sleep disturbance. Two of the papers used dosages outside the UK licence (Sachs *et al*, Stapleton *et al*). Stapleton reported that 'Those in the active group experienced significantly less sleep disturbance during the first week …. After this time there were no differences between the groups'. In discussing the withdrawal symptoms data, Tønneson stated that as the populations were not comparable at weeks 1 and 6, 'statistical analysis was not valid' and did not show any data for sleep disturbance.

Fagerström *et al* (1993) used a table to compare treatment effects of placebo, nicotine gum, nicotine patch and a combination of patch and gum. All subjects had increased sleeping difficulties compared to baseline ($p<0.01$ for placebo) and no statistically significant difference was found between treatments. So, although Nicorette was no different from placebo in this regard, this did not make it a benefit.

The claim was alleged to be misleading in breach of Clause 7.2 in that it was not made clear to the reader that sleep disturbance was a common consequence of nicotine withdrawal.

RESPONSE

Pharmacia referred to the summary of the safety data from placebo-controlled studies which clearly showed that Nicorette 16 hour Patches had not been associated with an increase in sleep disturbances. The claim did not imply no sleep disturbances but only that the use of the patch did not cause sleep disturbances.

GlaxoSmithKline Consumer Healthcare's assertion that being equivalent to placebo meant that sleep was disturbed was not supported by references. In clinical studies, sleep disturbances were not demonstrated by all or even the majority of smokers who quit. In clinical trials of 16 hour nicotine patches, sleep disturbances were seen in only up to 16% of patients on placebo. Pharmacia referred to its submission at point 2 above.

The reference to studies by Sachs *et al* and Stapleton *et al* that used Nicorette 15mg/16hour patch for longer than 8 weeks did not invalidate the conclusions that could be reached about adverse events. Both the placebo group and the active treatment group used the patch for the same length of time. It was more reasonable to assume that a longer duration biased the results against the Nicorette 16 hour Patch since there was more opportunity for adverse events to arise over the longer treatment period than during the shorter 8-week usage period approved for Nicorette 16 hour Patch in the UK.

PANEL RULING

The Panel considered its ruling at point 2 above was relevant here. The Panel did not accept Pharmacia's submission that the claim did not imply no sleep disturbances but only that use of the patch did not cause sleep disturbance. The Panel noted that sleep disturbance might be a consequence of nicotine withdrawal. The claim, within the context of the advertisement as a whole, gave the impression that a patient on the Nicorette patch would not experience sleep disturbance and that was not necessarily so. A breach of Clause 7.2 was ruled.

6 Claim '… and then look forward to a comfortable night's sleep –'

COMPLAINT

GlaxoSmithKline Consumer Healthcare was not aware of data showing no sleep disturbance on Nicorette Patch. As discussed above 'the same as placebo' did not necessarily equate to a comfortable night's sleep. If a patient awoke three times in the night from nicotine withdrawal, being equivalent to this did not constitute a comfortable night's sleep. Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Pharmacia did not believe this claim was either misleading in breach of Clause 7.2 of the Code or was incapable of substantiation in breach of Clause 7.4 of the Code. The advertisement was not claiming that there was no sleep disturbance when Nicorette 16 hour Patch was used but rather that a more comfortable night's sleep was achievable as there was no nocturnal nicotine dosing with its related side effect of sleep disturbance.

PANEL RULING

The Panel considered that its ruling at points 2 and 5 were relevant here. The claim was misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **7 June 2002**

Case completed **12 August 2002**

CHIEF PHARMACIST v SANOFI-SYNTHELABO

Arixtra advisory board meeting

A chief pharmacist complained on behalf of a trust medicine management group about a meeting organised by Sanofi-Synthelabo. The meeting was to discuss the health economics of Arixtra (fondaparinux) in thromboprophylaxis. The invitation to the meeting explained that Sanofi-Synthelabo had created a health economic model in relation to the use of Arixtra in the NHS. Such models were quite complex and the company was in the process of producing one that allowed the required data to be accessed more easily and which met health professionals' needs. To that end the company was arranging an advisory board of health professionals who had expressed an interest in this area. Invitees were told that they would be sent five clinical papers for review which would probably take them an hour to digest; in recognition of the time taken to prepare for and attend the meeting an honorarium of £400 plus travel expenses was offered.

The complainant alleged that the honorarium plus travelling expenses was an excessive payment and not in line with the Code regarding gifts and inducements. Neither was it considered that this amount could be classed as reasonable expenses.

The Panel noted Sanofi-Synthelabo's submission that the purpose of the meeting was to provide a simplified version of the health economic model. The Panel considered that the letter could have been clearer about the precise role of the invitees. The agenda indicated that during the three hour meeting there would be four presentations each lasting ten or fifteen minutes. A total of one hour was allowed for discussion and questions and answers. On balance the Panel decided that the overall arrangements for the meeting were not unreasonable. Given the pre-meeting reading and the agenda it was not inappropriate to pay an honorarium. The fee of £400 was not unreasonable given rates previously suggested by the BMA. In the Panel's view the honorarium was not a payment to attend a promotional meeting. It was a payment for advice. No breach of the Code was ruled. No breach of Clause 2 was also ruled.

A chief pharmacist complained on behalf of a trust medicine management group about a meeting organised by Sanofi-Synthelabo Limited.

The letter of invitation was headed 'Health Economics Advisory Board'. It thanked recipients for expressing an interest in Arixtra (fondaparinux) and in particular the cost and health economic implications of thromboprophylaxis and stated that based on the clinical trial results for Arixtra, the company had created a health economic model to allow the potential effects of Arixtra to be modelled in the context of the NHS. Such models were quite complex and therefore Sanofi-Synthelabo was in the process of producing a health economic presentation tool in order that the required data was more easily accessible. It hoped to produce a tool which retained the high level of credibility but which had sufficient ease of use to allow health professionals to readily access data. In order to ensure that the health economic presentation tool met health professionals' needs, Sanofi-Synthelabo was arranging an advisory board in May with health professionals who had expressed an interest in this area. To prepare for this meeting invitees were told that they would be sent five clinical papers for review which would probably take them an hour to digest. The letter stated that in recognition of the time taken to prepare for and attend the meeting, an honorarium of £400 plus travel expenses was offered.

COMPLAINT

The medicine management group alleged that the honorarium of £400 plus travelling expenses was an excessive payment and not in line with the Code regarding gifts and inducements. Neither was it considered that this amount could be classed as reasonable expenses.

In considering this matter Sanofi-Synthelabo was asked to respond in relation to the provisions of Clauses 18.1, 9.1 and 2 of the Code.

RESPONSE

Sanofi-Synthelabo submitted that the arrangements and materials for this meeting were appropriate and that the meeting was not in breach of the Code.

Sanofi-Synthelabo explained that venous thromboembolism (VTE) ie deep vein thrombosis (DVT) and pulmonary embolism (PE), remained a significant cause of morbidity and mortality, particularly in patients undergoing major surgery. Arixtra was the first approved member of a new class of anticoagulants (Factor Xa inhibitors). It was recently launched in the UK and offered significantly improved efficacy in preventing VTE in patients undergoing orthopaedic surgery of the lower limb compared with existing therapies. However, some health professionals and NHS budget holders had expressed concern over the potential effects on local budgets of recommending widespread use of Arixtra.

Following the publication of results from the international, pivotal phase III clinical trial programme for fondaparinux in 2001, and in response to the concerns raised by health professionals and budget holders, Sanofi-Synthelabo embarked on producing a health economic model to provide information on the clinical and cost effectiveness of Arixtra relevant to its future use in clinical practice in the UK and Ireland. To achieve this, Sanofi-Synthelabo worked closely with a widely respected academic unit to produce a health economic model which was subsequently validated by a broad range of health professionals and others with expertise in health economics and/or assessment of new medicines. The output of this process was a complex model and an extensive internal company report which summarised the methodology and results.

Sanofi-Synthelabo was currently submitting the results for publication in a peer-reviewed journal and producing a simplified version of the model which would allow the generalised UK results to be applied to local circumstances, thus supporting health professionals and budget holders in making informed decisions.

The intended purpose of the Advisory Board meeting was to identify the factors required to produce a simplified version of the health economics model. This would take the form of software known as a graphical user interface (GUI). In particular, Sanofi-Synthelabo wished to find out the most useful way to present the results of the health economic model to the medical community and considered that this would be best achieved by bringing together a group of relevant experts and practitioners who would be given background information on Arixtra studies and participate in a discussion on the development and content of the health economic model.

The specific topics to be covered were a brief review of the clinical development programme leading to the approval of Arixtra; and reviews of the internal health economic report, the validation process for the health economic model to date, the results of the health economic model and the proposed content of the GUI. A copy of the agenda was provided.

In order to achieve a representative cross-section of different specialities and geographical locations, the meeting was organised for 12 delegates. All advisers were identified for their relevance to this type of project. The senior medical adviser for Arixtra requested that the sales team nominated potential advisers with relevant expertise. Forty-seven names were submitted, including specialists in orthopaedic surgery and primary care, pharmacy managers, anticoagulation pharmacists, drug information pharmacists, NHS business managers and clinical services managers representing a range of individuals with an interest and expertise in the therapeutic area and in making decisions locally relating to drug formularies and budgets. The senior medical adviser selected 30 of these individuals to be invited to the meeting in the expectation that 50-60% would decline initially or would subsequently be unavailable on the day in question. The decision on who to invite rested solely with the senior medical adviser. Invitations, in the form of a personal letter, were sent from the senior medical adviser to each of 30 nominees.

There were eight attendees from England, Scotland and Ireland, these being a clinical pharmacologist, a senior lecturer in primary care, a health authority pharmaceutical adviser, three senior pharmacists and a procurement officer.

The meeting was chaired by a senior medical adviser of the company. The meeting was also attended by a medical education manager to the company and a medical education officer who was responsible for meeting logistics and travel arrangements. A member of the venous thrombosis specialist sales team also sat in on the meeting and took notes – this had been agreed as a training opportunity on the understanding that she took no active part in the meeting.

Sanofi-Synthelabo stated that the meeting was the first in a planned series of three Advisory Board meetings. A second Advisory Board meeting was planned for September 2002 to review the first draft of the GUI, and a third meeting, to approve the final version of the GUI, was planned for November 2002.

Since delegates travelled from as far afield as the West Midlands, the Channel Islands, Scotland and Ireland (details were provided), the meeting was held at a central venue and was scheduled to commence at 2pm in order to allow delegates to travel to and from the meeting in one day, thus avoiding the need to provide overnight accommodation. Since all but one of the delegates would have been travelling all morning to attend the meeting, lunch was provided prior to the meeting. The budgeted cost of the meeting for 12 was £1,417, inclusive of travel, meeting room, lunch and beverages. A full breakdown of the costs was provided.

Participants had spent at least one hour reading literature that Sanofi-Synthelabo had provided in preparation for the meeting, at least three hours (and up to 4.5 hours) at the meeting itself and, on average, spent at least four hours travelling to and from the meeting.

Although initial correspondence to advisers suggested about one hour's work was required prior to the meeting in the form of reading five published clinical papers (approximately 47 pages of text, excluding contents and reference lists), the binder of pre-meeting reading material that was sent to the advisers actually contained more than 275 pages (excluding contents and reference lists and appendices) of complex information to read and consider. Sanofi-Synthelabo submitted that this would certainly have taken substantially longer than the suggested one hour to read and digest.

Based on the overall amount of work required, Sanofi-Synthelabo believed the honorarium offered was in line with current consultancy rates or fees charged for professional services within the private sector and was, therefore, a reasonable amount to offer participants, and was certainly not excessive. This payment could not be perceived as either a gift or as an inducement to prescribe, supply, administer or recommend Arixtra.

Sanofi-Synthelabo submitted that it was clear that the purpose of the meeting was to provide appropriate information to a select group of health professionals in order to stimulate discussion and elicit expert advice on the health economic model. Sanofi-Synthelabo believed it was entirely reasonable that a pharmaceutical company should have access to well-informed experts with experience in a relevant field.

The meeting was set up and run by a senior medical adviser of the company. The letter of invitation clearly stated the nature and objectives of the meeting. The meeting was not promotional in nature but represented a legitimate exchange of scientific and health economic information between experts. No aspect of the arrangements for the meeting could be construed as providing an inducement to prescribe, supply, administer or recommend a particular medicine.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. The selection of attendees had to stand up to independent scrutiny and the arrangements had to comply with the Code. The impression created by invitations to advisory board meetings such as the meeting in question should be borne in mind; it should be sufficiently clear that the honorarium represented payment for professional advice and the participatory role and amount of work involved should be clear.

The Panel noted Sanofi-Synthelabo's submission that the purpose of the meeting was to provide a simplified version of the health economic model. The letter of invitation made reference to a health economic presentation tool and to pre-reading for the meeting which consisted of five clinical papers. There was little mention of the interactive nature of the meeting in the letter of invitation. The agenda indicated that during the three hour meeting there would be four presentations. These being: a summary of the trial data, a summary of the principles upon which the health economic model was based, an explanation of the validation steps and the health economics tool itself. Each of these four presentations lasted either ten or fifteen minutes. A total of one hour was allowed for discussion and questions and answers.

The meeting in question was one in a series of three. The Panel considered that it was difficult in such cases to determine precisely where the boundary lay. The letter could have been clearer about the precise role of the invitees, how much work would be involved and that the payment was for the invitees' contribution and participation. On balance the Panel decided that the overall arrangements for the meeting were not unreasonable. Given the pre-meeting reading and the agenda for the meeting it was not inappropriate to pay an honorarium. The fee of £400 was not unreasonable given rates previously suggested by the BMA. In the Panel's view the honorarium was not a payment to attend a promotional meeting. It was a payment for advice. No breach of Clause 18.1 of the Code was ruled. The Panel did not consider that Sanofi-Synthelabo had failed to maintain a high standard and no breach of Clause 9.1 of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **12 June 2002**

Case completed **25 July 2002**

CASES AUTH/1331/6/02 and AUTH/1332/6/02 *NO BREACH OF THE CODE*

CONSULTANT PSYCHIATRIST v JANSSEN-CILAG and SHIRE

Reminyl booklet

A consultant psychiatrist at a primary care NHS trust complained about a 'Questions and Answers' booklet on Reminyl (galantamine) issued by Janssen-Cilag and Shire. Reminyl was indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type.

The complainant was concerned about the question 'How quickly will Reminyl start to take effect?' and its answer 'You may notice an improvement in the first month of treatment, but in some patients this may take several months. You may notice no improvement but that does not mean that Reminyl isn't helping. It may be slowing down any worsening of your symptoms. The doctor will assess the level of symptoms and adjust the dose accordingly'.

The complainant noted that guidance issued by the National Institute for Clinical Excellence (NICE) stated 'A further assessment should be made, usually two to four months after reaching maintenance dose of the drug. Following this assessment the drug should be continued only where there has been an improvement or no deterioration in MMSE score, together with evidence of global improvement on the basis of behavioural and/or functional assessment'. The NICE guidance made the point that improvement must be demonstrated for the medicine to be continued. The complainant alleged that the answer to the question, 'How quickly will Reminyl start to take effect' was misleading and inaccurate.

The Panel noted the Reminyl summary of product characteristics (SPC) stated that maintenance treatment could be continued for as long as therapeutic benefit existed and that the clinical benefit of the medicine should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect was no longer present. The section at issue was not inconsistent with the SPC. It advised that doctors would assess symptoms and adjust the dose accordingly. The booklet clearly stated that Reminyl would not cure the disease.

The Panel noted that there was a difference between the product's SPC and the NICE guidance; this

appeared to have given rise to the complainant's concerns. In the Panel's view the slowing down in the rate of deterioration was consistent with the Reminyl SPC and in this regard considered that the booklet was not misleading and inaccurate as alleged. The Panel therefore ruled no breach of the Code.

A consultant psychiatrist at a Primary Care NHS Trust, complained about a booklet (ref 032/0105) on Reminyl (galantamine) entitled 'Questions and Answers' issued by Janssen-Cilag Limited and Shire Pharmaceuticals Limited.

According to its summary of product characteristics (SPC), Reminyl was indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type.

The complainant was concerned about the question 'How quickly will Reminyl start to take effect?' which appeared on page 8 of the booklet. The answer given was that 'You may notice an improvement in the first month of treatment, but in some patients this may take several months. You may notice no improvement but that does not mean that Reminyl isn't helping. It may be slowing down any worsening of your symptoms. The doctor will assess the level of symptoms and adjust the dose accordingly'.

COMPLAINT

The complainant alleged that the information on page 8 was misleading and inaccurate and was concerned that it would cause difficulties between patients, their families and carers and doctors prescribing cognitive enhancers such as Reminyl.

The complainant stated that as an old age psychiatrist he spent an increasing amount of time discussing with patients and their families the whole issue of cognitive enhancers, the benefits they brought and also the need to carefully evaluate the patient's response to medication. The complainant referred to the guidelines issued by the National Institute for Clinical Excellence (NICE) which had been adopted by the Health Technology Board for Scotland (HTBS).

The complainant noted that the NICE guidance stated in Section 1.15 'A further assessment should be made, usually two to four months after reaching maintenance dose of the drug. Following this assessment the drug should be continued only where there has been an improvement or no deterioration in MMSE score, together with evidence of global improvement on the basis of behavioural and/or functional assessment'. The NICE guidance made the point that improvement must be demonstrated for the medicine to be continued. It was with this in mind that the complainant drew attention to the answer given to the question 'How quickly will Reminyl start to take effect'.

The complainant objected to the fact that the reader was not made aware that the prescribing doctor would need to make a judgement, and have some evidence that the patient was improving on at least one of the areas assessed, in the case of the NICE guidance this being the requirement for evidence of global improvement on the basis of behavioural and/or functional assessment. The complainant was concerned that the book was aimed at increasing carer demand for the medicine to be continued even in the absence of improvement and thought that the companies involved had been irresponsible in allowing the booklet to be circulated.

RESPONSE

Shire replied on behalf of itself and Janssen-Cilag.

The Authority had not specified any clauses of the Code. Shire's view was that the complaint appeared to relate most closely to Clauses 7.2 and 20.2.

The complainant made two references to the NICE guidance. The Reminyl Questions and Answers booklet made no such reference and its content was based on the patient information leaflet (PIL) and the SPC. At the outset the importance of reading the PIL was emphasised. While NICE issued guidance on many topics, these were simply the opinions of NICE and the guidance did not necessarily reflect either the PIL or SPC for any medicine. All promotional materials were required to be compliant with the SPC, which in the case of copy was seen as the 'gold standard'.

Shire stated that throughout the booklet, there was a consistent theme which encouraged the patient to communicate with, and seek guidance from, the treating doctor. The final sentence on page 8 indicated that the prescribing doctor made a judgement, from assessment of the level of symptoms, on whether to adjust the dose.

Shire firmly contended that the information in the booklet was fully consistent with the PIL, which stated that 'Your doctor will decide whether this medicine is suitable for you. Your doctor may adjust the amount of medicine you take'. The PIL described the dose escalation regimen over at least 8 weeks to reach an appropriate final maintenance dose and that the doctor, after starting a low dose 'may then slowly increase the amount of Reminyl that you take to find the most suitable dose for you'.

Shire also firmly contended that the statements in the final paragraph on page 8 were consistent with Section 4.2 of the SPC, which also fully described the dose escalation regimen over a period of at least two months to reach an appropriate maintenance dose. It was axiomatic that the assessment of clinical benefit described at length in Section 4.2 was performed by the treating physician.

The final paragraph of page 8 of the booklet referred to a sometimes slow improvement, that no improvement might still represent slowing down of worsening symptoms and that it was the doctor who would assess symptoms and adjust the dose accordingly.

It was common for improvement on Reminyl to occur slowly over several months. A large placebo-controlled, randomised trial with 978 patients showed that those on the SPC dose escalation schedule (8mg a day for the first 4 weeks, 16mg a day for at least the next 4 weeks and 24mg a day thereafter) were clearly continuing to show more improvement at 3 months

than at one month on the ADAS-cog 11 scale (Tariot *et al* 2000). The importance of this was that patients and their carers might need to be warned to expect relatively slow improvement, so that if they felt little benefit early on, they were not tempted to stop the medicine by themselves without the doctor's assessment.

Alzheimer's disease was a chronic deteriorating condition. Therefore Reminyl could reasonably be continued in the absence of symptomatic improvement if the doctor assessed the treatment as beneficial compared with no treatment and when, in the absence of treatment, deterioration would otherwise be expected. 'Therapeutic benefit' might therefore include the halting or reduction of symptomatic decline.

The adjustment of dose referred to in the booklet included the possibility of adjusting the dose up or down according to the doctor's assessment of response to treatment, or indeed stopping the medication in the event of the doctor assessing no therapeutic effect of treatment.

Shire submitted that the booklet accurately and correctly reflected the prescribing information. It also reflected relevant data from clinical studies and allowed for dose escalation, dose reduction or stopping of treatment by the doctor based on their own assessment of symptoms.

In Shire's opinion, the part of the complaint regarding the booklet being aimed at increasing carer demand for the medicine even in the absence of improvement could refer to the need for the booklet to present information about medicines to the general public factually and in a balanced way (Clause 20.2). This part of the complaint could also relate to the necessity not to raise unfounded hopes of successful treatment (Clause 20.2).

The booklet fully supported the standard approach to patient management, encouraging all prescribing decisions to be taken by the doctor. The booklet also discussed the reality of the treatment for Alzheimer's disease, where cure was not the objective with available medicines. Page 6 of the booklet stated 'It is important to realise that Reminyl is not a cure, but may help some of the symptoms of early to middle stage Alzheimer's for a limited period of time'. Shire submitted that this statement and those on page 8 did not aim to increase carer demand for the medicine and that the information was presented both factually and in a balanced manner.

There were no statements within the booklet which could be construed as encouraging members of the public to ask their doctors to prescribe Reminyl. The booklet was offered to health professionals at memory clinics who were invited to give them to patients/carers after Reminyl was prescribed. The briefing notes for representatives described this booklet as being 'for use only with patients who are prescribed Reminyl' and the booklet clearly stated at the top of page 2 that it was for 'Patients and carers of patients who have been prescribed Reminyl'.

In addition, Shire specifically denied that it had been irresponsible in circulating the booklet. The booklet was distributed solely as a service to medicine.

PANEL RULING

The Panel noted that the companies had not been advised which clauses of the Code to consider. This was an error. Shire had responded in relation to Clauses 7.2 and 20.2. The relevant clause for the material aimed at the general public and/or patients was Clause 20.2.

The Panel noted Section 4.2 of the Reminyl SPC stated that maintenance treatment could be continued for as long as therapeutic benefit existed and that the clinical benefit of the medicine should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect was no longer present.

The Panel noted that it was not unusual for the NICE guidance to make recommendations for use of a product that were inconsistent with the SPC. Clause 3.2 of the Code required that the promotion of a medicine had to be in accordance with the terms of its marketing authorization and not be inconsistent with its SPC. In this instance, Section 1.15 of the NICE guidance required that a further assessment should be made, usually two to four months after reaching maintenance dose of the medicine. Following this the medicine should be continued only where there had been an improvement or no deterioration in MMSE score together with evidence of global improvement on the basis of behavioural and/or functional assessment whereas the SPC simply referred to therapeutic benefit for the patient. In the Panel's view, slowing down of worsening of symptoms would be a therapeutic benefit and maintenance treatment could continue.

No mention was made in the booklet about the NICE guidance. Companies were not obliged to make such mention in their materials. The section at issue was not inconsistent with the SPC. It advised that doctors would assess symptoms and adjust the dose accordingly. The booklet clearly stated that Reminyl would not cure the disease.

The Panel noted that there was a difference between the product's SPC and the NICE guidance; this appeared to have given rise to the complainant's concerns. In the Panel's view the slowing down in the rate of deterioration was consistent with the Reminyl SPC and in this regard considered that the booklet was not misleading and inaccurate as alleged. The Panel therefore ruled no breach of Clause 20.2 of the Code.

Complaint received **13 June 2002**

Case completed **24 July 2002**

CASE AUTH/1333/6/02

AVENTIS PASTEUR MSD v GLAXOSMITHKLINE

'Dear Nurse' letter

Aventis Pasteur MSD complained about a 'Dear Nurse' letter about Hepatyrix (combined hepatitis A and typhoid vaccine) sent by GlaxoSmithKline. The first section, headed 'Removal of the Black Triangle', advised the reader that the Special Reporting Directive symbol had now been removed by the Medicines Control Agency (MCA). The section stated that '… sufficient doses of Hepatyrix have now been administered to allow the MCA to be confident about its safety profile' and was followed in an emboldened typeface by a separate paragraph which read '… This represents an important milestone for Hepatyrix, and makes it the only combined vaccine for hepatitis A and typhoid to have achieved this 'tried and trusted' status'.

Aventis Pasteur MSD noted that the black triangle scheme, run by the Committee on Safety of Medicines (CSM) and the MCA, indicated a period of intensive surveillance and agreed that its removal indicated that product safety had been well established. However by making a claim that Hepatyrix was the only product to have achieved 'this 'tried and trusted' status' implied that Aventis Pasteur MSD's combined hepatitis A and typhoid vaccine, Viatim (the only other such product on the market), was in some way neither 'tried' nor 'trusted'. Aventis Pasteur MSD alleged that the claim attempted to discredit Viatim in breach of the Code. Aventis Pasteur MSD also considered that making a claim around the removal of black triangle status was effectively making a claim about definitive product safety, when in fact pharmacovigilance was an ongoing process. A further breach of the Code was alleged.

The Panel noted that Aventis Pasteur MSD's product Viatim was the only other combined vaccine for hepatitis A and typhoid. The Panel considered that the claim at issue 'This represents an important milestone for Hepatyrix and makes it the only combined vaccine for hepatitis A and typhoid to have achieved this 'tried and tested' status' and previous comments such as '… to allow the MCA to be confident about its safety profile' implied more than the satisfaction of the criteria for the removal of the black triangle. The Panel considered it implied that Hepatyrix had an additional safety benefit compared to Viatim. The Panel thus considered the claim misleading about the comparative safety of Hepatyrix and Viatim as alleged; a breach of the Code was ruled.

The Panel was also concerned that the claim implied that continuing pharmacovigillance was no longer required for Hepatyrix. In the Panel's view nurses should have been reminded that suspected serious adverse reactions still needed to be reported. The Panel considered that the claim was misleading with regard to the safety of Hepatyrix. A breach of the Code was ruled.

Aventis Pasteur MSD Ltd complained about a 'Dear Nurse' letter (ref HPX/LTR/02/1971) about Hepatyrix (combined hepatitis A and typhoid vaccine) sent by GlaxoSmithKline UK Ltd.

The letter stated that its purpose was to communicate important new information about Hepatyrix and to remind the reader of other significant clinical benefits. The first section, headed 'Removal of the Black Triangle', advised the reader that the Special Reporting Directive symbol had now been removed by the Medicines Control Agency (MCA). The section stated that '… sufficient doses of Hepatyrix have now been administered to allow the MCA to be confident about its safety profile' and was followed in an emboldened typeface by a separate paragraph which read '… This represents an important milestone for Hepatyrix, and makes it the only combined vaccine for hepatitis A and typhoid to have achieved this 'tried and trusted' status'.

COMPLAINT

Aventis Pasteur MSD stated that it took issue with the claim that the removal of the black triangle from Hepatyrix '… makes it the only combined vaccine for hepatitis A and typhoid to have achieved this tried and trusted status'.

Aventis Pasteur MSD stated that the black triangle scheme, run by the Committee on Safety of Medicines (CSM) and the MCA, indicated a period of intensive surveillance during the first two years after a product was licensed. Aventis Pasteur MSD agreed that the removal of the black triangle indicated that the CSM/MCA believed that the safety of a product had been well established. However by making a claim that Hepatyrix was the only product to have achieved 'this 'tried and trusted' status' implied that Aventis Pasteur MSD's combined hepatitis A and typhoid vaccine, Viatim (the only other such product on the market), was in some way neither 'tried' nor 'trusted'. Aventis Pasteur MSD believed that any medicine granted a licence by the MCA should be considered to be 'tried', by virtue of having undergone extensive trials and 'trusted', by virtue of having undergone extensive clinical and pre-clinical safety testing. In intercompany correspondence, GlaxoSmithKline stated that it had made no attempt to denigrate Viatim by virtue of the fact that it was a licensed product and had therefore satisfied safety standards pre-licence. However, this was in sharp contrast with the tone of the claim at issue which effectively claimed that Hepatyrix was the only product to have achieved tried and trusted status. Aventis Pasteur MSD alleged a breach of Clause 7.3 of the Code in that the claim in question attempted to discredit Viatim by implying that it was in some way not tried and trusted.

Making a claim around the removal of black triangle status was effectively making a claim about product safety. GlaxoSmithKline was attempting to imply that the removal of black triangle status was, in some way, a definitive statement that the safety of the product had been proven once and for all, when in fact pharmacovigilance was an ongoing process. Aventis Pasteur MSD emphasised this point by highlighting that a recent review revealed that 50% of safety problems with licensed medicines came to light long

after the first two years of usage had passed. A breach of Clause 7.9 of the Code was alleged.

RESPONSE

GlaxoSmithKline stated that it was certainly not its intention to imply that Viatim was in some way neither tried nor tested. The letter made no reference to Viatim. What GlaxoSmithKline was seeking to do was to inform its customers that the black triangle had been removed from its product, Hepatyrix. It was a fact that the MCA only allowed a black triangle to be removed when it had a level of confidence about the safety record of a product following licensure. In the letter the phrase 'tried and trusted' was in inverted commas, implying a more colloquial use, rather than a literal statement of absolute fact. The letter was a one-off mailing, pointing out this milestone and was not part of an ongoing promotional campaign. GlaxoSmithKline did not accept that this constituted a breach of the Code.

GlaxoSmithKline stated that it had explained in the letter that the removal of the black triangle meant that sufficient doses of Hepatyrix had been administered to allow the MCA to be confident about its safety profile. This was not the same thing as saying that the product was completely safe and it believed that recipients of the letter would understand this. In addition the use of inverted commas around the words 'tried and trusted' implied relative, rather than absolute safety.

PANEL RULING

The Panel noted that the use of the black triangle symbol on promotional material to denote that special reporting was required in relation to adverse reactions was not a Code of Practice or statutory requirement. It reflected an agreement between the CSM and the ABPI. The supplementary information to Clause 4.3 of the Code made reference to the use of the symbol.

The Panel noted that the BNF (No 43; March 2002) gave information regarding the reporting of adverse reactions to medicines. Regarding the use of the black triangle symbol to identify medicines that were monitored intensely by the CSM/MCA, it stated that there was no standard time for which products retained the black triangle; safety data were usually reviewed after two years. During the period that a product retained its black triangle all suspected reactions should be reported via the yellow card scheme. On removal of the black triangle then only serious suspected reactions should be reported.

The Panel noted Aventis Pasteur MSD conceded that the removal of the black triangle indicated that the CSM and the MCA believed that the safety of Hepatryrix had been well established. The Panel noted that Aventis Pasteur MSD's product Viatim was the only other combined vaccine for hepatitis A and typhoid. The Panel considered that the claim at issue 'This represents an important milestone for Hepatyrix and makes it the only combined vaccine for hepatitis A and typhoid to have achieved this 'tried and tested' status' and previous comments such as '… to allow the MCA to be confident about its safety profile' implied more than the satisfaction of the criteria for the removal of the black triangle. The Panel considered it implied that Hepatyrix had an additional safety benefit compared to Viatim. The Panel thus considered the claim misleading about the comparative safety of Hepatyrix and Viatim as alleged; a breach of Clause 7.3 was ruled.

In addition, the Panel was concerned that the claim implied that continuing pharmacovigillance was no longer required for Hepatyrix. In the Panel's view nurses should have been reminded that suspected serious adverse reactions still needed to be reported. The Panel considered that the claim was misleading with regard to the safety of Hepatyrix. A breach of Clause 7.9 was ruled.

Complaint received **14 June 2002**

Case completed **19 July 2002**

CASE AUTH/1334/6/02

ANONYMOUS GENERAL PRACTITIONER v GLAXOSMITHKLINE

Avandia e-detail

An anonymous general practitioner complained about the promotion of Avandia (rosiglitazone) by GlaxoSmithKline through an Internet service established by a third party. The complainant was concerned that an Avandia e-detail was preceded by the statement that 'The information in each module is provided through an educational grant by the manufacturer of the product presented'. The complainant failed to see how a promotional presentation could contain information that was provided through an educational grant. This was inaccurate and misleading. The complainant stated that on completing the presentation he was asked to complete a questionnaire to qualify for an incentive which seemed strange for so-called market research when the presentation looked very similar to that used by the representatives. In addition the complainant questioned the adequacy of the website's security.

The Panel noted that the material at issue was an e-detail for Avandia which appeared on an Internet website owned by a third party. A market research questionnaire had followed the e-detail, the first page of which was headed with the Avandia product logo. GlaxoSmithKline had provided the promotional material and had reviewed, and had an opportunity to amend, the questionnaire prior to it being made available on the website. It appeared from a hard copy provided by GlaxoSmithKline that the company had submitted the material to its copy approval system. In the Panel's view although the website was organised by a third party the provision of the material and the arrangements between the parties meant that GlaxoSmithKline was responsible, with regard to the provisions of the Code, for the Avandia e-detail as well as those pages which introduced the e-detail and the subsequent questionnaire.

The first web page headed 'Medicines interactive: market research programme' thanked the viewer for agreeing to participate in the market research exercise. Viewers were told that although the information they were about to view was promotional the aim of the survey was to gain views on the Medicines Interactive service. The survey was not intended to be promotional. They were also told that to complete the Medicines Interactive module they would need to have visited all the core pages and completed the questionnaire. Once the questionnaire was completed and submitted viewers would receive £30 as gift vouchers by return.

The third web page headed 'Medicines Interactive' and sub-headed 'Introduction' stated 'Welcome to the 'Medicines Interactive' index from which you can visit a 'Medicines Interactive' module of your choice. Each module is provided through an educational grant by the manufacturer of the product presented'. The product highlighted on the page was Avandia. The pages that followed consisted of the e-detail for the product. The Panel considered that it was misleading to state that the module had been provided through an educational grant when the information therein was clearly promotional. It was immaterial that viewers had previously been told that the material they were about to see was promotional. The Panel considered that the promotional nature of the modules had been disguised and that high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that another page was headed 'Avandia'. A pro-forma below stated 'You have chosen Avandia' and requested an address to which to send a cheque. A 'button' in the bottom right-hand corner of the page stated 'Start presentation'. Viewers thus were made aware of the payment which they would receive if they read the Avandia material and completed the questionnaire. In the Panel's view they were being offered an incentive to view the Avandia e-detail.

The Code stated that representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview. In the Panel's view the same principle applied to e-details. In this case doctors were told, before they viewed the e-detail, that if they viewed it and completed the questionnaire they would receive £30.

The Panel noted that the market research had not been accessed from a separate and dedicated part of the website. In the Panel's view it was not unreasonable to conduct research into the acceptability of the website, however, the way in which this had been done gave the impression that doctors were being offered an incentive to view the Avandia e-detail. The Panel noted that the first page of the questionnaire was headed with the Avandia product logo. In the Panel's view the arrangements for the market research were such that it constituted disguised promotion of Avandia. The Panel therefore ruled a breach of the Code. As the study was considered to be disguised promotion it followed that payments for participation were inappropriate and a further breach of the Code was ruled.

Clause 21 of the Code required that access to promotional material directed to a UK audience provided on the Internet in relation to, *inter alia*, prescription only medicines, must be limited to health professionals and appropriate administrative staff. The Guidance on the Internet published in the May 1996 Review (upon which Clause 21 was based) referred to a 'secure closed system'. The Authority usually advised companies to provide passwords via conventional mail to avoid providing a password electronically to somebody posing as a doctor. The Panel considered that the arrangements for access to the website were on the limits of acceptability with regard to security. The Panel noted that in order to gain access to the website

doctors had to provide their name and GMC number. On balance the Panel did not consider that the inclusion of the Avandia e-detail on the website constituted promotion of a prescription only medicine to the general public. No breach of the Code was ruled.

An anonymous general practitioner complained about the promotion of Avandia (rosiglitazone) by GlaxoSmithKline UK Ltd. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

COMPLAINT

The complainant was concerned about the promotion of Avandia by GlaxoSmithKline through an Internet service. In a section headed 'Prescribe' a subsection termed 'Medicines Interactive' contained an online presentation of Avandia. The complainant was concerned that on clicking to enter the list of presentations the text stated: 'The information in each module is provided through an educational grant by the manufacturer of the product presented'.

The complainant failed to see how a promotional presentation could contain information that was provided through an educational grant and alleged that this was inaccurate and misleading as it suggested an educational presentation, rather than a promotional one.

On completing the presentation, the complainant was asked to complete a questionnaire to qualify for an incentive. The complainant was unsure how this worked, but it seemed strange to be offered an incentive on completion for so-called market research when the presentation looked very similar to material the complainant had viewed from a representative.

In addition, the complainant was not convinced of the adequacy of the website's security. It seemed that on acquiring a General Medical Council (GMC) number from the GMC website, by searching for an individual's surname, you were able to enter as another person. There was no validation process relating to information unavailable on the GMC website. For example, other secure websites used registered postcode as a safety check. Was this considered satisfactory to avoid promotion to people who were not health professionals? The complainant stated that his teenage son pointed out this security breach after a few minutes!

GlaxoSmithKline was asked to bear in mind the requirements of Clauses 9.1, 10.1, 10.2, 18.1 and 20.1 of the Code.

RESPONSE

GlaxoSmithKline provided background information to help to put the complainant's comments into context.

The website at issue, which had been established by a third party, was an educational website for health professionals. It provided information on medical news, clinical networks, guidelines, calculators, conferences etc. with links to external medical databases and key medical references. The third party had developed a new service called Medicines Interactive which aimed to provide doctors with access to companies' promotional materials such that it could be viewed at the customer's convenience. The complainant had commented on a pilot website within the website and Avandia was the material chosen for assessment supplied by GlaxoSmithKline to the third party. The service was being evaluated by the third party for feasibility and usefulness to its customers. Both the internet website and Avandia materials were reviewed in light of the Code prior to the start of the pilot. The contract for this pilot ceased at the end of June and the material in question would be withdrawn in the near future.

GlaxoSmithKline provided a hard copy of a number of pages from the website. These included pages introducing the Medicines Interactive part of the website, the Avandia e-detail and the subsequent questionnaire.

With regard to the allegation that the phrase 'provided through an educational grant' was misleading as the material was promotional, GlaxoSmithKline stated that on entering the section entitled 'Medicine Interactive' it was clearly stated that the material that was about to be viewed was of a promotional nature that had been sponsored by the pharmaceutical industry. The statement that information was provided through an educational grant was merely a statement of sponsorship, as required by Clause 18.1 of the Code, relating to the entire diabetes clinical network website.

By informing the internet user that they were about to view promotional material, GlaxoSmithKline had clearly identified what was going to be available. It was not disguised in any way. GlaxoSmithKline therefore believed that there had been no breach of Clauses 10.1, 10.2 and 18.1 of the Code.

With regard to the complaint about the offering of an incentive on completion of market research when the presentation looked very similar to material viewed with a representative, GlaxoSmithKline stated that on entering the Medicines Interactive page a clear explanation of the website was provided. The title of the page was 'medicines interactive: market research programme' and explained that the research being undertaken was to evaluate a new service to be delivered by the third party. It went on to state 'Although the material you are about to view is of a promotional nature [ie the e-detail], the aim of the survey is to gain your views on the Medicines Interactive service. This survey is not intended to be promotional and, as such, this survey is restricted to the first 200 participants'.

The survey content was about the service, and asked questions about the length of the presentation and where the presentation was viewed, whether the viewer liked the way it was presented and whether the service might be used on a regular basis when it became widely available.

The description of the market research on the first page, along with the nature of the questions in the survey, made it clear that this was a market research project for the third party and the service it provided. It was highlighted that the material to be seen was of a promotional nature. GlaxoSmithKline therefore, did

not believe that this was disguised promotion, and thus there had been no breach of Clauses 10.1 or 10.2 of the Code.

As an additional point, the third party stated that once the survey had been completed the user would received £30 in gift vouchers (these were from a named high street store paid for by the third party). This was a thank you for the time and effort involved with completing with questionnaire. It was not an incentive to view the materials that were presented on Avandia. GlaxoSmithKline did not pay for these gift vouchers.

Because the gift vouchers were provided by the third party for completion of the questionnaire and not as an encouragement to view the promotional material GlaxoSmithKline did not consider that there had been a breach of Clause 18.1.

With regard to the complainant's concerns about the security of the website GlaxoSmithKline noted that the internet website was specifically designed for health professionals. GlaxoSmithKline was involved in numerous discussions with the third party regarding the security of the website and was assured that it would be adequately protected and that to access it the internet user would have to have provided a GMC number and their surname. This was the standard method of security for most internet websites designed specifically for health professionals. Examples of other websites which used this method were provided.

GlaxoSmithKline noted the complainant's comments that it was easy to access a GMC number and surname from the GMC website. The company believed that this was not something that was widely known; the general public would be unlikely to know what a GMC number was, let alone that a GMC website existed from which these details could be obtained.

With regard to postcode validation to enhance security, the GMC had informed GlaxoSmithKline that a doctor's postcode could be obtained directly from it and potentially used to breach the security of these websites.

GlaxoSmithKline considered that the website had adequate security and as such was not in breach of Clauses 9.1, or 20.1. The information provided was suitable for a medical audience and every attempt to limit access to the website to doctors meant that GlaxoSmithKline was not promoting to the general public.

On all three points GlaxoSmithKline did not consider that there had been any breach of Clauses 9.1, 10.1, 10.2, 18.1 or 20.1 of the Code. GlaxoSmithKline hoped this clarified all the points made by the complainant and reassured the Panel that the company had tried to ensure that the website was appropriate for the audience and suitably reviewed with respect to the Code.

In response to a request for further information GlaxoSmithKline noted that at the time of the complaint, the Avandia pilot was the only electronic detailing and market research pilot available to doctors accessing the third party website. However, market research questionnaires had since been included for other companies' products. These had all been made available on the relevant Medicines Interactive pages of the website, which clearly stated that their purpose was to research a new service. Each of these pieces of research had involved less than 200 GPs, and the total number of GPs taking part in all pilots would be no more than 400.

The education website was promoted by the third party itself through e-mail, post and conventional advertising. GlaxoSmithKline did not promote the website in any way, nor was the Avandia market research specifically mentioned in any promotional activity conducted by the third party or GlaxoSmithKline. Some information regarding the general market research exercises had been included in e-mails to doctors by the third party. This information applied to all of the market research undertaken, including that for other companies' products.

On logging on to the website, doctors were given the option of entering a section called 'Clinical Networks'. The Diabetes Clinical Network was listed within this section as an area of interest. Once in the Network itself, the doctor could view a number of sections incorporating information relevant to the disease area (eg the National Service Framework (NSF) for diabetes, news items, journals abstracts, etc). One such section was called 'Medicines Interactive'. This was specifically noted to be a pilot section, with the aim of enabling doctors to learn more about medicines. Similarly, a clear indication was given to users that promotional items might be included in this section. The Avandia market research exercise was found here, although it had since been removed, as the contract had now expired. It should be noted that each user had to make a positive decision to access it.

There was no communication from GlaxoSmithKline drawing attention to the website in any way. Indeed, not even its field-force was notified of the existence of this exercise.

To register for the website, doctors were asked to provide a surname and a GMC number, a level of security in common use for medical websites. The doctor's surname and GMC number were then used as the username and password, respectively, for subsequent access. Once logged on, no further passwords were required to access the Medicines Interactive section, which incorporated the market research and electronic detailing.

GlaxoSmithKline paid a global sum of money to the third party for sponsorship of the educational Diabetes Clinical Network part of the website. GlaxoSmithKline's role in sponsoring the website was clearly specified. No specific payments were made regarding the electronic detail pilot, nor for the market research relating to it. GlaxoSmithKline did not underwrite any 'thank you' payments in cash or kind to doctors completing the market research. As noted above, such payments were made by the third party only to the first 200 doctors who completed the market research evaluation (this procedure had since been adopted on the website with other companies' products). Thereafter, it was intended that the

Avandia-specific materials would be viewable as an 'e-detail', with the appropriate warnings. No pecuniary or other incentives would be offered for accessing these materials.

GlaxoSmithKline reviewed the questionnaire prior to it being available to doctors on the website, and was able to make appropriate changes. This review was to ensure that it complied in all respects with the Code. The market research exercise itself was intended to help assess the value and efficacy of providing an e-detailing service, and was not instigated or conducted on behalf of GlaxoSmithKline. The third party was a member of the British Healthcare and Business Information Association and, as such, complied with the Code specifically relating to market research.

The questionnaire was entered into a standard template that incorporated the Avandia logo. While GlaxoSmithKline did not believe that the appearance of the logo represented, in itself, a breach of the Code, the company considered in retrospect that this might not have been appropriate, particularly in view of the fact that the market research in question was not conducted on GlaxoSmithKline's behalf.

The data from the market research questionnaire were made available in an anonymised format to GlaxoSmithKline. However, as noted above, the market research was conducted by the third party, to evaluate the services provided on its website.

GlaxoSmithKline noted that its contract with the third party had now expired, and all materials relating to Avandia had been withdrawn from the website.

PANEL RULING

The Panel noted that the complaint was about an e-detail for GlaxoSmithKline's product Avandia, which appeared on an Internet website owned by a third party. A market research questionnaire had followed the e-detail. The first page of the questionnaire was headed with the Avandia product logo. GlaxoSmithKline had provided the promotional material and had reviewed, and had an opportunity to amend, the questionnaire prior to it being made available on the website. The Panel noted that the hard copy of pages from the website which had been provided by GlaxoSmithKline had a handwritten note in the top right hand corner which read 'Final sign off copy'. It appeared that the company had thus submitted the material to its copy approval system. In the Panel's view although the website was organised by a third party the provision of the material and the arrangements between the parties meant that GlaxoSmithKline was responsible, with regard to the provisions of the Code, for the Avandia e-detail as well as those pages which introduced the e-detail and the subsequent questionnaire.

The Panel examined the web pages provided by GlaxoSmithKline.

The first web page headed 'Medicines interactive: market research programme' thanked the viewer for agreeing to participate in the market research exercise. Viewers were told that although the information they were about to view was promotional the aim of the survey was to gain views on the Medicines Interactive service. They were told that the survey was not intended to be promotional and as such was restricted to the first 200 participants. They were also told that to complete the Medicines Interactive module they would need to have visited all the core pages and completed the questionnaire. Once the questionnaire was completed and submitted viewers would receive £30 as gift vouchers by return.

The third web page headed 'Medicines Interactive' and sub-headed 'Introduction' stated 'Welcome to the 'Medicines Interactive' index from which you can visit a 'Medicines Interactive' module of your choice. Each module is provided through an educational grant by the manufacturer of the product presented'. The product highlighted on the page was Avandia. The pages that followed consisted of the e-detail for the product. The Panel noted GlaxoSmithKline's submission that it had sponsored the entire Diabetes Clinical Network part of the website which included the e-detail section at issue. It had not made any specific payment regarding the e-detail section. The Panel considered that it was misleading to state that the module had been provided through an educational grant when the information therein was clearly promotional. In the Panel's view it was immaterial that on a previous page viewers had been told that the material they were about to see was promotional. The Panel considered that the promotional nature of the modules had been disguised and that high standards had not been maintained. Breaches of Clauses 9.1 and 10.1 were ruled.

The Panel noted that another page was headed 'Avandia'. A pro-forma below stated 'You have chosen Avandia' and requested address details of the viewer. Viewers were told that the address specified would be the address to which the cheque was sent. A 'button' in the bottom right-hand corner of the page stated 'Start presentation'. Viewers thus were made aware of the payment which they would receive if they read the Avandia material and completed the questionnaire. In the Panel's view they were thus being offered an incentive of £30 to view the Avandia e-detail.

The Panel noted that Clause 15.3 of the Code stated that representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview. In the Panel's view the same principle applied to e-details ie health professionals should not be offered an incentive to view them. In this case doctors were told, before they viewed the e-detail, that if they viewed it and completed the questionnaire they would receive £30.

The Panel noted that participants for the market research exercise had not been recruited as such, it was open to the first 200 'entrants'. The market research had not been accessed from a separate and dedicated part of the website. In the Panel's view it was not unreasonable for the third party to conduct research into the acceptability of its website, however, the way in which this had been done gave the impression that doctors were being offered an incentive to view the Avandia e-detail. The Panel noted that the first page of the questionnaire was

headed with the Avandia product logo. In the Panel's view the arrangements for the market research were such that it constituted disguised promotion of Avandia. The Panel therefore ruled a breach of Clause 10.2 of the Code. As the study was considered to be disguised promotion it followed that payments for participation were inappropriate and a breach of Clause 18.1 was ruled in this regard.

Clause 21 of the Code required that access to promotional material directed to a UK audience provided on the Internet in relation to, *inter alia*, prescription only medicines, must be limited to health professionals and appropriate administrative staff. The Panel noted that it had received very few complaints about the Internet. The Panel had to decide whether the arrangements for access to the website were such that access was limited to health professionals. There was no advice in the Code on this point. The Guidance on the Internet published in the May 1996 Review (upon which Clause 21 was based) referred to a 'secure closed system'. The Authority usually advised companies to provide passwords via conventional mail to avoid providing a password electronically to somebody posing as a doctor. The Panel considered that the arrangements for access to the website were on the limits of acceptability with regard to security. The Panel noted that in order to gain access to the website doctors had to provide their name and GMC number. On balance the Panel did not consider that the inclusion of the Avandia e-detail on the website constituted promotion of a prescription only medicine to the general public. No breach of Clause 20.1 was ruled.

Complaint received **17 June 2002**

Case completed **22 August 2002**

CASE AUTH/1335/6/02

GENERAL PRACTITIONER v NAPP

Promotion of Transtec

A general practitioner complained that a placebo version of a Transtec 35mcg/h transdermal patch issued by Napp, which had been attached to the front cover of MIMS, seemed to be used as a promotional device. However, neither the approved name of Transtec, buprenorphine, nor abridged details from the summary of product characteristics (SPC) were included.

The Panel considered that the placebo patch had been used to promote Transtec 35mcg/h. It was designed to be removed from the front cover of MIMS. The Panel's view was that given the context in which it was presented the placebo patch had to be considered as a loose insert. Prescribing information should have been included. The Panel noted that the non-proprietary name did not appear immediately adjacent to the most prominent display of the brand name. The Panel ruled breaches of the Code as acknowledged by Napp.

A general practitioner complained about the promotion of Transtec (buprenorphine) 35mcg/h transdermal patch by Napp Pharmaceuticals Limited. The material at issue was a placebo Transtec 35mcg/h transdermal patch which had been attached to the front cover of MIMS, June 2002.

COMPLAINT

The complainant stated that the imitation patch seemed to be used in this context as a promotional device, whose purpose it was to bring Transtec to his attention. However, the printing did not include the approved name of Transtec, buprenorphine, nor were there any abridged details from the summary of product characteristics (SPC). The complainant queried whether the provision and use of this item under the circumstances constituted a breach of the Code.

Napp was asked to respond in relation to Clauses 4.1 and 4.3 of the Code.

RESPONSE

Napp stated that the production of the item had highlighted an oversight in the approval process specific to this item. The individual components, the placebo patch and MIMS entries (including 'New This Month', and index entry and abbreviated advertisements), all followed the appropriate approval process and the Code requirements.

However, the use of the Transtec placebo patch in this manner, affixed to the front cover of MIMS, was not approved through Napp's normal system. Napp accepted that the use of the placebo in this context constituted a breach of Clauses 4.1 and 4.3 of the Code.

Napp stated that it had taken immediate steps to ensure that the correct approval process was followed in future and that this event was not repeated.

PANEL RULING

The Panel considered that the placebo patch had been used to promote Transtec 35mcg/h. It was therefore an advertisement and had to comply with the Code. It was designed to be removed from the front cover of MIMS. The Panel's view was that given the context in which it was presented the placebo patch had to be

considered as a loose insert. Prescribing information should have been included as required by Clause 4.1 of the Code. The Panel noted that the non-proprietary name did not appear immediately adjacent to the most prominent display of the brand name as required by Clause 4.3. The Panel ruled breaches of Clauses 4.1 and 4.3 of the Code as acknowledged by Napp.

Complaint received **20 June2002**

Case completed **17 July 2002**

CASE AUTH/1336/6/02 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v ASTRAZENECA

Seroquel mailing

A general practitioner complained about a Seroquel (quetiapine) mailing sent by AstraZeneca. Seroquel was an atypical antipsychotic for the treatment of schizophrenia.

The complainant was concerned that in the mailing AstraZeneca had quoted the National Institute of Clinical Excellence (NICE) as stating that atypicals should be used in newly diagnosed patients. The guidance summary from NICE stated that the oral atypical antipsychotics, including quetiapine, should be 'considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia'. The wording of the mailing seemed to deliberately imply that the atypicals should be used in all newly diagnosed patients to the exclusion of the typical agents and the complainant alleged that this was misleading.

The Panel had some sympathy with the complainant and considered that Section 1.2 of NICE guidance to which he referred was not sufficiently clear about the place of the atypical antipsychotics in the treatment of newly diagnosed schizophrenics; it was unclear whether the choice referred to was the choice between one of the five atypical antipsychotics listed or the choice between typical and atypical agents. The position was clarified by other parts of the guidance which demonstrated that in the view of NICE all patients newly diagnosed with schizophrenia should be treated with an atypical antipsychotic. The Panel thus did not consider that the mailing was misleading as alleged and no breach of the Code was ruled. The mailing did not quote from the NICE guidance and so there could be no breach of the Code in that regard. The Panel ruled accordingly.

A general practitioner complained about a Seroquel (quetiapine) mailing (ref 02/10549) sent by AstraZeneca UK Limited. Seroquel was an atypical antipsychotic for the treatment of schizophrenia.

COMPLAINT

The complainant was concerned that in the mailing AstraZeneca had quoted the National Institute of Clinical Excellence (NICE) as stating that atypicals should be used in newly diagnosed patients. The guidance summary from NICE stated that the oral atypical antipsychotic medicines, including quetiapine, should be 'considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia'. The wording of the mailing seemed to deliberately imply that atypicals should be used in all newly diagnosed patients to the exclusion of the typical agents and the complainant considered that this was a deliberate attempt to mislead readers, especially if they had not read the paragraph in the NICE guidance.

It was this deliberate manipulation of words in pharmaceutical advertising which made the complainant increasingly cynical about claims for new medicines, even when those claims might be well justified and he considered that this approach to advertising could only bring the pharmaceutical industry into disrepute, which was unfortunate considering the excellent service that it provided in many aspects of patient care.

When writing to AstraZeneca, the Authority drew attention to Clauses 7.2 and 11.2 of the Code.

RESPONSE

AstraZeneca stated firstly that it genuinely regretted a health professional considered there had been a deliberate attempt to mislead. The company was committed to ethical promotion and took stringent measures to ensure that its promotional campaigns met the highest possible standards. The item was a direct mailing to GPs and was posted on the day following the NICE guidance issued on atypical antipsychotics in schizophrenia.

The wording used in the mailing was as follows:

[In schizophrenia:]

'Atypicals should be used in:

- Newly diagnosed patients
- Existing or relapse patients for whom typical antipsychotics:
  - Offer unsatisfactory management (inadequate symptom control)
  - Cause unacceptable side effects
- Those unable to make an informed decision about their drug therapy.'

With regard to Clause 11.2, the mailing did not contain any quotations from the original document; it summarised its contents without actually quoting it.

AstraZeneca therefore did not believe that Clause 11.2 was relevant.

AstraZeneca's intention was not to mislead the audience. The item was not intended as a direct quote of NICE and was instead a very brief summary of the major points raised in the overall NICE guidance document. However, AstraZeneca considered that the summary accurately reflected the main points of this document.

The NICE guidance document consisted of 21 pages. The complainant quoted from Section 1 of the guidance, which constituted the first two pages. Section 1 stated that 'It is recommended that the oral atypical antipsychotic drugs amisulpride, olanzapine, quetiapine, risperidone and zotepine are considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia'. However it was important that Section 1 was read in the context of the rest of the document.

AstraZeneca believed the spirit of the NICE guidance was such that the overall thrust was that atypical antipsychotics should be more widely prescribed than they were currently (approximately 31% of patients). The spirit of the guidance therefore suggested the use of atypicals, rather than simply the consideration of the use of atypicals, as the wording of Section 1 might suggest. There were numerous Sections of the guidance document which supported this view:

Section 4.3.2 stated 'On balance, the Committee concluded that more widespread use of the atypical antipsychotics would benefit individuals with schizophrenia because of the likelihood of a reduced incidence of EPS'. In conjunction with Section 2.7 'Individuals experiencing a first episode of schizophrenia are known to be more susceptible to the adverse effects of treatment, which may subsequently impact on their adherence to future therapy and on their longer-term prognosis', this would appear to show that NICE believed newly diagnosed patients would benefit from being prescribed atypicals.

In Section 5.4, there was a statement that implied that NICE expected atypicals to be adopted as first-line therapy in schizophrenia. 'Adoption of atypicals as first-line therapy is expected to involve a shift away from inpatient care to residential or community care, which are less expensive' and in Section 7.1 that 'All clinicians treating individuals with schizophrenia should review their current practice of prescribing antipsychotic drugs in line with the guidance set out in Section 1'.

One particular feature of the guidance suggested that atypicals should be used in newly diagnosed patients: Section 7.4, headed 'Implementation', stated that 'To measure compliance locally with the guidance set out in Section 1, the following criteria should be used. Further details of suggestions, for audit are presented in Appendix D'. Further on in Section 7.4, it was restated that 'An oral atypical antipsychotic drug is considered for prescription in the following circumstances: an individual is newly diagnosed with schizophrenia'.

One of the stated objectives of the audit in Appendix D was that 'atypical antipsychotic drugs are prescribed appropriately for individuals with schizophrenia'. It was stated that the audit could either include all patients with schizophrenia or could be undertaken on specific groups such as people with newly diagnosed schizophrenia, people previously diagnosed with schizophrenia and people with treatment-resistant schizophrenia. One of the measures to be used as a basis for the audit referred directly to newly diagnosed schizophrenia patients. Importantly, the standard recommended for use in the audit was that 100% of individuals newly diagnosed with schizophrenia were prescribed an oral atypical antipsychotic drug.

In practical terms, clinicians would be expected to read the entire NICE guidance document. With this in mind and taking into account the above, AstraZeneca believed its summary wording was neither inaccurate nor misleading in the overall context of the NICE document. AstraZeneca did not believe that it had breached Clause 7.2.

PANEL RULING

The Panel noted that the NICE guidance at issue (Technology Appraisal Guidance No. 43) was entitled 'Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia'. It was thus specifically about the use of atypical antipsychotics and not about the treatment of schizophrenia generally. The document consisted of a number of sections and appendicies; Section 1 constituted the Institute's guidance on the use of the atypical antipsychotics. Section 1.2 stated 'It is recommended that the oral atypical antipsychotic drugs amisulpride, olanzapine, quetiapine, risperidone and zotepine are considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia'. Section 7 of the guidance was entitled 'Implementation'. Section 7.1 stated that doctors treating patients with schizophrenia should review their current practice of prescribing antipsychotics in line with the guidance set out in Section 1. Section 7 referred readers to Appendix D where audit details were presented which would allow doctors to measure their compliance with the guidance. One of the criteria to be measured was 'The individual who is diagnosed with schizophrenia for the first time is prescribed an oral atypical antipsychotic drug' the standard for which was '100% of individuals newly diagnosed with schizophrenia'.

The Panel had some sympathy with the complainant and considered that Section 1.2 of NICE guidance to which he referred was not sufficiently clear about the place of the atypical antipsychotics in the treatment of newly diagnosed schizophrenics. It was not entirely clear from Section 1.2 as to whether the choice referred to was the choice between one of the five atypical antipsychotics listed or the choice between typical and atypical agents. The position was clarified by other parts of the guidance such as Sections 5.4 and 7. Section 7 and Appendix D of the guidance demonstrated that in the view of NICE all patients newly diagnosed with schizophrenia should be treated with an atypical antipsychotic. The Panel thus did not consider that the mailing was misleading as alleged and no breach of Clause 7.2 was ruled. The

mailing did not quote from the NICE guidance and so there could be no breach of Clause 11.2. The Panel ruled accordingly.

Complaint received **24 June2002**

Case completed **12 August 2002**

CASE AUTH/1337/6/02

TAKEDA/DIRECTOR v GLAXOSMITHKLINE

Promotion of Avandia

Takeda complained about the promotion of Avandia (rosiglitazone) for type 2 diabetes by GlaxoSmithKline. The complaint appeared to involve a possible breach of undertaking and this aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board. The claim at issue 'Avandia has favourable effects on lipid profile' had been used in a number of promotional items. Takeda supplied Actos (pioglitazone).

In Case AUTH/1123/1/01 the Panel ruled SmithKline Beecham in breach of the Code because its claim for a reduction in the TC:HDLC ratio relied on data where concomitant statin therapy might have affected the outcome (Fonsecca *et al* 2000). GlaxoSmithKline no longer used that study to support its claim for positive effects on the lipid profile, but instead now cited the Avandia summary of product characteristics (SPC).

Takeda stated that the Panel had previously noted that the Avandia SPC stated that '… total cholesterol:HDLc ratio was unchanged or improved' and referred to increases in both LDL-C and HDL-C during treatment with no mention of any beneficial effects on triglycerides. Earlier in the same section the following adverse events were listed: hyperlipaemia and hypercholesterolaemia in combination with metformin, and hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia in combination with sulphonylureas.

Takeda stated that GlaxoSmithKline had elected to replace a specific claim for reduction in TC:HDLC ratio that had been found in breach of the Code with a claim implying overall lipid benefit when there was no scientific data to support any beneficial effects on LDL-C or triglycerides. Changing the wording and the reference from that previously found in breach did not alter the fact that a global lipid benefit claim for Avandia was in disagreement with the main body of scientific evidence.

The Panel noted that the Section 4.8 of the Avandia SPC, Undesirable Effects, stated that 'Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone plus sulphonylurea and rosiglitazone plus metformin respectively. The elevated total cholesterol levels were associated with increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment'. Thus plasma lipids were raised in only a minority of patients but, when they were, the ratio of total cholesterol: HDLC was unchanged or improved suggesting that there should be no resultant adverse cardiovascular effects.

The Panel noted that one of the pages of a detail aid was headed 'Avandia has positive effects on a range of cardiovascular risk factors'. One of the positive effects listed, under a sub-heading of 'Dyslipidaemia' was the claim in question 'Avandia has favourable effects on lipid profile' referenced to the SPC. In the Panel's view the favourable effects listed in the SPC related only to those few patients in whom hypercholesterolaemia occurred.

The claim in question referred to the lipid profile; the lipid profile was composed of many lipid fractions. In the Panel's view most readers would assume from the claim that in all patients Avandia had positive effects on all aspects of the lipid profile which was not so. The Panel noted that the effects of Avandia on the total cholesterol: HDL-C ratio were complicated in that a significant proportion of the patients included in the trials were, at the same time, taking statins. Overall the Panel considered that the claim 'Avandia has favourable effects on lipid profile' was misleading. A breach of the Code was ruled.

The Panel noted that the claim now at issue in Case AUTH/1337/6/02 referred to the lipid profile as a whole and not just to one aspect of it as in Case AUTH/1123/1/01. The Panel considered that the new claim was sufficiently different from the old one not to be caught by the undertaking and assurance given in Case AUTH/1123/1/01. No breach of the Code was ruled in that regard.

On appeal by GlaxoSmithKline the Appeal Board noted that the relevant section of the SPC to which the claim 'Avandia has favourable effects on lipid profile' was referenced was that relating to undesirable effects wherein it was stated that hypercholesterolaemia had been reported in some patients. By way of explanation and mitigation it was further stated that 'the elevated total cholesterol levels were associated with increase in both LDL and HDL, but the ratio of total cholesterol:HDL was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment'. The Appeal Board was concerned that a statement included in the SPC to place an adverse reaction in its clinical context was being used to support a claim in promotional material for a favourable effect in general. The

Appeal Board considered that referencing the claim to the SPC gave it a credence which was not justified. The Appeal Board accepted that there was data to show that Avandia clearly had beneficial effects on specific aspects of the plasma lipid profile, for example HDL-C, however the claim for a favourable effect on the plasma lipid profile overall was too broad given the data. The Appeal Board considered that the claim was misleading as alleged and upheld the Panel's ruling of a breach of the Code.

Takeda UK Limited complained about the promotion of Avandia (rosiglitazone) by GlaxoSmithKline UK Limited. The claim at issue 'Avandia has favourable effects on lipid profile' had been used in a number of promotional items. Takeda supplied Actos (pioglitazone).

COMPLAINT

Takeda stated that it had a number of concerns about GlaxoSmithKline's promotion of Avandia for the treatment of type 2 diabetes; on two occasions the company had to resort to complaints to the Authority.

In Case AUTH/1123/1/01 the Panel ruled SmithKline Beecham, in breach of Clause 7.2 of the Code because its claim for a reduction in the TC:HDLC ratio relied on data where concomitant statin therapy might have affected the outcome. (Fonsecca *et al* 2000). In its current materials GlaxoSmithKline no longer used this study to support its claim for positive effects on the lipid profile, but instead cited the Avandia summary of product characteristics (SPC).

The Panel had previously noted the contents of the Avandia SPC Section 4.8 Undesirable Effects. This section stated that '… total cholesterol:HDLc ratio was unchanged or improved' and referred to increases in both LDLc and HDLc during treatment with no mention of any beneficial effects on triglycerides. Earlier in the same section the following adverse events were listed: hyperlipaemia and hypercholesterolaemia in combination with metformin, and hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia in combination with sulphonylureas.

The Avandia SPC stated: 'Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone and sulphonylurea and rosiglitiazone and metformin respectively. The elevated total cholesterol levels were associated with increase in both LDLc and HDLc, but the ratio of total cholesterol:HDLc was unchanged or improved in long term studies'.

Takeda stated that GlaxoSmithKline had elected to replace a specific claim for reduction in TC:HDLC ratio that had been found in breach of the Code with a claim implying overall lipid benefit when there was no scientific data to support any beneficial effects on LDLC or triglycerides. In Takeda's opinion this was a worse breach than GlaxoSmithKline's previous offence. The Avandia SPC did not support a claim that the product had a favourable effect on lipid profile. Changing the wording and the reference from that previously found in breach did not alter the fact that a global lipid benefit claim for Avandia was in disagreement with the main body of scientific evidence. Takeda therefore alleged that this claim was in breach of Clause 7.2.

* * * * *

The Authority noted that the complaint appeared to involve a possible breach of undertaking. This aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board. When writing to GlaxoSmithKline to advise it of the complaint the company was requested to consider, in addition to Clause 7.2 cited by Takeda, the provisions of Clauses 22, 9.1 and 2 of the Code.

* * * * *

RESPONSE

GlaxoSmithKline noted that Takeda cited Clause 7.2 of the Code as the basis for its complaint. Given, however, that the nature of its concerns related to the substantiability of the claim, and to its referencing, GlaxoSmithKline maintained that Clauses 7.4 and 7.6 were also of relevance. GlaxoSmithKline emphatically rejected the implication made by Takeda that the claim in question represented a breach of undertaking (and therefore of Clause 22 of the Code), inasmuch as GlaxoSmithKline had never given any undertaking with respect to claims concerning the general effects of Avandia on the lipid profile.

As the claim in question was a general one, and therefore did not refer to particular published studies (Clause 7.6), there was no obligation under the Code to specify every reference underpinning it. GlaxoSmithKline chose, in this instance, to provide the SPC for Avandia as a single overall reference; but, as would be seen below, there was a considerable body of additional data supporting the claim.

GlaxoSmithKline raised two questions: Firstly was the claim substantiable by available data, so as to comply with Clauses 7.2 and 7.4 of the Code, and secondly if so, did the citation of the SPC as a sole reference for the claim somehow render it misleading, or otherwise in breach of the Code?

Was the claim substantiable? In assessing the effects of an agent on the lipid profile, a variety of different parameters must be considered, and some consideration given as to which were the most clinically significant in relation to their impact on cardiovascular risk. The generally accepted view was that the most important measures were HDL-cholesterol (HDL) and its subfractions; LDL-cholesterol (LDL), both absolute levels and particle size; and the ratio between total cholesterol and HDL-cholesterol (TC-HDL ratio). High levels of HDL were considered to be beneficial (atheroprotective); whereas higher levels of LDL, smaller denser LDL particles, and an increased TC-HDL ratio were believed to be harmful (atherogenic). Other lipid parameters included triglycerides and non-esterified fatty acids

(NEFAs), although the linkage between these and cardiovascular risk was far more debatable.

These parameters would be discussed individually below, with particular reference to the effects of Avandia.

HDL-cholesterol: Major morbidity/mortality trials had confirmed that raising low levels of HDL was an important target of therapy. A 6% increase in HDL was associated with a 22% reduction in the risk of myocardial infarction and death from coronary artery disease. More specifically, in type 2 diabetics (the target population for Avandia), low HDL levels had been shown to be a consistent predictor of coronary heart disease mortality and morbidity.

The highly beneficial effects of Avandia on HDL levels had been documented in numerous studies. Avandia monotherapy increased HDL levels by 25% after 100 weeks, compared to baseline. In combination with metformin over 18 months, there was a 19% increase in HDL levels over baseline; the corresponding increase in combination with glibenclamide over the same time-period was 11%. Furthermore, in an abstract presented at the 2002 conference of the American Diabetes Association, the increases in HDL levels observed with Avandia administration were reported as being significantly greater than those seen with pioglitazone.

The protective role of HDL was believed to be mainly mediated through the HDL_2 subfraction, and Avandia monotherapy had been shown to lead to a 12.6% increase in this atheroprotective subfraction.

LDL-cholesterol: The benefits of reducing LDL levels were all accepted, and underlaid the use of statins in reducing cardiovascular risk. More recently, it had been recognised that as smaller LDL particles were able to penetrate the blood vessel wall more rapidly, increasing the size of the LDL particles themselves might be more important than reducing the overall level of LDL-cholesterol in terms of altering the progression of coronary artery disease. Thus, the presence of small, dense LDL particles was associated with a 3.6-fold increase in the risk of cardiovascular disease. The lipid profile of type 2 diabetics was characterised by the presence of small, dense, atherogenic LDL particles; and the prevalence of such particles might be doubled in diabetic patients.

Inasmuch as insulin resistance had been shown to correlate inversely with LDL particle size, one might expect that administration of an insulin-sensitising agent such as Avandia would result in a beneficial increase in particle size. This had indeed been shown to be the case. Treatment with Avandia led to a shift from small atherogenic LDL particles towards larger, less atherogenic particles. In one study, the proportion of particles with a relative flotation greater than 0.2632 was increased from approximately 45% at study entry to approximately 70% after eight weeks on Avandia. This Avandia-induced shift in LDL particle size resulted in a small, short-term increase in total LDL levels, which stabilised over the longer term.

TC-HDL ratio: The TC-HDL ratio (the ratio between total cholesterol [the sum of HDL-plus LDL-cholesterol] and HDL-cholesterol) was a strong predictor of cardiovascular risk, and the Joint British Societies' recommendations on the prevention of coronary heart disease in clinical practice used the TC-HDL ratio to estimate coronary risk.

The effects of Avandia on this parameter were complicated by the fact that – as might be expected in trials conducted in dyslipidaemic diabetics – a significant proportion of the patients included in the trials were concomitantly being treated with a statin. The significance of the data concerned had been the subject of a previous case between Takeda and SmithKline Beecham (Case AUTH/1123/1/01). Nevertheless, the fact remained that, in evaluating these data, the regulators were of the opinion that they demonstrated that 'the TC-HDL ratio was unchanged or improved in long-term studies', and this statement was included in the SPC for Avandia. Independent regulatory assessment of the long-term effects of Avandia on this ratio was thus that they were neutral or beneficial. Taken in conjunction with Avandia's unambiguously beneficial effects on HDL and LDL, as referred to above, GlaxoSmithKline contended that Avandia administration led to a marked overall improvement in the most clinically significant elements of the lipid profile, fully substantiating the claim at issue.

Other lipid parameters: GlaxoSmithKline noted that Takeda was particularly keen to put forward the importance of triglycerides, inasmuch as administration of its agent, pioglitazone, had been shown to reduce triglyceride levels in overtly hypertriglyceridaemic patients. Unfortunately, the balance of medical opinion and evidence suggested that triglycerides were unlikely to be an independent risk factor for cardiovascular disease. Thus, in the VA-HIT study to evaluate the efficacy of gemfibrozil, a 31% reduction in triglycerides was not associated with a reduction in coronary events, whereas HDL was observed to be an independent risk factor (Miller, 2000). Likewise, the United Kingdom Prospective Diabetes Study (UKPDS), the largest and most significant study yet conducted in type 2 diabetes, failed to show triglycerides to be an independent risk factor (Turner *et al* 1998). Notably, triglyceride levels were not included in the recently published UKPDS cardiovascular risk model, unlike the TC:HDL ratio.

The overall effects of Avandia on triglycerides appeared to be neutral. However, it should be noted that (unlike the corresponding pioglitazone studies), patients in these trials were predominantly normotriglyceridaemic, and the effect of thiazolidinediones on plasma triglycerides appeared to depend heavily on baseline levels. The definitive effects of Avandia on this parameter in high-baseline patients remained to be determined.

Avandia had also been shown to cause significant reductions in NEFA levels although the clinical significance of such a reduction was uncertain.

In summary: GlaxoSmithKline noted that Avandia had been shown to be associated with the following lipid effects: highly significant increases in overall HDL levels; significant increases in HDL_2, the most atheroprotective HDL subfraction; significant

increases in LDL particle size, and reductions in LDL density, without long-term increases in absolute LDL levels; no change or improvement in the TC-HDL ratio over the long term; significant reductions in NEFA levels and a neutral effect on triglycerides in predominantly normotriglyceridaemic patients.

Taken as a whole, GlaxoSmithKline believed that these data incontrovertibly substantiated the claim that Avandia had favourable effects on the lipid profile, and this view had been confirmed by recent independent evaluation (Wagstaff and Goa 2002). GlaxoSmithKline thus contended that, contrary to Takeda's allegations, the claim complied in all respects with Clauses 7.2 and 7.4 of the Code.

Did the citation of the SPC as the sole reference for the claim in question render it misleading, or otherwise in breach of the Code? Given that the claim in question was substantiable independently of the SPC, and that the SPC itself did not contradict any of the above conclusions, it was difficult to see how citation of the SPC as a reference could, in and of itself, represent a breach of the Code as GlaxoSmithKline understood it. Equally, it was at first sight hard to understand why Takeda should so vehemently protest this course of action. If anything, referencing the SPC alone provided a less comprehensive impression of the lipid effects of Avandia than would be achieved by citing the totality of the studies referred to above.

As already noted, the SPC stated that 'the ratio of total cholesterol:HDLc was unchanged or improved in long term studies'. It likewise noted that 'elevated cholesterol levels were associated with increase in both LDLc and HDLc', again as noted above. The references to hyperlipidaemia in the SPC, raised by Takeda, referred to uncommon adverse effects, and could not be taken as representative of the general effect of Avandia on the lipid profile.

Inasmuch as HDL levels and the TC-HDL ratio represented the two most clinically significant lipid parameters for cardiovascular risk, and as the SPC noted the increases in the former seen with Avandia, and its long-term neutral or beneficial effects on the latter, GlaxoSmithKline believed that it was perfectly appropriate to cite the SPC as a 'minimal' reference for the claim that Avandia had favourable effects on the lipid profile. However, GlaxoSmithKline reiterated that the claim was substantiable independently of the SPC.

GlaxoSmithKline believed that Takeda sought to prevent GlaxoSmithKline from making a claim included in its SPC, namely that the TC-HDL ratio was unchanged or improved following long-term treatment with Avandia. Insofar as one of the primary functions of the Code was precisely to ensure that promotional claims were consistent with product SPCs, GlaxoSmithKline believed that such an approach was by its very nature, without merit.

Takeda wished to interpret the outcome of Case AUTH/1123/1/01, referred to above, as implying that no claim for Avandia with respect to the TC-HDL ratio could legitimately be made. This certainly did not accord with GlaxoSmithKline own interpretation. In its ruling in Case AUTH/1123/1/01, the Panel did not give an opinion on whether the SPC statement was a fair reflection of the study data. The particular promotional item found to be in breach on that occasion had, wrongly, failed to include the 'unchanged' portion of the 'unchanged or improved' wording of the SPC statement on the effects of Avandia on the TC-HDL ratio, and it was for this reason that the piece was found to be in breach of Clause 7.2. GlaxoSmithKline had accepted this ruling and as a result undertook to ensure that the full wording would be employed in all future promotional materials, and this undertaking had been scrupulously observed, thus ensuring complete consistency with the SPC wording.

Takeda also took the view that it was improper to make 'a claim implying overall lipid benefit [for Avandia] when there was no scientific data to support beneficial effects on LDLc or triglycerides'. For LDLc, as noted above, Takeda's assertions were simply wrong. For triglycerides, the effects of Avandia were at worst neutral; and the clinical relevance of this parameter was, in any event, questionable. The claim at issue 'Avandia has favourable effects on lipid profile', did not necessarily imply that favourable effects had been unequivocally demonstrated with every possible lipid parameter; but rather that the balance of evidence, especially for the clinically more important measures, was overwhelmingly in favour of the claim.

In summary GlaxoSmithKline did not accept that citation of the SPC as a reference for the claim at issue could represent a breach of the Code, given that the claim was fully substantiated by other evidence, and was consistent with the SPC wording. Indeed, it was difficult to see what clause of the Code could possibly be breached by this approach.

PANEL RULING

The Panel noted that Section 4.8 of the Avandia SPC, Undesirable Effects, stated that 'Adverse experiences of hypercholesterolaemia were reported in 3.6% and 2.1% of patients treated with rosiglitazone + sulphonylurea and rosiglitazone + metformin respectively. The elevated total cholesterol levels were associated with increase in both LDLc and HDLc, but the ratio of total cholesterol: HDLc was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment'. Thus plasma lipids were raised in only a minority of patients but, when they were, the ratio of total cholesterol: HDLC was unchanged or improved suggesting that there should be no resultant adverse cardiovascular effects.

The Panel noted that in a detail aid (ref 20278693), page 13 was headed 'Avandia has positive effects on a range of cardiovascular risk factors'. One of the positive effects listed, under a sub-heading of 'Dyslipidaemia', was the claim in question 'Avandia has favourable effects on lipid profile' referenced to the SPC. In the Panel's view the favourable effects listed in the SPC related only to those few patients in whom hypercholesterolaemia occurred.

The claim in question referred to the lipid profile; the lipid profile was composed of many lipid fractions. In

the Panel's view most readers would assume from the claim that in all patients Avandia had positive effects on all aspects of the lipid profile which was not so. The Panel noted that the review by Wagstaff and Goa, cited by GlaxoSmithKline in support of the claim, stated that rosiglitazone improved lipid profile but continued by qualifying that statement in brackets with '(decreased small dense LDL, increased HDL)'. The Panel noted that the effects of Avandia on the total cholesterol: HDLC ratio were complicated in that a significant proportion of the patients included in the trials were, at the same time, taking statins.

Overall the Panel considered that the claim 'Avandia has favourable effects on lipid profile' was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that in the previous case cited by Takeda, Case AUTH/1123/1/01, the claim for a reduction in TC-HDLC ratio at 18 months in Avandia treated patients was ruled in breach of the Code because it was based on the results of studies in which a statin might have been added to a patient's therapy. The claim now at issue in Case AUTH/1337/6/02 was different to that in the previous case; it referred to the lipid profile as a whole and not just one aspect of it. The Panel considered that the new claim was sufficiently different from the old one not to be caught by the undertaking and assurance given in Case AUTH/1123/1/01. No breach of Clauses 22, 9.1 and 2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline noted that the Panel concluded that 'most readers would assume from the claim 'Avandia has favourable effects on lipid profile' that in all patients Avandia had positive effects on all aspects of the lipid profile, which was not so'. GlaxoSmithKline believed that this represented an unreasonable and impossibly rigorous criterion against which to judge promotional claims; and, furthermore, that to employ such a criterion was patently inconsistent with universally accepted practice. Indeed, were it to be applied generally, it would effectively render impermissible any promotional claim for any product.

GlaxoSmithKline did not accept that any reasonable clinician would infer from the claim that administration of Avandia would necessarily lead, in all patients, to improvements in all lipid parameters. On the contrary, a more reasonable interpretation would be that, in properly conducted clinical trials, administration of Avandia had been shown to lead to statistically and clinically significant improvements in a range of lipid parameters, particularly those generally considered to be most important with respect to cardiovascular risk, leading to an overall beneficial effect on the lipid profile as a whole. Without reiterating here the details of its response, GlaxoSmithKline believed that the clinical trials data obtained from Avandia overwhelmingly supported this interpretation, and thus the claim itself. GlaxoSmithKline noted in its response, this view was supported in independent reviews of the effects of Avandia.

GlaxoSmithKline also noted that, in the view of the Panel, 'the favourable effects [on lipid parameters] listed in the SPC related only to those few patients in whom hypercholesterolaemia occurred'. The favourable effects specifically mentioned in the SPC were increases in HDL, on the one hand; and no change or improvement in the TC:HDL ratio, on the other.

While the SPC statement on increases in HDL might have related only to those patients in whom hypercholesterolaemia was noted, the overall claim could only be misleading under Clause 7.2 of the Code if significant increases in HDL were not observed in the generality of patients. However, an extensive body of robust and consistent evidence demonstrated an unequivocally positive effect of Avandia on HDL and its most atheroprotective subfraction. The Code did not mandate citation of every reference relating to a claim, only that the claim itself be substantiable. In this case, it was difficult, if not impossible, to see how the SPC statement on HDL could be considered misleading if the beneficial effects of Avandia on this parameter were fully supported by the evidence, as GlaxoSmithKline believed they were.

With respect to the TC:HDL ratio, the Panel seemed to have misinterpreted the SPC wording relating to this parameter. This stated that the 'the ratio of total cholesterol:HDLc was unchanged or improved in long-term studies'. These studies were general in nature, and were not solely carried out on 'those few patients in whom hypercholesterolaemia occurred', as stated erroneously in the Panel's ruling.

GlaxoSmithKline did not accept the view that the SPC statements on the effects of Avandia on HDL and the TC:HDL ratio could be considered in any way misleading. GlaxoSmithKline considered that the SPC was an appropriate 'minimal' overall reference for the claim in question; the SPC did not provide as positive an impression of the global effects of Avandia on the lipid profile as would be conveyed by citing the totality of the evidence available (an option open to GlaxoSmithKline in preparing the relevant materials), GlaxoSmithKline could not understand why referencing the SPC alone rendered the claim in breach of the Code.

The third point GlaxoSmithKline wished to raise related to the Panel's interpretation of the admissibility of using the SPC statement on the effects of Avandia on the TC:HDL ratio in promotional materials, either implicitly or explicitly. This had been the subject of prior dispute between Takeda and GlaxoSmithKline; the ruling issued by the Panel in Case AUTH/1123/1/01 had evidently been interpreted quite differently by the two companies. GlaxoSmithKline had always believed that the reason that a breach was ruled in that particular case was that in the promotional material in question at the time, the word 'unchanged' had wrongly been omitted from the SPC statement that the TC:HDL ratio was 'unchanged or improved in long-term studies'.

GlaxoSmithKline was therefore very concerned to read the Panel's opinion in the current case that 'the claim for a reduction in TC:HDL ratio at 18 months in Avandia-treated patients was ruled in breach of the Code because it was based on the results of studies in

which a statin might have been added to a patient's therapy'.

While the concomitant administration of statins in Avandia-treated patients was undoubtedly a confounding factor, there were strong reasons for believing that the clinically significant long-term reductions in TC-HDL ratio seen in the studies in question might not be due to the effects of the statin alone. Whereas statins exerted their main effect in lowering LDL, and had a more modest effect on increasing HDL, the effect of Avandia was predominantly to raise HDL levels. This effect might be associated with a small quantitative increase in LDL levels, although there was a qualitative shift towards less dense, and hence less atherogenic, LDL particles. In quantitative terms, then, the effects of Avandia and statins were complementary.

In considering the evidence the regulatory authorities clearly took the view that the data warranted the SPC statement referred to above: that the TC-HDL ratio was unchanged or improved in long-term trials with Avandia. As this statement formed part of the licence for Avandia, GlaxoSmithKline believed it could not, by definition, be held in breach of the Code by referring to it, whether such reference was direct or (as in the current case) indirect. Given that the wording of a product's licence was the bedrock on which the Code was founded, GlaxoSmithKline did not accept that it was within the remit of the Panel – still less that of a competitor company – to decide which particular statements in a licence might be deemed 'acceptable' and which might not. Were such a principle to be upheld, it would have serious and potentially far-reaching implications. GlaxoSmithKline therefore submitted it was justified in asking the Appeal Board to make a specific and unambiguous ruling on this issue.

COMMENTS FROM TAKEDA

Takeda maintained that the claim 'Avandia has favourable effects on lipid profile' was a broad, unqualified claim which implied that favourable effects were seen on the whole lipid profile. When the effects of rosiglitazone on the individual lipids were examined this was clearly not the case.

In the two main studies used in GlaxoSmithKline's promotional material, rosiglitazone in combination with metformin or a sulphonylurea had increased LDL-C, HDL-C and triglycerides with no significant change in the total cholesterol-HDL ratio.

A review of rosiglitazone written by GlaxoSmithKline's Medical Information Department (USA) (Werner, 2001) stated that rosiglitazone was associated with mean increases in LDL-C and HDL-C compared with baseline, with a variable but overall neutral effect on triglycerides at 52 weeks. This review also stated that the increase in LDL-C occurred primarily during the first 1-2 months of therapy, remained elevated above baseline through 52 weeks, and that the total cholesterol: HDL ratio was unchanged from baseline in a 1 year study.

As previously noted in Case AUTH/1123/1/01, in the two data on file references used to support the long-term effect of rosiglitazone in combination with metformin or sulphonylureas on plasma lipids it was clearly stated that the return of LDL-C towards baseline levels after long-term treatment was largely attributable to initiation of lipid lowering therapy. Patients who did not receive lipid-lowering therapy had an increase in LDL-C that plateaued but did not appear to diminish appreciably with long-term treatment (mean increase at 18 months 8.7mg/dl in combination with metformin and 6.6mg/dl in combination with sulphonylurea).

There were also seven published prospective head to head studies of rosiglitazone vs Actos in addition to the retrospective study EVIDENT (Boyle *et al* 2002). The lipid effects seen with rosiglitazone in these seven studies included increases in triglycerides and total cholesterol and varying effects on LDL-C and HDL-C. In EVIDENT rosiglitazone was associated with reductions in triglycerides, total cholesterol, HDL-C and an increase in LDL-C.

Takeda noted that in GlaxoSmithKline's original response it commented that the clinical relevance of triglycerides was questionable. A number of studies had concluded that high triglyceride levels, independent of HDL-C, were a significant risk factor for cardiovascular disease (Austin *et al* 1998). Several studies (Framingham Heart Study, the Prospective Cardiovascular Munster Study, the Helsinki Heart Study and the Baltimore Coronary Observational Long-term study) suggested that triglyceride levels should be considered in coronary heart disease assessment and that the current goals for triglycerides should be reduced. It was clear that a cohort of patients with low HDL cholesterol levels or a high LDL-HDL cholesterol ratio in association with elevated triglyceride levels might be at increased risk. Many patients with Type 2 diabetes fitted this pattern. It was difficult to uncouple the increase in HDL cholesterol from the reduction in triglycerides because these lipids were physiologically linked in a 2-way exchange pathway mediated by cholesterol ester transfer protein.

Taken as a whole, the effects of rosiglitazone on the lipid profile could not be considered to be favourable.

In relation to GlaxoSmithKline's concern that the Panel considered the favourable effects on lipid parameters listed in the SPC related only to patients in whom hypercholesterolaemia occurred, Takeda noted that GlaxoSmithKline acknowledged that this was the case but suggested that there were additional data that supported the claim in the generality of patients. As discussed above Takeda did not believe that the current body of evidence had supported the claim in the generality of patients.

In relation to GlaxoSmithKline's third point, Takeda was not in a position to comment on the EMEA's reasoning behind it authorising the statement that rosiglitazone's effects on TC:HDL-C ratio were *'unchanged or improved'* within the safety section of the rosiglitazone SPC. However it was not unknown for product labelling to contain data or claims that could not be used as blanket statements or out of context in promotional material. The statement GlaxoSmithKline referred to was made only in the

safety section of the SPC where it was intended to be read within the context of patients with hypercholesterolaemia.

Takeda did not believe that there was any foundation to support GlaxoSmithKline's appeal.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Avandia has favourable effects on lipid profile' was referenced to the Avandia SPC. The section of the SPC in question was that relating to undesirable effects wherein it was stated that hypercholesterolaemia had been reported in some patients. By way of explanation and mitigation it was further stated that 'the elevated total cholesterol levels were associated with increase in both LDL and HDL, but the ratio of total cholesterol:HDL was unchanged or improved in long term studies. Overall, these increases were generally mild to moderate and usually did not require discontinuation of treatment'. The Appeal Board was concerned that a statement included in the SPC to place an adverse reaction in its clinical context was being used to support a claim in promotional material for a favourable effect in general. The Appeal Board considered that referencing the claim to the SPC gave it a credence which was not justified. The Appeal Board accepted that there was data to show that Avandia clearly had beneficial effects on specific aspects of the plasma lipid profile, for example HDL-C, however the claim for a favourable effect on the plasma lipid profile overall was too broad given the data. The Appeal Board considered that the claim was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal was unsuccessful.

Complaint received **24 June 2002**

Case completed **7 October 2002**

CASE AUTH/1338/6/02

SANOFI-SYNTHELABO v GLAXOSMITHKLINE

Lamictal journal advertisements

Sanofi-Synthelabo complained about two journal advertisements issued by GlaxoSmithKline which promoted the use of Lamictal (lamotrigine) in epilepsy. Sanofi-Synthelabo marketed Epilim (sodium valproate).

The first advertisement featured a photograph of a young woman shopping for shoes. Two claims read 'Controls seizures' and 'Has no effect on shopping'. The Lamictal product logo appeared with the claim 'Epilepsy treatment with women in mind'.

Sanofi-Synthelabo stated that Lamictal was licensed for use as monotherapy in adults and children over 12 years of age for simple and complex partial seizures, secondarily generalised tonic-clonic seizures and primary generalised tonic-clonic seizures. The claim 'Controls seizures' was all-embracing and implied that Lamictal was licensed for all types of seizures including absences (petit mal) and myoclonic seizures. The claim had not been cross-referenced to the summary of product characteristics (SPC) nor had it been attributed to any quoted literature and therefore remained unsubstantiated. Lamictal was not licensed for use as add-on therapy in children under 2 years of age and could not be used as monotherapy in children under 12 years. The claim 'Controls seizures' implied suitability for all age groups.

Lamotrigine monotherapy was unlikely to provide freedom from seizures in more than 60.4% of patients with partial and/or generalised tonic-clonic seizures (Reunanen *et al* 1996). Sanofi-Synthelabo alleged, therefore, that the claim 'Controls seizures', was an exaggeration and a generalisation.

Additionally Sanofi-Synthelabo alleged that the claim 'Has no effect on shopping' was misleading and exaggerated. The claim implied that Lamictal had no effect on activities of daily living, which was clearly false as the side effects listed in the SPC included drowsiness, agitation, unsteadiness, nystagmus, confusion and hallucinations etc.

A major concern of Sanofi-Synthelabo was that the advertisements encouraged the belief that Lamictal was safe in women of childbearing potential despite the caution in the SPC: 'There are insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus'.

In the Panel's view the claim 'Controls seizures' implied that Lamictal could be used successfully in all types of seizures; this was not so. The claim was too general given the indications for the product. The Panel considered that the claim was inconsistent with the SPC, misleading, not capable of substantiation and exaggerated as alleged. Breaches of the Code were ruled.

The Panel did not consider that the claim meant that patients would be seizure-free. Control could mean that seizures were less frequent and/or less severe. The Panel did not consider that use of the word 'control' meant that the claim was exaggerated as alleged. No breach of the Code was ruled on this narrow point.

The Panel noted that Lamictal was indicated as add-on therapy in children between age 2 and 12. The

claim 'Controls seizures' could be read as implying that Lamictal was suitable for all epileptic patients but the Panel considered that in association with a photograph of a young woman the claim did not imply suitability in all age groups. The Panel thus ruled no breach of the Code.

The Panel considered that the claim 'Has no effect on shopping' was a strong claim. The side effects for the product were such that they could have an effect on activities such as shopping. The Panel considered that the claim was misleading, not capable of substantiation and exaggerated. Breaches of the Code were ruled.

The Panel considered the claim 'Epilepsy treatment with women in mind', would encourage readers to think that Lamictal was particularly suited to the treatment of women. One aspect of such treatment was use in pregnancy which was of particular concern when treating epilepsy. According to the SPC Lamictal could be used in pregnancy if in the opinion of the physician the potential benefits outweighed any possible risk to the developing foetus. The Panel did not accept that the advertisement implied that Lamictal was safe for use in pregnancy. However, although the product might cause less problems in pregnancy than other antiepileptics it was not entirely without risk. The Panel considered that the claim in effect concealed this risk and was misleading in that regard. The Panel ruled a breach of the Code.

The Panel did not consider that the claim 'Epilepsy treatment with women in mind' was inconsistent with the particulars listed in the SPC. Lamictal was not contraindicated in pregnancy. No breach of the Code was ruled.

The second Lamictal advertisement featured a photograph of three young girls in a bedroom pretending to be pop stars or applying make-up. Two claims read 'Controls seizures' and 'Has no effect on sleepovers'. The Lamictal product logo appeared with the claim 'Epilepsy treatment with girls in mind'. The claim 'Controls seizures' was alleged to be an all-embracing claim implying the applicability for all seizure types despite Lamictal's limited licensed indications; suitability for all patient groups, and given the imagery of the advertisement, particularly children; and complete seizure freedom (ie absolute seizure control). The claim 'Controls seizures' had not been qualified by reference to the SPC or to medical literature and was therefore an unsubstantiated claim. Lamictal's marketing authorization did not include monotherapy for children under the age of 12 years, whereas the advertisement depicted girls who could be perceived to be under 12 years of age.

Sanofi-Synthelabo alleged that the claim 'Epilepsy treatment with girls in mind' appeared to confirm concerns that GlaxoSmithKline was promoting outside the licensed indication when, in girls under 12 years of age, the SPC recommended that Lamictal could only be prescribed as add-on treatment; this was not clearly stated.

Sanofi-Synthelabo alleged that the claim 'Has no effect on sleepovers' was a misleading and exaggerated claim, which implied that Lamictal did not disrupt recreational or group activities and had no effect on sleep. The SPC, however, listed a whole host of side effects, which could interfere with activities of daily living as well as effects on sleep.

The Panel noted its ruling regarding the claim 'Controls seizures' and seizure type above and considered that its ruling that the claim was too general given the indications for the product also applied to this advertisement. Breaches of the Code were ruled.

The Panel also considered that its rulings with regard to the use of the word 'control' in relation to patients being seizure-free also applied to this advertisement. No breach of the Code was ruled on this narrow point.

The Panel considered that the advertisement would be read as referring only to the use of Lamictal in children. It therefore decided that in this context the claim 'Controls seizures' referred only to children; it was not a claim for suitability in all patient groups. The Panel ruled no breach of the Code. The Panel considered whether it was appropriate for the company to claim that Lamictal controlled seizures in girls. In this regard, the Panel noted GlaxoSmithKline's response that all the models were over 12 years old. Lamictal could be used in children under 12 but only as add-on therapy not monotherapy. The Panel considered that the depiction of girls who could be perceived as under 12 years old was not inconsistent with the SPC and no breach of the Code was ruled. However the Panel considered that the advertisement was misleading as it did not make it clear that in this age group Lamictal could only be used as add-on therapy. A breach of the Code was ruled. The Panel did not consider that the artwork *per se* failed to comply with the Code and no breach was ruled.

The Panel considered that the claim 'Has no effect on sleepovers' was a strong claim. The Panel noted its comments above with regard to the claim 'Has no effect on shopping' and considered that they were relevant here. The Panel considered that the claim was misleading, not capable of substantiation and exaggerated. Breaches of the Code were ruled. The Panel did not consider that the claim was a specific claim about side effects and thus no breach of the Code was ruled.

No breach of the Code was ruled with regard to allegations that both advertisements were disguised promotion.

Sanofi-Synthelabo Limited complained about two journal advertisements (refs LAM/FPA/02/692 and LAM/DPS/02/693) for Lamictal (lamotrigine) issued by GlaxoSmithKline UK Limited. The advertisements had appeared in Hospital Doctor (18 April and 25 April).

Both advertisements promoted the use of Lamictal in epilepsy and Sanofi-Synthelabo's concerns related to the advertisements implying the applicability of Lamictal not just for the licensed indications but all seizure types; the suitability of Lamictal for all groups

of patients, including children; and the inference that treatment with Lamictal provided complete seizure freedom (ie absolute seizure control).

Sanofi-Synthelabo marketed Epilim (sodium valproate).

1 Lamictal journal advertisement LAM/FPA/02/692

The advertisement featured a photograph of a young woman trying on some shoes in a shoe shop. Two claims in the top left-head corner read 'Controls seizures' and 'Has no effect on shopping'. The Lamictal product logo appeared in the bottom left-hand corner with the claim 'Epilepsy treatment with women in mind'.

COMPLAINT

Sanofi-Synthelabo stated that Lamictal was licensed for use as monotherapy in adults and children over 12 years of age for simple and complex partial seizures, secondarily generalised tonic-clonic seizures and primary generalised tonic-clonic seizures. The claim 'Controls seizures' was an all-embracing claim, which implied that Lamictal was licensed for all types of seizures including absences (petit mal) and myoclonic seizures. The claim 'Controls seizures' had not been cross-referenced to the summary of product characteristics (SPC) nor had it been attributed to any quoted literature and therefore remained unsubstantiated despite correspondence with GlaxoSmithKline. Sanofi-Synthelabo alleged a breach of Clauses 3.2, 7.2, 7.4 and 7.10 of the Code.

Lamictal was not licensed for use as add-on therapy in children under 2 years of age and could not be used as monotherapy in children under 12 years. The claim 'Controls seizures' alone implied suitability for all age groups. Sanofi-Synthelabo alleged a breach of Clauses 3.2, 7.2 and 7.10.

Brodie *et al* (1995) which examined lamotrigine monotherapy in newly diagnosed epilepsy, reported that the proportion of seizure-free patients during a 24-week period was 35% for those with partial seizures with or without generalisation, 47% for those with primary generalised tonic-clonic seizures and 39% for all seizures. A broader review of the literature indicated that lamotrigine monotherapy was unlikely to provide freedom from seizures in more than 60.4% of patients with partial and/or generalised tonic-clonic seizures (Reunanen *et al* 1996). Sanofi-Synthelabo alleged, therefore, that the claim 'Controls seizures', was an exaggeration and a generalisation in breach of Clauses 7.2, 7.4 and 7.10.

Additionally Sanofi-Synthelabo alleged that the claim 'Has no effect on shopping' was misleading and exaggerated in breach of Clauses 7.2, 7.4 and 7.10. The claim implied that Lamictal had no effect on activities of daily living, which was clearly false as the side effects listed in the SPC included drowsiness, agitation, unsteadiness, nystagmus, confusion and hallucinations etc. All of these could have a significant impact on activities of daily living including shopping and therefore the claim that there was 'no effect' was misleading.

A major concern was that the advertisements encouraged the belief that Lamictal was safe in women of childbearing potential and therefore also in pregnancy despite the SPC caution about safety in pregnancy: 'There are insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus'. There was no clear evidence that the newer anticonvulsants were safe in pregnancy and Lamictal was no exception in this respect. Sanofi-Synthelabo alleged a breach of Clauses 3.2, 7.2 and 10.1 of the Code.

RESPONSE

GlaxoSmithKline did not agree that the claim Lamictal 'Controls seizures' was incompatible with the terms of the marketing authorization or inconsistent with the particulars listed in the SPC. Lamictal was an antiepileptic medicine, and had been licensed as such in the UK since October 1991. By definition all antiepileptic medicines, including Lamictal, had the ability to control seizures. The types of seizures for which Lamictal was licensed were clearly set out in the prescribing information, which formed an integral part of the advertisement. Therefore GlaxoSmithKline did not consider it necessary to also reference the SPC. Neither did GlaxoSmithKline consider the advertisement to be misleading, exaggerated, all-embracing or incapable of substantiation, since no claim was made that Lamictal was effective in all types of seizure.

GlaxoSmithKline disagreed with Sanofi-Synthelabo's interpretation that the claim, 'Controls seizures', implied Lamictal was suitable for use in all age groups. Lamictal was licensed as add-on therapy in patients aged over 2 years and as monotherapy in patients aged over 12 years. Again this point was explicitly covered in the prescribing information, which formed an integral part of the advertisement. GlaxoSmithKline therefore maintained that this advertisement was not misleading, exaggerated or all-embracing, and was fully compatible with the terms of the marketing authorization and the SPC.

With reference to only two clinical papers (Brodie *et al*, Reunanen *et al*) Sanofi-Synthelabo suggested that control of seizures was synonymous with seizure-freedom. Based on these limited data Sanofi-Synthelabo alleged that the claim 'Controls seizures' implied that all patients who received Lamictal would become seizure-free. GlaxoSmithKline disagreed with this interpretation and maintained that the advertisement did not claim that patients receiving Lamictal would be seizure-free. The papers referenced by Sanofi-Synthelabo only considered lamotrigine used as monotherapy. As stated in the prescribing information, Lamictal was also licensed for use as add-on therapy in patients over 2 years of age, including patients with Lennox-Gastaut Syndrome. The advertisement, therefore, clearly covered the use of Lamictal as add-on therapy as well as monotherapy, ie use of Lamictal in patients with more refractory epilepsy who were unresponsive or inadequately controlled on monotherapy alone. It

was inappropriate to consider seizure-freedom as a measure of seizure control in these patient groups, and therefore in this advertisement. Furthermore, guidelines published by the International League Against Epilepsy for the clinical evaluation of anti-epileptic medicines recognised the following endpoints as parameters of efficacy, ie seizure control: change in seizure frequency, duration, pattern; change in seizure free interval; change in functional capacity; change in behaviour and performance (children only) and percentage of responders.

As patients with epilepsy often had to make lifestyle adjustments in order to adapt to the uncertainty of seizures, it was important to consider the impact that seizure control had on quality of life. Van Hout *et al* (1997) demonstrated in a cohort of patients with stable epilepsy that seizure frequency was inversely related to quality of life, particularly activities of daily living. GlaxoSmithKline stated that it had attempted to illustrate this point in the advertisement by selecting a common daily activity ie shopping. The claim 'Has no effect on shopping' therefore reflected the efficacy of Lamictal as an antiepileptic medicine. Clearly patients with epilepsy could better undertake such activities of daily living once their seizures were controlled. The claim neither stated nor implied that Lamictal had no adverse effects. Once again the prescribing information clearly listed all the adverse effects described by Sanofi-Synthelabo. GlaxoSmithKline therefore did not agree that this advertisement was misleading or exaggerated.

GlaxoSmithKline noted that Lamictal was licensed as monotherapy in females aged over 12 years, and as add-on therapy in females over 2 years. However, this advertisement in no way encouraged the use of Lamictal in pregnancy, and GlaxoSmithKline found it hard to understand why Sanofi-Synthelabo had come to this opinion. Again the prescribing information specifically stated 'There are insufficient data available on the use of Lamictal in human pregnancy to evaluate its safety. Lamictal should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risk to the developing foetus'. Consequently GlaxoSmithKline did not believe the advertisement was incompatible with the terms of the marketing authorization or inconsistent with the particulars listed in the SPC. Neither did GlaxoSmithKline believe the advertisement to be misleading in this respect. GlaxoSmithKline had difficulty understanding Sanofi-Synthelabo's complaint about disguised promotion, since this material appeared in the format of an advertisement in a medical journal and GlaxoSmithKline's sponsorship was clearly visible.

PANEL RULING

The Panel noted that Lamictal was indicated as monotherapy for children over 12 and adults for partial epilepsy with or without secondarily generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. It was indicated as add on therapy in adults and children over 2 for partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures and seizures associated with Lennox-Gastaut Syndrome.

In the Panel's view the claim 'Controls seizures' implied that Lamictal could be used successfully in all types of seizures; this was not so. The claim was too general given the indications for the product. It was an accepted principle under the Code that misleading claims could not be qualified by reference to the prescribing information. The Panel considered that the claim was inconsistent with the SPC, misleading, not capable of substantiation and exaggerated as alleged. Breaches of Clauses 3.2, 7.2, 7.4 and 7.10 were ruled.

The Panel did not consider that the claim 'Controls seizures' meant that patients would be seizure-free. Control could mean that seizures were less frequent and/or less severe. The Panel did not consider that use of the word 'control' meant that the claim was exaggerated as alleged. No breaches of Clauses 7.2, 7.4 and 7.10 were ruled on this narrow point.

The Panel noted that Lamictal was indicated as add on therapy in children between age 2 and 12. The claim 'Controls seizures' could be read as implying that Lamictal was suitable for all epileptic patients. The Panel considered that the advertisement referred only to adults. It therefore decided that overall the claim 'Controls seizures' with the photograph of a young woman did not imply suitability in all age groups. The Panel thus ruled no breach of Clauses 3.2, 7.2 and 7.10.

The Panel considered that the claim 'Has no effect on shopping' was a strong claim. The side effects for the product were such that they could have an effect on activities such as shopping. The Panel also noted GlaxoSmithKline's submission that patients with epilepsy could better undertake activities of daily living once their seizures were controlled. As noted above, if a patient's seizures had been controlled it did not mean that they were seizure-free. The Panel considered that the claim was misleading, not capable of substantiation and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 of the Code were ruled.

The Panel considered the claim 'Epilepsy treatment with women in mind', would encourage readers to think that Lamictal was particularly suited to the treatment of women. One aspect of such treatment was use in pregnancy which was of particular concern when treating epilepsy. The Panel noted that some of the older antiepileptics had been associated with an increased risk of neural tube defects (Ref BNF 43 March 2002). According to the SPC Lamictal could be used in pregnancy if in the opinion of the physician the potential benefits outweighed any possible risk to the developing foetus. The Panel did not accept that the advertisement implied that Lamictal was safe for use in pregnancy. However, although the product might cause less problems in pregnancy than other antiepileptics it was not entirely without risk. The Panel considered that the claim in effect concealed this risk and was misleading in that regard. The Panel ruled a breach of Clause 7.2.

The Panel did not consider that the claim 'Epilepsy treatment with women in mind' was inconsistent with the particulars listed in the SPC. Lamictal was not

contraindicated in pregnancy. No breach of Clause 3.2 of the Code was ruled.

The Panel also ruled no breach of Clause 10.1 as the advertisement was not disguised.

2 Lamictal journal advertisement LAM/DPS/02/693

This advertisement featured the photograph of three young girls in a bedroom pretending to be pop stars or applying make-up. Two claims in the top left-hand corner read 'Controls seizures' and 'Has no effect on sleepovers'. The Lamictal product logo appeared in the bottom left-hand corner with the claim 'Epilepsy treatment with girls in mind'.

COMPLAINT

Sanofi-Synthelabo was concerned about this advertisement for similar reasons but made a number of specific points.

The claim 'Controls seizures' was alleged to be an all-embracing claim implying the applicability for all seizure types despite Lamictal's limited licensed indications; suitability for all patient groups, and given the imagery of the advertisement, particularly children; and complete seizure freedom (ie absolute seizure control). The claim 'Controls seizures' had not been qualified by reference to the SPC or to medical literature and was therefore an unsubstantiated claim. Lamictal's marketing authorization did not include monotherapy for children under the age of 12 years, whereas the advertisement depicted girls who could be perceived to be under 12 years of age. Sanofi-Synthelabo alleged a breach of Clauses 3.2, 7.2, 7.8 and 7.10 of the Code.

The claim 'Epilepsy treatment with girls in mind' appeared to confirm concerns that GlaxoSmithKline was promoting outside its licensed indication when, in girls under 12 years of age, the SPC recommended that Lamictal could only be prescribed as add-on treatment; this was not clearly stated. Sanofi-Synthelabo alleged a breach of Clauses 3.2, 7.2 and 10.1.

The claim 'Has no effect on sleepovers' was a misleading and exaggerated claim, which implied that Lamictal did not disrupt recreational or group activities and had no effect on sleep. The SPC, however, listed a whole host of side effects, which could interfere with activities of daily living as well as effects on sleep for example irritability, aggression and insomnia. Sanofi-Synthelabo alleged a breach of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

GlaxoSmithKline stated that the claim 'Controls seizures' had already been addressed in point 1 above.

GlaxoSmithKline submitted that the models used in the advertisement were over 12 years of age. This was a specific requirement of the brief GlaxoSmithKline gave to the agency responsible for executing the campaign. If required, the identity cards of the models could be produced. GlaxoSmithKline therefore denied that the advertisement was incompatible with the terms of the marketing authorization or inconsistent with the particulars listed in the SPC. Neither did GlaxoSmithKline believe the advertisement, including the artwork, was misleading in this respect, and had taken trouble to ensure that this was not so. Again GlaxoSmithKline had difficulty understanding Sanofi-Synthelabo's complaint about disguised promotion, since this material appeared in the format of an advertisement in a medical journal and its provenance was clear.

The claim 'Epilepsy treatment with girls in mind' did not seek to promote Lamictal outside the licensed indications or age groups. Again both were clearly contained within the prescribing information that formed an integral part of this advertisement. The purpose of the claim was to remind paediatricians that Lamictal could be used as add-on therapy in girls aged over 2 years and as monotherapy in girls aged over 12 years. The decision not to have a similar advertisement for boys simply reflected market forces. Again GlaxoSmithKline had difficulty understanding Sanofi-Synthelabo's complaint about disguised promotion, since this material appeared in the format of an advertisement in a medical journal and was clearly attributable to GlaxoSmithKline.

Since quality of life in children with epilepsy could be dramatically affected by seizures. GlaxoSmithKline submitted it was important to consider the beneficial impact of seizure control in this age group. Camfield *et al* (2001) found that quality of life in patients aged 2-16 years was inversely and significantly related to seizure frequency. In this study quality of life was assessed by a variety of parameters, including social activities and relationships with peers. GlaxoSmithKline had attempted to illustrate this point in its choice of artwork and corresponding claim. The claim therefore reflected the efficacy of Lamictal as an antiepileptic medicine, and clearly patients with epilepsy could better undertake such activities once their seizures were controlled. The claim neither stated nor implied that Lamictal had no adverse effects. The prescribing information clearly listed all the adverse effects described by Sanofi-Synthelabo, including those on sleep. GlaxoSmithKline therefore did not agree that the advertisement was misleading, all-embracing or exaggerated.

PANEL RULING

The Panel noted its ruling regarding the claim 'Controls seizures' and seizure type in point 1 above and considered that its ruling that the claim was too general given the indications for the product also applied to this advertisement. Breaches of Clauses 3.2, 7.2, 7.4 and 7.10 were ruled.

The Panel also considered that its rulings with regard to the use of the word 'control' in relation to patients being seizure-free also applied to this advertisement. No breach of Clauses 7.2, 7.4 and 7.10 was ruled on this narrow point.

The Panel noted that Lamictal could be used as add-on therapy in children between age 2 and 12.

Children over 12 years of age and adults could receive Lamictal as monotherapy. The Panel considered that the advertisement would be read as referring only to the use of Lamictal in children. It therefore decided that in this context the claim 'Controls seizures' referred only to children; it was not a claim for suitability in all patient groups. On this very narrow point the Panel ruled no breach of Clauses 3.2, 7.2, 7.8 and 7.10. The Panel went on to consider the point as to whether it was appropriate for the company to claim in effect that Lamictal controlled seizures in girls. In this regard, the Panel noted GlaxoSmithKline's response that all the models were over 12 years old but considered that they might be seen as being younger than 12, particularly given their portrayal of dressing up and the claim 'Epilepsy treatment with girls in mind'. Lamictal could be used in children under 12 but only as add-on therapy not monotherapy. The Panel considered that the depiction of girls who could be perceived as under 12 years old was not inconsistent with the SPC and no breach of Clause 3.2 was ruled. However the Panel considered that the advertisement was misleading as it did not make it clear that in this age group Lamictal could only be used as add-on therapy. Inclusion of the prescribing information was not sufficient in this regard. A breach of Clause 7.2 was ruled. The Panel did not consider that the artwork *per se* failed to comply with the Code and no breach of Clause 7.8 of the Code was ruled. The Panel ruled no breach of Clause 10.1 of the Code as the advertisement was not disguised.

The Panel considered that the claim 'Has no effect on sleepovers' was a strong claim. The Panel noted its comments in point 1 above with regard to the claim 'Has no effect on shopping' and considered that they were relevant here. The Panel considered that the claim was misleading not capable of substantiation and exaggerated. Breaches of Clauses 7.2, 7.4 and 7.10 of the Code were ruled. The Panel did not consider that the claim was a specific claim about side effects and thus no breach of Clause 7.9 of the Code was ruled.

Complaint received **26 June 2002**

Case completed **15 August 2002**

CASE AUTH/1339/6/02

SCOTTISH MEDICINES CONSORTIUM v AVENTIS PHARMA

Letter about launch of Lantus

The Scottish Medicines Consortium (SMC) complained about a letter sent by Aventis Pharma regarding the launch of Lantus (insulin glargine). The letter explained that Lantus would be launched in late August but in the preceding three months limited stocks would be available such that consultant diabetologists could register for a service which would provide them with enough to treat up to 10 patients in that time. In order to monitor the situation Aventis requested brief anonymous details of the patients treated with the advance supply.

The letter had been sent to a wide range of diabetes hospital specialists in Scotland. The complainant was concerned that the company appeared to be wishing to seed use of the medicine in Scotland before the SMC had made a decision on it. Advocating such use of Lantus did not appear to be related to any particular extenuating circumstances and might be seen as promotional in advance of the launch and the complainant was concerned that this was in breach of the Code. No summary of product characteristics was provided with the letter nor was there any mention of costs. This seemed remarkably like a concealed marketing policy. Moreover, as the company had submitted data to the SMC which advised the NHS Boards and prescribers on all newly licensed products in Scotland, the letter sought to circumvent SMC advice even before it was promulgated.

The Panel considered that the letter, about the launch of a product and discussing arrangements for its supply, was not sufficiently similar to the examples of factual, accurate and informative announcements cited as exemptions to the definition of promotion to be able to take the benefit of that exemption. The Panel decided that the letter was subject to the Code. The Panel ruled a breach of the Code as no prescribing information had been included.

The Panel noted that the marketing authorizations for Lantus vials and cartridges had been received in January 2002 and June 2000 respectively. The letter in question was dated May 2002. The product had thus not been promoted prior to the grant of its marketing authorization. The Panel ruled no breach of the Code.

The letter explained the supply problems and the interim service provided by Aventis post licence but prior to launch. The stock was to be paid for but this had not been made clear or mentioned in the copy of the letter provided by the complainant, although the copy provided by Aventis included a paragraph about cost. The letter was sent to prescribers and required those that were interested in obtaining a supply of Lantus to contact Aventis. No medicine was supplied with the letter. The Panel ruled no breach of the Code with regard to the requirements regarding the provision of medicines and samples.

The Panel did not consider that Aventis had failed to meet a high standard and nor had it brought discredit on or reduced confidence in the pharmaceutical industry.

The Scottish Medicines Consortium (SMC) complained about a letter from Aventis, dated 22 May 2002 and signed by the medical director, which stated that Lantus would be launched on 28 August but that a limited amount of stock would be available from 1 June. Consultant diabetologists could register for a service which would provide them with one pack of 30 x 10ml vials. This would be sufficient to treat up to 10 patients for 3 months by which time the product would have been launched. In order to monitor the situation Aventis requested brief anonymous details of the patients treated with the advance supply.

The Chief Medical Officer, Health Department, Scottish Executive, had also contacted the ABPI about this matter.

COMPLAINT

The SMC stated that the letter in question had been sent to a wide range of hospital specialists in the diabetes field in Scotland. Aventis appeared to be wishing to seed use of this medicine in Scotland, bypassing a decision from the SMC. This did not appear to be related to any particular extenuating circumstances of need for patients with diabetes mellitus, and the SMC was concerned that this constituted a breach of the Code and might be seen as promotional in advance of the launch, which would then be in breach of the Medicines Act.

The SMC's major concern was that if this medicine gained widespread use before it had made a decision on it (and it would be considering it in the near future), then this was clearly a way that companies might choose to use in order to avoid the need for SMC advice to be taken into account.

No data sheet/summary of product characteristics (SPC) was provided and no mention of costs was involved. This seemed remarkably like a concealed marketing policy and was clearly outwith the spirit, if not the letter of the Code. Moreover, as the company had submitted data to the SMC which advised the NHS Boards and prescribers on all newly licensed products in Scotland, the letter sought to circumvent SMC advice even before it was promulgated. Given the excellent collaboration there had been between industry and the SMC, and given the substantial contribution to the development of SMC by the ABPI, the SMC was saddened by this development.

When writing to Aventis, the Authority invited it to bear in mind the requirements of Clauses 2, 4.1, 9.1 and 17 of the Code.

RESPONSE

Aventis noted that the allegations appeared to be two-fold.

Firstly, that Aventis might be acting in a manner that could be regarded as promotional in advance of the launch of Lantus and therefore in contravention of the Medicines Act. The SMC also appeared to have made a judgement concerning the value of the use of Lantus by doctors and patients ahead of the SMC Committee's consideration of the evidence and the Committee's subsequent advice to the NHS Boards and prescribers by stating that: 'This ['seeding use of this drug in Scotland'] does not appear to be related to any particular extenuating circumstances of need for patients with diabetes mellitus…'.

Secondly, that Aventis was acting in some underhand and/or improper manner in order to undermine the authority of the SMC by seeking to 'seed' the use of Lantus in Scotland ahead of any review of the product by the SMC.

Aventis stated that it took these allegations extremely seriously. Aventis refuted all direct allegations and implied suggestions of wrongdoing made by the complainants. The company addressed its responses to the clauses of the Code that were pertinent to the complaints.

Clause 3 Promoting a medicine in advance of launch

Lantus received marketing approval in June 2000. The medicine was licensed by way of the centralised European licensing procedure in accordance with the European Medicines Evaluation Agency's (EMEA) regulations. This was posted on the EMEA web-site and a copy was provided. Aventis noted that it had clearly made the point that it had a marketing approval for Lantus in the first paragraph of the letter at issue.

It appeared from the SMC's correspondence that some confusion existed between the legal status of the product and the notion of commercial launch. Aventis had had the marketing approval for more than two years and therefore providing information about Lantus was not in contravention of the Medicines Act, or Clause 3 of the Code.

Clauses 4.1 and 1.2 Allegation that Lantus had been promoted and required the provision of either abbreviated prescribing information or a copy of the SPC

The letter at issue made no claims regarding either the efficacy and/or the safety of Lantus. Indeed, the description of Lantus was specifically limited to the brand, generic and non-proprietary names: Lantus, insulin glargine and long-acting insulin analogue. As no claim was made, the letter did not represent promotion as defined by the Medicines Act and the Advertising Directive or the Code. Accordingly, there was no requirement to include either prescribing information or a copy of the SPC as questioned by the SMC.

Notwithstanding this, Clause 1.2 of the Code specifically excluded 'Factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse reaction warnings, trade catalogues and price lists provided they include no product claims' from the definition of promotion.

The letter was only sent to consultant diabetologists and it was certainly Aventis' intention to only inform the body of consultant diabetologists in the UK of the

small but important amount of Lantus supplies that had become available ahead of commercial launch. What the letter did not mention was the reason for limiting the supply to 30 vials for any individual consultant diabetologist from June until August. This occurred because Aventis had only secured sufficient stock to guarantee the treatment of 5,000 patients for 4 months at the average doses seen in the clinical trials.

Lantus was licensed throughout the EU, the USA and very many other markets around the world. Hoechst, one of the two companies that merged to form Aventis, did not appreciate the obvious clinical benefits that were now clearly apparent for Lantus. As a consequence the necessary increase in manufacturing capacity was not put in place early enough during the development of the medicine to satisfy true demand. As a consequence Aventis was faced with the decision of how best to control the limited production capacity. In brief, the decision was made to supply the USA and Germany only, as this would take all the supply capacity that could be guaranteed. Continuity of supply to patients once stabilised on insulin was critical. The reason for selecting Germany was because Hoechst had been a major supplier of insulins there for more than 80 years.

The last paragraph of the letter informed the recipients that only the UK would be in a position to launch Lantus in 2002. Quite simply, there was no 'concealed marketing policy' going on here as alleged. The truth of the matter could not be further from this assertion. Aventis had acknowledged that a severe mismatch of demand and supply forecasting led to a situation that was as regrettable as it was embarrassing.

While this was a trade availability issue, Aventis was so concerned about the possible medical consequences of the severe rationing being overlooked by physicians, in that they would initiate treatment on more than 10 patients and then expect an uninterrupted supply of Lantus, that it was decided that the announcement and the invitation to register for the supply service should come from its medical director.

Aventis provided copies of letters it had sent to the medical profession in June and October 2001 as part of its strategy of responsible communication about the supply shortfall.

Aventis acknowledged that no mention of price was made in the letter; recipients were invited to obtain more details of the scheme by contacting Aventis' medical affairs department. A copy of this pack was provided. It was decided to use the 'invitation followed by information pack' approach so that only clinicians who already knew what Lantus was, and also had a need for it, would obtain the additional information on the clinical particulars (SPC), price and distribution logistics. Aventis did this with the specific intention of not fuelling demand by trying to promote the benefits of Lantus to any consultants who did not already know what the product was and what it could do.

There was much debate with clinicians as to whether or not Aventis should charge for the limited supplies that could be made available. It was agreed by everyone that Aventis should charge. One of the main reasons for doing this was particularly poignant in the context of this complaint. Aventis, and the opinion leaders it discussed the matter with, wanted to be totally clear that by providing the much needed, but limited stock, Aventis was not engaged in some type of unworthy 'seeding' campaign as suggested but was offering a bona fide service for difficult to control diabetic patients and their doctors as soon as possible. The SMC's suggestion of seeding seemed to be a particularly disappointing reflection of the perceptions of the motives of an innovative pharmaceutical industry.

Clause 9.1 Format, suitability and causing offence, sponsorship

Lantus was a basal insulin and represented the only innovative advance in long-acting insulin technology in the last 35 years.

Lantus was unique in having a flat insulin activity profile and represented true pharmacological mimicry of the human's body basal insulin production and physiology. It was widely appreciated that the treatment of diabetes with insulin was not only a serious medical decision but also one that required an uninterrupted, long-term commitment to supply the insulin product that the patient was stabilised on.

Aventis believed that it was correct to limit the letter solely to consultant diabetologists who, by the nature of their training and ongoing education, were likely to know about insulin glargine. Aventis also considered that the content and tone of the letter was appropriate for the recipients. Interestingly Aventis had received a complaint from a hospital pharmacist who was aggrieved that Aventis had not sent him the same information as his consultant colleague and that he became aware of it only when his colleague had contacted him.

Clause 17 Provision of medicines and samples

Aventis noted that some might consider that the letter represented an invitation to receive a sample of Lantus. As the stock on offer was being charged at a commercial price that was clearly not the case and could not represent a breach of this clause.

Clause 2 Discredit to, and reduction in confidence in, the industry

Aventis took the fact that the SMC had complained about its activities very seriously indeed. In no way had Aventis sought to undermine the processes, decision and advice of the SMC in Scotland, nor it should also be said, had it sought to do this in England and Wales with the National Institute for Clinical Excellence (NICE).

Lantus was currently the subject of consideration by both the SMC and NICE. Aventis had tried to be as helpful as possible to both organisations during their different assessment processes. That being said, Aventis was not aware of any legislation and/or agreement between either of these bodies and the pharmaceutical industry in general or Aventis as a specific company, that either mandated or suggested

that Aventis could not go about its lawful business until such time as they had formulated their advice to the NHS in Scotland. It would appear that this was a subject in need of urgent clarification by the ABPI with the SMC for the benefit of all.

Aventis was a major global pharmaceutical company and it took its responsibilities to research, develop, manufacture and market very seriously indeed; it had very high standards of operation and professional expectation from its staff. It was true that during the early development phases of Lantus, Hoechst did not appreciate the considerable improvement to patient care that this innovation would bring and did not plan sufficient production capacity. Notwithstanding this, given the fact that there was a considerable world shortfall in the production capacity of insulin glargine, Aventis believed that everyone in Aventis had done all that was possible to manage the situation.

Aventis refuted in the strongest possible terms any allegation that it had acted in a manner that was unprofessional, unethical or in any other manner unworthy of a leading pharmaceutical company.

PANEL RULING

The Panel noted that it was only concerned with whether the activities were in accordance with the Code and not whether it was in accordance with the policies of the SMC.

The Panel noted that Clause 1.2 of the Code stated that the definition of promotion did not include factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse reaction warnings, trade catalogues and price lists provided they include no product claims. Although this list was not definitive, the Panel considered that the letter announcing the launch of a product and discussing arrangements for its supply was not sufficiently similar to the examples cited to be able to take the benefit of the exemption to the definition of promotion. The Panel decided that the letter was thus subject to the Code. The Panel ruled a breach of Clause 4.1 as no prescribing information had been included in the letter.

The Panel noted that Lantus had received its marketing authorization for vials in January 2002. The marketing authorization for Lantus cartridges had been received in June 2000 (ref SPC). The letter in question dated 22 May 2002 had been sent after the product had received its marketing authorization. The Panel ruled no breach of Clause 3.1 of the Code.

The letter explained the supply problems and the interim service provided by Aventis post licence but prior to launch. The stock was to be paid for but this had not been made clear or mentioned in the copy of the letter provided by the complainant although the copy provided by Aventis included a paragraph about cost. The letter was sent to prescribers and required those that were interested in obtaining a supply of Lantus to contact Aventis. No medicine was supplied with the letter. In the circumstances the Panel ruled no breach of Clause 17 of the Code.

The Panel did not consider that in the circumstances Aventis had failed to meet a high standard or brought discredit on or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

Complaint received **12 June 2002**

Case completed **16 August 2002**

CASE AUTH/1340/7/02

AVENTIS PHARMA v MERCK SHARP & DOHME

Promotion of Cozaar

Aventis Pharma complained that Merck Sharp & Dohme was making claims for Cozaar (lasartan) which were not consistent with the summary of product characteristics (SPC) and was therefore promoting its use outside the licensed indications.

Cozaar was an angiotensin-II antagonist. Aventis marketed Tritace (ramipril) an angiotensin-converting enzyme (ACE) inhibitor. The advertisement referred to the results of the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension).

A journal advertisement had a photograph of a lifebuoy within which appeared the claim 'Throw your high-risk * hypertensive patients a lifeline'. The explanation for the asterisk was 'LIFE trial patients entered with BP 160-200 mmHg systolic and/or 95-115 mmHg diastolic and ECG documented LVH'. Beneath the lifebuoy was the claim 'In the LIFE study COZAAR is the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator (atenolol) and showed a 25% reduction in stroke risk (p=0.001)'. A logo relating to the LIFE study in which the word 'LIIFE' was encircled by a claim 'Losartan intervention for end point reduction' appeared adjacent to the product logo in the bottom right-hand corner of the advertisement.

Aventis alleged that the use of the word 'lifeline' clearly suggested that treatment with Cozaar should positively improve the longevity of a hypertensive patient's lifespan. This claim went much further than the licensed indication of simple blood pressure lowering. Moreover, there was a claim that Cozaar treatment reduced the risk of a patient having a stroke by 25% compared with atenolol. Cozaar was not licensed for cardiovascular protection, it was only licensed for the treatment of hypertension.

The Panel noted that the aim of the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) was to establish whether the selective blocking of angiotensin II improved left ventricular hypertrophy (LVH) beyond reducing blood pressure and consequently reduced cardiovascular morbidity and death. The study was carried out on 9193 patients with essential hypertension and LVH. Patients took once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction or stroke). The results were interpreted as losartan prevented more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and was better tolerated. Losartan seemed to confer benefits beyond reduction in blood pressure.

The LIFE study was carried out on high-risk patients who were treated for hypertension. In the Panel's view the promotional material must make it clear that Cozaar was used to treat hypertension in high risk patients and all references to the LIFE study results must be set in that context.

The Panel did not consider that the use of the word 'lifeline' suggested that Cozaar would result in hypertensive patients living longer nor did its use go beyond the licensed indication for Cozaar. Throwing a lifeline did not guarantee survival but might improve the chance of avoiding harm. The Panel ruled no breach of the Code in this regard.

The advertisement clearly referred to high risk patients. The Panel did not consider that the journal advertisement was sufficiently clear in placing the CV outcome within the context of being a benefit of treating hypertension with Cozaar. It considered that the advertisement including the 'LIIFE' logo promoted Cozaar for its CV outcomes including reduction in stroke risk. This was inconsistent with the SPC and a breach of the Code was ruled.

A six page leavepiece gave details of the outcome of the LIFE study. Page 3 headed 'Outcome data are a major consideration when choosing an antihypertensive' included five bullet points describing some of the design characteristics of the LIFE study. Aventis stated that the claims on page 4 of the leavepiece that 'Cozaar produced significantly better cardiovascular protection than atenolol', 'Significantly greater reduction in combined stroke, MI and CV death', followed by '13% reduction in risk vs atenolol (p=0.021)', and 'Significantly lower incidence of stroke', followed by '25% reduction in risk vs atenolol (p=0.001)' were efficacy claims and Cozaar was not licensed for cardiovascular protection.

Page 6 of the leavepiece was headed 'Knowing that you've made an evidence-based choice for your high risk hypertensive patients'. In Aventis' view the leavepiece confirmed that evidence-based choices should be made for high risk, were important and should be defined by some of the dimensions of the LIFE study inclusion criteria.

The first two bullet points beneath the heading 'Cozaar is the only antihypertensive to demonstrate superior outcomes against an active comparator' and 'Significant reduction in the risk of stroke' were inconsistent with the SPC for Cozaar.

The Panel noted its comments above. As previously noted the results from the LIFE study had to be clearly placed within the context of treating hypertension. Further the results were in high risk patients. In the Panel's view the leavepiece did not make it sufficiently clear that Cozaar was licensed to treat hypertension. The leavepiece referred to antihypertensive treatment and to LIFE being a reduction in hypertension study. However, in the Panel's view, the layout and content of the leavepiece was not adequate in this regard. The reason to give Cozaar appeared to be to achieve the CV outcomes referred to, not to lower blood pressure *per se*. In this regard the Panel noted that on page 6 of the leavepiece it appeared that the first two reasons to choose Cozaar for high risk

hypertensives were because of outcome data. Blood pressure control was not referred to until the third of three bullet points. A breach of the Code was ruled.

A 'Dear Healthcare Professional' letter, sent to UK doctors, referred to establishing hypertension as a risk factor for stroke and documenting the benefits of treatment being milestones in the treatment of cardiovascular disease. It stated that there was 'evidence that how blood pressure is lowered can have a major impact on your patients' lives. The LIFE study now tells us the choice of drug is more important than just lowering blood pressure'. The letter gave a brief description of the study and its results. Aventis alleged that the overall impression left in the reader's mind was that the LIFE study results were important and that they should change current clinical practice. The claims made for Cozaar went far beyond the treatment of hypertension In addition there was a claim that use of Cozaar resulted in the 'reduced risk of onset of diabetes (–25%, p=0.001)'. This was alleged to be an efficacy claim for which Cozaar was not licensed.

Finally, the letter referred readers to a Merck Sharp & Dohme Internet site providing the results of the LIFE study. This represented promotion of an unlicensed indication as the reader had not asked for the results, they had been 'cold-called' prompted by the letter to seek them out.

The Panel considered that the letter placed the results from the LIFE study in the context of using Cozaar to treat hypertension and lower blood pressure. The second sentence referred to establishing hypertension as a risk factor for stroke, and documenting the benefits of treatment. The next sentence stated that how blood pressure was lowered could have a major impact and that choice of medicine was more important than just lowering blood pressure. The Panel considered that on balance the letter was not inconsistent with the Cozaar SPC. No breach of the Code was ruled.

The Panel did not consider that a reference to 'reduced risk of onset of diabetes (–25%, p=0.001)' was a claim for an unlicensed indication. No breach of the Code was ruled.

With regard to the reference to the Internet site where the full results from LIFE were available, the Panel did not consider that this constituted the promotion of an unlicensed indication. No breach of the Code was ruled.

Aventis stated that the promotion of indications that were not consistent with an SPC represented a serious breach of professionalism and commercial naivety and/or arrogance and had the potential to reflect adversely on the reputation of the whole pharmaceutical industry. A breach of Clause 2 was alleged.

Aventis drew attention to Case AUTH/1029/6/00 which concerned the placing of an advertisement in the UK edition of The Lancet for Tritace that was inconsistent with its SPC. At the time, the HOPE study had just shown that Tritace provided clinically relevant and statistically significant cardiac morbidity and mortality benefits. Nonetheless, Aventis accepted the Panel's ruling of a breach of the Code.

The Panel noted that the HOPE study had shown that Tritace reduced mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure. At that time Tritace was licensed for the treatment of mild to moderate hypertension and in congestive heart failure as an adjunctive to diuretics with or without cardiac glycosides. In Case AUTH/1029/6/00 the Panel had decided that the advertisement at issue promoted Tritace for cardio and cerebroprotection in a general high risk population and thus constituted promotion of an unlicensed indication in breach of the Code.

The Panel considered that the two cases were not comparable. Case AUTH/1029/6/00 concerned a study which was not within the Tritace licensed indication for the product whereas Case AUTH/1340/7/02 concerned a study on patients that were within the Cozaar current licensed indication.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. It decided that the material at issue did not warrant a ruling of a breach of Clause 2.

Aventis Pharma Ltd complained about a journal advertisement, a leavepiece and a 'Dear Healthcare Professional' letter for Cozaar (losartan) issued by Merck Sharp & Dohme Limited.

Cozaar was an angiotensin-II antagonist. Aventis marketed Tritace (ramipril) an angiotensin-converting enzyme (ACE) inhibitor.

A Alleged promotion outside the marketing authorization

Aventis noted that the promotion of a medicine outside the terms of its marketing authorization, or the promotion of a medicine that was inconsistent with its summary of product characteristics (SPC) was always a serious matter.

Aventis had no option but to bring a formal complaint that the current promotional campaign for Cozaar based on the results of the LIFE study (cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension: a randomised trial against atenolol, 2002), had been designed and carried out in such a fashion as to bring the industry into disrepute.

Aventis stated that the complaint was not intended to be a comprehensive critique of the materials produced by Merck Sharp & Dohme. The nub of the issue was that Merck Sharp & Dohme was making claims about Cozaar which were not consistent with the SPC and therefore promoting its use outside the licensed indications in contravention of Clause 3.2. Aventis drew attention to the UK legal requirements that framed the relationship of the promotional claims to the SPC in the positive unlike the Code. The relevant part stated: 'No person shall issue an advertisement relating to a relevant medicinal product unless that advertisement complies with the particulars listed in the summary of product characteristics'.

The Medical Director of Merck Sharp & Dohme, stated in his letter of 13 May that '… the aim of treating hypertension is to reduce cardiovascular death, CHD morbidity, stroke and renal dysfunction amongst others'.

Aventis agreed that treating hypertension was a good thing. But this was not the same as saying that treating hypertension would necessarily reduce the incidence or risk of a patient experiencing cardiac mortality, morbidity, stroke, renal dysfunction, etc. The only way to be certain of this was to conduct outcome studies such as LIFE. If the claim was proved that morbidity, etc, were beneficially improved then the product could be licensed for the specific indication.

It was important to note that hypertension was only a surrogate endpoint for cardiac mortality, stroke, etc. There was a good body of evidence to link the impact of treating hypertension with benefit to patients and reduce the risk of them experiencing such hard endpoints as morbidity from whatever end organ damage, but having a marketing authorization for lowering blood pressure was not the same as having a marketing authorization for various cardiovascular disease hard endpoints.

Aventis did not believe that Merck Sharp & Dohme did not know of these issues because the HOPE study (the Heart Outcomes Prevention Evaluation study (2000)) that was conducted using Tritace, an ACE inhibitor that modified the renin-angiotensin system in similar fashion to Cozaar, was the source data of a successful marketing authorization variation to include hard mortality and myocardial infarct type endpoints into the licensed indications for Tritace more than a year ago.

Furthermore, due to the error of an international colleague placing an advertisement for Tritace/HOPE in the UK editions of The Lancet, Aventis wrote to the Medicines Control Agency (MCA) and the Authority pointing out the error and Aventis was ruled in breach of the Code, Case AUTH/1029/6/00. Although the MCA let the Authority deal with the matter, it did prior vet all Tritace materials for almost a year after this error.

The HOPE study and the changes to the licence of Tritace had been made very widely known within the healthcare environment and the relevant parts of the pharmaceutical industry. From personal communication with Merck Sharp & Dohme executives Aventis knew that Merck Sharp & Dohme knew of the issues and must have decided to ignore the precedent. Aventis directly asked Merck Sharp & Dohme if the MCA had changed its position. For whatever reason Merck Sharp & Dohme had not replied on this point.

1 Journal advertisement

The journal advertisement had a photograph of a lifebuoy within which appeared the claim 'Throw your high-risk * hypertensive patients a lifeline'. The explanation for the asterisk (given below the copy and above the prescribing information) was 'LIFE trial patients entered with BP 160-200 mmHg systolic and/or 95-115 mmHg diastolic and ECG documented LVH'.

Beneath the lifebuoy was the claim 'In the LIFE study COZAAR is the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator (atenolol) and showed a 25% reduction in stroke risk (p=0.001)'.

A logo relating to the LIFE study in which the word 'LIIFE' was encircled by a claim 'Losartan intervention for end point reduction' appeared adjacent to the product logo in the bottom right-hand corner of the advertisement.

COMPLAINT

Aventis alleged that the use of the word 'lifeline' clearly suggested that treatment with Cozaar should positively improve the longevity of a hypertensive patient's lifespan. This claim of comparative mortality improvement went much further than the licensed indication of simple blood pressure lowering.

Moreover, in smaller font text in the lower left of the advertisement was a claim that Cozaar treatment reduced the risk of a patient having a stroke by 25% compared with atenolol. This was an efficacy claim and the issue was that Cozaar was not licensed for cardiovascular protection, it was only licensed for the treatment of hypertension. A breach of Clause 3.2 was alleged.

RESPONSE

Merck Sharp & Dohme stated that the use of the word 'lifeline' was intended as a pun on the study title, in the same way as many of the Tritace materials had played on the word 'HOPE'. Indeed, Merck Sharp & Dohme would have thought that 'throwing a patient a lifeline' and 'giving a patient HOPE' were synonymous! Throwing someone a lifeline did not constitute a guarantee of survival but it did improve their chance of avoiding harm and, as such, was consistent with the LIFE data.

The advertisement clearly described Cozaar as an antihypertensive, and the population as a hypertensive one, and Merck Sharp & Dohme believed therefore set the LIFE results in the context of treating hypertension. This advertisement was nonetheless amended in light of the Appeal Board's previous ruling. The current advertisement (05-03 CZR etc) had gone one step further to address blood pressure reduction before describing the reduction in stroke that ensued.

Merck Sharp & Dohme did not consider that either of the advertisements promoted Cozaar outside its licensed indication. Reduction in stroke was the *raison d'être* of antihypertensive treatment. In licensing treatments for hypertension *per se*, the assumption was made that lowering blood pressure had the potential to reduce stroke. As a result of the LIFE study, Merck Sharp & Dohme knew the actual stroke reduction with Cozaar (compared to atenolol), and was referring to this in its advertisements.

Merck Sharp & Dohme refuted any suggestion of a breach of Clause 3.2.

PANEL RULING

The Panel noted that Cozaar was indicated for the treatment of hypertension. There was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

Clause 3.2 of the Code required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel noted Merck Sharp & Dohme's comments about the previous case, Case AUTH/1262/12/01. The case report had not yet been published. The case concerned the promotion of Cozaar in relation to the results of the RENAAL study which looked at the effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes with nephropathy. The Appeal Board noted that Cozaar was not licensed for renal protection, it was only licensed to lower blood pressure. In the material at issue the renoprotective effects had been given undue emphasis and had not been placed sufficiently within the context of treating hypertension such that Cozaar was promoted for its renoprotective effect. Breaches of the Code had been ruled including Clause 3.2.

The aim of the LIFE study was to establish whether the selective blocking of angiotensin II improved left ventricular hypertrophy (LVH) beyond reducing blood pressure and consequently reduced cardiovascular morbidity and death. The study was carried out on 9193 patients with essential hypertension and LVH diagnosed by electrocardiography (ECG). Patients took once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction or stroke). LVH was described as a cardinal manifestation of preclinical cardiovascular disease and an independent risk factor for all cardiovascular complications in hypertension, reversal of LVH had possible prognostic benefits that were independent of blood pressure, angiotensin II was associated with development of LVH and blocking angiotensin II could be especially effective in reversing LVH. The study stated that blocking the actions of angiotensin II might confer protective benefits beyond lowering of blood pressure. The findings of the study were that blood pressure fell by 30.2/16.6 (SD 18.5/10.1) and 29.1/16.8 mmHg (SD 19.2/10.1) in the losartan and atenolol groups, respectively. The primary composite endpoint occurred in 508 losartan (23.8 per 1000 patient-years) and 588 atenolol patients (27.9 per 1000 patient-years; relative risk 0.87, 95% CI 0.77-0.98, p=0.021). 204 losartan and 234 atenolol patients died from cardiovascular disease (0.89, 0.73-1.07, p=0.206); 232 and 309, respectively, had fatal or non-fatal stroke (0.75, 0.63-0.89, p=0.001); and myocardial infarction (non-fatal and fatal) occurred in 198 and 188, respectively (1.07, 0.88-1.31, p=0.491). New-onset diabetes was less frequent with losartan.

The results were interpreted as losartan prevented more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and was better tolerated. Losartan seemed to confer benefits beyond reduction in blood pressure. Participants were derived from a high-risk population of hypertensive patients and the study stated that the outcome should be interpreted in this context. The study concluded that losartan had already been established as an effective once-daily antihypertensive with excellent tolerability, effective blocking of angiotensin II at the type 1-receptor, and protective properties in diabetic nephropathy. The greater clinical benefit in high-risk patients and enhanced tolerability with losartan than atenolol suggested that broader application would improve outcome for hypertensive patients. The results were directly applicable in clinical practice and should affect future guidelines.

The Panel noted that the LIFE study was carried out on high-risk patients. Patients were treated for hypertension and the benefits of that treatment were investigated with differences between losartan and atenolol being established. In the Panel's view the promotional material must make it clear that Cozaar was used to treat hypertension in high risk patients and all references to the LIFE study results must be set in that context.

With regard to the journal advertisement the Panel did not consider that the use of the word 'lifeline' suggested that Cozaar would result in hypertensive patients living longer nor did its use go beyond the licensed indication for Cozaar of treatment of hypertension. Throwing a lifeline did not guarantee survival but might improve the chance of avoiding harm. The Panel ruled no breach of Clause 3.2 of the Code in this regard.

The advertisement clearly referred to high risk patients. The Panel did not consider that the journal advertisement was sufficiently clear in placing the CV outcome within the context of being a benefit of treating hypertension with Cozaar. It considered that the advertisement including the 'LIIFE' logo promoted Cozaar for its CV outcomes including reduction in stroke risk. This was inconsistent with the SPC and a breach of Clause 3.2 of the Code was ruled.

The Panel did not consider the amended advertisement.

2 Leavepiece

The six page leavepiece gave details of the outcome of the LIFE study.

COMPLAINT

Aventis drew attention to a number of claims. Firstly the heading to page 3 that 'Outcome data are a major consideration when choosing an antihypertensive'. This page included five bullet points describing some of the design characteristics of the LIFE study. Aventis stated that the claims on page 4 of the leavepiece that 'Cozaar produced significantly better cardiovascular protection than atenolol', 'Significantly greater reduction in combined stroke, MI and CV death', followed by '13% reduction in risk vs atenolol (p=0.021)', and 'Significantly lower incidence of stroke', followed by '25% reduction in risk vs atenolol (p=0.001)' were efficacy claims and Cozaar was not

licensed for cardiovascular protection, it was licensed only for the treatment of hypertension.

Page 6 of the leavepiece was headed 'Knowing that you've made an evidence-based choice for your high risk hypertensive patients'. The first two bullet points beneath the heading 'Cozaar is the only antihypertensive to demonstrate superior outcomes against an active comparator' and 'Significant reduction in the risk of stroke' were alleged to be inconsistent with the SPC for Cozaar in breach of Clause 3.2.

The third bullet point 'Effective blood pressure control and excellent tolerability' was the only one that was consistent with the efficacy statements of the SPC although use of the word excellent was perhaps overstating the matter.

RESPONSE

As stated above, Merck Sharp & Dohme's understanding was that it was acceptable to promote the benefits of treating blood pressure where they had clearly been established in clinical trials and provided they were detailed in the context of treating hypertension. Nothing in the claims was inconsistent with the SPC, and there was no positive requirement for every promotional item to be included in the SPC, provided it could be substantiated. The LIFE study was peer reviewed and published in The Lancet, so any claims made were capable of substantiation.

Aventis took a number of claims from the leavepiece out of context but, it was the overall context that was important. The leavepiece referred to: Outcome data '… when choosing an antihypertensive', '9193 patients with hypertension…', 'Cozaar is the only antihypertensive…', 'Use Cozaar first-line for high risk hypertensive patients' and 'Effective blood pressure control and excellent tolerability'. Indeed, it even spelled out the LIFE study title in full: Losartan Intervention For Endpoint Reduction in Hypertension Study.

Merck Sharp & Dohme believed therefore that the leavepiece clearly set the results in the context of treating hypertension and Merck Sharp & Dohme did not consider that it promoted Cozaar outside its licensed indication. The layout and context of the leavepiece made it quite clear the reason for prescribing Cozaar was for the treatment of hypertension and that the presentation of outcome data clarified the consequences of the treatment.

PANEL RULING

The Panel noted its comments in point A1 above. As previously noted the results from the LIFE study had to be clearly placed within the context of treating hypertension. Further the results were in high risk patients. In the Panel's view the leavepiece did not make it sufficiently clear that Cozaar was licensed to treat hypertension. The leavepiece did refer to antihypertensive treatment and to LIFE being a reduction in hypertension study. However, in the Panel's view, the layout and content of the leavepiece was not adequate in this regard. The reason to give Cozaar appeared to be to achieve the CV outcomes referred to, not to lower blood pressure *per se*. In this regard the Panel noted that on page 6 of the leavepiece it appeared that the first two reasons to choose Cozaar for high risk hypertensives were because of outcome data. Blood pressure control was not referred to until the third of three bullet points.

A breach of Clause 3.2 of the Code was ruled.

3 'Dear Healthcare Professional' letter

The 'Dear Healthcare Professional' letter from the Cozaar marketing manager was delivered to UK doctors. It referred to establishing hypertension as a risk factor for stroke and documenting the benefits of treatment being milestones in the treatment of cardiovascular disease. It stated that there was 'evidence that how blood pressure is lowered can have a major impact on your patients' lives. The LIFE study now tells us the choice of drug is more important than just lowering blood pressure'. The letter gave a brief description of the study and its results.

COMPLAINT

Aventis alleged that the overall impression left in the reader's mind was that the LIFE study results were important and that they should change current clinical practice.

The claims made for Cozaar went far beyond the treatment of hypertension. For example 'The results highlight the superiority of Cozaar (losartan) as the only ever antihypertensive to demonstrate significant benefits over the established gold standard beta blocker atenolol, in the reduction of cardiovascular morbidity and mortality in the primary end points of stroke, heart attack and cardiovascular death'. In addition to this claim, which was similar in nature to the other promotional material, a new claim not seen in other material appeared to be made, namely that use of Cozaar resulted in the 'reduced risk of onset of diabetes (–25%, p=0.001)'. This was alleged to be an efficacy claim for which Cozaar was not licensed.

Finally, the letter referred readers to a Merck Sharp & Dohme Internet site providing the results of the LIFE study. This represented promotion of an unlicensed indication as the reader had not asked for the results, they had been 'cold-called' prompted by the letter to seek them out.

RESPONSE

Merck Sharp & Dohme stated that given that the LIFE study was newsworthy, Merck Sharp & Dohme anticipated significant media interest and therefore considered it was important that UK physicians should have received a short concise communication immediately after the results were presented in May, to avoid them being in the awkward position of patients reading about the results and their doctor being unaware of them. This letter was therefore delivered to as many UK doctors as possible. As such, it was intended to be very focussed. It clearly set the scene of treating hypertension, the association of raised blood pressure with stroke and equivalent

blood pressure reductions and superior tolerability profile of Cozaar compared with atenolol. The headline results were set clearly in context and Merck Sharp & Dohme did not consider that it promoted Cozaar outside its licensed indication. It was clear that, to be eligible for treatment with Cozaar, the patient had to be hypertensive. The reference to the web site pointed doctors to a source of scientific information which Merck Sharp & Dohme believed to be within the current licence. In any event, the active seeking out of this information by a doctor on the internet implied a specific desire to have the information, similar to a phone call to medical information. This letter was no longer in use, now that reprints of the peer reviewed paper were available.

PANEL RULING

The Panel noted its comments in points 1 and 2 above.

The Panel considered that the letter placed the results from the LIFE study in the context of using Cozaar to treat hypertension and lower blood pressure. The second sentence referred to establishing hypertension as a risk factor for stroke, and documenting the benefits of treatment. The next sentence stated that how blood pressure was lowered could have a major impact and that choice of medicine was more important than just lowering blood pressure. The Panel considered that on balance the letter was not inconsistent with the Cozaar SPC. No breach of Clause 3.2 of the Code was ruled.

The Panel did not consider that the reference to 'reduced risk of onset of diabetes (–25%, p=0.001)' was a claim for an unlicensed indication. In the Panel's view the claim was set within the context of lowering blood pressure with losartan-based therapy as opposed to atenolol based therapy. No breach of Clause 3.2 was ruled.

With regard to the reference to the internet site where the full results from LIFE were available, the Panel did not consider that this constituted the promotion of an unlicensed indication. No breach of Clause 3.2 of the Code was ruled.

During the consideration of this case, the Panel noted that no reference had been made in the letter to the fact that the LIFE study was on high risk patients. It considered that it was misleading to fail to make this clear. There was no allegation in this regard. The Panel requested that Merck Sharp & Dohme be advised of its concerns.

B Alleged breach of Clause 2

COMPLAINT

Aventis alleged a breach of Clause 2. Aventis stated that the promotion of indications that were not consistent with an SPC represented a serious breach of professionalism and had the potential to reflect adversely on the reputation of the whole pharmaceutical industry.

The granting of a marketing authorization for a product or an indication demonstrated that the competent authorities had been satisfied by the quantity and quality of a medicine's efficacy, safety and pharmaceutical product quality data. Without a marketing authorization for a product or an indication for a product, health professionals and the general public had no independent basis for their confidence in the appropriate use of medicines. This confidence must be maintained at all costs.

In considering this case, Aventis drew attention to Case AUTH/1029/6/00, Director v Aventis, which had some important parallels to the present complaint and some important differences.

The case concerned the placing of an advertisement in the UK edition of The Lancet for Tritace that was inconsistent with its SPC. Tritace, at the time of placing of the advertisement, had just been shown to provide clinically relevant and statistically significant cardiac morbidity and mortality benefits in a high quality, very large clinical trial published in the New England Journal of Medicine: the HOPE study.

The point of major importance that separated the behaviour of Aventis and Merck Sharp & Dohme was that an international colleague had placed the advertisement in the Aventis case in The Lancet unknown to the UK company. Regrettably, the international product manager was ignorant of UK practices and requirements and had failed to follow the company's relevant standard operating procedure.

As soon as Aventis UK became aware of the advertisement in The Lancet, it immediately informed the Authority of the error and undertook a detailed internal communication and training programme for all relevant UK and international medical and marketing departments.

Aventis deeply regretted the incident. It was important also to note that the HOPE study had been in the public domain for several months prior to the placing of the advertisement and that the company was in the process of applying for a marketing authorization variation, which was granted a few months later for a new indication of cardiovascular mortality and morbidity protection. Equally Aventis agreed with the Panel ruling that the company had breached Clause 3.2 of the Code and that it had also failed to maintain a high standard of promotional material approval in breach of Clause 9.1.

What appeared clear about the current Merck Sharp & Dohme campaign for Cozaar based on the LIFE study was that it was not the case of an isolated advertisement. The campaign used many types of media in a concerted fashion (advertisements, leavepieces, direct mailings and internet posting) and alleged and/or implied and/or stated a broad scope of cardiovascular benefit and claims, namely; morbidity and mortality risk reduction, stroke risk reduction and diabetes prevention.

Aventis contended that there was no obvious mitigation in this case. There was no evidence that Merck Sharp & Dohme's systems for the approval of promotional pieces had been woefully inadequate. Instead Aventis contended that executives of Merck Sharp & Dohme had knowingly supported this campaign and had not been mindful to stop the promotional inaccuracies and excesses as soon as it

became aware of them. For this reason, Aventis did not believe that bringing a claim under the terms of promotional certification set out in Clause 14 was sufficiently strong to represent what had happened in this case.

RESPONSE

Merck Sharp & Dohme believed that there were fundamental differences between the HOPE study and the LIFE study which made the previous case irrelevant. The population under study in HOPE was a mixture of patients at varying degrees of cardiovascular risk, namely over 55 years with: history of coronary artery disease, stroke or peripheral vascular disease (outside licence at the time), diabetes plus hypertension (inside licence at the time, although not the reason for the prescription), diabetes plus abnormal cholesterol (outside licence at the time), diabetes plus smoking (outside licence at the time) and diabetes plus microalbuminuria (outside licence at the time).

As a result of these selection criteria, fewer than half of the patients in the HOPE study had hypertension or heart failure and would have been considered as within the licence of the day. It was therefore very easy to see why the promotion of HOPE prior to the grant of a licence was unacceptable, and why the Panel considered that Aventis' 'system for the approval of the advertisement was inadequate' and that it had failed to maintain high standards contrary to Clause 9.1. This conclusion was reinforced by a recently reported case (Case AUTH/1268/12/01) regarding a Diovan Detail Aid in which the study data was considered inappropriate when only 39% of the population of the study had hypertension, the licensed indication for Diovan.

Merck Sharp & Dohme considered this case to be entirely irrelevant to the current complaint about the LIFE study. Losartan was licensed for hypertension which was a pre-requisite for entry into the LIFE study. Every single patient in the LIFE study was within the current product licence. The results of the LIFE study – blood pressure reduction, left ventricular hypertrophy regression and reduction in clinical events such as stroke were therefore the results that prescribers could expect when using losartan to treat hypertension in a population similar to the LIFE cohort (hypertension plus LVH).

HOPE was essentially a phase V clinical trial, seeking evidence to treat a patient group hitherto excluded from the ramipril licence. LIFE was a phase IV (post licence) clinical trial seeking to establish the relative merits of two antihypertensive agents being used within the product licence. Not only was Merck Sharp & Dohme aware of the HOPE situation, it was aware of its relevance to the ramipril licence.

In summary Clause 3.2 stated that promotion must be in accordance with the terms of the marketing authorization (ie for patients with hypertension) and must not be inconsistent with the SPC. The Panel and the Appeal Board had ruled on previous occasions that inclusion in promotional material of a clinical benefit (stroke in this case) was not necessarily unacceptable but must be clearly set in the context of the licensed indication (hypertension in this case). Merck Sharp & Dohme believed its materials complied on both these points. Nothing in its promotional material suggested that the LIFE study was anything other than a hypertension study and Merck Sharp & Dohme believed that its materials did no more than report the expected benefits of treatment with a specific antihypertensive therapy.

There was no inconsistency between the promotion and the SPC and Merck Sharp & Dohme believed there was no requirement for it to change the licensed indication from hypertension. It might, in due course, seek the inclusion of the LIFE data in one of the sections of the SPC, but the clinical reason for treating these patients would remain hypertension.

As for the comments about standards within Merck Sharp & Dohme UK bringing the industry into disrepute, Merck Sharp & Dohme firmly denied that this was the case and continued to believe that its standards were as high as anywhere else in the UK pharmaceutical industry. Finally, it noted that Aventis had not specifically brought an allegation under Clause 14, so it had not addressed this in its response.

PANEL RULING

The Panel noted that the HOPE study included patients who had a history of coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking or documented microalbuminuria). At that time, Tritace was licensed for the treatment of mild to moderate hypertension and in congestive heart failure as an adjunctive to diuretics with or without cardiac glycosides. Tritace had been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure. In the previous case, Case AUTH/1029/6/00, the Panel had decided that the advertisement at issue promoted Tritace for cardio and cerebroprotection in a general high risk population and thus constituted promotion of an unlicensed indication in breach of Clause 3.2 of the Code.

The Panel considered that the two cases were not comparable. Case AUTH/1029/6/00 concerned a study which was not within the Tritace licensed indication for the product whereas Case AUTH/1340/7/02 concerned a study on patients that were within the Cozaar current licensed indication.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. It decided that the material at issue did not warrant a ruling of a breach of Clause 2.

Complaint received **3 July 2002**

Case completed **29 August 2002**

CASE AUTH/1341/7/02

DOCTOR v MERCK SHARP & DOHME

Cozaar journal advertisement

A doctor complained about a journal advertisement for Cozaar (losartan) issued by Merck Sharp & Dohme which referred to the results of the LIFE study (cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension: a randomised trial against atenolol).

The complainant alleged that the claim 'In addition, Cozaar is the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator and Cozaar showed a 25% reduction in stroke risk (p=0.001)' gave the misleading impression that Cozaar reduced a wide range of cardiovascular (CV) outcomes in addition to reducing stroke by 25%. The data from the LIFE study, however, showed that only stroke was reduced, and this was the sole and only driver for the combined CV outcome claim. The complainant alleged that this was irresponsible advertising intended to increase the sales of Cozaar by implying a wider range of benefits than the data showed.

The Panel noted that in the LIFE study CV outcomes were defined as a composite of cardiovascular death, stroke and myocardial infarction. The differences between losartan and atenolol with regard to the individual endpoints of cardiovascular death and myocardial infarction did not show statistically significant differences. The reduction in stroke was the main driver for the reduction in the primary composite endpoint. The Panel considered that the claim implied two distinct benefits as alleged and this was misleading. Breaches of the Code were ruled.

The complainant alleged that the claim '… Cozaar is the only hypertensive to demonstrate superior CV outcomes versus an active comparator …' was a lie intended to put Cozaar in a unique position; the Medical Research Council (MRC) trials of 1985 and 1992, comparing diuretics and beta-blockers, clearly showed a superior outcome with diuretics over beta-blockers.

The Panel noted that the 1985 MRC trial stated 'Neither of the two drug regimens had any clear overall advantage over the other'. The 1992 MRC trial on older adults concluded that with regard to all-cause mortality the trial did not have sufficient power to detect small effects of treatment and overall the trial suggested that treatment of hypertension with the diuretic combination reduced the risk of strokes and all cardiovascular events at least in non-smokers.

In the Panel's view Cozaar was the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator, atenolol, as reported in the LIFE study. The claim was not a claim for a special merit that could not be substantiated. It was not an unreasonable claim and no breach of the Code was ruled.

A doctor complained about a journal advertisement for Cozaar (losartan) issued by Merck Sharp & Dohme Limited which referred to the results of the LIFE study (cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension: a randomised trial against atenolol).

When writing to Merck Sharp & Dohme, the Authority drew attention to Clauses 7.2, 7.3 and 7.10 of the Code.

1 Claim 'In addition, Cozaar is the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator and Cozaar showed a 25% reduction in stroke risk (p=0.001)'

COMPLAINT

The complainant alleged that the totally misleading claim was obviously intended to give the impression that Cozaar reduced a wide range of cardiovascular (CV) outcomes in addition (the word 'and' clearly included for this purpose) to reducing stroke by 25%. The data from the LIFE study, however, showed very clearly that only stroke was reduced, and this was the sole and only driver for the combined CV outcome claim.

The complainant alleged that this was irresponsible advertising which was intended to increase the sales of Cozaar by implying a wider range of benefits than the data showed.

RESPONSE

Merck Sharp & Dohme noted that the complainant was concerned that the claim implied two distinct benefits – one a wide range of cardiovascular outcomes and, separately, stroke. He was, of course, correct in pointing out that the reduction in stroke was part of reduction of cardiovascular events and was the main driver for the total reduction. Merck Sharp & Dohme was very concerned by this allegation and sought to assure the complainant and the Authority that this was not its intention.

The claim was presented in the context of a summary of the recently published LIFE study results; a study of two antihypertensive treatment regimes, with 'cardiovascular morbidity and mortality' as the primary endpoint. This was defined as a composite of cardiovascular death, stroke and myocardial infarction. Cardiovascular death would include such causes as aortic aneurysms and heart failure in addition to fatal strokes and myocardial infarctions. This was a commonly used composite endpoint, reflecting the major adverse vascular events that might be improved by hypertensive treatment. This was statistically significantly reduced by losartan, when compared with atenolol, both treatments being used to lower blood pressure.

As was pre-specified in Merck Sharp & Dohme's data analysis plan and as published in the protocol design paper, the components of the primary endpoint were also analysed as individual secondary endpoints. It was not scientifically acceptable to present positive

secondary endpoints unless the primary endpoint of a trial was positive, and it was always preferable to detail the result of the primary objective of the study before describing the results at a lower level. Indeed, many would view it as misleading to present a very favourable secondary endpoint result without also presenting the primary outcome of the trial.

Merck Sharp & Dohme therefore disagreed that use of the phrase 'superior CV outcomes' was irresponsible, as this was the pre-specified primary endpoint of the LIFE study, and the result was positive. Merck Sharp & Dohme's intention was not to imply two distinct benefits, and it believed that most prescribers would understand that stroke would also be included in a count of adverse cardiovascular events.

PANEL RULING

The Panel noted the outcomes of the LIFE study. The CV outcomes were defined as a composite of cardiovascular death, stroke and myocardial infarction. The differences between losartan and atenolol with regard to the individual endpoints of cardiovascular death and myocardial infarction did not show statistically significant differences. The reduction in stroke was the main driver for the reduction in the primary composite endpoint.

The Panel considered that the claim implied two distinct benefits as alleged and this was misleading. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

2 Claim '… Cozaar is the only hypertensive to demonstrate superior CV outcomes versus an active comparator …'

COMPLAINT

The complainant alleged that the claim was a lie intended to put Cozaar in a unique position; the Medical Research Council (MRC) trials comparing diuretics and beta-blockers published in 1985 and 1992 clearly showed a superior outcome with diuretics over beta-blockers.

The complainant presumed that the Merck Sharp & Dohme marketing department was either trying to influence the medical profession by lying about the data or was too young to remember 1985. The complainant's view was that an awful lot of GPs and junior doctors took in a lot of information or formed opinions on products through advertising without reading the data.

RESPONSE

Merck Sharp & Dohme stated that no hypertension trial designed with the primary objective of showing superiority in CV outcomes of one class of agent over another class had ever succeeded to do so, until LIFE. The two MRC trials were both designed with the primary objective of showing a benefit in treating hypertensive patients with active therapy over placebo. Whilst the trials certainly attempted to compare beta-blockers with thiazides, Merck Sharp & Dohme did not believe that they 'clearly show a superior outcome with diuretics over beta-blockers'. Merck Sharp & Dohme summarised the main points of these two trials.

MRC Trial of treatment of mild hypertension (1985): The main objective of this trial was to determine whether medical treatment of mild hypertension reduced CV events ie active treatment versus placebo. Patients were randomised in a single blind fashion to one of three groups:- bendrofluazide (10mg), propranolol (up to 240mg) or placebo. A secondary aim of the study was to compare the blood pressure changes between the two active treatment groups and also to compare the incidence of suspected adverse reactions in the treatment groups. The primary results of the study confirmed that active treatment significantly reduced the incidence of stroke versus the placebo treated group, and the incidence of all CV events was significantly reduced on active treatment group versus placebo. There was no obvious difference in total mortality and no obvious difference in rates of coronary events. Additional sub group results were presented with the warning that these 'require very cautious interpretation'. The paper stated 'the rate of all cardiovascular events was not reduced by bendrofluazide'. Merck Sharp & Dohme did not believe that this supported the complainant's view that this trial clearly showed a superior outcome with diuretics over beta-blockers.

MRC Trial of treatment of hypertension in older adults (1992): As with the previous MRC trial, the primary objective of this trial was to establish whether active treatment (with a diuretic or a beta-blocker) reduced the risk of stroke, CHD and death, versus placebo in older hypertensive patients. A secondary aim of the study was to compare the effects of the two active medicines. The primary results were 'compared with the placebo group, actively treated subjects (diuretic and beta-blocker groups combined) had a 25% reduction in stroke, 19% reduction in coronary events, and 17% reduction in all cardiovascular events'. The sub group results, when comparing differences between the two active treatments (intention to treat), showed that for 'all CV events the rate was also significantly lower in the diuretic than in the beta-blocker group (p=0.007)'. However the text of the article advised that 'p values associated with subgroup analyses should be interpreted conservatively as numerous comparisons have been made and selection by interest might have occurred'. Further studying of the text revealed additional weaknesses of the trial, limiting the ability to make comparisons between the two classes of medicines. Firstly, when patients required additional antihypertensive control the medicine they were originally randomised to was first increased and then the other trial medicine was used to supplement the medicine allocated by randomisation. The primary results of the trial were based on a comparison of groups according to their randomised treatment. But the text reported that there was a 'substantial proportion of patient years in which the assigned treatment was not followed'. In fact, 52% of those randomised to receive beta-blockers had additional medicine added (including diuretic), and 38% of those randomised to diuretic had additional medicine added (including atenolol). Another widely recognised weakness of these studies related to the

large numbers of patients who did not complete the study. 48% of the diuretic group stopped taking randomised treatment, 63% of the beta blocker group stopped and 53% of the placebo group. Again, Merck Sharp & Dohme did not believe that this supported the complainant's view that this trial clearly showed a superior outcome with diuretics over beta-blockers.

These limitations had been noted in current British Hypertension Society guidelines 'Few trials have compared different classes of drugs directly as regards reduction in cardiovascular events and none is entirely satisfactory, but they have shown no consistent differences between regimens based on different drug classes'.

The recommendation supporting the use of thiazide diuretics as first line therapy was therefore based as much on cost as on clinical evidence. The MRC studies were clearly landmark studies at the time, establishing the benefit of treating raised blood pressure, but they were not well designed to reliably assess differences between the medicines.

In summary, Merck Sharp & Dohme appreciated these matters being brought to its attention, and assured both the complainant and the Authority that there was certainly no intention to mislead with these claims, nor did Merck Sharp & Dohme believe that they were likely to mislead. Merck Sharp & Dohme would nonetheless bear the comments in mind when it reviewed promotional materials to ensure clarity.

PANEL RULING

The Panel noted Merck Sharp & Dohme's comments about the MRC trials referred to by the complainant. The 1985 MRC trial stated 'Neither of the two drug regimens had any clear overall advantage over the other'. The 1992 MRC trial on older adults concluded that with regard to all-cause mortality the trial did not have sufficient power to detect small effects of treatment and overall the trial suggested that treatment of hypertension with the diuretic combination reduced the risk of strokes and all cardiovascular events at least in non-smokers.

In the Panel's view on the information before it, Cozaar was the only antihypertensive to clearly demonstrate superior CV outcomes versus an active comparator, atenolol, as reported in the LIFE study. The claim was not a claim for a special merit that could not be substantiated. It was not an unreasonable claim and no breach of Clause 7.10 was ruled.

Complaint received **8 July 2002**

Case completed **29 August 2002**

CASES AUTH/1342/7/02 and AUTH/1343/7/02

MERCK SHARP & DOHME v ASTRAZENECA and TAKEDA

Press release

Merck Sharp & Dohme alleged that a press release, issued by AstraZeneca and Takeda, was misleading, unbalanced and not an accurate reflection of the available evidence. The press release detailed some of the results of the SCOPE trial which compared the effects of candesartan (Amias, co-marketed by AstraZeneca and Takeda) and placebo on cardiovascular events and cognitive function in elderly patients with mild hypertension. The press release had been circulated to the medical and pharmaceutical press and a selection of national newspapers.

The press release was headed 'Largest ever study of mild hypertension in the elderly shows 28% reduction in stroke with Amias …'. This result was described as statistically significant. The press release also stated that the SCOPE trial had reported '… an 11% risk reduction in major cardiovascular events, and also suggested a beneficial trend in delay in onset of Type 2 diabetes (20% risk reduction), although neither of these trends achieved statistical significance against the control group'.

The primary endpoint of the SCOPE trial was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Pre-specified secondary endpoints were cognitive function, total mortality, cardiovascular mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, impaired renal function, hospitalisation, quality of life and health economics.

The results showed that overall there was a non-significant decrease of 11% in the primary composite endpoint. Of the components of the composite endpoint, cardiovascular death was not significantly reduced, myocardial infarction showed a non-significant increase of 10% and non-fatal stroke was reduced by 28% (p=0.04). None of the secondary endpoints reached statistical significance.

Of the three components of the primary endpoint, only cardiovascular mortality was specified as a stand-alone secondary endpoint. Stroke and myocardial infarction were to be dealt with as total (fatal and non-fatal) events. Merck Sharp & Dohme argued that analysing components of the composite, when the composite itself was not significantly reduced, gave an understanding of what might have gone on within the trial, but did not constitute robust evidence upon which promotion could be based; the study failed to show that candesartan was superior to placebo at preventing the composite endpoint or the pre-specified endpoints.

The press release gave undue prominence to the reduction in non-fatal stroke and played down the negative results for the primary and all pre-specified cardiovascular endpoints. The headline of the press release '… shows 28% reduction in stroke with Amias' failed to point out that anyone who died from their stroke had been excluded. The total number of strokes was not significantly reduced.

Furthermore, where there was a non-significant trend to reduction in an endpoint, this had been included (eg an 11% reduction in major CV events) but not where there were trends to increase of a similar magnitude (eg 10% non-significant increase in myocardial infarction). As such Merck Sharp & Dohme considered that the press release was not balanced and did not reflect all of the components of the composite equally.

Finally, Merck Sharp & Dohme was confused by the statement that 'Treating hypertension is clearly vital in … delaying the onset of diabetes'. Amias was not indicated for delaying the onset of diabetes.

The press release was entitled 'Largest ever study of mild hypertension in the elderly shows 28% reduction in stroke with Amias (candesartan cilexetil)'. The Panel noted that the 28% reduction was only with regard to the risk of non-fatal strokes. In the Panel's view the headline implied that there was a 28% risk reduction in all strokes which was not so. Although the first paragraph of text referred to non-fatal stroke it was an accepted principle under the Code that otherwise misleading headlines or claims could not be qualified by the small print. The risk reduction in major cardiovascular events and delay in the onset of Type 2 diabetes were referred to in the second paragraph as trends which did not achieve statistical significance against the control group.

The Panel considered that the press release was misleading, unbalanced and did not accurately reflect the evidence. The results referred to had not been placed in the context of the overall study results such that readers could assess their clinical significance. Readers were not told what the primary and secondary endpoints of the trial had been. Much had been made of the reduction in non-fatal stroke which was not the primary endpoint. Although readers were told of the non-significant risk reduction in major cardiovascular events they were not told that this was the primary composite endpoint which included non-fatal stroke. The press release did not state that the total number of strokes was not significantly reduced. Although the non-significant risk reduction in major cardiovascular events was reported in the press release no mention was made of the similarly non-significant increase in non-fatal myocardial infarction. The press release implied that Amias could be beneficial in delaying the onset of type 2 diabetes which was not a licensed indication for the product. Breaches of the Code were ruled.

Merck Sharp & Dohme Limited complained about a press release issued by AstraZeneca UK Limited and Takeda UK Limited which detailed some of the results of the SCOPE trial (The Study on Cognition and Prognosis in the Elderly). The SCOPE trial compared the effects of candesartan (Amias, co-marketed by AstraZeneca and Takeda) and placebo on

cardiovascular events and cognitive function in elderly patients with mild hypertension. The press release had been circulated to the medical and pharmaceutical press, as well as to a selection of national newspapers.

The press release was headed 'Largest ever study of mild hypertension in the elderly shows 28% reduction in stroke with Amias …'. This result was described as statistically significant. The press release also stated that the SCOPE trial had reported '… an 11% risk reduction in major cardiovascular events, and also suggested a beneficial trend in delay in onset of Type 2 diabetes (20% risk reduction), although neither of these trends achieved statistical significance against the control group'.

COMPLAINT

Merck Sharp & Dohme alleged that the press release was misleading, unbalanced and did not accurately reflect the available evidence in breach of Clauses 7.2 and 20.2 of the Code. By disseminating this press release widely, AstraZeneca and Takeda had ensured inaccurate and sensationalised press coverage of the results of SCOPE. Merck Sharp & Dohme's requests to AstraZeneca and Takeda for the immediate issue of a retraction was met with delaying tactics by both companies, although both had now confirmed that no further press release would be issued. Merck Sharp & Dohme considered this was inadequate as the misleading impression formed by the dissemination of the press release would remain unchallenged and given the time sensitive nature of press materials of this kind it was unlikely that AstraZeneca and Takeda would need to issue any further press release announcing the results of the SCOPE study.

The SCOPE study design, Hansson *et al* (1999) was a comparison of candesartan vs placebo in elderly hypertensive patients. During the course of the study, many patients were also prescribed a diuretic. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Pre-specified secondary endpoints were cognitive function, total mortality, cardiovascular mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, impaired renal function, hospitalisation, quality of life and health economics.

The SCOPE study results were presented in June 2002 at the International Society of Hypertension. The results indicated the following:

- primary endpoint – risk reduction 11% p=0.19, non-significant;
- pre-specified secondary endpoints – none of those presented (including total stroke) reached statistical significance;
- components of the composite – CV death not significantly reduced, myocardial infarction non-significant increase by 10%, non-fatal stroke reduced by 28% (p=0.04).

Of the three components of the primary endpoint, only cardiovascular mortality was specified as a stand-alone secondary endpoint. Stroke and myocardial infarction were to be dealt with as total (fatal and non-fatal) events. Merck Sharp & Dohme argued that analysing components of the composite, when the composite itself was not significantly reduced, was valuable hypothesis generating activity and contributed to the understanding of what might have gone on within the trial, but did not constitute robust evidence upon which promotion could be based. As such, the SCOPE study failed to prove convincingly that candesartan was superior to placebo at preventing the composite endpoint or the pre-specified endpoints.

The press release gave undue prominence to the reduction in non-fatal stroke and played down the negative results for the primary and all pre-specified cardiovascular endpoints so far presented. Indeed the headline of the press release '… shows 28% reduction in stroke with Amias' failed to point out that anyone who was unfortunate enough to die from their stroke had been excluded. The total number of strokes was not significantly reduced.

Furthermore, where there was a non-significant trend to reduction in an endpoint, this had been included (eg an 11% non-significant reduction in major CV events) but not where there were trends to increase of a similar magnitude (eg 10% non-significant increase in myocardial infarction). As such, the press release was not balanced and did not reflect all of the components of the composite equally.

Merck Sharp & Dohme stated that the misleading press release had resulted in unbalanced press coverage and examples were provided.

Finally, Merck Sharp & Dohme was confused by the statement that 'Treating hypertension is clearly vital in … delaying the onset of diabetes'. Amias was not indicated for delaying the onset of diabetes.

When asked to act quickly to rectify the matter, AstraZeneca and Takeda both responded with holding letters, delaying further communication for another week. Whilst this timescale might be acceptable in routine inter-company issues, press materials were far more time-sensitive and Merck Sharp & Dohme considered this an unacceptable delaying tactic, calculated to allow press coverage to go ahead and to maximise its impact.

Although both companies had now given an undertaking not to reissue the press release, Merck Sharp & Dohme sought the issue of a retraction making it clear that there was no significant reduction in any pre-specified cardiovascular endpoints. It also wanted a ruling that the use of a non-specified sub-group which reached statistical significance in the absence of a positive primary or pre-specified secondary endpoint did not constitute the robust substantiation necessary for promotion under the Code.

RESPONSE

AstraZeneca responded on behalf of both companies.

The SCOPE study was the largest ever study of mild hypertension in the elderly. It involved almost 5000 patients followed up for a period of 3 - 5 years. The primary objective of the study was to assess the effect of candesartan, an angiotension II receptor antagonist

(AIIRA), on major cardiovascular events, with secondary objectives of the study assessing effects on events including cognitive function, myocardial infarction, renal function, fatal and non-fatal stroke. The impression given was that Merck Sharp & Dohme had a number of underlying concerns with the SCOPE study itself. However, it was the press release which was the subject of the complaint, not the study.

Merck Sharp & Dohme alleged that of the three components of the primary endpoint, only cardiovascular mortality was specified as a stand-alone secondary endpoint. The SCOPE working protocol listed one of the secondary endpoints as 'fatal and non-fatal stroke'. The statistical analysis plan (SAP) which was endorsed by the SCOPE steering committee and finalised before any analysis performed, stated that all stroke, fatal stroke and non-fatal stroke should be analysed separately. AstraZeneca requested that the SAP remained a confidential document. Two independent members from the SCOPE steering committee confirmed that non-fatal stroke was definitely a pre-specified secondary endpoint. The SAP stated the following variables, without any order of importance, will be considered as secondary variables. Fatal or non-fatal stroke; the time from randomisation to a fatal or non-fatal stroke, whichever occurs first; the time from randomisation to a fatal stroke; the time from randomisation to a non-fatal stroke; and the number of non-fatal strokes per 1000 patient years after the first occurrence of a non-fatal stroke.

Furthermore, as non-fatal stroke was an important component of the primary endpoint, it was logical to include non-fatal stroke in the analysis of secondary endpoints.

AstraZeneca did not believe the data was unbalanced and misleading as alleged since it was clear from the analysis of robust data that candesartan reduced the risk of non-fatal stroke by 28% and this was of statistical significance. Although the total number of strokes was not significantly reduced, since non-fatal stroke was defined as a component of the primary endpoint and as a separate secondary endpoint, it was included in the press release as a significant outcome. It was also clear within the press release that the 11% risk reduction in the primary endpoint (reduction in major cardiovascular events), in the candesartan group did not achieve statistical significance, providing a balanced view of the available data. The companies therefore refuted the allegation of a breach of Clause 7.2 and 20.2 of the Code.

In order to address and provide information on the primary endpoint of the study, the 11% risk reduction in major cardiovascular events (a composite of cardiovascular death, non-fatal MI and non-fatal stroke) was reported. However, the press release also stated that the result was not statistically significant compared with the control group. AstraZeneca did not consider it was necessary to provide results of all the individual components of the composite primary endpoint and secondary endpoints since the purpose of issuing a press release was primarily to provide information about the most prominent outcomes of the study in a balanced and appropriate manner. The subsequent press cuttings provided by Merck Sharp & Dohme reflected the information provided in the press release and all mentioned the reduction in non-fatal stroke by 28% and two of the three supplied mentioned the 11% risk reduction in major cardiovascular events.

AstraZeneca was not clear as to the precise nature of the complaint in relation to the statement 'Treating hypertension is clearly vital in … delaying the onset of diabetes'. However, to clarify, this was part of the guidelines issued by the National Service Framework for Coronary Heart Disease and AstraZeneca did not make any claims for candesartan being indicated for delaying the onset of diabetes. Two references which demonstrated that lowering blood pressure could potentially delay the onset of diabetes were provided.

AstraZeneca believed that the results of SCOPE presented in the press release were sufficiently balanced and not intended to mislead the medical and lay media and therefore refuted the alleged breaches of Clauses 7.2 and 20.2.

A copy of the presentation given at the International Society of Hypertension/European Society of Hypertension in Prague was provided on a confidential basis as the trial investigators had not given their permission to release the data beyond the presentation at Prague. The results for SCOPE were released two weeks prior to the conference and therefore an abstract could not be submitted in time. The presentation of the data was therefore provided in the Hotline session in Prague since it was considered to be of newsworthy interest to all delegates present.

AstraZeneca had been given access to this data on the strict instructions that they were not to be disclosed to a third party until publication which was anticipated in September.

PANEL RULING

The press release was entitled 'Largest ever study of mild hypertension in the elderly shows 28% reduction in stroke with Amias (candesartan cilexetil)'. The Panel noted that the 28% reduction was only with regard to the risk of non-fatal strokes. In the Panel's view the headline implied that there was a 28% risk reduction in all strokes which was not so. Although the first paragraph of text referred to non-fatal stroke, and that the 28% risk reduction was statistically significant, it was an accepted principle under the Code that otherwise misleading headlines or claims could not be qualified by the small print. The risk reduction in major cardiovascular events and delay in the onset of Type 2 diabetes were referred to in the second paragraph as trends which did not achieve statistical significance against the control group.

The description of the SCOPE study published in 1999 stated that the primary objective was to assess the effect of candesartan on major cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension. The secondary objectives were to assess the effects on a number of factors including cardiovascular mortality, fatal and non-fatal myocardial infarction and fatal and non-fatal stroke.

The Panel considered that on the information available to Merck Sharp & Dohme non-fatal stroke

was not a secondary endpoint. The Panel noted AstraZeneca's submission that the statistical analysis plan stated that all stroke, fatal stroke and non-fatal stroke should be analysed separately. The Panel accepted AstraZeneca's submission that non-fatal stroke was a secondary endpoint.

The Panel noted that the statistical analysis plan stated that the results of the analysis of the secondary variables would not automatically be considered as confirmatory but rather as exploratory in the sense that they might support the results from the confirmatory analyses or indicate other effects of treatment.

The Panel considered that the press release was misleading, unbalanced and did not accurately reflect the evidence. The results referred to in the press release had not been placed in the context of the overall study results such that readers could assess their clinical significance. Readers were not told what the primary and secondary endpoints of the trial had been. Much had been made of the reduction in non-fatal stroke which was not the primary endpoint. Although readers were told of the non-significant risk reduction in major cardiovascular events they were not told that this was the primary composite endpoint which included non-fatal stroke. The press release did not state that the total number of strokes was not significantly reduced. Given the reduction in non-fatal strokes and the fact that total stroke stayed roughly constant the Panel queried whether this meant there had been an increase in the number of fatal strokes. Although the non-significant risk reduction in major cardiovascular events was reported in the press release no mention was made of the similarly non-significant increase in non-fatal myocardial infarction. The press release implied that Amias could be beneficial in delaying the onset of type 2 diabetes which was not a licensed indication for the product. No details about the comparator were given. At enrolment all patients on current antihypertensive therapy had their medication standardized to hydrochlorothiazide after an appropriate reduction of prior treatment.

The Panel considered that the press release failed to meet the requirements of Clause 20.2 and a breach of that clause was ruled. The Panel also considered that the press release failed to meet the requirements of Clause 7.2 as alleged and a breach of that clause was ruled.

With regard to Merck Sharp & Dohme's request for AstraZeneca and Takeda to issue a retraction, the Panel noted that it had no authority to require companies to issue a retraction. Paragraph 12.2 of the Constitution and Procedure stated that where a report was made to the ABPI Board of Management, the ABPI Board could require a company to publish a corrective statement. The Panel did not consider that the circumstances were such that it should make a formal report about the matter to the Code of Practice Appeal Board for the Appeal Board to consider whether to report the matter on to the ABPI Board.

The Panel was concerned that AstraZeneca and Takeda had issued the press release when the data was confidential and could not be provided on request. Clauses 7.4 and 7.5 required that information, claims and comparisons must be capable of substantiation and such substantiation must be available at the request of health professionals or appropriate administration staff. The Panel requested that its concerns be passed on to the companies.

Complaint received **11 July 2002**

Case completed **6 September 2002**

PRESCRIBING ADVISER v SERVIER LABORATORIES

Coversyl Plus journal advertisement

A prescribing adviser complained about a journal advertisement for Coversyl Plus (perindopril and indapamide) issued by Servier Laboratories which bore the main claim 'Two great antihypertensives come together'. The bottom right-hand corner featured the claim 'Evidence-based combination therapy' beneath 'New Coversyl Plus' in logo format.

The complainant alleged that the advertisement was misleading as it inferred a link to the PROGRESS study in which perindoril and indapamide had been used. However, the dose of indapamide in that study was 2.5mg (2mg in Japanese patients) whereas in Coversyl Plus the dose was 1.25mg.

The complainant stated that when he saw the word 'evidence' he understood it to mean evidence of an effect on outcomes such as strokes, heart attacks etc. No such evidence was presented or referred to in this advertisement and he thought it was thus disingenuous.

The Panel did not accept the complainant's view that 'Evidence-based combination therapy' inferred a link to the PROGRESS study. The complainant also alleged that the claim inferred evidence of an effect on outcomes; the Panel considered that the claim would be read within the context of the main claim 'Two great antihypertensives come together' and the visual of two large waves cascading towards each other. In the opinion of the Panel the reader would gain the overall impression that two established products were now combined in one medicine. Within this context the Panel did not consider the claim misleading, unsubstantiable or exaggerated as alleged and ruled no breach of the Code.

A prescribing adviser complained about an advertisement for Coversyl Plus (perindopril and indapamide) issued by Servier Laboratories Ltd which appeared in Prescriber, 19 June. The advertisement bore the main claim 'Two great antihypertensives come together'. The bottom right-hand corner featured the claim 'Evidence-based combination therapy' beneath 'New Coversyl Plus' in logo format.

COMPLAINT

The complainant alleged that the advertisement was misleading. He noted that the claim 'Evidence-based combination therapy', was not referenced to any evidence. Evidence was no doubt available that it was an effective antihypertensive – it had a product licence which said so, but the complainant believed that the advertisement inferred a link to the PROGRESS study in which these two medicines were used. However, the dose of indapamide in that study was 2.5mg (2mg in Japanese patients) whereas in Coversyl Plus the dose was 1.25mg.

The complainant stated that when he saw the word 'evidence' he understood it to mean evidence of an effect on outcomes such as strokes, heart attacks etc. No such evidence was presented or referred to in this advertisement and he thought it was thus disingenuous.

When writing to Servier the Authority asked it to respond in relation to Clauses 7.2, 7.4, 7.5 and 7.10 of the Code.

RESPONSE

Servier noted that the complainant stated that the word 'evidence' meant evidence of an effect on outcomes such as strokes, heart attacks etc; there was certainly no intention on Servier's part for the advertisement to be interpreted in this way and, in its view, the advertisement did not encourage this interpretation in the general reader. No evidence on outcomes was presented or referred to, either directly or indirectly.

Servier stated that in its view, the term 'evidence-based' was clearly linked to 'combination therapy'. The advertisement announced the launch of Coversyl Plus, a combination of the ACE inhibitor, perindopril, and the diuretic, indapamide. The headline in the advertisement was 'Two great antihypertensives come together'. The whole thrust of the advertisement was thus related to combination therapy for hypertension.

There was a wealth of evidence supporting the use of the combination of an ACE inhibitor and a diuretic in the treatment of hypertension, so much so that the combination was now one of the most popular in the UK.

The combination of an ACE inhibitor and a diuretic was a significant element in all guidelines on the treatment of hypertension, including those issued in America by the sixth Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI 1999), those issued jointly by the World Health Organisation and the International Society for Hypertension (WHO-ISH 1999) and those issued by the British Hypertension Society (BHS 1999). The definitions of blood pressure normalisation had slowly moved to lower values (BP<140/90mmHg according to the WHO-ISH and JNC-VI recommendations or BP<140/85mmHg in the BHS guidelines) and all of the guidelines advocated the use of suitable combinations of agents in order to achieve these targets. In fact, to emphasise this point even further, low-dose fixed-combination therapy had been recognised as a suitable first-line treatment in JNC-VI.

Key quotes from the guidelines included:

'Combinations of … two agents from different classes have been shown to provide additional efficacy, thereby minimising the likelihood of dose-dependent adverse effects. Very-low doses of a diuretic can potentiate the effect of the other agent without producing any adverse metabolic effects.' JNC-VI

'It is often preferable to add a small dose of a second drug rather than increasing the dose of the original drug. This allows both the first and second drugs to be used in the low-dosage range that is more likely to be free of side effects.' WHO-ISH

'Less than half of all hypertensives will be controlled on monotherapy and one third will require three or more drugs' and 'Submaximal doses of two drugs result in larger blood pressure responses and fewer side-effects than maximal doses of a single drug.' BHS

There was also considerable evidence for the efficacy of both perindopril and indapamide as single agents in the treatment of hypertension. Servier provided a list of references.

Perindopril monotherapy had been shown to be effective in mild to moderate hypertension. Perindopril also had demonstrated excellent efficacy in elderly patients, Type I and Type II diabetic patients, patients with renal disease and patients with left ventricular hypertrophy. Perindopril had also been shown to be at least as effective as other antihypertensive agents, including calcium antagonists, ß-blockers and other ACE-inhibitors.

Indapamide monotherapy had also been studied in a wealth of patients, with mild to moderate hypertension, Type II diabetic patients, patients with renal impairment, patients with left ventricular hypertrophy and the elderly. Indapamide had been shown to be at least as effective as other antihypertensive agents, including calcium antagonists, ß-blockers, ACE-inhibitors and other diuretics.

The fact that Coversyl Plus had been licensed for the 'Treatment of essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone' indicated that there was adequate evidence for the efficacy of the combination.

Servier therefore denied any breach of Clauses 7.2, 7.4, 7.5 and 7.10 of the Code; it did not consider the advertisement misleading (Clause 7.2) or exaggerated (Clause 7.10) and it considered the claim 'Evidence-based combination therapy' capable of substantiation, as described above (Clause 7.4). As it had not received a request for substantiation in relation to this advertisement it did not consider Clause 7.5 relevant.

PANEL RULING

The Panel did not accept the complainant's view that 'Evidence-based combination therapy' inferred a link to the PROGRESS study. The complainant also alleged that the claim inferred evidence of an effect on outcomes; the Panel had some sympathy in this regard but considered that the claim would be read within the context of the main claim 'Two great antihypertensives come together' and the visual of two large waves cascading towards each other. In the opinion of the Panel the reader would gain the overall impression that two established products were now combined in one medicine. Within this context the Panel did not consider the claim misleading, unsubstantiable or exaggerated as alleged and ruled no breach of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted that Servier had not received a request for substantiation from a health professional and thus there could be no breach of Clause 7.5 of the Code. There was no complaint in this regard. It appeared that this clause had been raised in error by the Authority.

Complaint received **15 July 2002**

Case completed **10 September 2002**

CASE AUTH/1345/7/02

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

Zocor journal advertisement

Bristol-Myers Squibb and Sankyo Pharma jointly complained about a journal advertisement for Zocor (simvastatin) presented in the style of an advertorial and issued by Merck Sharp & Dohme. The complainants co-marketed Lipostat (pravastatin).

Bristol-Myers Squibb and Sankyo alleged that the claim 'Zocor: The statin of choice in the Heart Protection Study' claimed special merit for Zocor which was not substantiated. Zocor was chosen by the investigators for the Heart Protection Study, which was part-funded by Merck Sharp & Dohme, but their motives for this decision were not stated and did not support the special merit implied.

The Panel considered that the heading was ambiguous. Although Zocor had been chosen for use in the Heart Protection Study this did not automatically mean that it had some special merit compared to the other statins. Zocor was the only statin examined in the study. The Panel considered that the claim was misleading as alleged and had not been substantiated. Breaches of the Code were ruled.

Bristol-Myers Squibb and Sankyo alleged that the claims 'Zocor: outcomes data that's second-to-none', 'No other statin has been studied in these settings and to this extent' and 'It is the only statin to have demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study' did not fairly represent all the available data. They appeared to ignore data from large clinical trials LIPID, CARE and WOSCOPs and their combined trial, the Pravastatin Pooling Project. In the latter study Lipostat demonstrated comparable benefits and tolerability to those shown by Zocor in the Heart Protection Study.

The complainants stated that 'only' in the claim 'It is the only statin to have demonstrated significant clinical benefit and excellent tolerability in the recent Heart Protection Study' was misleading. Zocor was the only statin that could show benefit in the study because it was the only statin used. If the context was broadened outside the Heart Protection Study, Lipostat had demonstrated comparable benefit in large clinical trials such as LIPID, CARE, WOSCOPs and the Pravastatin Pooling Project and the claim was, therefore, inaccurate.

Firstly in relation to the claim 'Zocor: outcomes data that's second-to-none' the Panel noted that there were two double-blind, randomised, placebo-controlled studies which provided outcome data for Zocor – the Heart Protection Study and the 4S study. Three double-blind, randomised, placebo-controlled studies provided outcome data for pravastatin (WOSCOPs, LIPID and CARE). A fourth study, the Pravastatin Pooling Project, combined the results of the other three. The Panel considered that the claim 'Zocor: outcomes data that's second-to-none' implied that clinically Zocor had demonstrated outcome data that were not surpassed by that of any other statin. No data had been submitted which directly compared Zocor with other statins. The Panel noted that no primary prevention data for Zocor had been provided by Merck Sharp & Dohme – the Heart Protection Study was a mixture of primary and secondary prevention and the 4S study was a secondary prevention study. Pravastatin on the other hand had primary prevention data from the WOSCOPs study. The Panel considered that data from the different trials could not be directly compared. Without direct comparisons of Zocor and the other statins it was not possible to be certain that Zocor had outcomes data that was second-to-none. The Panel thus considered that the claim was not accurate or fair. A breach of the Code was ruled.

The Panel noted that the claim 'No other statin has been studied in these settings and to this extent' appeared immediately after reference to the Heart Protection Study and the 4S study; 'these settings' thus referred to primary and secondary prevention. The Panel noted that pravastatin had also been studied in primary and secondary prevention. It was thus not accurate to state that, with regard to Zocor, 'No other statin has been studied in these settings and to this extent'. A breach of the Code was ruled.

The Panel noted that Zocor was the statin chosen to be used in the Heart Protection Study. 'Only' in the claim '[Zocor] is the only statin to have demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study' suggested that other statins had also been used but that Zocor was the only one to have demonstrated significant clinical benefits and excellent tolerability. The Panel noted its comments above with regard to the headline 'Zocor: The statin of choice in the Heart Protection Study'. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

In the claim '… over 20,000 patients with existing or at high risk of CHD were studied†', the obelus referred the reader to the footnote 'Zocor is not licensed in the UK for the prevention of stroke or primary prevention of CHD'. Bristol-Myers Squibb and Sankyo stated that if, as Merck Sharp & Dohme claimed, the advertorial was limited to discussing secondary prevention in patients with established CHD the total would be 13,348 patients. The remainder of patients did not have established CHD and therefore fell outside the marketing authorization for Zocor. The advertorial informed the reader that Zocor now had clinical trial data demonstrating event reduction in primary prevention patients, which was an unlicensed indication. The footnote stating that simvastatin was not indicated for primary prevention simply emphasised the unlicensed nature of the information presented. The advertorial was also alleged to be disguised promotion.

The Panel noted that the claim was in a paragraph headed 'HPS – an impressive trial on an impressive scale' and thus referred to the patients included in the Heart Protection Study. 20,000 referred to the number of patients randomised to either Zocor or placebo; of these patients 35% had no history of coronary disease. The sentence following the claim stated 'Zocor 40mg reduced, among other end-points, MI and revascularisation by approximately one third, at the same time demonstrating excellent tolerability'. This efficacy claim thus related to all patients included in the Heart Protection Study including those with no prior history of coronary disease in whom Zocor was being used for primary prevention. The Panel noted that an obelus next to the claim at issue and the following efficacy claim referred to the footnote 'Zocor is not licensed in the UK for the prevention of stroke or primary prevention of CHD'. The Panel considered that the context of the claim at issue, by referring to patients without CHD, immediately followed by results on the entire patient population, albeit for indications within the current Zocor SPC, in effect promoted Zocor for primary prevention as alleged. The Panel did not consider that the subheading to the advertisement 'Zocor – proven efficacy in more CHD patients than any other statin' negated this impression. The Panel considered that the material was not in accordance with the terms of the Zocor marketing authorization; a breach of the Code was ruled.

The Panel did not consider that the advertorial was disguised promotion, it was clearly an advertisement, and so ruled no breach of the Code.

Bristol-Myers Squibb and Sankyo noted that the claim 'Zocor has been recommended for use as routine first-line therapy for the prevention of CHD events …' was a quote from a Drug and Therapeutics Bulletin review of statins, which referred to secondary prevention only for simvastatin. This was not made clear in the advertisement, leaving the reader to assume that simvastatin was for primary and secondary prevention. The complainants alleged that this was both misleading and outside the licence for the product.

The Panel noted its ruling above and considered that despite the subheading to the advertisement and contrary to Merck Sharp & Dohme's submission, the advertisement would not be read as referring only to CHD patients. The Panel noted that the article from the Drug and Therapeutics Bulletin was published in 2001 before the publication of the results from the Heart Protection Study. The Drug and Therapeutics Bulletin article clearly stated that simvastatin was licensed for secondary prevention of CHD events. In the Panel's view the article referred to the use of simvastatin in both primary and secondary prevention. It was not clear that the recommendation for use was limited to secondary prevention. The Panel considered that some readers would interpret '… first-line therapy for the prevention of CHD events …' to mean primary prevention of CHD for which Zocor had no licence. The Panel thus ruled a breach of the Code.

The Panel did not consider that the claim constituted disguised promotion as alleged. No breach of the Code was ruled.

Bristol-Myers Squibb and Sankyo alleged the advertisement was misleading 'in spirit' and disregarded the industry's special relationship with medical professionals. The advertisement was placed in several publications where the audience would not be expected to know the trials in sufficient detail to appreciate the subtleties of the phrasing.

Notwithstanding its rulings above, the Panel did not consider that the advertisement failed to recognise the special nature of medicines nor the professional standing of the audience to which it was directed. It was not likely to cause offence. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited and Sankyo Pharma UK Limited jointly complained about a journal advertisement for Zocor (simvastatin) issued by Merck Sharp & Dohme Limited. The advertisement was presented in the style of an advertorial.

Bristol-Myers Squibb and Sankyo jointly marketed Lipostat (pravastatin).

1 Claim 'Zocor: The statin of choice in the Heart Protection Study'

This claim appeared as the headline to the advertisement.

COMPLAINT

Bristol-Myers Squibb and Sankyo Pharma alleged that the heading 'Zocor: The statin of choice in the Heart Protection Study' claimed special merit for Zocor which was not substantiated. It implied that in the Heart Protection Study Zocor was chosen over other statins. More correctly stated Zocor was chosen for the Heart Protection Study, which was part-funded by Merck Sharp & Dohme, and was the only statin used in the trial. This would be equivalent to claiming Lipostat was the statin of choice for the LIPID trial or in fact any medicine studied in a trial was the 'medicine of choice'. It implied that some special merit led to Zocor being the 'statin of choice' but failed to substantiate this. Zocor was chosen by the investigators for the Heart Protection Study but their motives for this decision were not stated and did not support the special merit implied by this heading. Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Merck Sharp & Dohme stated that the driving force behind the initiation of the study was a meta-analysis by the Clinical Trials Service Unit in Oxford which showed that lowering cholesterol by medicine was associated with a reduction in cardiovascular events. It therefore proposed a prospective study to confirm its hypothesis that cholesterol lowering by medicine was beneficial in reducing cardiovascular events and deaths. The Clinical Trials Service Unit therefore wished to use the most potent agent available at the

time and at its highest dosage, to achieve maximal cholesterol lowering during the study. At the time the agents available were pravastatin, fluvastatin and simvastatin; clearly simvastatin 40mg was the most obvious choice. The Clinical Trials Service Unit did a pilot study using this dose of simvastatin which confirmed its efficacy and safety profile and this, plus the availability of independent support from Merck and Merck Sharp & Dohme UK, made simvastatin its statin of choice.

Merck Sharp & Dohme thus did not consider that the claim was in breach of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel considered that the claim 'Zocor: The statin of choice in the Heart Protection Study' was ambiguous. It could be interpreted as meaning that, of the statins studied in the Heart Protection Study, the best results were achieved with Zocor, thus making it the statin of choice. Although Zocor had been chosen as the statin to be used in the Heart Protection Study this did not automatically mean that it had some special merit compared to the other statins. There were a number of reasons why any medicine was chosen for use in a clinical trial. Zocor was the only statin examined in the study. The Panel considered that the claim was misleading as alleged and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claims 'Zocor: outcomes data that's second-to-none'
'No other statin has been studied in these settings and to this extent'
'It is the only statin to have demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study'

COMPLAINT

Bristol-Myers Squibb and Sankyo alleged that the above claims did not fairly represent all the available data and were therefore inaccurate in breach of Clause 7.2 of the Code. They appeared to ignore data from LIPID, CARE and WOSCOPs and their combined trial, the Pravastatin Pooling Project, which comprised 19,768 patients with or at risk of coronary heart disease (CHD), Lipostat demonstrated comparable benefits and tolerability in the Pravastatin Pooling Project compared to Zocor in the Heart Protection Study.

Bristol-Myers Squibb and Sankyo stated that the use of the word 'only' in the claim 'It is the only statin to have demonstrated significant clinical benefit and excellent tolerability in the recent Heart Protection Study' was misleading. Zocor was the only statin that could show benefit in the Heart Protection Study because it was the only statin used. In fact Zocor was compared to placebo and to date there were no major trials published comparing two statins. If the context was broadened outside the Heart Protection Study, Lipostat had demonstrated comparable benefit in large clinical trials such as LIPID, CARE, WOSCOPs and the Pravastatin Pooling Project and the claim was, therefore, inaccurate.

RESPONSE

Merck Sharp & Dohme stated that it did not consider that the claims at issue were in breach of Clause 7.2 of the Code. The company noted that the complainants alleged that it had ignored data from three large studies ie LIPID, CARE and WOSCOPs. This was incorrect, the company was aware of the large amount of data these studies provided on the use of pravastatin in patients with, or at risk of developing CHD. However Merck Sharp & Dohme considered that simvastatin had data on a larger number of patients overall and more substantial data on the different patient sub-groups which supported its claims.

'Zocor: outcomes data that's second-to-none.'

Simvastatin and pravastatin were the only statins to have randomised, placebo-controlled trials looking at treatment outcomes on mortality in patients with CHD. The two large secondary prevention studies, CARE and LIPID, which used pravastatin, included a total of 13,173 patients with CHD. The Scandinavian Simvastatin Survival Study (4S) and Heart Protection Study combined looked at the effect of simvastatin treatment in over 17,000 patients with CHD. This meant that about 25% more patients had been studied using simvastatin compared to pravastatin, providing a larger amount of data overall plus additional evidence on the safety profile and tolerability of simvastatin.

On comparing outcomes, the larger of the two secondary care studies involving pravastatin, LIPID, which included patients with unstable angina and a history of myocardial infarction (MI), saw reductions in all cause mortality of 22% compared to placebo. The 4S study which looked at a similar population group (patients with a history of MI or angina) saw an overall reduction in all cause mortality of 30%. Risk reductions for death from CHD were 24% (LIPID) and 42% (4S) respectively. The combined endpoint of death due to CHD or non-fatal MI saw a 24% risk reduction in the LIPID study compared to the 34% risk reduction seen in the 4S study.

The other major trial in secondary prevention with pravastatin was CARE which displayed a similar 24% reduction in coronary events, again less than seen in 4S, though admittedly at a lower risk. Comparison of the Heart Protection Study with CARE was inappropriate as they studied very different patient populations: the Heart Protection Study had a large element of primary prevention, CARE was secondary prevention but in a low cholesterol population.

Not only had simvastatin been studied overall in more CHD patients than pravastatin, the only other statin to have long-term outcome data, but when assessing the outcomes measured (and comparing similar patient groups) it could be seen that they were superior for simvastatin.

Other statins had been studied in patients with CHD but the outcomes measured had tended to be reductions in cholesterol levels and the treatment in acute coronary syndromes. Thus lacking evidence on long-term morbidity and mortality outcomes.

For this reason Merck Sharp & Dohme considered that Zocor had outcomes data that was second-to-none.

'No other statin has been studied in these settings and to this extent'

Merck Sharp & Dohme stated that following an internal review of the advertisement this claim was changed to read 'No other statin has been studied to this extent' (a revised advertisement which had subsequently also been withdrawn as stated earlier was provided).

Merck Sharp & Dohme noted that the complainants alleged that the company had ignored the data from the Pravastatin Pooling Project which had combined the data from LIPID, CARE and WOSCOPS. The Pravastatin Pooling Project looked at a large number of patients, over 19,000, who were at risk of having or had established CHD. When this figure was broken down to look at the various groups of patients studied within the trial (women, diabetics, over 65s, Hypertension, PVD and Stroke/TIA) and hence the extent of the data available, it was possible to see the true discrepancy between these trials and the fact that simvastatin had been studied in a much larger number of the same important groups of patients in the Heart Protection Study. One of the goals of the Heart Protection Study was to provide convincing evidence in the areas that required further work ie patients at risk of CHD. This table had not looked at the number of patients studied in 4S: if included this would further illustrate the wealth of data simvastatin now had on these groups of patients.

'It is the only statin to have demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study'

Merck Sharp & Dohme stated that the clinical benefits and tolerability findings from the Heart Protection Study could only be applied to simvastatin 40mg, the statin and dose that was used in the Heart Protection Study. Whilst some competitors considered that the results could be applied to statins in general, Merck Sharp & Dohme did not consider that the safety and tolerability data from the Heart Protection Study could be extrapolated to other statins. The company's concerns had been heightened as it was clear from journal advertising that this was happening.

However, Merck Sharp & Dohme conceded that the statement could be open to interpretation and it had now changed the claim to read 'Zocor: demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study in addition to the landmark 4S study'.

Merck Sharp & Dohme suggested that the materials in circulation continue with the original strapline for reasons as outlined above but that all new pieces would use the revised strapline.

PANEL RULING

The Panel considered each of the claims at issue separately.

'Zocor: outcomes data that's second-to-none'

The Panel noted that there were two double-blind, randomised, placebo-controlled studies which provided outcome data for Zocor – the Heart Protection Study and the 4S study. The Heart Protection Study included patients with no history of coronary disease (35%), a history of MI (41%) or some other history of coronary disease (24%). Patients were eligible for entry into the study if, *inter alia*, their non-fasting total plasma cholesterol was at least 3.5mmol/l provided they were considered to be at substantial 5-year risk of death from CHD. At the initial screening visit before any statin treatment had started, those participants who were subsequently randomised had a mean non-fasting blood concentration of total cholesterol of 5.9mmol/l. The number of patients randomised to receive simvastatin 40mg daily was 10,269. The 4S study was a secondary prevention study. 4444 patients with angina or previous MI and serum cholesterol 5.5-8.0mmol/l were randomised to double-blind treatment with simvastatin or placebo. 2221 patients received simvastatin and at baseline their total cholesterol was 6.74mmol/l; total cholesterol in the placebo group was 6.75mmol/l.

Three double-blind, randomised, placebo-controlled studies provided outcome data for pravastatin (WOSCOPs, LIPID and CARE). A fourth study, the Pravastatin Pooling Project, combined the results of the other three. WOSCOPs was a primary prevention study in which 3,302 patients received treatment with pravastatin; baseline total cholesterol in both the pravastatin and placebo groups was 7mmol/l. The LIPID and CARE studies were secondary prevention studies. In the LIPID study 4,512 patients were treated with pravastatin; median baseline total cholesterol in the treatment and placebo groups was 5.6mmol/l. In the CARE study 2,081 patients were randomised to treatment with pravastatin. One of the entry criteria was a total cholesterol of <6.2mmol/l. At baseline total cholesterol in both the pravastatin and placebo groups was 5.4mmol/l.

The Panel noted that in terms of the number of patients treated in the outcome studies with either simvastatin or pravastatin, more patients had been treated with simvastatin – 12,490 (10,269 from the Heart Protection Study and 2,221 from 4S) compared with 9,895 respectively. Not all patients in the Heart Protection Study had a history of CHD although they were considered to be at substantial risk of death from CHD.

The Panel considered that the claim at issue 'Zocor: outcomes data that's second-to-none' implied that clinically Zocor had demonstrated outcome data that were not surpassed by that of any other statin. No data had been submitted which directly compared Zocor with other statins. The Panel noted that no primary prevention data for Zocor had been provided by Merck Sharp & Dohme – the Heart Protection Study was a mixture of primary and secondary prevention and the 4S study was a secondary prevention study. Pravastatin on the other hand had primary prevention data from the WOSCOPs study. The 4S study (simvastatin) and the LIPID study (pravastatin) included similar patient groups (angina or previous MI) and demonstrated a decrease in all

cause mortality of 30% and 22% respectively. The Panel noted, however, that the patients in the LIPID study had a lower baseline total cholesterol than those in the 4S study (5.6mmol/l vs 6.74mmol/l) and therefore might have been considered to be at lower risk. Patients in the CARE study (pravastatin) were only those with a history of MI; these patients had a mean total cholesterol of 5.4mmol/l.

The Panel considered that data from the different trials could not be directly compared. Without direct comparisons of Zocor and the other statins it was not possible to be certain that Zocor had outcomes data that was second-to-none. The Panel thus considered that the claim was not accurate or fair. A breach of Clause 7.2 was ruled.

'No other statin has been studied in these settings and to this extent'

The Panel noted that this claim appeared immediately after reference to the Heart Protection Study and the 4S study; 'these settings' thus referred to primary and secondary prevention. The Panel noted that pravastatin had also been studied in primary and secondary prevention. It was thus not accurate to state that, with regard to Zocor, 'No other statin has been studied in these settings and to this extent'. A breach of Clause 7.2 was ruled.

'[Zocor] is the only statin to have demonstrated significant clinical benefits and excellent tolerability in the recent Heart Protection Study'

The Panel noted that Zocor was the statin chosen to be used in the Heart Protection Study. The use of the word only in the claim above suggested that other statins had also been used but that Zocor was the only one to have demonstrated significant clinical benefits and excellent tolerability. The Panel noted its comments in point 1 above with regard to the headline 'Zocor: The statin of choice in the Heart Protection Study'. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

3 Claim '… over 20,000 patients with existing or at high risk of CHD were studied†.'

The obelus referred the reader to a footnote which read 'Zocor is not licensed in the UK for the prevention of stroke or primary prevention of CHD'.

COMPLAINT

Bristol-Myers Squibb and Sankyo stated that if, as Merck Sharp & Dohme claimed the advertorial was limited to discussing secondary prevention in patients with established CHD the total would be 13,348 patients. The remainder of patients did not have established CHD and therefore fell outside the marketing authorization for Zocor. The advertorial informed the reader that Zocor now had clinical trial data demonstrating event reduction in primary prevention patients, which was an unlicensed indication. The footnote stating that simvastatin was not indicated for primary prevention simply emphasised the unlicensed nature of the information presented. The advertorial could also be considered to constitute disguised promotion.

The complainants alleged breaches of Clauses 3.2 and 10.1 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the claim at issue was part of a sentence which when read in its entirety, was a brief description of the types of patients who were recruited into the Heart Protection Study. The company did not consider this breached Clause 3.2 of the Code; it was merely there to inform health professionals about this important trial. When describing any study it seemed fundamental to include the total number and various type of patients who were recruited, along with the primary endpoints studied. The following sentence went on to mention the outcomes from the Heart Protection Study but only referred to the outcomes for which Zocor had a licensed indication.

The results of the Heart Protection Study showed that the 'proportional reduction in the rate of major vascular events was about one-quarter in each of the sub-category of participants studied'. Patients with pre-existing CHD were one such category and, after allowance for non-compliance, treatment with 40mg of simvastatin would probably reduce the rate by a third.

Merck Sharp & Dohme stated that, as previously mentioned, when looking at the advertisement as a whole it was made clear from the start that the types of patients that the claims were referring to were patients with CHD. To clarify matters further and not to disguise promotion, it was clearly stated in a footnote linked to this section that Zocor was not licensed in the UK for the prevention of stroke or the primary prevention of CHD.

PANEL RULING

The Panel noted that the claim at issue was in a paragraph headed 'HPS – an impressive trial on an impressive scale'. The claim thus referred to the patients included in the Heart Protection Study. 20,000 referred to the number of patients randomised to either Zocor or placebo; of these patients 35% had no history of coronary disease. The sentence following the claim stated 'Zocor 40mg reduced, among other end-points, MI and revascularisation by approximately one third, at the same time demonstrating excellent tolerability'. This efficacy claim thus related to all patients included in the Heart Protection Study including those with no prior history of coronary disease in whom Zocor was being used for primary prevention. The Panel noted that an obelus next to the claim at issue and the following efficacy claim referred to a footnote which read 'Zocor is not licensed in the UK for the prevention of stroke or primary prevention of CHD'. The Panel considered that the context of the claim at issue, by referring to patients without CHD, immediately followed by results on the entire patient population, albeit for indications within the current Zocor SPC, in effect promoted Zocor for primary prevention as

alleged. The Panel did not consider that the subheading to the advertisement 'Zocor – proven efficacy in more CHD patients than any other statin' negated this impression. The Panel noted Merck Sharp & Dohme's submission that the reduction in the rate of major vascular events in patients with pre-existing CHD would probably be about a third. The efficacy claim was not limited to patients with pre-existing CHD. The Panel considered that the material was not in accordance with the terms of the Zocor marketing authorization. A breach of Clause 3.2 was ruled.

The Panel did not consider that the advertorial was disguised promotion, it was clearly an advertisement, and so ruled no breach of Clause 10.1.

4 Claim 'Zocor has been recommended for use as routine first-line therapy for the prevention of CHD events …'

COMPLAINT

Bristol-Myers Squibb and Sankyo noted that the claim was a quotation from a Drug and Therapeutics Bulletin review of statins, which referred to secondary prevention only for simvastatin. This was not made clear in the advertisement, leaving the reader to assume that simvastatin was for primary and secondary prevention. The complainants alleged that this was both misleading and outside the licence for the product. The Drug and Therapeutics Bulletin also expressly forbade the use of its materials for advertising purposes. Breaches of Clauses 3.2 and 10.1 were alleged.

RESPONSE

Merck Sharp & Dohme stated that the claim quoted the text from the Drug and Therapeutics Bulletin Vol 39 No 3 March 2001 headed 'Statin Therapy – what now?'. The company had been given permission from the Consumer's Association to use this quotation provided it was referenced to the Drug and Therapeutics Bulletin, which had been done in the advertisement.

Merck Sharp & Dohme stated that in response to the allegation that it was trying to use the claim to promote the use of Zocor in primary prevention, this was not the case. At no juncture in the advertisement did the company advocate the use of Zocor in primary prevention. From the start of the advertisement, in the sub-heading it was made clear that the population referred to in the advertisement were those patients with CHD. This was clarified in this section by the sentence which followed on from the quote, reporting the results of the GOALS study. It stated that '93% of patients with coronary heart disease achieved a target LDL-C level of <3.0mol/l'.

Merck Sharp & Dohme considered that this section was not in breach of the Code as it initially quoted an independent recommendation, which the company had approval to use, and substantiated this with evidence from the GOALS study in patients with CHD.

PANEL RULING

The Panel noted that the claim at issue appeared in the paragraph of text which followed on from that considered at point 3 above. The Panel noted its ruling in point 3 and considered, despite the subheading to the advertisement, that contrary to Merck Sharp & Dohme's submission, the advertisement would not be read as referring only to CHD patients. The Panel noted that the article from the Drug and Therapeutics Bulletin was published in 2001 before the publication of the results from the Heart Protection Study. The Drug and Therapeutics Bulletin article clearly stated that simvastatin was licensed for secondary prevention of CHD events. In the Panel's view the article did not refer only to the use of simvastatin in secondary prevention. The article referred to both primary and secondary prevention. It was not clear that the recommendation for use was limited to secondary prevention. The Panel considered that some readers would interpret '… first-line therapy for the prevention of CHD events …' to mean primary prevention of CHD for which Zocor had no licence. The Panel thus ruled a breach of Clause 3.2 of the Code.

The Panel did not consider that the claim constituted disguised promotion as alleged. No breach of Clause 10.1 was ruled.

The Panel noted Merck Sharp & Dohme's submission that it had obtained permission to quote from the Drug and Therapeutics Bulletin. This was not a matter covered by the Code.

5 Alleged breach of Clause 9.1

COMPLAINT

Bristol-Myers Squibb and Sankyo noted that intercompany correspondence had resolved some but not all of the differences of opinion with regard to the advertisement at issue. Overall the advertisement was misleading 'in spirit' and disregarded the industry's special relationship with medical professionals. The advertisement was placed in several publications where the audience would not be expected to know the trials in sufficient detail to appreciate the subtleties of the phrasing. A breach of Clause 9.1 was alleged.

RESPONSE

Merck Sharp & Dohme disagreed that the advertisement was misleading 'in spirit' and was inappropriately placed in publications. The advertisement was first placed in GP, 15 April, to provide health professionals with important information about the Heart Protection Study. The Heart Protection Study was the largest statin trial to date and included large numbers of patient groups who had previously not been studied to such a great extent. All of the patient groups looked at in the Heart Protection Study were extremely relevant in clinical practice and of interest to health professionals, the audience of publications such as GP, not breaching Clause 9.1 of the Code.

Merck Sharp & Dohme stated that following internal review and the publication of the LIPID eight year

survival data the initial advertisement was withdrawn and alterations made, including the removal of the statements 'No other statin has eight-year survival data' and 'No other statin has been studied in these settings or to this extent' being amended to 'No other statin has been studied to this extent'.

Due to further review and in light of the then forthcoming publication of the Heart Protection Study it was decided to withdraw the advertisement completely.

PANEL RULING

Notwithstanding its rulings above, the Panel did not consider that the advertisement failed to recognise the special nature of medicines nor the professional standing of the audience to which it was directed. It was not likely to cause offence. No breach of Clause 9.1 of the Code was ruled.

Complaint received **19 July 2002**

Case completed **29 August 2002**

CASE AUTH/1347/7/02

CHAIRMAN, DRUGS & THERAPEUTICS COMMITTEE v MERCK SHARP & DOHME

Conduct of representative

The chairman of a hospital drugs & therapeutics committee complained about mail received from a Merck Sharp & Dohme medical representative.

The envelope was handwritten with the complainant's name and hospital address and marked 'Private – Confidential'. Inside the envelope was an Arcoxia (etoricoxib) leavepiece, a questions and answers booklet, clinical data overview and the representative's business card. The complainant noted that the contents of the envelope were anything but private and confidential and was forced to conclude that this was an attempt to gain his attention for this promotional material.

The Panel considered that the impression given by the envelope was that it contained a personal letter to the complainant which was not so; the promotional material had been disguised as a personal communication. The Panel ruled a breach of the Code. The representative had failed to comply with all the relevant requirements of the Code and a further breach of the Code was ruled.

The chairman of a hospital drugs & therapeutics committee complained about mail received through the post from a medical representative of Merck Sharp & Dohme Limited.

The A4 envelope was handwritten with the complainant's name and hospital address and marked 'Private – Confidential'. Two first class stamps had been used. Inside the envelope was a leavepiece for Arcoxia (etoricoxib), a questions and answers booklet for Arcoxia and an etoricoxib clinical data overview with CD-ROM. The representative's business card was also enclosed.

COMPLAINT

The complainant stated that as chairman of a hospital drugs & therapeutics committee, he had a rigid policy that he would not see pharmaceutical representatives. He noted, however, that some company representatives were willing to revert to subterfuge to gain his attention!

The complainant provided an envelope and its contents and noted that the envelope was labelled 'Private – Confidential', but its contents, including the card of the pharmaceutical representative, were anything but. The complainant was forced to conclude that this was an attempt to gain his attention for this promotional material and as such a direct breach of Claude 10.1 of the Code.

In addition to Clause 10.1 cited by the complainant, the Authority requested Merck Sharp & Dohme to consider the requirements of Clause 15.2.

RESPONSE

Merck Sharp & Dohme stated that the representative concerned admitted that she had posted the promotional material for Arcoxia to the complainant in an envelope marked 'Private – Confidential' in order to ensure that the material would be received by him; she had had previous experiences of communications being misplaced when she had used the hospital's internal mail.

Merck Sharp & Dohme accepted that this action was undoubtedly in breach of Clause 10.1 of the Code. The company would be taking appropriate disciplinary action against the representative and apologised unreservedly to the Authority and the complainant for this breach. The company would also take this opportunity to remind all of its representatives of their obligations under Clause 10 of the Code.

PANEL RULING

Clause 10.1 of the Code stated that promotional materials and activities must not be disguised. The

supplementary information advised *inter alia* that promotional material sent in the guise of personal communications, for example, using envelopes or postcards addressed in real or facsimile handwriting, was inappropriate.

The Panel noted that the representative had sent the promotional material by post in an effort to ensure that the complainant received it. This was not necessarily a breach of the Code. However, the envelope in which it had been sent was handwritten and marked 'Private – Confidential'. The impression given by the envelope was that it contained a personal letter to the complainant which was not so. As a result of the representative's actions the promotional material had been disguised as a personal communication. The Panel ruled a breach of Clause 10.1. The representative had failed to comply with all the relevant requirements of the Code and a breach of Clause 15.2 was ruled.

Complaint received **31 July 2002**

Case completed **5 September 2002**

CASE AUTH/1348/8/02

PHARMACIA/DIRECTOR v GLAXOSMITHKLINE CONSUMER HEALTHCARE

Breach of undertaking

Pharmacia complained that a NiQuitin advertisement ruled in breach of the Code in Case AUTH/1253/11/01 had subsequently been reissued by GlaxoSmithKline Consumer Healthcare. Pharmacia had been the complainant in the previous case. As the complaint involved a breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The Panel noted that Case AUTH/1253/11/01 had concerned, *inter alia*, a NiQuitin CQ journal advertisement feature which it had ruled in breach of the Code. GlaxoSmithKline Consumer Healthcare had accepted the Panel's rulings and provided the requisite form of undertaking and assurance in February 2002. However, the advertisement reappeared in the NHS Journal of Healthcare Professionals July 2002 and as a consequence the company had failed to comply with its undertaking. A breach of the Code was ruled as acknowledged by GlaxoSmithKline Consumer Healthcare.

The Panel noted that the agency had received a copy of the Panel's rulings in Case AUTH/1253/11/01 in March. Subsequently the account manager left the agency and was replaced and GlaxoSmithKline Consumer Healthcare appointed a new brand manager. In May the brand manager was asked by the account manager to provide material to fill an advertisement space and was advised by the account manager, on the basis of an old e-mail, that the NiQuitin CQ patch advertisement at issue was approved. Neither party checked the status of the advertisement with senior personnel within their organisations and no reference was made to the original job bag which was archived and 'no longer current'. A copy of the advertisement which was stored electronically was issued.

The Panel considered that it was beholden upon a company to ensure that its procedures for the withdrawal of material pursuant to the provision of an undertaking encompassed all forms in which it was stored, including the electronic version of the material. Written instruction should be provided to advertising agencies regarding the return or destruction of electronic images. The Panel considered that the circumstances were such that they brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

Pharmacia Limited complained that a NiQuitin advertisement ruled in breach of the Code in Case AUTH/1253/11/01 had subsequently been reissued by GlaxoSmithKline Consumer Healthcare. Pharmacia had been the complainant in the previous case. As the complaint involved a breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

COMPLAINT

Pharmacia stated that a NiQuitin CQ advertisement, which appeared to be unaltered from that ruled in breach in Case AUTH/1253/11/01, had been published in the July 2002 edition of the NHS Journal of Healthcare Professionals.

When advising it of the complaint the Authority asked GlaxoSmithKline Consumer Healthcare to consider the requirements of Clauses 22, 9.1 and 2.

RESPONSE

GlaxoSmithKline Consumer Healthcare acknowledged that an unaltered reprint of an advertisement that was previously found to be in breach of the Code appeared in the July 2002 edition of the NHS Journal of Healthcare Professionals. The company sincerely regretted this happening and took the matter very seriously. It stressed that this was not a deliberate breach of undertaking by the company or by any individual. Rather it was a result of a very

unfortunate and unlikely combination of events occurring with the company and at the agency responsible for developing the advertisement. GlaxoSmithKline Consumer Healthcare noted that prior to this occasion, the advertisement last ran on 22 November 2001 and that this was a single isolated occurrence.

GlaxoSmithKline Consumer Healthcare noted that this was not a failure to withdraw offending material. This was undertaken rigorously in accordance with the Guidelines on Company Procedures Relating to the Code of Practice. Despite this, on this occasion an electronic file of the artwork was sent in error to the journal concerned.

GlaxoSmithKline Consumer Healthcare had required the agency concerned to undertake a thorough review of its processes to ensure that such an event could never happen again, allowing for recent developments in technology which meant that advertisements were now issued to journals electronically rather than as films. This would include ensuring that all job bags for items found in breach were sealed with a sticker to that effect. Release of any material for production, in any form, would require physical checking (which would be recorded) against the job bag to confirm that the item was still approved for use. The company had also required all other agencies to undertake a similar review.

GlaxoSmithKline Consumer Healthcare had also reviewed its own internal processes to ensure they were watertight. The company was in the process of ensuring that its standard operating procedure for recall of material was completely rigorous and consistent with that for GlaxoSmithKline Pharmaceuticals.

GlaxoSmithKline Consumer Healthcare stated that in summary, it regretted this unfortunate error and had taken a number of steps to ensure that it did not happen again. The company continued to take very seriously its commitment to the Code, always endeavouring to ensure that promotion of its medicines to members of the health professions was carried out in a responsible, ethical and professional manner.

In response to a request for further information, GlaxoSmithKline Consumer Healthcare explained that after the Panel ruling, and in fact throughout the complaint procedure, both the account director and account manager at the advertising agency were kept informed of the situation through telephone and face to face conversations. A copy of the Panel ruling was given to them at a routine update meeting on 5 March. Everybody was clear that the advertisement in question was not to be used in future, in any case it had not been booked to run in any journal after November the previous year, so the company was happy that it would not be appearing anywhere in the future. The job bag at the agency had already been archived in line with its procedures to ensure only 'live' job bags were available for use. As the vast majority of journals now printed digitally, traditional films were not held and did not need to be recalled or destroyed. All other relevant material was reviewed to ensure it did not contain similar material and therefore need to be withdrawn.

GlaxoSmithKline Consumer Healthcare stated that the account manager left the advertising agency on 28 March and a replacement was brought on to the account. Having reviewed the hand-over notes provided to the incoming account manager, the fact that the advertisement had been found in breach was unfortunately not communicated. Also in March a new brand manager was appointed. On 13 May the brand manager was asked for artwork by 16 May to fill an advertisement space booked by the previous brand manager. As the marketing manager was absent, the brand manager asked the agency account manager which advertisements were approved for use. The account manager found an old e-mail stating that the NiQuitin CQ patch advertisement was approved and advised the brand manager accordingly. Regrettably, no one more senior in the agency reviewed the advertisement, and as advertisements were issued electronically, he did not refer back to the original job bag. Had he done so he would have found it archived and therefore 'no longer current'. Also, the brand manager accepted the account manager's advice without checking with any more senior company personnel and without submitting it for formal copy approval by the appropriate people. Had either of them done this, they would have been made aware of the status of the advertisement and it would not have run.

GlaxoSmithKline Consumer Healthcare submitted that although it was clearly in breach of Clause 22, it was not because the company was lax in implementing the undertaking which it took extremely seriously and tried to apply stringently. However, this occurrence had led to a further review of procedures and processes (in particular the destruction of all electronically held copies of items found in breach) in an effort to ensure this could not happen again, even if all personnel changed overnight. In this case, the initial error occurred at the advertising agency and was compounded by the company not submitting the advertisement for internal approval and therefore the expected high standards were not met on this occasion.

Although human error clearly did occur, the company hoped that it had provided reassurance that it took the matter extremely seriously, had not been lax in implementing its undertaking and did not behave in a way to bring discredit upon or reduce confidence in the pharmaceutical industry. The agency concerned had taken this matter equally seriously – it had admitted significant shortcomings and as a result was currently undertaking a thorough review of its processes to ensure that such an event should never happen again. GlaxoSmithKline Consumer Healthcare denied a breach of Clause 2 of the Code.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Case AUTH/1253/11/01

concerned, *inter alia*, a NiQuitin CQ journal advertisement feature which was ruled in breach of the Code by the Panel; these rulings were accepted by GlaxoSmithKline Consumer Healthcare which provided the requisite form of undertaking and assurance on 15 February 2002. The advertisement had, however, appeared again in the NHS Journal of Healthcare Professionals July 2002 and as a consequence the company had failed to comply with its undertaking. A breach of Clause 22 was ruled as acknowledged by GlaxoSmithKline Consumer Healthcare.

The Panel noted that the agency had received a copy of the Panel's rulings in Case AUTH/1253/11/01 on 5 March. On 28 March the account manager left the agency and was replaced. In the same month, GlaxoSmithKline Consumer Healthcare appointed a new brand manager. On 16 May, with three days' notice, the new brand manager was asked by the new account manager to provide material to fill an advertisement space. The brand manager had asked the account manager which advertisements were approved for use and was advised, on the basis of an old e-mail, that the NiQuitin CQ patch advertisement at issue was so approved. Neither party checked the status of the advertisement with senior personnel within their organisations and no reference was made to the original job bag which was archived and 'no longer current'. A copy of the advertisement which was stored electronically was issued. The Panel noted that GlaxoSmithKline Consumer Healthcare had subsequently reviewed its procedures and processes to include the destruction of all electronically held copies found in breach of the Code.

The Panel considered that it was beholden upon a company to ensure that its procedures for the withdrawal of material pursuant to the provision of an undertaking encompassed all forms in which it was stored, including the electronic version of the material. It appeared that GlaxoSmithKline Consumer Healthcare's procedures did not specifically address the withdrawal of material stored electronically independently of the original job bag.

The procedure should be such that newly appointed personnel could readily identify which promotional materials were current without reference to senior staff or an outside agency. Written instruction should be provided to advertising agencies regarding the return or destruction of electronic images. It was unclear who owned the electronic images retained at the agency; nonetheless in the event that they were not owned by GlaxoSmithKline Consumer Healthcare the company should still be able to demonstrate that it had provided adequate instruction regarding their destruction or storage and the consequences of further use. The Panel considered that the circumstances were such that they brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel considered that consideration of the requirements of Clause 9.1 was covered by this ruling.

Complaint received **1 August 2002**

Case completed **16 September 2002**

CODE OF PRACTICE REVIEW – NOVEMBER 2002

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1250/11/01	**Pharmacia v Alcon Laboratories**	**Invitation to a scientific symposium**	**Breaches Clauses 2 and 3.1 Two breaches Clause 19.1 Audit of Alcon's procedures required by ABPI Board**	**No appeal Report from Appeal Board to ABPI Board**	**Page 3**
1264/12/01	**AstraZeneca v Wyeth**	**Promotion of Zoton including breach of undertaking**	**Breaches Clauses 2 and 4.3 Nine breaches Clause 7.2 Breach Clause 7.3 Five breaches Clause 7.4 Breaches Clauses 7.8, 7.10 and 22 Audit of Wyeth's procedures required by Appeal Board**	**Appeal by respondent**	**Page 5**
1290/3/02	Primary Care Trust Prescribing Adviser v Norgine	Letter about Movicol	No breach	Appeal by respondent	Page 26
1298/4/02	**AstraZeneca v GlaxoSmithKline**	**Promotion of Seretide**	**Two breaches Clause 7.2 Breach Clause 7.4**	**No appeal**	**Page 30**
1300/4/02	Consultant Manager of an Intensive Care Unit v INO Therapeutics	Promotion of Nitric Oxide	No breach	No appeal	Page 36
1304/4/02	**Schwarz Pharma/Director v Schering-Plough**	**Promotion of NeoClarityn including breach of undertaking**	**Breaches Clauses 2, 7.10, 12.1 and 22**	**No appeal Report from Panel to Appeal Board**	**Page 40**
1305/4/02	**Voluntary admission by Wyeth**	**Breach of undertaking**	**Breach Clause 22**	**Appeal by respondent**	**Page 47**
1314/5/02	**General Practitioner v Merck Sharp & Dohme**	**Cozaar (losartan) press information**	**Breaches Clauses 9.1, 20.1 and 20.2**	**No appeal**	**Page 51**
1315/5/02	Anonymous v AstraZeneca	Corporate journal advertisement to health professionals	No breach	No appeal	Page 55
1316/5/02	**Novartis v Fujisawa**	**Article in Kidney Life magazine**	**Breach Clause 9.9**	**No appeal**	**Page 58**
1319/5/02	Boehringer Ingelheim v GlaxoSmithKline	Promotion of Serevent	No breach	No appeal	Page 61
1324/5/02	**Consultant Psychiatrist v Janssen-Cilag**	**Risperdal Consta advisory board meeting**	**Breach Clause 9.1**	**Appeal by respondent**	**Page 65**
1325/5/02	**Janssen-Cilag/Director v Lilly**	**Promotion and medical information relating to Zyprexa**	**Six breaches Clause 7.2 Breach Clause 8.1**	**No appeal**	**Page 68**

1327/5/02	**Schwarz Pharma v Aventis Pharma**	**Telfast 120 leavepiece**	**Breach Clause 7.2**	**No appeal**	**Page 84**
1329/6/02	**GlaxoSmithKline Consumer Healthcare v Pharmacia**	**Nicorette Patch journal advertisement**	**Breaches Clauses 7.2, 7.3 and 7.4**	**No appeal**	**Page 85**
1330/6/02	Chief Pharmacist v Sanofi-Synthelabo	Arixtra advisory board meeting	No breach	No appeal	Page 91
1331/6/02 & 1332/6/02	Consultant Psychiatrist v Janssen-Cilag and Shire	Reminyl booklet	No breach	No appeal	Page 93
1333/6/02	**Aventis Pasteur MSD v GlaxoSmithKline**	**'Dear Nurse' letter**	**Breach Clause 7.3 and 7.9**	**No appeal**	**Page 96**
1334/6/02	**Anonymous General Practitioner v GlaxoSmithKline**	**Avandia e-detail**	**Breaches Clauses 9.1, 10.1, 10.2 and 18.1**	**No appeal**	**Page 98**
1335/6/02	**General Practitioner v Napp**	**Promotion of Transtec**	**Breaches Clauses 4.1 and 4.3**	**No appeal**	**Page 102**
1336/6/02	General Practitioner v AstraZeneca	Seroquel mailing	No breach	No appeal	Page 103
1337/6/02	**Takeda/Director v GlaxoSmithKline**	**Promotion of Avandia**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 105**
1338/6/02	**Sanofi-Synthelabo v GlaxoSmithKline**	**Lamictal journal advertisements**	**Breach Clause 3.2 Five breaches Clause 7.2 Three breaches Clause 7.4 Three breaches Clause 7.10**	**No appeal**	**Page 111**
1339/6/02	**Scottish Medicines Consortium v Aventis Pharma**	**Letter about launch of Lantus**	**Breach Clause 4.1**	**No appeal**	**Page 116**
1340/7/02	**Aventis Pharma v Merck Sharp & Dohme**	**Promotion of Cozaar**	**Two breaches Clause 3.2**	**No appeal**	**Page 120**
1341/7/02	**Doctor v Merck Sharp & Dohme**	**Cozaar journal advertisement**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 127**
1342/7/02 & 1343/7/02	**Merck Sharp & Dohme v AstraZeneca and Takeda**	**Press release**	**Breaches Clauses 7.2 and 20.2**	**No appeal**	**Page 130**
1344/7/02	Prescribing Adviser v Servier Laboratories	Coversyl Plus journal advertisement	No breach	No appeal	Page 134
1345/7/02	**Bristol-Myers Squibb and Sankyo Pharma v Merck Sharp & Dohme**	**Zocor journal advertisement**	**Breach Clause 3.2 Three breaches Clause 7.2 Breach Clause 7.4**	**No appeal**	**Page 136**
1347/7/02	**Chairman, Drugs and Therapeutics Committee v Merck Sharp & Dohme**	**Conduct of representative**	**Breaches Clauses 10.1 and 15.2**	**No appeal**	**Page 142**
1348/8/02	**Pharmacia/Director v GlaxoSmithKline Consumer Healthcare**	**Breach of undertaking**	**Breaches Clauses 2 and 22**	**No appeal**	**Page 143**

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).