PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 35 FEBRUARY 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.

Upward blip in number of complaints

There were 138 complaints under the Code of Practice in 2001 as compared with 121 in 2000 and 127 in 1999.

The number of cases arising from the complaints was also greater in 2001 than in 2000. The number of cases usually differs from the number of complaints because some complaints involve more than one respondent company and because complaints sometimes do not become cases at all, usually because no *prima facie* case is established. There were 147 cases in 2001 as compared with 134 in 2000.

The number of complaints from pharmaceutical companies slightly exceeded the number of complaints from health professionals, 60 coming from pharmaceutical companies and 57 from health professionals. It is generally the case that the greatest number of complaints come from health professionals, though this was not so in 1996 and 1999.

There was an unusually large number of anonymous complaints in 2001 and if these are allowed for it is likely that the total number of complaints from health professionals was higher than the number from pharmaceutical companies. Of the ten anonymous complaints, five stated that they were from health professionals (which may or may not be true), one was received by a newspaper and passed on to the Authority, one stated that it was from employees of the company involved and three were silent as to their origin.

Nine complaints were nominally made by the Director of the Authority, three relating to breaches of undertakings, two concerning media criticism, one arising from a voluntary admission by a company and three dealing with further matters noted during the consideration of complaints. Two complaints were made by members of the public.

The number of complaints each year has varied widely since the Authority was established in 1993, ranging from 92 in 1993 to 145 in both 1994 and 1997.

Public reprimand for Pfizer

Pfizer Limited has been publicly reprimanded by the ABPI Board of Management as a consequence of the activities of its medical liaison executives who had been promoting unlicensed medicines and indications.

Pfizer was also required by the ABPI Board to submit to an audit by the Prescription Medicines Code of Practice Authority of its procedures relating to the medical liaison executive function.

Full details can be found at page 10 in this issue of the Review in the report for Case AUTH/1186/5/01.

Be clear about meetings

Companies should ensure that the nature of their meetings, and the arrangements for them, are made clear to potential participants in advance.

It happens on occasion that a meeting which is otherwise acceptable under the Code of Practice is blighted by the fact that the invitation and associated documents fail to make matters clear.

For example, the offer of overnight accommodation should be justifiable on the basis of the information given, such as that the meeting takes place on both the day before and the day after, or that it starts early or finishes late, with some of those invited having to travel significant distances. Similarly, if an honorarium is offered it should be made quite clear why it is being offered and what is expected in return.

Attention to such detail can help to avoid complaints about hospitality, or the offer of an honorarium etc, which arise because of misunderstandings.

Chief executives must authorize inter-company complaints

Companies are reminded that Paragraph 5.2 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority states that when a complaint is made by a pharmaceutical company, the complaint must be signed or authorized in writing by the company's chief executive and must state the clauses of the Code which are alleged to have been breached.

Time is sometimes wasted because these requirements are not complied with and companies are asked to bear them in mind.

CODE OF PRACTICE TRAINING

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

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

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

Monday, 10 June

Monday, 1 July

Monday, 29 July

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.

CASES AUTH/1183/5/01 and AUTH/1184/5/01

BIOGEN v TEVA and AVENTIS PHARMA

'Dear Healthcare Professional' letter about Copaxone

Biogen complained about a 'Dear Healthcare Professional' letter from Teva and Aventis Pharma entitled 'Copaxone (glatiramer acetate) – Now Available in UK'. Copaxone was for use in relapsing-remitting multiple sclerosis (MS). Three bullet points on the first page discussed the reduction in relapse rates shown in large controlled clinical trials, six year efficacy data and tolerability and side effects. Subsequent paragraphs discussed cost and the product's launch and approval status in other countries.

The first bullet point stated 'In large controlled clinical trials, Copaxone has clearly shown important reductions in relapse rates that are unsurpassed by any other currently available treatment for people with multiple sclerosis (MS)' and was referenced to Johnson *et al* (2000) and Johnson *et al* (1998). Biogen stated that the references were to a pivotal randomised controlled trial and its extension phase. The total recruitment for the original trial was 251 patients and after the placebo-controlled trial 208 elected to enter the open-label extension, even though some of these were re-entered patients who had previously dropped out of the study. Biogen did not believe this number was 'large', and it was smaller than the pivotal trials for all the nearest competitors, the beta-interferons (eg Avonex trial 301 patients, Betaferon trial 372 patients and Rebif trial 560 patients). Neither should the wording 'multiple trials' be used as the references related to one placebo-controlled trial and its extension trial and the extension trial only contained a sub-set of the 251 patients recruited into the original trial.

The Panel noted that Johnson *et al* (1998) was a placebo-controlled multicentre double-blind study assessing the clinical effect of Copaxone on MS relapse rate, degree of disability and tolerability. A total of 251 patients were treated (Copaxone n=125; placebo n=126) for 24 months followed by an 11 month blinded extension phase. Johnson *et al* (2000) was an open-label extension of the aforementioned study whereby patients in the placebo group were switched to active drug. Whilst the study authors acknowledged reservations about open-label studies they stated 'No other licensed MS therapy has been evaluated this rigorously for this duration'. The Panel considered that the claim gave the impression that there were two or more separate Copaxone trials and in this regard noted that in addition to Johnson *et al* (1998) and its extension Johnson *et al* (2000) the respondent companies also referred to a further study of 239 patients, Comi *et al* (1999). The Panel noted that it was not necessary to cite every trial needed to substantiate a claim. The Copaxone summary of product characteristics (SPC) stated that in clinical trials a significant reduction in the number of relapses compared with placebo was seen. The SPC also stated that patients had been treated in three controlled trials involving 50, 251 and 239 patients respectively. The Panel considered that it was not misleading to refer to 'trials' in plural form in the claim at issue and ruled no breach of the Code on this point.

The Panel considered that the claim invited the reader to compare the Copaxone 'large clinical trials' with those for other currently available multiple sclerosis treatments. Whether a trial was considered large was subjective and depended on context, such as disease area. The patient numbers in the studies cited and Comi *et al* were smaller than the pivotal trials for Avonex, Betaferon and Rebif. The Panel considered that, on balance, the use of 'large' in this context was misleading and a breach of the Code was ruled. Upon appeal the Appeal Board's view was that readers would assume that the use of the word large to describe the Copaxone trials meant that there was some special merit with regard to their size; either the Copaxone trials involved more patients than the trials for other MS treatments or the trials of other MS treatments were regarded as small. Neither was the case. The Appeal Board considered that, on balance, the use of the word large in this context was misleading and upheld the Panel's ruling of a breach of the Code.

The second bullet point stated 'Copaxone is the only drug to have shown sustained efficacy over six years of treatment in people with MS. Published results in a large study show that more than 80% of patients continued treatment for six years. This group showed a reduction of at least 85% in relapse rates in the sixth year'. The claim was similarly referenced to Johnson *et al* (2000) and Johnson *et al* (1998). Biogen alleged that these claims were unjustified. Open-label extension studies were designed to test safety; placebo-controlled or blinded comparator trials were designed to test efficacy. The use of open-label studies to support efficacy overlooked the importance of maintaining high scientific standards in evidence-based medicine. The open-label part of the trial exaggerated the treatment effect previously observed in the placebo-controlled part due to several well recognised scientific problems which placebo-controlled trials were intended to avoid. The claims made failed to make it clear that the reduction in relapse rates was derived from such an unreliable methodology. The data on compliance with treatment cited in the letter was simply incorrect. The clinical paper showed precisely the compliance in both the active and placebo groups as followed through the trial. This error was acknowledged by Teva, although Biogen still disputed the corrected figure.

The Panel noted that the authors in Johnson *et al* (2000) acknowledged that open-label studies lacked the scientific rigour of double-blind placebo-controlled trials and stated that it was unethical to maintain patients on placebo when therapies of proven value were available. They submitted that there was substantial value in these long-term observations; continued study of a well chosen cohort educated to the requirements of the study was a clear improvement over natural history studies. The continued use of the same examining

and treating neurologist substantially improved the validity of the disability results. The Panel noted that whilst open-label studies did not have the scientific rigour of controlled, randomised trials the results could be considered generally supportive of such trials. The Panel was, however, concerned that the limitations of the study were not reflected in the claim at issue. The reader would assume that there was controlled, randomised data for a six year period to support the claim at issue and that was not so. The Panel considered the claim misleading in this regard and a breach of the Code was ruled.

Beneath the three bullet points the second paragraph opened with the claim 'The robust scientific data for Copaxone, together with its annual average cost per patient of £6,650 demonstrates its clinical and cost-effectiveness'. Biogen stated that no reference was offered for any health economic study for Copaxone nor any measure used in the letter that could be used in health economics (such as cost per clinical event, cost per quality adjusted life year (QALY) or suchlike). After a second letter to Teva in relation to this claim Biogen was sent an abstract of unknown origin which discussed the cost effectiveness of Copaxone. In addition, for reasons set out above, Biogen disputed that the data referenced was either 'robust' or that it 'demonstrates clinical and cost-effectiveness'. There might be other data supporting these claims, but none was referenced.

The Panel noted that the claim was not one that required a reference as it did not refer to a published study. Teva and Aventis had provided an abstract, Lavelle, which introduced an economic model for Copaxone based upon its clinical trial data. Very limited methodology was provided. The data showed that based upon analysis over 8 years, cost per relapse avoided and cost per disability unit avoided were £11,208 and £9,035 respectively. The author concluded that using patient data for Copaxone for a long-term period indicated that the cost per QALY gained was considerably less than that based upon short time periods such as 2 years. Based upon the strong clinical data over the long-term and the cost per QALY ratio reported being favourable compared to accepted standards for cost-effectiveness in the UK, this analysis provided economic justification for the prescribing of Copaxone for appropriate patients with relapsing-remitting MS. It was unclear whether Johnson *et al* discussed above was part of clinical trial data referred to by Lavelle. The abstract did not refer to comparable products; it was not clear whether the same economic model developed from Copaxone trial data could be applied to comparators. The claim and the response implied that the clinical trial data and the purchase price of the medicine alone demonstrated its cost-effectiveness and there was only limited data provided. In the Panel's view this was not sufficient. The claim was misleading and a breach of the Code was ruled.

The Panel noted that Biogen had also alleged a failure to provide substantiation pursuant to a written request. The Lavelle abstract was provided by Teva and Aventis following Biogen's request. The Panel noted its comments on the Lavelle abstract above. The Panel considered that Teva and Aventis had failed to substantiate the claim and a breach of the Code was ruled. Upon appeal of this ruling, the Appeal Board noted that in response to requests for further information regarding the broad claim for the cost-effectiveness of Copaxone enquirers would be sent the Lavelle abstract together with a Question and Answer document. At the end of that document recipients were informed that if they wanted a more detailed presentation then they could organise a visit from the companies' health economics team. The Lavelle abstract stated that the cost per QALY was between £23,026 and £65,896; the Question and Answer document, however, included a table of data which, in bold, referred to the cost per QALY for Copaxone of £23,026. The Appeal Board considered that the data regarding the cost effectiveness of Copaxone was not clear and that the results from Lavelle had been selectively quoted in the Question and Answer document such that attention had been drawn to the lower cost per QALY. The Appeal Board considered that Teva and Aventis had failed to substantiate the claim and upheld the Panel's ruling of a breach of the Code.

The final paragraph stated 'Copaxone was launched in the USA in 1997 and is now the fastest growing therapy for MS. It is also approved in 17 other countries including Canada, Australia, Israel and Switzerland and has been used worldwide in over 30,000 patients'. Biogen noted that the claim 'fastest growing therapy for MS' was not referenced nor was it clear whether it referred to absolute numbers of new patients, or new patient numbers relative to existing patients. Biogen alleged a failure to provide substantiation.

The Panel noted that the IMS America data submitted by Teva and Aventis showed that between June and October 2000 the market share (total prescriptions) of Copaxone had increased by 3.4% whilst that for Avonex and Betaferon had decreased by 2.3% and 1.2% respectively. At 20 October 2000 Avonex held the largest market share at 53% compared to Copaxone (25.8%). The sample 'Dear Healthcare Professional' letter provided was dated 12 December 2000. The Panel considered that the construction of the paragraph was such that it was unclear whether Copaxone was the fastest growing therapy for MS in the USA or worldwide in those countries in which Copaxone had been approved. The Panel considered the claim misleading and thus not capable of substantiation. A breach of the Code was ruled.

Biogen Limited complained about a 'Dear Healthcare Professional' letter sent jointly by Teva Pharmaceuticals Ltd and Aventis Pharma Ltd and entitled 'Copaxone (glatiramer acetate) – Now Available in UK'. The letter was signed by a senior product manager from each company. Copaxone was for use in relapsing-remitting multiple sclerosis (MS). Three bullet points on the first page discussed the reduction in relapse rates shown in large controlled clinical trials, six year efficacy data and tolerability and side effects. Subsequent paragraphs discussed cost and the product's launch and approval status in other countries.

Teva and Aventis Pharma each submitted an identical response to the complaint.

1 The first bullet point

The first bullet point stated 'In large controlled clinical trials, Copaxone has clearly shown important reductions in relapse rates that are unsurpassed by any other currently available treatment for people with multiple sclerosis (MS)' and was referenced to Johnson *et al* (2000) and Johnson *et al* (1998).

COMPLAINT

Biogen stated that the two references referred to a pivotal randomised controlled trial and its extension phase. The total recruitment for the original trial was 251 patients and after the placebo-controlled trial 208 elected to enter the open-label extension, even though some of these were re-entered patients who had previously dropped out of the study. Biogen did not believe this number was 'large', and was smaller than the pivotal trials for all the nearest competitors, the beta-interferons (eg Avonex trial 301 patients, Betaferon trial 372 patients and Rebif trial 560 patients). Neither should the wording 'multiple trials' be used as the references related to one placebo-controlled trial and its extension trial and the extension trial only contained a sub-set of the 251 patients recruited into the original trial. In inter-company correspondence Teva had cited a further clinical paper which was not referenced in the letter in question, and was thus irrelevant to this claim. Biogen alleged a breach of Clause 7.2.

RESPONSE

Teva and Aventis stated that the pivotal study of Copaxone incorporated 251 patients. This was similar in size to studies of other disease modifying agents for MS. Indeed, the study of Biogen's Avonex included 301 patients, which was of the same order of magnitude as the Copaxone study.

Teva and Aventis noted that Biogen also objected to the use of the plural 'trials'; this did not appear in its initial complaint and was only raised in subsequent correspondence. In reply, the companies drew Biogen's attention to a further study of Copaxone involving 239 patients. Biogen claimed that this study was 'irrelevant' because a reference for the work was not given. Whilst Biogen was correct in pointing out that the references quoted in the 'Dear Healthcare Professional' letter referred to the pivotal study and to an extension trial, it was surely unreasonable to claim that a further major study was 'irrelevant'. On the contrary, this additional trial provided clear evidence supporting the use of the plural 'trials' and this substantiation was provided to Biogen without delay following its request.

Teva and Aventis therefore denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that Johnson *et al* (1998) was a placebo-controlled multicentre double-blind study assessing the clinical effect of Copaxone on MS relapse rate, degree of disability and tolerability. A total of 251 patients were treated (Copaxone n=125; placebo n=126) for 24 months followed by an 11 month blinded extension phase. Johnson *et al* (2000) was an open-label extension of the aforementioned study whereby patients in the placebo group were switched to active drug. The data reported were from approximately six years of organised evaluation, including the initial double-blind phase of up to 35 months. Whilst the study authors acknowledged reservations about open-label studies they further stated 'No other licensed MS therapy has been evaluated this rigorously for this duration'.

The Panel considered that the claim gave the impression that there were two or more separate Copaxone trials and in this regard the Panel noted that in addition to Johnson *et al* (1998) and its extension Johnson (2000) the respondent companies also referred to a further study of 239 patients, Comi *et al* (1999). The Panel noted that the Comi study investigated the effect of Copaxone on MRI detected disease activity in patients with relapsing-remitting MS.

The Panel noted that whilst the studies cited should be relevant to a claim it was not necessary to cite every trial needed to substantiate a claim. The Copaxone summary of product characteristics (SPC) stated that in clinical trials a significant reduction in the number of relapses compared with placebo was seen. Copaxone had also demonstrated beneficial effects on MRI parameters of MS. The SPC also stated that patients had been treated in three controlled trials involving 50, 251 and 239 patients respectively. The Panel considered that it was not misleading to refer to 'trials' in plural form in the claim at issue and ruled no breach of Clause 7.2 on this point. This was accepted.

The Panel considered that the claim invited the reader to compare the Copaxone 'large clinical trials' with those for other currently available multiple sclerosis treatments. The Panel considered that whether a trial was considered large was subjective and depended on context, such as disease area. The Panel noted that the patient numbers in the studies cited and Comi *et al* were smaller than the pivotal trials for Avonex, Betaferon and Rebif. The Panel considered that, on balance, the use of 'large' in this context was misleading and a breach of Clause 7.2 was ruled. This ruling was appealed by Teva and Aventis.

APPEAL BY TEVA AND AVENTIS PHARMA

Teva and Aventis noted that the use of the word large to describe the Copaxone trials had been considered misleading because the patient numbers in the studies cited (Johnson, 251) and Comi *et al* (239) were smaller than the pivotal trials of Avonex (301), Betaferon (372) and Rebif (560). The use of the word large was not meant as a comparison, but rather to reflect that the Johnson and Comi studies were pivotal registration trials sufficiently powered to demonstrate a statistically significant difference between the two treatment arms. Teva and Aventis produced a table of data which showed that the number of patients involved in the placebo and treatment arms of the

various trials were as follows: Copaxone, 126 placebo, 125 active; Avonex, 143 placebo, 158 active; Betaferon, 128 placebo, 125 active (dose a) and 124 active (dose b); Rebif, 187 placebo, 184 active (dose a) and 189 (dose b). The companies noted that the number of patients in the treatment arms were of the same magnitude. Such exposure numbers per study in the field of multiple sclerosis were generally regarded as large. Teva and Aventis refuted the allegation that the use of the word large in this context was misleading and denied a breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the letter in question was sent to hospital specialists, pharmacists and MS nurses; it was not sent to general practitioners. The Appeal Board noted that the size of the Copaxone trials had been determined by study design, statistical power and patient population. The trials had been sufficiently large to detect the primary endpoint and the numbers of patients involved were not dissimilar to those included in the trials for other MS therapies. In the Appeal Board's view, however, readers would assume that the use of the word large to describe the Copaxone trials meant that there was some special merit with regard to their size; either the Copaxone trials involved more patients than the trials for other MS treatments or the trials of other MS treatments were regarded as small. Neither was the case. The Appeal Board considered that, on balance, the use of the word large in this context was misleading and upheld the Panel's ruling of a breach of Clause 7.2.

The appeal on this point was unsuccessful.

2 Open-label study

The second bullet point stated 'Copaxone is the only drug to have shown sustained efficacy over six years of treatment in people with MS. Published results in a large study show that more than 80% of patients continued treatment for six years. This group showed a reduction of at least 85% in relapse rates in the sixth year'. The claim was similarly referenced to Johnson *et al* (2000) and Johnson *et al* (1998).

COMPLAINT

Biogen alleged that these claims were unjustified and in breach of Clause 7.2 for the following reasons:

Open-label extension studies were designed to test safety; placebo-controlled or blinded comparator trials were designed to test efficacy. The use of open-label studies to support efficacy overlooked the importance of maintaining high scientific standards in evidence-based medicine.

The open-label part of the trial exaggerated the treatment effect previously observed in the placebo-controlled part due to several well recognised scientific problems which placebo-controlled trials were intended to avoid: selection bias (severe cases dropping out, reducing the 'average' severity of remaining patients) which was acknowledged by the authors in the paper and described in data tables; regression to the mean (a statistical effect where extreme observations reduced in later follow-up); and the well documented reduction in relapse rate associated with disease progression in MS.

The claims made failed to make it clear that the reduction in relapse rates was derived from such an unreliable methodology.

The data on compliance with treatment cited in the letter was simply incorrect. The clinical paper showed precisely the compliance in both the active and placebo groups as followed through the trial. This error was acknowledged by Teva, although Biogen still disputed the corrected figure.

RESPONSE

Teva and Aventis stated that Biogen made extensive criticisms of the design of the study reported by Johnson *et al* (2000) in the August issue of Multiple Sclerosis. This was a highly reputable peer-reviewed journal and the authors of the paper were amongst the foremost MS specialists in the world with international reputations.

This particular paper reported the follow-on study to a double-blind randomised controlled trial which compared the incidence of relapses in patients randomised to Copaxone compared to placebo. The methodology employed in this study was similar to that used in the pivotal beta-interferon studies. The objective of the follow-on study was to observe patients over the long term. This information was regarded as supportive to the initial double-blind placebo controlled trial, but was nevertheless very important as MS was a chronic disease and long-term data was lacking.

The paper was very open and clear about the methodology employed and the authors discussed many of the points raised by Biogen. They stated 'We acknowledge that open-label studies lack the scientific rigour of double-blind, placebo-controlled trials; however, it is obviously unethical to maintain patients on placebo when therapies of proven value were available. We believe there is substantial value in these long-term observations, because this is a well-characterised cohort of patients who have become accustomed to returning regularly for neurological evaluation and who are aware of the need to report new symptoms and potential MS relapses or adverse events promptly to their investigative centres'. Furthermore, the authors stated 'In our view, this open-label study is a rigorous, efficient and useful way to obtain long-term efficacy and safety data for an MS drug such as glatiramer acetate and can provide useful comparisons with the natural course of untreated MS. No other licensed MS therapy has been evaluated this rigorously for this duration'.

It was apparent, therefore, that this eminent group of highly experienced neurologists did not accept Biogen's contention that open-label extension studies should not be used to support efficacy. The randomised placebo-controlled trials had demonstrated a clinically relevant and statistically significant benefit of Copaxone on relapse rate and therefore a six-year placebo-controlled trial would be unethical. In this situation, valuable long-term

efficacy and safety data was provided by this carefully conducted study, as pointed out by the authors.

The issue of drop-outs was specifically addressed in the paper and the authors described the painstaking means adopted to deal with this, which included a critical evaluation of potential bias and examining questionnaires from patients who had left the study. Biogen alleged that regression to the mean had occurred in this study, but there was no evidence for this nor did Biogen provide anything to support its allegation. Biogen suggested that the reduction in relapse rate seen in this long-term study was due to disease progression. This was also addressed in the paper which stated 'Over time, relapsing-remitting MS patients without treatment experience fewer relapses but are known to display increasing fixed disability'. Hence, particular attention had been paid to the disability status of the patients. These evaluations 'show that the majority of patients have remained unchanged (or improved) over 6 years of careful scrutiny'. Thus the benefit in relapse rate was not due to disease progression.

Biogen claimed that the results seen in this study arose from an 'unreliable methodology'. On the contrary, as already explained, the world-respected authors of this peer-reviewed paper from an authoritative journal had taken special care to ensure the validity of their work.

Biogen insisted that in calculating a continuation rate it was necessary to use the original recruitment cohort as the denominator. Teva and Aventis accepted this and gave an undertaking that a figure of 60% would be used in future. This was taken directly from the publication, which stated 'In fact, 60% of the patients (152/251) originally recruited in 1991-92 continue in the study'. From the complaint it seemed that Biogen did not accept this figure, although Teva and Aventis did not understand its reasons.

Teva and Aventis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the study authors in Johnson *et al* (2000) acknowledged that open-label studies lacked the scientific rigour of double-blind placebo-controlled trials and stated that it was unethical to maintain patients on placebo when therapies of proven value were available. The authors submitted that there was substantial value in these long-term observations; continued study of a well chosen cohort educated to the requirements of the study was a clear improvement over natural history studies. The continued use of the same examining and treating neurologist substantially improved the validity of the disability results. The Panel noted that whilst open-label studies did not have the scientific rigour of controlled, randomised trials the results could be considered generally supportive of such trials.

With regard to selection bias the study authors stated that the 43 patients who chose not to participate in the open-label study were doing less well in terms of relapse rate and neurological disability than those who joined the open phase. The potential bias created by a subgroup of patients electing not to continue was critically evaluated and the study authors noted that the data did suggest a bias in that the patients who chose to continue in the open-label phase were a large subset who responded to and tolerated a known effective agent for a long follow-up period. A questionnaire sent to willing patients who were no longer participating showed no major bias between groups during the open-label study. The Panel noted, however, that only 62% of patients responded to this questionnaire. The Panel noted that Biogen had provided no data to substantiate the allegation of regression towards the mean. The Panel noted that Aventis and Teva argued that although relapse rate was known to reduce with disease progression this was usually associated with increasing fixed disability. Most patients in the study did not show an increase in disability, suggesting that the reduction in relapse rate was not due to disease progression. The Panel noted that Aventis and Teva accepted that it was not correct to say that 80% of patients continued treatment for six years; the figure should be calculated using the number of patients originally recruited as the denominator which gave a continuation rate of 60%. The Panel noted that Biogen disputed the revised figure of 60% but gave no explanation why.

The Panel considered that a controlled study would be more robust than an uncontrolled one, however it was not always possible to conduct such a study. Well conducted uncontrolled studies could provide useful data, however it was necessary to take the limitations of the methodology into account in relation to the claims being made. The Panel noted that the study authors conceded a selection bias, and that, as acknowledged by Teva and Aventis, the figure of 80% was incorrect. The Panel noted that the study had been cited in support of quantitative claims. The Panel was concerned that the limitations of the study were not reflected in the claim at issue. The reader would assume that there was controlled, randomised data for a six year period to support the claim at issue and that was not so. The Panel considered the claim misleading in this regard. A breach of Clause 7.2 was ruled.

3 Cost effectiveness claim

Beneath the three bullet points the second paragraph opened with the claim 'The robust scientific data for Copaxone, together with its annual average cost per patient of £6,650 demonstrates its clinical and cost-effectiveness'.

COMPLAINT

Biogen stated that no reference was offered for any health economic study for Copaxone nor any measure used in the letter that could be used in health economics (such as cost per clinical event, cost per quality adjusted life year (QALY) or suchlike). After a second letter to Teva in relation to this claim Biogen was sent an abstract of unknown origin which discussed the cost effectiveness of Copaxone. In addition, for the reasons set out at point 2 above, Biogen disputed that the data referenced was either 'robust' or that it 'demonstrates clinical and cost-effectiveness'. There might be other data supporting these claims, but none was referenced. Biogen alleged

a breach of Clause 7.2 in relation to the claim and a breach of Clause 7.3 in the failure to provide substantiation as requested in its letter of 16 January. Biogen further believed that companies had a particular responsibility to exercise sensitivity and care with claims on cost-effectiveness during the well publicised National Institute for Clinical Excellence (NICE) appraisal of beta-interferons and glatiramer which was still ongoing.

RESPONSE

Teva and Aventis stated that Biogen implied that the response sent following its initial letter ignored its concerns about the cost-effectiveness of Copaxone. This was not so, but it only became apparent from Biogen's subsequent letter that it regarded the reply as inadequate. When this became clear, however, Biogen was provided with an abstract discussing the issues in some detail. Biogen acknowledged this in its complaint.

The price of Copaxone and of Avonex had a bearing on this matter. Prices stated in MIMS February 2001 resulted in the following costs per patient per annum, exclusive of VAT: Avonex 30mcg once weekly = £9,061 and Copaxone 20mg per day = £6,650.04.

In addition under this point, Biogen repeated the allegation that the clinical trial reported by Johnson *et al* was not scientifically valid. As explained previously, this was in fact a carefully considered study which had been reported in a very measured way.

Teva and Aventis therefore denied breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the claim was not one that required a reference under Clause 7.5 of the 1998 Code; it did not refer to a published study. The Panel noted that Aventis and Teva had provided an abstract, Lavelle, which introduced an economic model for Copaxone based upon its clinical trial data. Very limited methodology was provided in the abstract. The data showed that based upon analysis over 8 years, cost per relapse avoided and cost per disability unit avoided were £11,208 and £9,035 respectively. The author concluded that using patient data for Copaxone for a long-term period indicated that the cost per QALY gained was considerably less than that based upon short time periods such as 2 years. Based upon the strong clinical data over the long-term and the cost per QALY ratio reported being favourable compared to accepted standards for cost-effectiveness in the UK, this analysis provided economic justification for the prescribing of Copaxone for appropriate patients with relapsing-remitting MS. It was unclear whether Johnson *et al* discussed at point 2 above was part of clinical trial data referred to by Lavelle. The abstract did not refer to comparable products; it was not clear whether the same economic model developed from Copaxone trial data could be applied to comparators.

The claim and the response implied that the clinical trial data and the purchase price of the medicine alone demonstrated its cost-effectiveness and there was only limited data provided. In the Panel's view this was not sufficient. The claim was misleading and a breach of Clause 7.2 was ruled. This ruling was accepted.

The Panel noted that Biogen had also alleged a breach of Clause 7.3 in relation to the failure to provide substantiation pursuant to a written request. The Panel noted that Clause 7.3 required that material was capable of substantiation. Clause 7.4 however required substantiation to be provided without delay at the request of members of the health professions or appropriate administrative staff. The Panel noted that the Lavelle abstract was provided by Teva and Aventis following Biogen's request. The Panel noted its comments on the Lavelle abstract above. The Panel considered that Teva and Aventis had failed to substantiate the claim and a breach of Clause 7.3 (1998 Code) was ruled. This ruling was appealed.

APPEAL BY TEVA AND AVENTIS PHARMA

Aventis and Teva considered that the claim of cost effectiveness for Copaxone was substantiable given the setting of health economics.

Recipients of the 'Dear Health Professional' letter at issue were given the choice of further information or advice if they so required. A Question and Answer document was generated by the companies' health economics team in conjunction with medical information to deal specifically with any request for further information. The companies also extended an invitation to Biogen to explain the health economics data.

The initial evidence provided to Biogen (Lavelle) was based on sound and accepted health economic principles ie the construction of a robust model into which the acquisition cost of the health technology was then incorporated. Based on the author's criteria for this model Copaxone was regarded as cost effective. The Panel commented on the paucity of methodology information in the abstract cited; this was due to the word limitation imposed on summaries of this nature. A full paper was now nearing completion.

Aventis and Teva presented further health economics data for the cost per quality adjusted life year for commonly used interventions these being: coronary artery bypass grafting for males age 55 with good ventricular function (£17,800); Copaxone for MS (£23,026 at 2000 prices); renal dialysis in a specialist renal unit (£23,099) and breast cancer screening for women aged 45-65 (£54,016).

In conclusion, the companies considered that their data was substantiable and that they went to all reasonable measures to allow recipients of the letter, as well as Biogen, access to further information or clarification.

APPEAL BOARD RULING

The Appeal Board noted that the abstract by Lavelle introduced an economic model for Copaxone. In response to requests for further information regarding the broad claim for the cost-effectiveness of Copaxone enquirers would be sent the abstract together with a Question and Answer document. At the end of that

document recipients were informed that if they wanted a more detailed presentation then they could organise a visit from the companies' health economics team.

The Lavelle abstract stated that the cost per QALY was between £23,026 and £65,896; the Question and Answer document, however, included a table of data which, in bold, referred to the cost per QALY for Copaxone of £23,026. The Appeal Board considered that the data regarding the cost effectiveness of Copaxone was not clear and that the results from Lavelle had been selectively quoted in the Question and Answer document such that attention had been drawn to the lower cost per QALY. The Appeal Board considered that Teva and Aventis had failed to substantiate the claim and upheld the Panel's ruling of a breach of Clause 7.3 (1998 Code).

The appeal on this point was unsuccessful.

4 Market share

The final paragraph on page 1 of the letter stated 'Copaxone was launched in the USA in 1997 and is now the fastest growing therapy for MS. It is also approved in 17 other countries including Canada, Australia, Israel and Switzerland and has been used worldwide in over 30,000 patients'.

COMPLAINT

Biogen noted that the claim 'fastest growing therapy for MS' was not referenced nor was it clear whether it referred to absolute numbers of new patients, or new patient numbers relative to existing patients. As with the above claim, Biogen alleged a breach of Clause 7.3 in the failure to provide substantiation as requested in its letter to Teva of 16 January.

Biogen regretted the need to bring this dispute before the Authority, but it believed these claims were flawed and would mislead health professionals in their choices of treatments for patients with MS.

RESPONSE

Teva and Aventis stated that the letter at issue referred to the launching of Copaxone in the USA. The mention of the fastest growing therapy in MS appeared in the same sentence, clearly referring to its performance in the USA. The companies' first reply to Biogen's initial letter voicing this complaint stated that this claim was supported by data from IMS and it seemed reasonable to assume that Biogen had access to this information. When Biogen insisted on seeing the data, a copy of the Weekly Prescription Analysis produced by IMS America was sent to it without undue delay.

Teva and Aventis therefore denied a breach of Clause 7.3.

PANEL RULING

The Panel noted that the IMS America data submitted by Teva and Aventis showed that between June and October 2000 the market share (total prescriptions) of Copaxone had increased by 3.4% whilst that for Avonex and Betaferon had decreased by 2.3% and 1.2% respectively. At 20 October 2000 Avonex held the largest market share at 53% compared to Copaxone (25.8%). The sample 'Dear Healthcare Professional' letter provided was dated 12 December 2000. The Panel considered that the construction of the paragraph was such that it was unclear whether Copaxone was the fastest growing therapy for MS in the USA or worldwide in those countries in which Copaxone had been approved. The Panel considered the claim misleading and thus not capable of substantiation. A breach of Clause 7.3 was ruled (1998 Code).

Complaint received **8 May 2001**

Case completed **29 November 2001**

CASE AUTH/1186/5/01

ANONYMOUS v PFIZER

Promotion of unlicensed medicines/indications

An anonymous complaint was received about the promotion of unlicensed indications/medicines by Pfizer. The complainants stated that as employees of Pfizer they felt duty bound to draw attention to a matter that not only brought the pharmaceutical industry into disrepute but, more seriously, potentially compromised patient safety and well being. Further, they believed that this issue also undermined the credibility of those who had dedicated themselves to delivering a truly professional service to health professionals.

It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

The complainants stated that Pfizer employed a team of regionally based medical liaison executives (MLEs) whose function was deemed to be 'medical'; however, it was important to note that it was only 'medical' insofar as it reported to the medical director. The complainants' view was that the MLE role was most definitely that of sales promotion. The majority of the MLE team comprised sales representatives with no specific experience, relevant training or qualifications to justify their appointment to this specialist role other than the possession of a basic science degree, which was often a basic prerequisite for sales representatives within the industry. There were only three medically qualified MLEs.

The complainants stated that the primary role of the MLEs was to canvass support for Pfizer's products with doctors, pharmaceutical advisers, formulary committees and any member of the NHS who could influence prescribing. This was often achieved through sharing of data on file and significantly, data that was off-licence.

The complainants stated that a specific MLE responsibility was to promote unlicensed products, such as ziprasidone, and off-licence indications for products such as atorvastatin, sildenafil and gabapentin. In the medical department report for March 2001, there was clear evidence that off-licence data was being shared with health professionals to promote ziprasidone and to secure agreement for inclusion onto formularies. The complainants were not confident that the health professionals had been informed about some of the safety concerns regarding this particular medicine. There was also mention of discussions about switching patients from existing licensed therapy and about the comparative benefits of an as yet unlicensed product.

The complainants emphatically believed that the current MLE role was unethical. It was irresponsible for Pfizer to use sales staff essentially to promote off-licence products and indications. Patient safety was being compromised.

Pfizer stated that the allegations made were extremely serious and were absolutely refuted by the individual Pfizer managers named in the complaint. Pfizer prided itself on the company value of integrity and it was beyond credibility that they, or members of the medical department, would countenance the scenario portrayed by the complainants.

Firstly the Panel had to decide whether the role of the MLE was a promotional role as alleged, or one of responding to requests for information as submitted by Pfizer. The Panel noted that the definition of promotion excluded replies made in response to individual enquiries from members of the health professions or in response to specific communications, whether of enquiry or comment, 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 purpose of the MLE role was 'To provide local specialist support to key customers. Developing and managing relationships, appropriate to business needs and implementing strategies to increase product growth'. The Panel considered that the role of the MLE appeared broader than that allowed by the limited exemption to the definition of promotion in the Code.

The Panel was concerned that the description of the MLE activities gave the impression that the MLEs were doing more than responding to requests for information from health professionals and others. It referred to 'proactively building relationships', 'increasing product growth' and information provision in line with 'marketing and sales direction'. The document also stated that MLEs would provide specialist product information to external customers to ensure the successful managed entry of new Pfizer products. One of the slides used to train MLEs responded to the question 'Why Medical Liaison?'. The listed reasons were 'Exchange of information to leverage product growth', 'Attached to medical therefore able to exchange information in off licence areas on request', 'Competitive advantage', 'Customer focus' and 'Successful model'.

The Panel queried the submission that the MLEs only responded to requests from health professionals and others when the MLE 'Plan of Action' document for 2000/2001 gave very detailed instructions about immediate priorities. This included a list of products that did not have MLE support. The Panel thought this was inconsistent with Pfizer's submission that the role of the MLEs was very similar to that of medical information with the main difference being that the MLEs were field-based. It also appeared that the MLEs only supported key customers whereas medical information would respond to anyone who requested information. The additional activities referred to developing and maintaining opinion leader networks. This again seemed strange given the submission that MLEs were supposed to only respond to request for information.

Materials had been prepared for the MLEs to use. This was not necessarily unacceptable. The supplementary information to the Code allowed for replies intended for use in response to enquiries which were received on a regular basis to be drafted in advance provided that they were only used when they directly and solely related to the particular enquiry.

The Panel noted that Pfizer stated that the MLE's role was very similar to the medical information role. The Panel queried whether this was so. Prescribers and others viewed medical information departments as the independent face of the industry; the MLEs, however, had a dotted line reporting relationship with the regional healthcare managers, were associated with sales and marketing and were expected to present data 'in line with marketing and sales direction'. It did not appear that the reactive role of MLEs had been very clearly addressed in the training materials.

The MLE briefing document for Istin listed key actions as access opportunities being created ideally in the first instance via the cardiovascular hospital specialist team and the customer healthcare consultants as they visited customers. The opportunity would present itself via a request for information on the PREVENT study. These opportunities would ideally take the form of a meeting at which the MLE was invited to share the data or it could take the form of a one to one call with a key customer if the meeting opportunity was not possible or was deemed unsuitable. This would depend on the nature of the interest of the key customer. The hospital sales representatives and customer healthcare consultants were to attend the meeting in order to maintain continuity and 'build on rapport with key customers'. The document referred to the MLEs being dependent on the assistance of the hospital sales representatives and the customer healthcare team to provide invitations to present and 'if these are not forthcoming the process must be reviewed and other options discussed'. The MLEs would feed back to regional colleagues. Intercompany emails referred to MLEs and the hospital sales representatives working well together to shift certain customers.

The MLE and Zeldox materials referred to the Pfizer mental health team and customer healthcare consultants' efforts in identifying customers who had requested information on Zeldox and handing on the leads to the MLEs in order that they could provide the information as being crucial to make the Zeldox launch as successful as possible. Access opportunities could be identified by the customer healthcare consultants and the Pfizer mental health team and would ideally take the form of a departmental meeting at which the MLE was invited to present information on Zeldox. Again the representatives were to attend these meetings. The role of the Pfizer mental health team was to begin to develop rapport with future key customers. One of the critical success factors stated was that if a stream of invitations was not forthcoming then the process had to be reviewed and other options discussed.

The Code defined a representative as someone calling upon members of the health professions and administrative staff in relation to the promotion of medicines. Representatives might frequently be asked about the unlicensed use of a product. It was of course unacceptable under the Code for companies to promote medicines that were not licensed or to promote unlicensed indications, doses, combinations etc. The provision of such information by the company had to comply with the Code. The Panel considered that health professionals would associate sales representatives with promotional activity.

The Panel noted that representatives were instructed to attend the meetings at which MLEs presented. The role of the representative was to promote products and their presence at such meetings was inconsistent with Pfizer's submission that such presentations were non- promotional. Representatives when asked for information about unlicensed products or unlicensed indications would normally forward such requests to their medical information department. The Panel was concerned about the activities of MLEs and at the amount and nature of the pre-prepared material provided to them. The Panel had no way of knowing the degree to which MLEs tailored the material to answer the request. There was, in the Panel's view, a difference in providing a scientific paper or a response from the medical information department to giving a presentation about the data following a specific request from the clinicians with representatives also attending. The Pfizer documents positively encouraged requests for information to be answered by means of a meeting at which the MLE responded. The Panel queried whether every member of every audience would have made an unsolicited individual request for information and whether every request for information needed a meeting.

The Panel considered that the boundary between the representatives and the MLEs was not sufficiently separate. The briefing material was not sufficiently clear that there must be unsolicited requests from health professionals. There was an implication in some MLE briefing documents for Istin and Lipitor that representatives should generate requests.

It was of concern that the instructions were always to arrange a meeting with a number of attendees. A one to one meeting with a key customer was considered second best. The possibility of sending material by post was never mentioned. The Panel considered that on the papers before it the MLE role was broader than that envisaged by the limited exemption to the definition of promotion in the Code which described a reactive, rather than proactive, role.

The Panel considered that the overall arrangements meant that the MLEs were representatives as defined in the Code. The consequence of this was that their activities constituted the promotion of a product which did not have a marketing authorization (Zeldox) and other products (Lipitor and Istin) for indications that were not licensed. Breaches of the Code were ruled.

The Panel considered that Pfizer had failed to maintain a high standard of ethical conduct and ruled a breach of the Code.

The Panel considered that the MLEs had been following the company's instructions. Nevertheless the MLEs had not complied with all the requirements of the Code and a breach of the Code was ruled.

With regard to the allegation regarding compromising patient safety in relation to ziprasidone and switching patients, the Panel noted the submission that patient safety had not been compromised and that patients had not been switched. On the evidence before it the Panel ruled no breach of the Code.

Clause 2 was used as a sign of particular censure and reserved for such occasions. The Panel considered that Pfizer's activities brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Pfizer accepted that it had breached the Code in respect of failing to maintain high standards. It appealed the other rulings of breaches of the Code.

The Appeal Board noted that the Code permitted certain activities in relation to products or indications not yet licensed. The supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion. The supplementary information, Advance Notification of New Products or Product Changes, allowed limited information on products with a significant budgetary implication to be provided to those responsible for making policy decisions on budgets ahead of the grant of the marketing authorization. The definition of 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.

In the Appeal Board's view it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Appeal Board noted Pfizer's submission that the MLEs were not representatives and that their role was wider than the exemption in the Code in relation to replies made in response to individual enquiries from members of the health professions. Pfizer did not believe that this rendered their activities unacceptable provided they otherwise complied with the Code. The Appeal Board noted that the MLEs were responsible for liaising with key customers in order to manage drug safety issues. Generally the matters discussed by the MLEs did not have significant budgetary implications. The MLEs also facilitated the identification of clinical trial investigators and assisted in clinical research projects.

The Appeal Board considered that whether the MLEs satisfied the definition of a representative was not the heart of the issue. In the Appeal Board's view it was likely that company personnel who held primarily non-promotional roles, such as clinical research physicians, might, on occasion, fulfil a promotional function; any promotional aspect of their role must comply with the Code.

The Appeal Board noted the limited exemption to the definition of promotion in relation to responding to enquiries from health professionals. The Appeal Board considered that in principle it was not necessarily unacceptable for a field based team such as MLEs to respond to such individual requests but their activities had to comply with the Code or be such that they came within the limited exemption to the definition of promotion. To come within the exemption the MLE's response should relate solely to the subject matter of the enquiry, be accurate, not mislead and not be promotional in nature. The enquiry should not be solicited.

The Appeal Board noted the submissions regarding the MLE role profile and the acknowledgement that the role profile and other documents were poorly written. The Appeal Board noted the company's view that it was what the MLEs actually did and were encouraged to do that was the issue. The Appeal Board considered that the documentation gave a very clear view of what the MLEs were encouraged to do. In the Appeal Board's view the documentation was not sufficiently clear about the reactive nature of the MLE job. The Appeal Board noted the company representatives' submission that the MLEs had not been formally judged against the criteria set out in the role profile although they had probably not been told that this would be the case. The MLEs had been given other additional information wherein their roles and activities were explained. Nonetheless the Appeal Board considered that the MLEs would reasonably rely on the role profile as one of several documents describing their job. The Appeal Board considered that the activities of the MLEs as described in the role profile went beyond the limited exemption to the definition of promotion.

The Appeal Board was concerned about the tone of the medical department reports; the company representatives accepted that the wording of the internal documents was regrettable and submitted that such inappropriate phrases were not a fair reflection of what the MLEs did in practice. The Appeal Board queried why errors had not been spotted and corrected prior to circulation, particularly given the company representatives' submission that staff had received training on the Code. The reports gave a flavour of the role of the MLEs and how it was perceived by Pfizer staff. The reports were not consistent with the limited exemption to the definition of promotion in the Code. The reports encouraged a proactive rather than a reactive role.

The Appeal Board considered that the activities of the MLEs went beyond responding to unsolicited

enquiries. The phraseology of the internal documentation was inconsistent with a role which responded to unsolicited enquiries. The documents did not reflect the requirements of the Code regarding the provision of such information. There was no clear and unequivocal message to the MLEs that they could not promote an unlicensed medicine or an unlicensed indication and no acknowledgement of the constraints placed on such activities. The Appeal Board considered that the activities were such that they constituted promotion of an unlicensed medicine, Zeldox, and unlicensed indications for Istin and Lipitor contrary to the Code. The Appeal Board upheld the Panel's rulings of a breach. The appeal on these points was unsuccessful.

The Appeal Board considered that the documentation was such that the MLEs had not been directed to maintain a high standard of ethical conduct in relation to their activities. However, the Appeal Board considered that Clause 15 applied solely to those employed as representatives and considered that technically the MLEs were not representatives. The Appeal Board thus ruled no breach of the Code. The appeal on this point was successful.

The Appeal Board was extremely concerned about the documentation before it. The supervision and accountability of the MLEs appeared to be wholly inadequate. There was insufficient separation of the MLEs from the sales force. The arrangements 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 the circumstances justified reporting the company to the ABPI Board of Management in accordance with Paragraph 11.1 of the 1998 Constitution and Procedure for the Authority.

The ABPI Board of Management agreed that this was a serious matter that necessitated further action. The Board decided that Pfizer should be reprimanded and details of that reprimand published. It also decided that the company should undergo an audit of the MLE function. This would be carried out by the Authority.

On receipt of the audit report the ABPI Board decided that, on the basis that Pfizer implemented the audit report recommendations, no further action was necessary.

An anonymous complaint was received about the promotion of unlicensed indications/medicines by Pfizer Limited. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

COMPLAINT

The complainants stated that as employees of the Pfizer Pharmaceuticals Group they felt duty bound to draw to the Authority's attention a matter that they believed constituted a very serious breach of professional and ethical standards of conduct by Pfizer senior management.

The complainants emphasised that their motivation to share this information was based on their conviction that this matter not only brought the pharmaceutical industry into disrepute but also, more seriously, potentially compromised the safety and well being of patients. Further, they believed that this issue also undermined the credibility of those who had dedicated themselves to delivering a truly professional service to health professionals.

Pfizer employed a group of sixteen regionally based medical liaison executives (MLEs). The MLE function was deemed to be a 'medical' one, however, it was important to note that it was in fact only 'medical' insofar as it reported to the medical director.

In the complainants' view the MLE role was most definitely a sales promotion role. The majority of the MLE team comprised sales representatives with no specific experience, relevant training or qualifications to justify their appointment to this specialist role other than the possession of a basic science degree, which was often a basic prerequisite for employment as sales representatives within the pharmaceutical industry. Only three MLEs were medically qualified.

The complainants stated that the majority of the MLEs had little or no experience of this role and this was further compounded by the failure to implement an ongoing programme of training to support this highly specialist medical role. Despite this the MLEs were required to discuss and impart complex scientific, technical and clinical data to a high standard with health professionals. The complainants' primary concern was that these health professionals might then make misguided prescribing and policy decisions based on their contacts with the MLEs.

The primary role of the MLEs was to canvass support for Pfizer's products with medical practitioners, pharmaceutical advisers, formulary committees and any member of the NHS who could influence prescribing. This was often achieved through sharing of data on file and significantly, data that was off-licence.

The complainants alleged that a specific MLE responsibility was to promote unlicensed Pfizer products, such as ziprasidone, and off-licence indications for products such as atorvastatin, sildenafil and gabapentin. The medical department report for March 2001 clearly indicated that the MLEs had been promoting ziprasidone which was currently not licensed in the UK. There was clear evidence that off-licence data was being shared with health professionals to promote this medicine and to secure agreement for inclusion onto formularies. The complainants were not confident that the health professionals had been informed about some of the safety concerns regarding this particular medicine. Worryingly, there was also mention of discussions about switching patients from existing licensed therapy and about the comparative benefits of an as yet unlicensed product.

This was a strategy that utilised principally staff with a sales background, with no relevant clinical or medical experience, to promote Pfizer's products off-licence. This, of course, also obviated the need to employ other more expensive resources to this role, such as registered medical practitioners.

The complainants stated that in the event of an enquiry regarding the dubious role of this team of MLEs, the Pfizer position was that the MLEs performed a definite 'medical' role. This was based on the simple rationale that the MLEs reported to the medical director via a field based MLE manager. Indeed the cynical view was that the token appointments of the three medically qualified MLEs further legitimised the 'medical' role of all of the other MLEs.

Indeed, if the reporting structure was an important substantiation for the 'medical' nature of the MLE role then this was currently compromised. The role of the MLE was developed by the medical director who had recently resigned. The MLE manager now reported directly to the general manager who was not medically qualified.

The complainants emphatically believed that the current MLE role was unethical. It was irresponsible for Pfizer to use sales staff essentially to promote off-licence products and indications. Patient safety was being compromised.

The complainants provided annotated copies of the December 2000 and March 2001 medical department monthly reports.

When writing to Pfizer, the Authority drew attention to Clauses 2, 3.1, 3.2, 7.7, 9.1 and 15.2 of the 1998 Code.

RESPONSE

Pfizer stated that the allegations made were extremely serious and were absolutely refuted by the individual Pfizer managers named in the complaint. Pfizer prided itself on the company value of integrity and it was beyond credibility that they, or members of the medical department, would countenance the scenario portrayed by the complainants.

As a preliminary point, Pfizer noted that the complaint had been made anonymously and that very sweeping allegations had been made. Many of the matters outlined in the complainants' letter were based on erroneous interpretations of matters in the medical department monthly reports, or were exaggerated, or simply untrue. The many apparent misunderstandings of the contents and context of the medical reports made it doubtful that the complaint emanated from the medical department.

Pfizer submitted that the allegations fell into two main parts. Firstly, it was alleged that the role of the MLEs was in reality that of promotion, rather than the provision of scientific information, and that they were not properly trained. Secondly, it was alleged that MLEs were encouraging the use of products off-label or without a marketing authorization and were thus compromising patient safety. Both of these were denied.

1 Allegations relating to the general role and activities of MLEs

1.1 Role of MLEs

The complainants alleged that MLEs performed a sales, rather than a medical, role. This was incorrect.

Pfizer provided a copy of the role profile for MLEs. Their role was summarised as follows: 'to provide local specialist support to key customers. Developing and managing relationships, appropriate to business needs and implementing strategies to increase product growth'.

The profile emphasised that the role of the MLE was to liaise with key customers. Details of the target external audience are set out below (point 1.3). Pfizer also provided an internal presentation describing the MLE role.

The primary role of the MLE was to respond to the requests of clinicians and NHS decision makers for information. Requests would usually come via the sales force who passed them on in the same way as they would pass on a request for references, for instance, to the medical information group, or a request for discussion with a medical adviser or a clinical research expert. The fact that a significant proportion of MLEs' requests for information came from the sales force should not be surprising – the same was true of medical information, which received on average about 40% of its requests from the sales force.

Another key accountability of the MLE role was to liaise with key customers in order to manage safety issues emanating from the region, or of a national or international nature. This was very much part of a regionally based medical role, which enabled optimal contact between Pfizer and health professionals over adverse event related issues.

Generally, the matters discussed by the MLEs did not have significant budgetary implications. The principal role of the MLEs was to provide and discuss clinical data at the request of health professionals. Sometimes, similar data were disclosed to prescribing advisers at their request. The role of the MLE was quite distinct from that of the Pfizer customer healthcare consultant who was specifically charged with the discussion of health economic issues and their budgetary implications.

The MLE role was very similar to the more familiar medical information role, the main difference being that, instead of being based centrally at head office, the MLEs' regional location allowed them more freedom to visit and interact with the health professionals who requested information and thus service their needs more effectively.

As the complainants acknowledged, the MLE role was a 'highly specialist medical role' and MLEs were 'required to discuss and impart complex scientific, technical and clinical data to a high standard with health professionals'.

The MLEs also liaised closely with the sales force, providing them with expertise on the interpretation of clinical data, assisting in constructing formulary applications and training the sales force in technical or specialist areas. The MLEs also liaised with clinical colleagues, facilitating the identification of clinical trial investigators and assisting in clinical research projects.

The MLEs sought to ensure that the sales force and other staff members referred requests for information to MLEs when appropriate, rather than seeking to deal with those requests themselves. Although in

these circumstances the MLEs would try to elicit referrals of the health professionals' questions received by other staff, there was no question of requests for information being actively solicited from health professionals.

Although Pfizer accepted that the MLE role profile referred to increasing both product growth and market share, this must be seen in context. Pfizer believed that the MLE service enabled a better understanding of its products and enhanced the company's reputation as an ethical pharmaceutical company. Pfizer certainly did not encourage practitioners to use its products off-label. Pfizer did not consider it objectionable that the activities of the MLEs might indirectly lead to greater prescribing of its licensed products. However, Pfizer stressed that the role of MLEs was not to promote products. That was the role of the sales force.

1.2 MLE organisation

Pfizer stated that the MLE role was established in Parke-Davis in 1998 and became part of the Pfizer organisation as a result of Pfizer's merger with Warner Lambert in 2000. There were 16 MLEs, organised on a regional basis, who reported in to a medical liaison manager.

The complainants alleged that Pfizer's belief that the MLEs performed a definite medical role was based simply on the rationale that the MLEs reported in to the medical director and on a few 'token' appointments of medically qualified staff. This was incorrect.

The MLEs' reporting line into the medical department was defined and one of substance. The MLEs' manager and 'acting head' was a full member of the medical department management team and, in turn, reported to the medical director (when in situ). Decisions about MLE recruitment, promotion, performance and pay were all made within the medical department. MLEs attended medical department meetings and training was received through the medical department.

The MLEs had a dotted line reporting relationship with the regional healthcare managers who helped to co-ordinate MLE activity on a regional basis. As the MLEs were the only members of the medical department who provided field-based medical support to sales force colleagues, co-ordination and prioritisation of their response to requests for information was needed at local level.

The fact that the MLE manager reported to a non-medically qualified general manager at the time of the complaint was cited by the complainants as evidence that the medical reporting line of the MLEs was 'compromised'. Since the departure of Pfizer's medical director in March 2001, all members of the medical department management team had reported to the general manager on a temporary basis until the appointment of a new medical director. The vast majority of medical directors reported in to a non-medically qualified general manager or chief executive and this in no way undermined their 'medical' credentials.

1.3 Target audience

Pfizer stated that the MLEs' target audience was a broad one of opinion leaders, clinicians, prescribers, prescribing advisers and health professionals in general. The common link would be that they had requested information from Pfizer. The approach of the MLEs was always reactive and never proactive.

The MLEs' primary contacts were opinion leaders and those persons responsible for formulary applications. The MLEs also provided specialised information on request to other practitioners.

In the case of opinion leaders and practitioners responsible for formulary applications, the MLEs participated in meetings and it was accepted that at those meetings wide-ranging scientific discussions took place concerning both licensed and unlicensed indications and products. Typically, a meeting would consist of 'round table' discussion where the MLE was responding to the specific questions raised by the attendees. It was Pfizer's view that these discussions were not prohibited by the Code.

In the case of opinion leaders, Pfizer was dealing with practitioners with a particular interest in a therapeutic field. These practitioners had an interest in working with Pfizer upon the future development of its products and would sometimes be involved in discussions about the results of clinical studies, or forthcoming studies in which they might be interested in acting as investigators. Pfizer provided, by way of example, various minutes of regional schizophrenia advisory board meetings, which are discussed further below (point 2.3.1). It was clear that such meetings were not promotional in tone and that practitioners were not being encouraged to use an unauthorized product. The same was true for meetings at which new trial data for authorized products were discussed.

Pfizer believed that there was nothing unusual in these arrangements and that many other companies provided equivalent information services without being considered to be in breach of the Code.

In the case of practitioners responsible for formulary applications, again Pfizer's arrangements were not unusual and reflected the practice of other pharmaceutical companies. These practitioners were involved in forward planning and needed to consider the impact of new products and new indications at the pre-authorization stage. Since the advent of NICE, there had been a trend towards earlier establishment of policy on new products by local formulary committees and this involved consideration of clinical effectiveness. In common with other companies, Pfizer was invited to provide data to those committees on its new products. It was certainly not the intention of the members of the formulary committees to consider the product for use before authorization, however, and they were not receiving the information for that purpose. Pfizer therefore believed that its arrangements complied fully with the Code.

In the case of other practitioners, Pfizer stressed that the MLE would only respond where a practitioner had requested information, for example relating to

clinical studies. The response provided in that case was scientific and not promotional. It was also individual.

1.4 MLEs: backgrounds, training and qualifications

The complainants alleged that 'the majority of the MLE team comprised sales representatives with no specific experience, relevant training or qualifications to justify their appointment to this specialist role, other than the possession of a basic science degree'. They also alleged that the MLEs were not supported by on-going training. These allegations were without foundation.

Eight of the MLEs had previous experience within the medical department, or were medically qualified. The others were differentiated from typical sales representatives by their background: having a long track record as either specialist hospital representatives or as highly specialised customer healthcare consultants.

The members of the MLE team either possessed postgraduate qualifications or had an excellent track record and highly developed scientific competencies. Three had PhDs. Pfizer emphasised that the medically qualified MLEs were not 'token appointments'. Pfizer did not consider it necessary for all MLEs to be medically qualified in order to carry out their duties, provided that they had other relevant qualifications, expertise and training.

Pfizer's position was clearly supported by the reaction of medical practitioners coming into contact with the MLEs. Doctors were very busy people and Pfizer believed that if they regarded the MLEs as inadequately qualified or performing a promotional role, they would not be prepared to have contact with the MLEs and would have complained either to the company or the Authority. Neither was the case.

The complainants' assertion that registered medical practitioners were 'more expensive resources' was also untrue. The fact that non-medically qualified MLEs could command salaries commensurate with (or in some cases higher than) their medically qualified colleagues was attributable to their valuable expertise and experience.

An anonymised list of the MLEs showing details of their background experience, qualifications and training was provided together with an outline of relevant product training initiatives and details of their status regarding the ABPI Medical Representatives Examination. Pfizer did not believe that the ABPI Medical Representatives Examination was relevant to the work of the MLEs as they were not engaged in promotional activity. In any event, only one of the team who had not passed the examination had been in the role for longer than two years.

In summary, Pfizer did not consider that the role of the MLE was 'unethical', or that it compromised patient safety in any way. Indeed Pfizer believed that the dissemination of accurate data by well-trained members of the medical department allowed for better understanding and safer use of Pfizer products.

2 Allegations relating to specific activities of MLEs

2.1 Agreed messages

Pfizer emphasised that the MLEs would only respond to specific questions raised by medical practitioners, so that each response would be individual. These questions were generally posed to members of the sales force during their day-to-day contact with medical practitioners. The requests for information were then referred to the local MLE who would provide the information requested to the practitioner at his or her convenience and be available to answer any further questions. Many such referrals from the sales force to the MLEs were verbal but an example of an email referral was provided.

There were, however, certain questions that arose very commonly and these were anticipated in slide sets. Some of these were prepared for use on a 'pick and mix' basis. In these cases, for any particular meeting, the MLEs selected from the pack only those slides necessary to respond to questions raised. Some of the presentations were either intended to answer common and general questions (such as 'What are the advantages of atypical anti-psychotics over typicals?'), or were prepared specifically for a single presentation, and so were designed to be used in their entirety. Copies of ziprasidone presentations that were used in this way were provided.

In addition, there were three slide sets dealing with the PREVENT, MIRACL and ASAP studies. These slides referred to the results of particular studies and so were self-contained and designed to be used in their entirety in response to the usual general request to hear about the results of the trial. Where a request was more specific than this, individual slides could be selected, but this was relatively uncommon. There was no 'electronic sales aid' as alleged by the complainants in their annotation to the March medical monthly report. Pfizer assumed that their comment referred to the presentations on the studies mentioned immediately above.

Pfizer also provided a slide set designed for use in its entirety for Neurontin, presented as part of a training day for GP registrars. Pfizer pointed out that this presentation related only to licensed indications.

The internal documents briefing Pfizer's sales force about the MLEs and Istin (amlodipine), Lipitor (atorvastatin) and Zeldox (ziprasidone) were provided and were divided into various sections for each product: a covering memorandum from the medical director, a briefing document and some related attachments:

- The covering memoranda explained the involvement of the medical liaison team with each product and described the role of MLEs in responding to requests for information from practitioners. It was emphasised that this role was distinct from that of promotion.
- The briefing documents emphasised that the MLE was responding to, and not initiating, requests for information. The goals for each product were set out. Although the details differed, the common aim was to provide scientific and clinical information in response to those requests.

- The other attachments included the referral protocol, an account selection form and a contact list.

The MLEs' plan of action for 2000/2001 (Q1/Q2) covering Istin, Lipitor and Zeldox was also provided. Pfizer stated that these products were seen as immediate priorities for the MLEs. Although some other products were listed for 'additional activities', as a matter of fact few of those activities developed and for some products no material had been prepared in anticipation of discussions with practitioners.

2.2 Allegations relating to promotion of unlicensed indications

Pfizer stated that it appeared that the following issues were relevant to the complainants' allegations relating to the promotion of unlicensed indications:

2.2.1 In relation to Lipitor, the MIRACL study looked at the effect of atorvastatin on the prevention of secondary coronary events. The ASAP study compared the effects of high dose atorvastatin with lower dose simvastatin on coronary atherosclerosis plaque regression in patients with familial hypercholesterolaemia. Lipitor was licensed (in summary) for the reduction of cholesterol. Health professionals often questioned whether by lowering cholesterol in the blood with atorvastatin the risk of heart disease was reduced. Prescribers and formulary committees made their decisions on the basis of such 'end point data'. MIRACL showed that patients with some common types of heart disease, treated aggressively with Lipitor, were less likely to suffer from further cardiac events. ASAP (like PREVENT) looked at the effects of Lipitor on atheromatous plaque progression. Both of these trials showed the effectiveness of Lipitor and so provided the evidence required and asked for by decision makers and prescribers. Again, no additional claims were being made for Lipitor. The data were shared in response to requests for information.

2.2.2 Istin was licensed for the treatment of hypertension and angina. Questions were commonly asked about the availability of end point data (ie did its effectiveness at lowering blood pressure correlate with a lower risk of heart disease/stroke). The PREVENT study showed that treatment with Istin reduced the patches of atheroma (intra-arterial fatty plaques) in the coronary and carotid arteries. Such end point data were the information sought by formulary committees so that they could make their decisions about which antihypertensive medications to include. Pfizer was therefore not making claims on the basis of this study for the product but was sharing the results so that the committee could be sure to assess products on the basis of the available evidence, which was its remit.

There was keen interest in receiving new data on atorvastatin and amlodipine, which it would be inappropriate for the sales force to deliver. The presentation of such data on request, specifically end point data, was unobjectionable. Pfizer emphasised that MLEs were discussing new data but were not discussing new indications and were in no way recommending the use of its products outside their licences. Medical practitioners were a very sophisticated audience and it was naïve for the complainants to suggest that they would characterise discussions of this nature as off-label promotion.

As stated above, the data that the MLEs held were only used in response to specific enquiries from medical practitioners who had an interest in this area.

With regard to Viagra and Neurontin, Pfizer did not know why these products were mentioned in the complainants' letter. While the complainants stated that evidence of off-label use of those products was illustrated in the monthly medical department reports, they had failed to highlight any activity involving these two products and Pfizer believed that the bald allegation in the complaint was completely without foundation.

So far as Pfizer was aware, Viagra had not been discussed at all by the MLEs.

With regard to Neurontin, the only issue raised related to alleged promotion of unlicensed indications. The Neurontin presentation was strictly limited to the product's licensed indications (a copy was provided). The only other Neurontin activity in which the MLEs had been involved in 2001 was liaison with physicians who were performing single-centre ('investigator-led') studies with the product. These were performed under the DDX procedure, a form of authorization exemption certificate granted by the MCA for clinical trials initiated by physicians. Such DDX support was very much the remit of the medical department and provided further evidence of the fact that the MLEs were a core group within the department.

It was certainly never agreed by the medical director, sales director and general manager that, 'as a specific responsibility', 'these MLEs would promote unlicensed Pfizer products … and off-licence indications'.

In summary, Pfizer strongly disagreed with the complainants' allegations relating to the use of scientific data by the MLEs.

2.3 Allegations relating to promotion of an unlicensed product (ziprasidone)

Pfizer stated that ziprasidone was an atypical anti-psychotic which currently did not have a marketing authorization in the UK. It was licensed in the US under the trademark 'Geodon' and was licensed as 'Zeldox' in Sweden, which was the reference member state in the mutual recognition procedure. It was actively marketed in both of these countries.

2.3.1 Unlicensed status

Pfizer stated that in response to demand for data, MLEs were legitimately discussing information about ziprasidone so that health professionals could make informed decisions about the comparative merits of atypical and typical anti-psychotics, and could consider the use of ziprasidone if and when it received a marketing authorization for the UK.

While the MLEs certainly discussed ziprasidone with opinion leaders, Pfizer did not accept that such

activity amounted to promotion of an unauthorized product. As stated above, the MLEs only used the data in response to specific enquiries from medical practitioners who had an interest and/or expertise in this area. The regional minutes of advisory board meetings illustrated this fact. The content of each meeting varied according to the particular interests of the participants. In some, but not all, the MLEs were asked to present on particular aspects of the data, but the initiative came from the participants and not the MLE. In each case, the nature of the discussion was broad and scientific. It was certainly not promotional in tone.

Health professionals had considerable interest in, and knowledge of, ziprasidone. Its withdrawal from the mutual recognition procedure resulted in a high level of concern and interest among those who had participated in the developmental clinical trials and generated an exceptional number of queries about its progress towards authorization. Pfizer considered that it was obliged to respond to the requests of trialists and opinion leaders for information. Clearly such people were familiar with both ziprasidone and with anti-psychotics generally and were well able objectively to evaluate and criticise data presented to them.

The complainants had expressed concern about references in the medical department monthly reports to 'switching patients from existing licensed therapy'. The specific issues mentioned in the reports were addressed by Pfizer in an appendix. As a general point, however, Pfizer regarded it as self-evident that these references must be to switching patients from typical to atypical anti-psychotics (which might include ziprasidone, if and when it obtained a marketing authorization, but not before).

Pfizer accepted that within certain of the ziprasidone presentations mentioned above there were clinical data relating to switching between atypical agents to ziprasidone, but these would only be presented in response to a specific request for those data and clearly no such switch was feasible pending the authorization of ziprasidone.

The advantages and possible risks of atypical anti-psychotics were well known and extremely topical. If the MLEs were sharing information beyond the requested level or in an unbalanced way Pfizer would have expected to receive at least one complaint from the recipients: none had been received.

2.3.2 Safety concern

Pfizer stated that during the mutual recognition procedure a number of regulatory authorities asked questions about ziprasidone, and sought additional data, raising the prospect of reference to arbitration. In order to answer the queries raised, and to submit further data, Pfizer withdrew ziprasidone from the mutual recognition procedure. A study looking at the duration of the QTc interval in patients with ziprasidone was mandated by the FDA in the USA as a result of concerns about the QTc interval in anti-psychotics in general. The result of the study was favourable and ziprasidone was granted a product licence in the USA. The dossier was now being finalised for assessment throughout the rest of Europe.

Pfizer assumed that the safety concerns referred to in the letter of complaint referred to the issue of the QTc interval with ziprasidone mentioned above. Contrary to the complainants' assertion, this issue was discussed when appropriate with health professionals. The first of the two 'pick and mix' ziprasidone presentations showed a slide of the low incidence of adverse events and depicted the incidence of QTc interval prolongation published by Tandon *et al*. Since study 054 (the study on QTc referred to above) was reported, a further presentation had been designed containing more details about the QTc issue; a copy was provided.

All health professionals with an interest in atypical anti-psychotic medication were aware of the issue of QTc prolongation and this issue would be raised routinely when discussing a new product of this type. The FDA conclusions on the point were in the public domain. If the QTc issue had not been addressed in specific presentations, this would be because it was not relevant to the data requested.

Pfizer had never at any time concealed any information from medical practitioners on this issue and it strongly denied that discussions by the MLEs of this safety issue had in any way been improper.

3 Specific points highlighted in medical department reports

Pfizer stated that the medical monthly reports were confidential internal documents circulated within the medical department and to the heads of other departments within Pfizer. Because they were intended to act as brief monthly updates upon issues with which the recipients were familiar, the reports contained statements which, upon a superficial reading, might appear ambiguous but which became clear when their context was understood. Detailed comments were submitted about both reports.

4 Conclusion

In summary, Pfizer believed very strongly that it was not in breach of the Code. The activities of the MLEs in providing information were not promotional. The MLEs were properly qualified and trained and provided a useful service to doctors. While Pfizer accepted that the MLEs had provided information about unlicensed medicines and unlicensed indications, this had to be seen in the correct context. This information was provided as part of a genuine scientific exchange of information and specifically in response to enquiries from medical practitioners. Further, it strongly denied any allegation that patient safety had been compromised in any way.

PANEL RULING

Firstly the Panel had to decide whether the role of the MLE was a promotional role as alleged or one of responding to requests for information as submitted by Pfizer. The Panel noted that the definition of promotion (Clause 1.2) excluded replies made in response to individual enquiries from members of the

health professions or in response to specific communications whether of enquiry or comment but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Panel noted Pfizer's submission that the MLE role was similar to the medical information role, the main difference being that the MLE's regional location assured more freedom for them to visit and interact with health professionals who requested information. The Panel noted the submission from Pfizer that its activities were similar to other companies' arrangements. The Panel noted that it had not previously received any complaints about this type of activity. Each case was of course considered on its own merits.

The Panel examined the documentation provided by Pfizer. The role profile of the MLE listed their key accountabilities together with their performance measures.

The purpose of the MLE role was described as 'To provide local specialist support to key customers. Developing and managing relationships, appropriate to business needs and implementing strategies to increase product growth'. The Panel considered that the role of the MLE appeared broader than that allowed by the limited exemption to the definition of promotion described in Clause 1.2 of the Code.

The first accountability listed was to provide local specialist support to the regions, 'proactively building relationships with external customers to establish strategic links that will increase product growth'. The relevant performance measures were feedback from customers regarding timeliness and quality of advice; and growth in market share. The second key accountability listed was to 'present new data on existing products and important scientific information on new products to key customers in line with marketing and sales direction, to ensure information is shared to meet local customer requirements'. The relevant performance measures were: data meets business needs; feedback from sales team and regional management; feedback from customers; sharing pertinent information with marketing colleagues. The eighth accountability referred to 'presenting information to key customers ... in order to assist in the achievement of sales objectives'.

The Panel was concerned that the description of the MLE activities gave the impression that the MLEs were doing more than responding to requests for information from health professionals and others. It referred to 'proactively building relationships', 'increasing product growth' and information provision in line with 'marketing and sales direction'. The document also stated that MLEs would provide specialist product information to external customers to ensure the successful managed entry of new Pfizer products. One of the slides used to train MLEs responded to the question 'Why Medical Liaison?'. The listed reasons were 'Exchange of information to leverage product growth', 'Attached to medical therefore able to exchange information in off licence areas on request', 'Competitive advantage', 'Customer focus' and 'Successful model'.

The Panel queried the submission that the MLEs only responded to requests from health professionals and others when the MLEs 'Plan of Action' document for 2000/2001 gave very detailed instructions about immediate priorities. This included a list of products that did not request MLE support. The Panel thought this was inconsistent with Pfizer's submission that the role of the MLEs was very similar to that of medical information with the main difference being that the MLEs were field-based. It also appeared that the MLEs only supported key customers whereas medical information would respond to anyone who requested information. In the Panel's view medical information would answer enquiries on all products whereas the MLEs' support of products was selective. The additional activities referred to developing and maintaining opinion leader networks. This again seemed strange given the submission that MLEs were supposed to only respond to request for information. How were they supposed to meet this target?

The Panel noted that materials had been prepared for the MLEs to use. This was not necessarily unacceptable. The supplementary information to Clause 1.2 of the Code allowed for replies intended for use in response to enquiries which were received on a regular basis to be drafted in advance provided that they were only used when they directly and solely related to the particular enquiry.

The Panel noted the submission that the MLEs did not generally discuss matters which had significant budgetary implications. Where there were no significant budgetary implications the supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, did not apply.

The Panel noted that every company employee would be working to increase appropriate use of the company's products. This was not unacceptable provided the requirements of the Code were met.

The Panel noted that Pfizer stated that the MLE's role was very similar to the medical information role. The Panel queried whether this was so. Prescribers and others viewed medical information departments as the independent face of the industry; the MLEs, however, had a dotted line reporting relationship with the regional healthcare managers. The MLEs were associated with sales and marketing and were expected to present data 'in line with marketing and sales direction'. It did not appear that the reactive role of MLEs had been very clearly addressed in the training materials.

The MLE briefing document for Istin listed key actions as access opportunities being created ideally in the first instance via the cardiovascular hospital specialist team and the customer healthcare consultants as they visited customers. The opportunity would present itself via a request for information on the PREVENT study. These opportunities would ideally take the form of a meeting at which the MLE was invited to share the PREVENT data or it could take the form of a one to one call with a key customer if the meeting opportunity was not possible or was deemed unsuitable. This would depend on the nature of the interest of the key customer. The hospital sales

representatives and customer healthcare consultants were to attend the meeting in order to maintain continuity and 'build on rapport with key customers'. The document referred to the MLE being dependent on the assistance of the hospital sales representatives and the customer healthcare team to provide invitations to present and 'if these are not forthcoming the process must be reviewed and other options discussed'.

The MLEs would feed back to regional colleagues and the Istin product team and were to identify opportunities for the clinical effectiveness consultants to present relevant health economic models.

Other material, on intercompany email, referred to MLEs and the hospital sales representatives working well together to shift certain customers.

The MLE and Zeldox materials referred to the Pfizer mental health team and customer healthcare consultants' efforts in identifying customers who had requested information on Zeldox and handing on the leads to the MLEs in order that they could provide the information as being crucial to make the Zeldox launch as successful as possible. Access opportunities could be identified by the customer healthcare consultants and the Pfizer mental health team. This opportunity would arise if a potential prescriber requested information on Zeldox or asked for information on Pfizer products in schizophrenia. These opportunities would ideally take the form of a departmental meeting at which the MLE was invited to present information on Zeldox. Again the representatives were to attend these meetings. The role of the Pfizer mental health team was to begin to develop rapport with future key customers. One of the critical success factors stated was that if a stream of invitations was not forthcoming then the process had to be reviewed and other options discussed.

The Panel noted that Clause 1.6 of the Code defined a representative as someone calling upon members of the health professions and administrative staff in relation to the promotion of medicines.

The Panel noted that representatives might frequently be asked about the unlicensed use of a product. It was of course unacceptable under Clause 3 of the Code for companies to promote medicines that were not licensed or to promote unlicensed indications, doses, combinations etc.

The provision of such information by the company had to comply with the Code. The Panel considered that health professionals would associate sales representatives with promotional activity.

The Panel noted that representatives were instructed to attend the meetings at which MLEs presented. The role of the representative was to promote products and their presence at such meetings was inconsistent with Pfizer's submission that such presentations were non- promotional. Representatives when asked for information about unlicensed products or unlicensed indications would normally forward such requests to their medical information department. The Panel was concerned about the activities of MLEs and at the amount and nature of the pre-prepared material provided to them. The Panel had no way of knowing the degree to which MLEs tailored the material to answer the request. There was, in the Panel's view, a difference between providing a scientific paper such as a report or a response from the medical information department and giving a presentation about the data with representatives also attending. The Panel noted that the presentations would only be made following a specific request from the clinicians. The Pfizer documents positively encouraged requests for information to be answered by means of a meeting at which the MLE responded. The Panel queried whether every member of every audience would have made an unsolicited individual request for information and whether every request for information needed a meeting.

The Panel considered that the boundary between the representatives and the MLEs was not sufficiently separate. Representatives were encouraged to attend MLE meetings. The MLEs were dependent on requests to representatives for information. The briefing material was not sufficiently clear that there must be unsolicited requests from health professionals. There was an implication in the MLE briefing documents for Istin and Lipitor that representatives should generate requests.

Genuine unsolicited requests could be answered in a variety of ways. In some instances it could be by simply sending the papers. It was of concern that the instructions were always to arrange a meeting with a number of attendees. A one to one meeting with a key customer was considered second best. The possibility of posting material was never mentioned. The Panel considered that on the papers before it the MLE role was broader than that envisaged by the limited exemption to the definition of promotion in Clause 1.2 of the Code which described a reactive, rather than proactive, role.

The Panel considered that the overall arrangements meant that the MLEs were representatives as defined in Clause 1.6 of the Code. The consequence of this was that their activities were promotional. Their activities constituted the promotion of a product which did not have a marketing authorization (Zeldox) and other products (Lipitor and Istin) for indications that were not licensed. This was not in accordance with Clauses 3.1 and 3.2 of the Code. The Panel therefore ruled breaches of Clauses 3.1 and 3.2 of the Code. The Panel also noted that the MLEs were required to have passed the ABPI Representatives Examination in accordance with the provisions of Clauses 16.2 and 16.4.

The Panel considered that Pfizer had failed to maintain a high standard of ethical conduct and a breach of Clause 9.1 of the Code was ruled.

The Panel considered that the MLEs had been following the company's instructions. Clause 15.2 required representatives to maintain a high standard of ethical conduct and comply with all relevant requirements of the Code. The Panel considered it was the company that was at fault and this had resulted in a breach of Clause 9.1. The MLEs were not acting on their own initiative they were following company instructions. Nevertheless the MLEs had not complied with all the requirements of the Code. A breach of Clause 15.2 was ruled.

With regard to the allegation regarding compromising patient safety in relation to ziprasidone and switching patients, the Panel noted the submission that patient safety had not been compromised and that patients had not been switched. On the evidence before it the Panel ruled no breach of Clause 7.7 of the Code.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such occasions. The Panel considered that Pfizer's activities brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY PFIZER

Pfizer stated that it accepted the Panel's ruling of a breach of Clause 9.1 of the Code on the basis set out in its response below and appealed the ruling in respect of Clauses 2, 3.1, 3.2 and 15.2 of the Code.

A number of specific comments and findings were made, and queries raised by, the Panel in its ruling. Pfizer responded to these individual points in the order in which they appeared in the Panel ruling.

Response to the Panel's finding of fact

1 Pfizer disagreed fundamentally with the approach taken by the Panel. Pfizer contended that a blanket decision should not be made about whether the MLEs' role was or was not promotional but rather that their activities should be examined individually to determine whether any of them breached the Code. Pfizer did not accept that if there were some isolated instances where the MLEs' activities might be considered promotional, this should render their role illegitimate as a whole. MLEs' individual activities could be ruled promotional or non-promotional by reference to particular prohibitions in the Code, but a sweeping overview of their role must by its nature be a subjective and impressionistic evaluation. Any such overview was likely to be arbitrary, and arbitrary rulings weakened confidence in the Code. Such overviews were also unhelpful to the industry; many companies were conducting similar activities to Pfizer's MLEs and those companies would be looking for constructive guidance about what activities were permitted and prohibited by the Code. Any ruling on this issue therefore needed to be of practical assistance to companies seeking to comply with the Code: making decisions about the application of the Code on the basis of an overview did not achieve this.

2 In relation to paragraph 4 of the Panel's ruling, Pfizer accepted that the MLEs' role as described in the role profile was wider than the exclusion in Clause 1.2 of the Code. However, it did not believe that this rendered their activities unacceptable, provided that they otherwise complied with the Code. It was clear from Pfizer's initial response to the complaint that it did not dispute that the MLEs engaged in activities beyond simply responding to specific questions.

3 Pfizer asked the Appeal Board to think very carefully before accepting the Panel's apparent reasoning that any activity beyond the exemption in Clause 1.2 of the Code must be promotional. Pfizer believed this approach to be flawed in principle: in order to fall within the definition of 'promotion' in Clause 1.2, the relevant activity must 'promote the prescription, supply, sale or administration of its medicines'. There were many activities which did not fall within the exemption in Clause 1.2 and yet were clearly not promotional in nature (for example, most clinical research).

4 In relation to paragraph 5 of the Panel's ruling, Pfizer accepted that the MLEs' role profile was poorly written but it contended that it was what the MLEs actually did and were encouraged to do that was the issue. The MLEs' role profile was inherited from Parke Davis in 2000 when Pfizer merged with Warner Lambert. The role profile was not reviewed at that time but was simply transposed into the standard Pfizer format. The MLEs' role profile had had very little use in practice. Within Pfizer, the main use of role profiles was in relation to performance management, particularly in annual staff performance appraisals. Since most of the members of the MLE team had been in their current role for less than a year, the role profile had not been used in respect of most of the MLEs' annual appraisals. In the two cases where the role profile was used, the MLEs' manager in fact made no reference to sales or product performance to measure performance. Following receipt of the complaint, the MLEs' role profile had been amended and reissued as further described below.

5 The MLEs' manager was adamant that in the MLEs' recruitment, training and in one to one conversations, it had been emphasised on many occasions that MLEs could only respond to specific requests for information from health professionals and that they should take care to distinguish themselves clearly from sales colleagues when meeting to share that information. The MLEs' manager also confirmed that there was no direction or interaction with members of the sales or marketing teams in either setting MLEs' objectives or conducting their appraisals. Indeed the MLEs' objectives were cascaded down from those of the medical director (in common with all other members of the medical department).

6 Pfizer provided explanations below in relation to the specific items of concern identified by the Panel in paragraph 6 of the ruling in relation to the MLEs' role profile.

6.1 In relation to 'proactively building relationships with external customers', this referred to the MLEs' efforts to ensure that all their interactions with healthcare professionals were positive and to build trust in their ability to respond to healthcare professionals' needs for information, so as to become a valued source of information for ongoing data requirements. If health professionals with an interest in a particular therapeutic area were impressed by the information provided by an MLE in one instance, they would often ask for further information or to be advised of any developments in that area. Pfizer believed that it was legitimate for MLEs to respond to such requests for information. The MLEs had other opportunities for contact with health professionals while carrying out other key medical department responsibilities under their role profile, such as managing drug safety issues and supporting clinical

research. It was by this ongoing contact, with repeated interactions, that the MLEs aimed to form positive relationships with health professionals. Pfizer denied absolutely that any of these activities was promotional or otherwise prohibited by the Code.

6.2 In relation to 'increasing product growth', Pfizer pointed out that the Panel itself accepted that all employees work to increase appropriate use of the company's products and that this was not unacceptable, provided the requirements of the Code were met. Despite the references to sales and product growth in the MLEs' role profile, the MLEs operated under the same basic contract and bonus scheme that applied to Pfizer's head office staff, including the medical department. Pfizer accepted that references to product growth were open to misinterpretation and, to avoid any possibility of confusion, it had since revised the MLEs' role profile to delete all reference to product growth.

6.3 In relation to 'providing information in line with sales and marketing direction', this wording appeared out of context in the ruling. What the role profile said was 'to present new data on existing products and important scientific information on new products to key customers, in line with sales and marketing direction, to ensure information is shared to meet local customer requirements'. Pfizer submitted that when the words were read in context, it was easier to see that the main thrust of this accountability was the presentation of certain data to customers, so that information was shared to meet their needs. There was no question of the MLEs acting under the orders of the sales and marketing departments. In practice there was no direction given to the MLE team by sales or marketing management at any level. The reference to 'in line with' sales and marketing direction meant 'consistent with' or 'not out of line with' their input, rather than 'as required by' or 'under the direction of' sales and marketing. Given that the MLE role was new to Pfizer and that the MLEs would be starting out in an unfamiliar region, it seemed sensible for them to try to avoid unnecessary clashes with sales and marketing colleagues who would be well-established in that territory (eg to avoid MLEs inadvertently duplicating medical information already provided by a sales representative, and to avoid causing unnecessary inconvenience to local sales force colleagues by competing with them for meeting time slots). In short, the phrase referred to co-ordination rather than control. Again, Pfizer accepted that the wording in the MLEs' role profile was open to misinterpretation, so reference to sales and marketing input had been deleted from the new version.

6.4 In relation to 'provide specialist product information to external customers to ensure the successful managed entry of new Pfizer products', this appeared in the MLEs' role profile as its twelfth and final accountability. Pfizer saw nothing inherently objectionable in it. Indeed, the industry was encouraged by Government to manage the entry of new products onto the market. There was no suggestion that this information was provided other than in response to requests. There were likely to be numerous questions about any new product which was reasonably close to being approved and marketed, for example from formularies which would need certain information in order to decide whether to include the new product and, if so, on what basis. It was part of the MLEs' job to respond to these and other requests in a timely fashion so that the launch of the product was as orderly as possible.

7 In relation to paragraph 6 of the Panel's ruling, Pfizer noted that one particular slide in the MLE presentation seemed to have worried the Panel. In answer to the question 'Why MLEs?' the following responses were picked out by the Panel as items of concern. Pfizer noted that the answers were all in bullet point format and it was evident from the language used that these were shorthand answers which might therefore require further explanation.

7.1 In relation to 'Exchange of information to leverage product growth', Pfizer noted the Panel's later acceptance that it was not necessarily unacceptable for employees to work to increase appropriate use of the company's products. It was also worth noting that the context here was clearly the 'exchange' of information: in addition to responding to requests from health professionals for specific information, the MLEs also relayed to other colleagues any common themes of concern among health professionals (eg perceived weaknesses of existing treatments). This feedback could then be taken into account when planning new clinical trials or assessing the market potential for new products, thus (indirectly) increasing product growth.

7.2 In relation to 'Attached to medical therefore able to exchange information in off licence areas on request', Pfizer stated that although not well expressed, this bullet point clearly acknowledged that the MLEs were part of the medical department and the need for a request for information prior to discussing off licence data.

7.3 In relation to 'Competitive advantage', this referred to management's belief that the service provided by the MLEs gave Pfizer an advantage over many of its competitors, largely due to the value that health professionals ascribed to the quality of data available from the MLEs. Pfizer did not see why the Panel should find this idea objectionable in principle.

7.4 In relation to 'Customer focus', this was one of Pfizer's company values. It referred to Pfizer's aim to concentrate on internal and external customers' needs and concerns. This answer attempted to make an association for staff between the company value of customer focus (which would be very familiar to them) and the MLEs' role, which would be less familiar. The association would not be difficult to make, since the MLEs were clearly intended to respond to customers' requests for information: this was the first responsibility mentioned in the list of functional responsibilities on the slide.

7.5 In relation to 'Successful model', this referred to the fact that the MLE concept had been tried before at other companies where the medical director had worked before joining Pfizer and the system was introduced there. The medical director considered the MLE model to have been of benefit to those other companies.

8 Pfizer was concerned that the Panel appeared to have construed certain documents in a light unfavourable to Pfizer without any grounds for doing so. In paragraph 7 of its ruling, the Panel had queried Pfizer's submission that the MLEs acted reactively in response to requests on the basis of the list of priorities in the Plan of Action. The Panel appeared to have misread this document. The Plan of Action described the immediate priorities for the MLEs in terms that made it clear that they would be responding reactively to requests for information, rather than proactively. The immediate priorities were stated as follows (with emphasis added):

'To be prepared to present PREVENT data ... *as requested by customers'*

'To be able to address any questions/issues in relation to PREVENT'

'To be prepared to present MIRACL and ASAP data ...'

'To use MIRACL, ASAP and AVERT to present outcomes evidence ... *as requested by customers'*

'To provide scientific and clinical information relating to ZELDOX and *address questions* raised ...'

'To feedback to sales and marketing the impressions of customers to the information presented ...'.

None of the priorities set out in the Plan of Action appeared to be inconsistent with Pfizer's submission that the MLEs responded to requests from health professionals rather than acting proactively. Pfizer was very concerned to see that the Panel appeared to have come to the opposite conclusion without stating its reasons for doing so.

9 The Panel had noted in paragraph 7 of its ruling that the Plan of Action included a list of product teams that had not requested MLE support. The Panel thought that this was inconsistent with the submission that the MLEs were similar to medical information, on the basis that MLE support was selective (prioritising certain products and supporting 'key customers') whereas medical information would cover all products and would respond to anyone requesting information. Pfizer accepted that there were differences between the MLEs and medical information but it did not accept that these undermined its position. It was evident from the introductory paragraphs of the Plan of Action that the MLEs were not expected to reach full strength until the end of 2001 and therefore the document stated that it set out 'immediate priorities for those members of the team who will be in place as at October 1st 2000'. In order to maintain a high level of product knowledge, each MLE generally concentrated on one or two products. Clearly there were insufficient MLEs to cover all Pfizer's products in sufficient depth at the time when the Plan of Action was written, given the geographical constraints imposed by their regional base. Pfizer had had plans to increase both the number of MLEs and the range of products covered by the team in 2001 but these had been halted, pending the outcome of the complaint.

10 In any event, the Panel's assumption that this differed from the position in the medical information department was wrong. Pfizer's medical information department contained medical information executives who responded to requests for information at a relatively superficial level across the entire product range by reference to standard documentation. It also contained medical information specialists who concentrated on one or two products and so had much deeper knowledge of those products and related therapy areas and could deal with more complex and novel queries. Like the MLEs, the medical information specialists would tend to respond selectively to certain queries and customers in order to make the best use of their particular experience. Pfizer believed that this confirmed rather than undermined its contention that there were similarities between these roles.

11 The Panel had noted in paragraph 7 of its ruling that the 'Additional activities' section of the Plan of Action referred to developing and maintaining opinion leader networks. As a preliminary point Pfizer pointed out that, as explained in its original response (point 2.1), few additional activities were in fact conducted. No opinion leadership activities took place in respect of Viagra or Vfend. Nonetheless, Pfizer addressed the Panel's concerns below.

12 The Panel had stated that the MLEs' development and maintenance of opinion leader networks seemed 'strange, given that the MLEs were supposed only to respond to requests for information'. The Panel had asked how the MLEs were supposed to achieve this. Pfizer explained that was to be done within the context of responding to requests for information and carrying out other aspects of the MLEs' role as described in item 1.1 of Pfizer's original submission (eg through contacts with opinion leaders in relation to potential clinical research programmes or to discuss drug safety). The contact between MLEs and opinion leaders was usually ongoing, because opinion leaders generally requested prompt notification and/or discussion of new clinical or scientific information within their specialist field. By responding promptly with the required information and by demonstrating credibility and expertise, the MLEs had a legitimate opportunity to build positive relationships with opinion leaders. MLEs could also make useful professional contacts through their provision of scientific and/or product information at advisory boards and investigator meetings. Pfizer believed that there was nothing objectionable in MLEs seeking to build positive relationships with healthcare professionals in this way and did not believe that it breached the Code in any way. In any event, in order to avoid any possibility of misunderstanding, Pfizer planned to omit any reference to developing such relationships from future MLE briefing materials.

13 In response to the particular issues raised by the Panel in paragraph 11 of its ruling:

13.1 Pfizer contended that the MLEs' role was very similar to the more familiar medical information role for the reasons set out in point 1.1 of its original response and points 9 and 10 above.

13.2 The Panel had also expressed concern about the perceived independence of the MLE role, on the basis of the MLEs' dotted line reporting relationship into the regional healthcare managers. In reality,

prescribers would not have been aware of this dotted line relationship and so Pfizer could not see how it could affect their perception of the MLEs' independence. In any event, the MLEs' reporting relationship with the regional healthcare managers was a dotted, not a solid, line. This reporting mechanism was commonly used within Pfizer for administrative convenience where (as was the case with MLEs) staff were based at a site that was remote from their functional manager. The local dotted line manager usually facilitated local communication (eg by imparting news of computer downtime or of VIP visitors at the site) and administration (eg by establishing local standards for equipment and processes) but did not exercise any significant influence over the functional content of the role. If there was any conflict between the solid and the dotted reporting lines, the solid line would prevail. Pfizer was aware that it was a common misconception that any staff who were regionally based must be part of the sales force. This assumption was not always correct: Pfizer had a number of staff who were regionally based but who did not form part of the sales force including the MLEs, clinical research associates and clinical research monitors. Although Pfizer contended that the dotted line relationship with the regional healthcare managers had no significant influence on the MLEs' role, it accepted that it might be open to misinterpretation and so had removed it.

13.3 Pfizer noted that the Panel had stated that the MLEs were 'associated with sales and marketing'. Pfizer referred to point 13.2 above and point 23 below.

13.4 The Panel's comments regarding the expectation for data to be presented by the MLEs 'in line with marketing and sales direction' was dealt with at point 6.3 above.

13.5 The Panel had stated that it did not appear that the reactive role of MLEs had been very clearly addressed in training materials. Pfizer drew attention to the MLE presentation submitted with its original response. Slide 7 set out the functional responsibilities of the MLEs and the very first words in the first bullet point were 'Respond to requests'. Later in this presentation, there were several slides explaining how the MLEs were to discharge their responsibilities (under the heading 'How do we do it?'). These referred by way of background to the law and Code and then in two slides headed 'The Enquiry' and 'The Answer' it was made clear that the MLEs needed to respond to specific questions: the need for a specific question was emphasised both by repetition and underlining. A third slide (headed 'Credibility') referred to the need for neutral, objective, evidence based and individualised data *in response to a specific question*. Slide 33 (headed 'Istin: MLE objectives') referred to providing 'scientific and clinical information relating to PREVENT, *as requested by customers*', and slide 35 (headed 'Key Responsibilities') stated as the MLEs' first responsibility 'To present the PREVENT data at the customer's request ...'. The reactive role of the MLEs was similarly described in the MLE briefing documents and was emphasised during their induction and ongoing training. Pfizer conceded that the training materials could have explicitly stated that such requests must not be solicited, but it was Pfizer's contention that this was understood and that the requests received were in fact unsolicited. If there had been any systematic attempt to solicit requests for information, given the number of requests received, Pfizer stated that it would surely have had at least one complaint to this effect from a health professional.

14 In paragraphs 12 and 13 of its ruling, the Panel referred to the MLE briefing document for Istin and quoted a number of extracts from the document without explaining the Panel's objections to the quoted items. Pfizer inferred from the mention of these items and the Panel's later conclusions that adverse conclusions were drawn from the quoted items but it was not told what these inferences were or why they were thought to be justified. It was impossible for Pfizer to have a fair opportunity to respond to the Panel's concerns if the Panel failed to articulate them clearly. Nonetheless, Pfizer had attempted to address the issues mentioned by the Panel.

14.1 The Panel had noted that the briefing document referred to 'access opportunities' being 'created' by members of the sales force. Pfizer acknowledged that the wording used was ambiguous and could be taken to imply that members of the sales force should proactively seek requests for information. However, Pfizer contended that it need not, and should not, be read in this way. Each referral by the sales force of an unsolicited request for information was an 'access opportunity' for the MLEs that would not otherwise exist. As explained in its original submission, in order to improve the quality of data available to health professionals it was necessary for the sales force to refer appropriate queries to the MLEs, rather than attempt to answer such queries themselves. The sales force thus created access opportunities for the MLEs by referring appropriate (unsolicited) requests for information to them.

14.2 The Panel had commented that the briefing document also referred to Pfizer's stated preference for information to be shared with health professionals in meetings, with one to one calls being suggested as an alternative if a meeting was not possible or was unsuitable. Pfizer stated that this preference for meetings resulted from the past experience of the Parke Davis MLE team which found that meetings were preferred by most of the health professionals who wanted information relating to clinical data. The health professionals who were most interested in emerging clinical data tended to be professors or senior consultants who were usually keen for that information to be shared with their junior colleagues but wished to be present when this was done, hence the popularity of group meetings. Usually the questions relating to clinical trial data were very standard (eg about basic design and results of a particular trial), so requests for the same data were often received from different specialists working in the same hospital. In both such cases, it was clearly more efficient for the MLE and the health professionals to have a single meeting of all the interested parties. The MLE only had to present the basic briefing once and the health professionals could hear each others' challenges to, and debate about, the data presented.

14.3 Reference was made by the Panel to the hospital sales representatives (HSRs) and customer healthcare consultants (CHCs) attending meetings with the MLEs to 'build on the rapport with key customers'. Pfizer stated that the HSRs and CHCs were to build on their existing rapport with the relevant health professional by introducing the MLEs. The act of bringing the health professional into contact with a useful local medical information resource was to be treated as a positive interaction in the HSRs' and CHCs' ongoing relationship with that health professional. This was all that was meant by the wording highlighted by the Panel. However, in recognition of the possible misunderstanding that the presence of representatives at such meetings might cause, guidance had since been issued to the MLEs that members of the sales team should not generally attend the MLEs' meetings with health professionals.

14.4 The Panel had noted that the briefing document referred to the MLEs' initial dependence on invitations being generated by members of the Pfizer sales force and stated that 'if these were not forthcoming the process must be reviewed and other options discussed'. Pfizer believed that this acknowledgement of the MLEs' dependence on referrals of requests for information supported its contention that the MLEs were clearly understood to be restricted to acting in response to such requests. The MLE role was new to Pfizer. As with any new system, the operation of the new MLE role would need to be checked to see if it was working as anticipated. The comment merely reflected the need for such review. In fact, the level of referrals of requests for information to MLEs was found to be generally satisfactory and so beyond attempting to publicise internally some unevenness in adopting the new system (which was detailed in Pfizer's original response), no other options were discussed.

14.5 The Panel had also noted that the MLEs would feed back to regional colleagues. Pfizer stated that it was clear from the preceding line in the briefing document that this would happen following a meeting at the customer's request to present PREVENT data. This feedback was necessary largely for reasons of co-ordination (eg in meetings not attended by a sales colleague to let him/her know when the meeting had occurred, so that he/she would know if the meeting request was outstanding at his/her next visit to the health professional concerned). Other information provided by the health professional might also be fed back to other colleagues. For example, if a health professional requested detailed information about the health economic or budgeting implications of a product then this would be referred to the regional clinical effectiveness consultant (CEC) who specialised in providing this information. Pfizer referred to point 7.1 above for other examples of potential feedback to colleagues.

14.6 In paragraph 13 of its ruling, the Panel also noted that the Istin product team was to identify opportunities for the CECs to present relevant health economic models. Pfizer did not see the relevance of this item to this case, since it did not relate to the MLEs but rather to a product team and the CECs. As previously explained, the MLEs did not generally discuss budgetary matters. If queries arose on financial, budgetary or other health economic issues, Pfizer thought it was legitimate for these to be referred by the product team to the CECs, who had specialised knowledge in this area.

15 In paragraph 14 of the ruling, the Panel quoted from an e-mail between one MLE and a sales force colleague a reference to MLEs and hospital sales representatives working well together to 'shift certain customers'. The MLE asked for evidence of such activity and suggested two possible examples. The sales force colleague replied by referring to two examples and providing further details: in both it seemed that the 'shift' referred to changing the consultants' attitudes to products by supplying information that addressed their particular concerns. Pfizer was concerned by this interaction which, although not conclusive, suggested some blurring of the boundary between the hospital sales representatives and the MLEs. Pfizer accepted that the exchange was unfortunate but asked the Appeal Board not to attach disproportionate weight to one isolated and informal e-mail exchange.

16 Pfizer had similar difficulties to those mentioned in point 14 above in relation to paragraph 15 of the Panel's ruling. Pfizer did not understand the Panel's concerns in relation to many of the issues highlighted by the Panel in paragraph 15 of its ruling. The points which appeared to require explanation are dealt with in points 14.1-14.6 above where similar considerations apply.

17 In relation to Zeldox specifically, Pfizer explained how questions about an unlicensed product would be received by the mental health team and CHCs. Sales representatives had an ongoing relationship with many health professionals (particularly psychiatrists) through their work with other Pfizer mental health products, such as Lustral and Aricept. Queries about ziprasidone would arise by virtue of health professionals' awareness of Pfizer's interest and activities in this area generally, and would be even more likely to arise following news about the launch of ziprasidone in other countries and the withdrawal of ziprasidone from the European mutual recognition procedure in 2000 (point 2.3.2 of original response). Concerns about the risk/benefit profile of ziprasidone had been raised by another pharmaceutical company with a commercially available product, and this led to many requests from health professionals for clarifying data. In addition, several developments in the mental health arena had prompted health professionals to seek information about the management of schizophrenia and particularly pharmacological management with atypical anti-psychotics (eg the NICE review of atypical anti-psychotics and the new National Service Framework for Mental Health). It was therefore inevitable that important medical questions about ziprasidone would be raised by health professionals during their contact with the mental health team and CHCs to discuss Pfizer's licensed mental health products.

18 Paragraph 18 of the Panel's ruling referred twice to Pfizer's instructions to members of its sales force to attend meetings with the MLEs. Pfizer sought to

clarify this: the representatives were to attend the initial meeting between health professionals and the MLEs in order to introduce the MLE, and certainly not to take part in the meeting. Pfizer did not believe that the presence of a member of the sales force at these meetings was, of itself, sufficient to make such meetings promotional. The MLE would not be familiar with the location of the meeting or the individual who had requested it. Pfizer contended that it was basic good manners for the representative who knew the health professional to make the initial introduction to the MLE. Far from being treated as if they were associated with Pfizer's sales force, the MLEs would typically be treated like an invited specialist from a different hospital and as such would be fitted into one of the health professional's regular educational meeting slots. From a management perspective, it was important to avoid any unnecessary friction between the new MLEs and their other colleagues in the same region. Allowing the HSRs and CHCs to make the introduction would help them to feel more comfortable with the new arrangement. The reference was clearly to attending 'the meeting' (ie in the singular). There was no suggestion that the HSRs or CHCs would attend later meetings with the MLEs once the introduction had been made. Pfizer did not consider that the brief initial introduction made the meeting promotional but, to avoid any possible confusion, guidance had since been issued to the MLEs that sales representatives should not generally attend such meetings.

19 The Panel had expressed concern about the activities of MLEs and the amount and nature of the pre-prepared information provided to them, saying that it had no way of knowing the degree to which MLEs tailored the material to answer the request. Pfizer acknowledged the Panel's difficulty here and noted the Panel's acknowledgement that pre-prepared material was not necessarily unacceptable. Pfizer referred to its submission on this point (point 2.1 of its original response) which explained that materials were pre-prepared for the MLEs to respond to the most common requests for information, to ensure that the core information presented would be accurate and consistent.

20 In paragraph 18 of its ruling, the Panel had queried whether every member of every audience would have made an unsolicited individual request for information. Pfizer conceded that they would not and referred to point 14.2 above. Group meetings were arranged with the most senior health professional of the group concerned, generally with a professor or a senior consultant in respect of a meeting held at his/her behest for members of his/her team with a special interest in the area concerned. In these circumstances, the senior health professional's request was made on behalf of his/her team.

21 Pfizer's response to the Panel's question in paragraph 18 of the ruling about whether every query needed a meeting, was that clearly it did not. Contrary to the Panel's assumption, the MLEs did not always respond to requests for information with meetings: requests for information were referred to the medical information department where appropriate. For example, there had been at least 575 enquiries to the medical information department so far this year (2001) regarding MIRACL data. Further, to date about 11% of this year's (2001) requests for information relating to Lipitor and ziprasidone received by the department had come from the MLEs. This proportion was unsurprising: as Pfizer had explained, most requests came via the sales force. If the sales force believed that the query could best be dealt with by the medical information department, then it would refer the query there directly.

22 In relation to paragraph 19 of the Panel's ruling, Pfizer disputed that the boundary between the MLEs and representatives was unclear. The MLEs were clearly part of the medical department. Their reporting line into the medical group was one of substance. The MLEs' manager and 'acting head' was a full member of the medical department management team and in turn reported to the medical director. Decisions about MLE recruitment, promotion, performance and pay were all made within the medical department. The MLEs attended medical department meetings and their training was received through the medical department. Unlike members of the sales force, the MLEs did not have sales targets, or attend the twice yearly briefing from the marketing group on its Plan of Action, or have their pay, performance or bonus directly determined by reference to sales growth. Pfizer also referred to points 1, 10, 13 and 18 above in particular.

23 With regard to the other issues raised in paragraph 19 of the Panel's ruling, Pfizer conceded that the representatives were encouraged to attend MLE meetings. However, this was only in respect of the initial meeting and the part played by the representatives in those meetings was confined to introducing the MLE to the health professional as a matter of courtesy. Pfizer acknowledged that the MLEs were not able to initiate contact with health professionals and therefore were initially dependent on appropriate requests for information being referred to them by the sales force. Pfizer also conceded that its documentation was inadequate and did not meet the high standards required by Clause 9.1 of the Code. As mentioned above, revised guidance had been issued, correcting the deficiencies identified by the Panel. A schedule of action taken and in progress was provided. However, Pfizer contended that it was not what the documentation said but what the MLEs actually did that mattered. After all, if the documentation had been better written, that would not exonerate the MLEs if their activities were in fact in breach of the Code. Pfizer noted that the Panel's findings were based on poor quality documentation rather than actual activity.

24 Paragraph 20 of the Panel's ruling stated that requests for information could be answered in a number of ways, in some instances by simply sending the papers. Pfizer agreed that this could sometimes be appropriate and indeed this happened in a number of instances. However, in most cases this would not be an appropriate response. Many of the MLEs' key contacts were opinion leaders. These people were expert in their field and greatly interested in any new

scientific developments in their therapeutic area. In many cases they were not prepared to wait for published data. For example the MIRACL data were not published until March 2001, some five months after the information was presented at the November 2000 American Heart Association meeting. Even where such papers did exist, it was often pointless to send them: experts in the field would usually already have copies of the relevant papers but would require much more detailed information. Often, receipt of a new paper would prompt opinion leaders to request a meeting with their local MLE to discuss it in more detail. The possibility of sending material in the post was not mentioned because it was not envisaged that this would be appropriate to the sort of queries that would be referred to the MLEs (as opposed to medical information executives – see point 10 above).

In the light of Pfizer's answers to the Panel's concerns above, it firmly maintained that the MLEs' role was reactive rather than proactive.

The Panel's reasoning and ruling on Clauses 3.1, 3.2 and 15.2

In relation to the issue of the extent of the exemption in Clause 1.2 of the Code, Pfizer referred to points 1, 2 and 3 above. Pfizer fundamentally disagreed with the Panel's reasoning, which appeared to be seriously flawed. In order to fall within the definition of 'representative' within Clause 1.6, the person concerned must call on health professionals and others 'in relation to the promotion of medicines'. The Panel's ruling asserted that the MLEs were representatives and therefore that their activities were promotional. Pfizer respectfully submitted that this begged the very question of whether the MLEs were representatives. The MLEs could only fall into the definition of 'representatives' if their activities were promotional, and yet the Panel decided that their activities were promotional because the MLEs were representatives. This reasoning was entirely circular.

Even if Pfizer was to accept (and it did not) that the MLEs were 'representatives' within the definition in Clause 1.6, it challenged the Panel's view that the MLEs' activities would automatically be promotional as a result. In order to fit within the definition of 'promotion' in Clause 1.2 of the Code, the activity concerned must 'promote the prescription, sale, supply or administration of its medicines'. Pfizer submitted that an action should not be promotional purely because the person committing it was a representative. It was possible, and indeed quite common in smaller pharmaceutical companies, for sales representatives to conduct many activities that were not promotional in nature. It therefore contended that the Panel was not entitled to condemn the MLEs' entire role but should instead have examined the individual activities they performed and ruled on the question whether any of these breached the Code.

Pfizer disputed absolutely the Panel's findings; it did not believe that there were sufficient grounds upon which to characterise the MLEs' overall as representatives or their activities overall as promotional. It denied that Clauses 3.1 and 3.2 of the Code were breached and the Panel's assertion that the MLEs were required to pass the ABPI Representatives Examination for the same reason: the MLEs role was not promotional and they were not representatives.

Pfizer accepted the Panel's ruling of a breach of Clause 9.1 of the Code on the basis set out in points 4, 6, 13, 14 and 23 above. It accepted that the company had failed to maintain high standards in its description of the MLEs' role and related guidance and documentation.

Pfizer contested the ruling of a breach of Clause 15.2 of the Code on the basis that this clause applied to representatives and, as explained above, it was Pfizer's contention that the MLEs were not representatives.

The Panel's ruling on Clause 2

Pfizer was greatly disturbed by, and particularly wished to appeal, the Panel's ruling of a breach of Clause 2 of the Code.

Clause 2 related to activities which 'bring discredit upon, or reduce confidence in, the pharmaceutical industry'. Pfizer did not consider that censure under Clause 2 was appropriate in this case.

For the reasons set out above, it did not believe that it had breached Clauses 3.1, 3.2 or 15.2 of the Code. However, if the Appeal Board ruled against it in respect of one or more of these clauses, it still took particular issue over whether a Clause 2 ruling was justified.

The MLEs were a relatively new concept at Pfizer, their activities had not given rise to complaint previously and other companies engaged in similar activities. It was its submission that these sorts of arrangements were in a grey area, where the rules for operation were far from clear: the Panel itself noted that many of the MLEs' activities were not necessarily unacceptable but had to be judged on their merits.

Even in those matters where the Panel ruled against Pfizer, it did so on the basis of an 'overview' of the arrangements or poor documentation and not on the basis of any clear breach of the Code.

The introduction of the MLE system at Pfizer resulted from the Pfizer/Warner Lambert merger in June 2000, when the MLE role was inherited from Parke Davis. The MLE role was adopted by Pfizer at the behest of the former medical director of Parke Davis. The MLE system was understood to have operated successfully at Parke Davis for several years and therefore did not undergo the same review that a new Pfizer initiative would have done. This, the massive disruption caused by the merger and the absence of a medical director, explained (but did not necessarily excuse) the apparent lack of management focus on the MLEs.

Pfizer accepted that the organisation, training and operations of the MLEs could have been much better implemented. However it remained convinced that any breach of the Code was inadvertent, and not a deliberate or cynical act of non-compliance. Senior management within the company, and at its parent company, was committed to ensuring that the MLEs operated within the Code and the law and viewed this complaint extremely seriously.

Once management was alerted to the matters complained of, prompt action was taken. Details of the various steps taken and in progress were outlined.

Clause 2 was stated to be 'a sign of particular censure and to be reserved for such cases'. In view of the circumstances described above, Pfizer believed that a Clause 2 ruling was not justified.

APPEAL BOARD RULING

The Appeal Board noted that the Code permitted certain activities in relation to products not yet licensed or indications not yet licensed. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited providing that any such information or activity did not constitute promotion prohibited by Clause 3 or any other clause. The supplementary information to Clause 3.1, Advance Notification of New Products or Product Changes, allowed limited information on products with a significant budgetary implication to be provided to those responsible for making policy decisions on budgets ahead of the grant of the marketing authorization. The definition of promotion in Clause 1.2 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.

In the Appeal Board's view it was not necessarily unacceptable for companies to have employees focussing on the provision of information prior to the grant of the marketing authorization or prior to the licensing of an indication. The arrangements and activities of such employees had to comply with the Code. Such employees should be comprehensively briefed about the Code. The area was difficult and companies needed to ensure that the arrangements and activities were very carefully controlled and managed. The importance of documentation and instruction could not be overestimated.

The Appeal Board noted Pfizer's submission that the MLEs were not representatives as defined by Clause 1.6 of the Code and that their role as described in the role profile was wider than the exemption in Clause 1.2 of the Code in relation to replies made in response to individual enquiries from members of the health professions. Pfizer did not believe that this rendered their activities unacceptable provided they otherwise complied with the Code. The Appeal Board noted that the MLEs were responsible for liaising with key customers in order to manage drug safety issues. Generally the matters discussed by the MLEs did not have significant budgetary implication. The MLEs also facilitated the identification of clinical trial investigators and assisted in clinical research projects.

The Appeal Board considered that whether the MLEs satisfied the definition of a representative at Clause 1.6 was not the heart of the issue. In the Appeal Board's view it was likely that company personnel who held primarily non-promotional roles, such as clinical research physicians, might, on occasion, fulfil a promotional function; any promotional aspect of their role must comply with the Code.

The Appeal Board noted the limited exemption to the definition of promotion in Clause 1.2 in relation to responding to enquiries from health professionals. The Appeal Board considered that in principle it was not necessarily unacceptable for a field based team such as MLEs to respond to such individual requests but their activities had to comply with the Code or be such that they came within the limited exemption to the definition of promotion at Clause 1.2. To come within the exemption the MLE's response should relate solely to the subject matter of the enquiry, be accurate, not mislead and not be promotional in nature. The enquiry should not be solicited.

The Appeal Board noted Pfizer's submission that its merger with Warner Lambert in June 2000 had caused a period of massive disruption. The medical director had resigned and left the company in the week beginning 26 February 2001. A new medical director had been in place since the beginning of September. A number of the activities at issue mentioned in the documentation had occurred whilst the medical director was present. The Appeal Board considered that it was nonetheless incumbent upon the company to ensure that standards were maintained in relation to the Code; that staff were appropriately supervised and directed in relation to the Code. On the documentation before it the Appeal Board queried whether sufficient control had been exercised in relation to the MLEs.

The Appeal Board noted the submissions of the company representatives regarding the MLE role profile and the acknowledgement that the role profile and other documents were poorly written. The Appeal Board noted the company's view that it was what the MLEs actually did and were encouraged to do that was the issue. The Appeal Board considered that the documentation gave a very clear view of what the MLEs were encouraged to do. In the Appeal Board's view the documentation was not sufficiently clear about the reactive nature of the MLE job. The Appeal Board noted the company representatives submission that the MLEs had not been formally judged against the criteria set out in the role profile although they had probably not been told that this would be the case. The MLEs had had one to one meetings with their manager and had been given other additional information wherein their roles and activities were explained. Nonetheless the Appeal Board considered that the MLEs would reasonably rely on the role profile as one of several documents describing their job. The Appeal Board considered that the activities of the MLEs as described in the role profile went beyond the limited exemption to the definition of promotion at Clause 1.2.

The Appeal Board noted the MLEs activities in relation to Zeldox and the company's submission that the enquiries from healthcare professionals were entirely spontaneous. At the appeal the company representatives stated that such enquiries arose from interest about the mutual recognition position, the QTc interval and the US sales position.

The Appeal Board noted that the March 2001 medical report referred to 180 key opinion leaders in region 2 having received presentations on Zeldox to date. The Appeal Board queried the number of key opinion leaders within one region. At the appeal the company representatives accepted that the term 'key opinion leader' was probably not a fair reflection of the status of those who had been seen. The Appeal Board noted that the December 2000 medical report referred to the provision of data on Zeldox prior to launch; it was reported that pharmacists were 'delighted' with Pfizer's service. The report also referred to the launch programme and mentioned issues in relation to the future prescribing of Zeldox. Similar comments appeared in the March 2001 medical report which also referred to 20 formulary acceptances to date. At the appeal the company representatives stated that this must be incorrect as the medicine was not yet licensed.

The December 2000 report referred to the lack of requests about the MIRACL and PREVENT studies in one particular region and to the strategies subsequently used to generate an interest in MIRACL data; one such strategy was to accompany field visits as a way to introduce the role and hopefully generate an interest in MIRACL data. The MIRACL study referred to an unlicensed indication for Lipitor and the PREVENT study referred to an unlicensed indication for Istin.

The Appeal Board was concerned about the tone of the medical department reports; at the appeal hearing the company representatives accepted that the wording of the internal documents was regrettable and submitted that such inappropriate phrases were not a fair reflection of what the MLEs did in practice. One purpose of the medical reports was to market the role of the MLEs internally to other departments. Each medical manager would contribute to his/her section. The Appeal Board noted the submission that in the absence of the medical director no one person took overall responsibility for the monthly report. The Appeal Board queried why errors had not been spotted and corrected prior to circulation of the reports, particularly given the company representatives' submission that staff had received training on the Code. The reports gave a flavour of the role of the MLEs and how it was perceived by Pfizer staff. The reports were not consistent with the limited exemption to the definition of promotion in Clause 1.2 of the Code. The reports encouraged a proactive rather than a reactive role.

The Appeal Board was also concerned that 14 doctors had attended the Regional Schizophrenia Advisory Board Meeting in Glasgow; at the appeal hearing the company representatives conceded that this group was too large; other advisory boards had consisted of 6 - 10 doctors.

The Appeal Board considered that on the evidence before it the activities of the MLEs went beyond responding to unsolicited enquiries. The phraseology of the internal documentation was inconsistent with a role which responded to unsolicited enquiries. The documents did not reflect the requirements of the Code regarding the provision of such information. There was no clear and unequivocal message to the MLEs that they could not promote an unlicensed medicine or an unlicensed indication and no acknowledgement of the constraints placed on such activities. The Appeal Board considered that the activities were such that they constituted promotion of an unlicensed medicine, Zeldox, and unlicensed indications for Istin and Lipitor, contrary to the provisions of Clauses 3.1 and 3.2 of the Code. The Appeal Board upheld the Panel's rulings of breaches of Clauses 3.1 and 3.2. The appeal on these points was unsuccessful.

The Appeal Board considered that the documentation was such that the MLEs had not been directed to maintain a high standard of ethical conduct in relation to their activities. However, the Appeal Board considered that Clause 15 applied solely to those employed as representatives and considered that technically the MLEs were not representatives. The Appeal Board thus ruled no breach of Clause 15.2 of the Code. The appeal on this point was successful.

The Appeal Board was extremely concerned about the documentation before it. The supervision and accountability of the MLEs appeared to be wholly inadequate. There was insufficient separation of the MLEs from the sales force. The arrangements 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 the circumstances justified reporting the company to the ABPI Board of Management in accordance with Paragraph 11.1 of the 1998 Constitution and Procedure for the Authority.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board of Management agreed that this was a serious matter that necessitated further action. The Board decided that Pfizer should be reprimanded and details of that reprimand published. It also decided that the company should undergo an audit of the MLE function. This would be carried out by the Authority.

On receipt of the audit report the ABPI Board decided that, on the basis that Pfizer implemented the audit report recommendations, no further action was necessary.

Complaint received	**10 May 2001**
PMCPA proceedings completed	**22 October 2001**
ABPI Board proceedings completed	**12 February 2002**

CASE AUTH/1204/7/01

ROCHE v ORTHO BIOTECH

Promotion of Eprex

Roche complained about four pieces of Eprex (epoetin alpha) promotional literature issued by Ortho Biotech.

A leavepiece announcing five new strengths of Eprex stated that the new presentations would bring further simplicity of dosing 'particularly for patients who would benefit from receiving Eprex once weekly'. Roche stated that the Eprex summary of product characteristics (SPC) did not contain a recommendation for once weekly dosing in any subgroup of patients. Although no dosing frequency was stated for adult haemodialysis patients in the maintenance phase, no change from the three weekly dose in the correction phase was mentioned or implied.

The Panel considered that the claim was such that it was implicit that not all patients receiving Eprex would receive a once weekly dose. The SPC stated that adult haemodialysis patients in the maintenance phase were recommended a total weekly dose of Eprex of between 75 and 300 IU/kg. There was no statement about frequency of dosing for these patients. In the Panel's view it was possible for them to receive a once weekly dose as could adult patients scheduled for major elective orthopaedic surgery. The Panel did not consider that a reference to some patients receiving a once weekly dose was inconsistent with the SPC as alleged. No breach of the Code was ruled. Upon appeal by Roche the Appeal Board did not consider that the dosage recommendation for adult haemodialysis patients in the maintenance phase excluded the possibility of using a once weekly dose; reference to such a dosage frequency was not inconsistent with the SPC. The Panel's ruling of no breach was upheld.

A leavepiece entitled 'Flexible dosing' stated that 'Emerging clinical evidence supports a flexible range of dosing regimens for [Eprex] with total weekly dose remaining unchanged whether receiving once weekly, twice weekly or three times fortnightly injections' Roche stated that only twice weekly dosing was licensed and then only for patients on peritoneal dialysis.

The Panel noted that the 'emerging clinical evidence' appeared to relate to patients receiving either haemodialysis or peritoneal dialysis. It did not relate to all patient subgroups. The type of patient and whether the dose was correction or maintenance was not made clear. Given the complexity of the dosing regimens and range of patient subgroups the Panel considered that the mention of once and twice weekly and thrice fortnightly dosing regimens in the leavepiece was misleading and thus inconsistent with the SPC; the emerging clinical evidence did not apply to all subgroups and in some, such as peritoneal dialysis patients, the dosing schedules in the leavepiece were not consistent with the SPC. A breach of the Code was ruled.

A booklet entitled 'Treatment Guide for Renal Patients' referred to the treatment of anaemia in dialysis patients and patients with renal insufficiency not yet on dialysis. With regard to maintenance therapy it was stated that the appropriate dose 'can be given as one*, two or three injections per week'. The asterisk referred to a footnote which read 'For adults on haemodialysis'.

Roche stated that the SPC for Eprex did not recommend one injection per week for any group of patients. Furthermore, the suggestion made that Eprex could be given twice weekly was only consistent with the SPC recommendations for adult patients on peritoneal dialysis, but no qualifying statement was made to this effect on the page in question or anywhere else in the booklet. Roche alleged a breach of the Code.

The Panel noted that the booklet referred to the treatment of anaemia in dialysis patients and in patients with renal insufficiency who were not yet on dialysis who would be given a maintenance dose either once, twice or three times a week. The Panel considered that its comments above were relevant. In the Panel's view the once, twice or thrice weekly maintenance dosage regimen for adult and paediatric patients with renal insufficiency was not inconsistent with the SPC for this patient population. No frequency of dosing was given in the relevant section of the SPC. No breach of the Code was ruled.

The first question of a quiz read, 'which of the following Eprex dosage regimens can be used during the maintenance phase in adult haemodialysis. Please tick'. The answer options were once, twice or three times per week or 'all of the above'. Roche stated that the only correct answer, consistent with the SPC, was three times per week. However, during a telephone conversation between the companies' medical departments, Ortho Biotech confirmed that the answer judged to be correct by Ortho Biotech was 'all of the above'. Roche alleged a further breach of the Code.

The Panel considered that its rulings above were relevant. The question identified the patient population as adults on haemodialysis. No breach of the Code was ruled.

Roche Products Limited submitted a complaint about the promotion of Eprex (epoetin alfa) by Ortho Biotech at the British Renal Society meeting held in Manchester 7-9 June 2001. Four promotional items were at issue.

According to its summary of product characteristics (SPC) Eprex was indicated for the treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis. The treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis. The treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (eg cardiovascular status, pre-existing anaemia at the

start of chemotherapy). Eprex could also be used to increase the yield of autologous blood from patients in a predonation programme and to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications.

1 Leavepiece (ref A4190701300)

A one page leavepiece subtitled 'Announcing five new strengths of Eprex' stated '… to bring further simplicity of dosing, particularly for patients who would benefit from receiving Eprex once weekly, we have introduced five new strengths'. This was followed by a table depicting the complete range of pre-filled syringes with reference to their strength and volume. Subsequent reference was also made to a survey of haemodialysis patients. The leavepiece took the form of a letter signed by the product manager.

COMPLAINT

Roche stated that the SPC for Eprex referred to a dosage of 50 IU/kg, 3 times per week intravenously (iv) or subcutaneously (sc) for the correction phase of treatment in adult haemodialysis patients. For the maintenance phase, a weekly dosage of 75-300 IU/kg was recommended but no change to the frequency of dosing or route of administration was mentioned nor implied. For paediatric haemodialysis patients, the same dosage as for adults was recommended but only the intravenous route was specified. For maintenance in paediatric haemodialysis patients, a table was provided showing dosing according to body mass; the dosage column was clearly marked 'Dose (IU/kg given 3x week)'.

For adult patients with renal insufficiency not yet undergoing dialysis the correction phase dosage was clearly recommended as 3 times per week by sc (preferred) or iv routes. For maintenance in these patients, the SPC stated that the 'maximum dosage should not exceed 200 IU/kg 3 times per week' and suggested a maintenance dosage of 17-33 IU/kg 3 times per week. For adult peritoneal dialysis, a correction dosage of 50 IU/kg sc, 2 times per week was recommended, with maintenance at the same dosing frequency.

Roche noted that the leavepiece made reference to 'patients who would benefit from receiving Eprex once weekly'. The SPC for Eprex did not contain a recommendation for once weekly dosing in any subgroup of patients. Roche alleged that Ortho Biotech had breached Clause 3.2 of the Code which required that the promotion of a medicine must be in accordance with the terms and conditions of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

RESPONSE

Ortho Biotech noted that the allegation related to a specific interpretation by Roche of the SPC wording regarding posology and method of administration of Eprex for management of anaemia in adult haemodialysis patients.

The SPC for Eprex clearly divided the management of anaemia associated with chronic renal failure in adult haemodialysis patients into two distinct phases, the correction phase, and the maintenance phase. The two phases were not synonymous, and therefore it was inappropriate to extrapolate recommendations from one phase into the other, in particular, with regard to dosing due to the consequent changes in haemoglobin (Hb). During the correction phase the aim was to elicit a gradual increase (in Hb) toward a physiological 'target' Hb (for which numerous national and international guidelines existed) and the maintenance phase which aimed to stabilise Hb around this physiological target level. Due to the different pharmacokinetic-pharmacodynamic relationships for Eprex with regard to the Hb changes during the two distinct phases of management, different dosing regimens were appropriate, as indicated within the SPC.

Ortho Biotech stated that for the correction phase in adult haemodialysis patients, the dosing recommendations given in the SPC (50 IU/kg three times weekly, with recommendations on dose adjustments) were well established in clinical practice.

For the maintenance phase however, there was not consistent practice amongst clinicians, in particular with regard to frequency of dosing, with individual clinicians using a variety of dosing regimens. The SPC for Eprex in adult haemodialysis patients for the maintenance phase stated 'the recommended total weekly dose is between 75 and 300 IU/kg'. This statement stood alone; it was not implied that recommendations for the dosing regimen during the correction phase of anaemia should be carried through to the maintenance phase. This element was notably different from recommendations elsewhere within the SPC and left the determination of frequency of dosing to the choice of the individual clinician. This, as highlighted above, was subject to a degree of individual variability. This being mirrored in clinical practice (see below).

Ortho Biotech noted the requirements of Clause 7.2 of the Code and its supplementary information, in particular that 'where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'.

Ortho Biotech stated that the clinical issue of dosing frequency during the maintenance phase for adult haemodialysis patients was an area where opinion differed and a generally accepted viewpoint was not established. There was however a gathering opinion amongst nephrologists that during the maintenance phase a once weekly injection was preferable to more frequent dose administrations and at the discretion of an individual clinician, if the total weekly dose was between 75-300 IU/kg it was not inconsistent with the particulars in the SPC for adult patients receiving haemodialysis.

Clause 7.2 of the Code required that promotional materials treated issues where differing viewpoints existed in an unambiguous manner, and did not mislead either directly or by implication. Ortho

Biotech stated that within the spirit of this element of the Code it had therefore sought not to be ambiguous with regard to this point and in a balanced way, had also stated that in addition to once weekly dosing, clinicians were also dosing twice weekly, three times weekly, and also using a dosing frequency of three times a fortnight. Providing the total weekly dose of any of these treatment regimens was between 75-300 IU/kg then that particular treatment regimen fell within the particulars listed within the SPC for Eprex for adult haemodialysis patients.

Clause 7.2 of the Code also required information to be based on an up-to-date evaluation of the evidence. The principal reference underpinning the promotional materials was the European Survey of Anaemia Management (ESAM) (Valderrabano *et al*, 2000). This survey which was undertaken by Ortho Biotech had undergone specific analysis such that data quoted referred to adult haemodialysis patients. A second reference used (Kwan and Povey, 2001) related to data presented at a renal association meeting and fell into the category of 'emerging clinical or scientific opinion' as alluded to under the supplementary information to Clause 7.2 of the Code.

Ortho Biotech stated that the leavepiece at issue was underpinned by Valderrabano *et al* in which haemodialysis patients (based on an average adult weight of 70kg) showed an average maintenance dose of erythropoietin of 7329 IU/week. This equated to a total weekly dose of 104.7 IU/kg, which was within the specifics outlined within the SPC for Eprex. Additional information within the survey indicated that 26% of adult patients receiving haemodialysis received their erythropoietin as a once weekly injection, hence the phrase 'patients who would benefit from receiving Eprex once weekly' allowed a clinician the option to follow this treatment regimen should they so desire. The leavepiece did not imply or state that all patients should receive once weekly dosing. The choice was left to the clinician, and within the spirit of Clause 7.2 allowed further debate on this issue.

PANEL RULING

According to Section 4.2 of the Eprex SPC, Posology and Method of Administration, the dosage regimen for several of the subgroups listed was divided into two stages; the correction phase and the maintenance phase. For adult haemodialysis patients the correction phase dosage was 50 IU/kg 3 times per week and during the maintenance phase the recommended total weekly dose was between 75 and 300 IU/kg. For paediatric haemodialysis patients the correction phase dosage was 50 IU/kg 3 times per week and for maintenance phase a table was provided illustrating the maintenance doses (IU/kg given 3 times a week) observed in clinical trials after 6 months of treatment. The doses ranged from 30-100 IU/kg for patients > 30kg to 75-100 IU/kg for patients < 10kg. For adult patients with renal insufficiency not yet undergoing dialysis the correction phase starting dosage was 50 IU/kg 3 times per week followed by dosage increments of 25 IU/kg thrice weekly until the desired goal was achieved. Maintenance phase dosage was between 17 and 33 IU/kg three times per week. The maximum dose should not exceed 200 IU/kg 3 times per week. For adult peritoneal dialysis patients the starting dose was 50 IU/kg 2 times per week in the correction phase and, subject to dose adjustment between 25 and 50 IU/kg 2 times per week in the maintenance phrase. For adult cancer patients receiving chemotherapy the initial dose was 150 IU/kg 3 times per week; subsequent dose adjustment was described in a diagram. For adult surgery patients in an autologous predonation programme mildly anaemic patients should be treated with 600 IU/kg 2 times weekly for 3 weeks. For adult patients scheduled for major elective orthopaedic surgery the recommended dosage regimen was 600 IU/kg given weekly for 3 weeks (days 21, 14 and 7) prior to and on the day of surgery.

The Panel thus considered that there were some patient groups who could receive Eprex weekly. At the doctor's discretion the total weekly maintenance dose recommendation in adult haemodialysis patients would allow a once weekly dose to be given. It was specifically stated that adult patients scheduled for major elective orthopaedic surgery should receive, if time allowed, weekly doses of Eprex for three weeks prior to surgery. It was not true that the Eprex SPC did not contain a recommendation for once weekly dosing in any subgroup of patients as stated by Roche.

According to Ortho Biotech's response the leavepiece at issue related to adult haemodialysis patients. The Panel considered that the leavepiece did not make this sufficiently clear; the first paragraph referred to patients who would benefit from receiving Eprex once weekly; the second paragraph, beneath the table depicting the Eprex product range, referred to a survey of haemodialysis patients showing an average maintenance dose of 7,329 IU per week based on a 70kg patient.

The Panel noted that it had to consider whether the reference to once weekly dosing was inconsistent with the SPC; the leavepiece announced five new strengths of Eprex. The Panel considered that the claim 'to bring further simplicity of dosing, particularly for patients who would benefit from receiving Eprex once weekly,…' implied that the five new strengths would bring simplicity of dosing to all patient subgroups and particularly so for those who would benefit from a once weekly dose.

The Panel considered that the claim was such that it was implicit that not all patients receiving Eprex would receive a once weekly dose. According to the Exprex SPC adult haemodialysis patients in the maintenance phase were recommended a total weekly dose of between 75 and 300 IU/kg. There was no statement about frequency of dosing for these patients. In the Panel's view it was possible for them to receive a once weekly dose as could adult patients scheduled for major elective orthopaedic surgery. The Panel did not consider that a reference to some patients receiving a once weekly dose was inconsistent with the SPC as alleged. No breach of Clause 3.2 was ruled.

APPEAL BY ROCHE

Roche's reasons for appeal were as follows:

1 Although the posology of Eprex was a complicated issue relating to various groups of patients, Roche had clearly emphasized that its complaint related to the *maintenance phase* for patients on haemodialysis suffering from chronic renal failure and not necessarily for all the other groups of patients mentioned in the SPC (eg orthopaedic patients mentioned by the Panel).

2 The Panel initially considered that the issue relating to adult haemodialysis patients had not been made sufficiently clear in the leavepiece but still ruled no breach of Clause 3.2. Roche considered this to be inconsistent.

The main dispute in this case was in the interpretation of the Eprex SPC. The Panel had found Ortho Biotech to be within the licence for Eprex by promoting once weekly administration. Roche noted that it had put its case and it did not intend to restate the reasons for its initial complaint. However in support of its case, it cited the British National Formulary (BNF) (March, 2001), which was quite clear and unambiguous about the maintenance dose of erythropoietin alfa in adults suffering from chronic renal failure; ie it was to be given three times per week (and not on a once weekly basis). The BNF recommendation would have been based on the Eprex SPC and clearly had made the same interpretation as Roche on this matter.

In addition, in the ruling the Panel accepted that 'the recommended total weekly dose' allowed for a once weekly administration. Roche believed that the word 'total' implied a summation of dosage during the week and that this followed on from the section on initial treatment which specified exact 'divided' dosing. If the SPC allowed for once weekly dosing there would be no need to use the word 'total'. This was common convention in the dosing of many medicines, particularly those requiring complex regimens.

That the leavepiece stated '… to bring further simplicity of dosing, particularly for patients who would benefit from receiving Eprex once weekly …' clearly showed that Ortho Biotech was promoting once weekly administration of Eprex, which was in breach of Clause 3.2.

3 Roche noted that Ortho Biotech stated that there was a difference in opinion among clinicians on the frequency of dosage recommendation in adult haemodialysis patients. However, the promotion of a once weekly administration without the marketing authorization was in breach of Clause 3.2 whether or not clinicians believed that the posology could be modified. Again Roche stressed that no data on once weekly administration were submitted for the registration of Eprex and that it was inconceivable that the regulatory authorities would licence once weekly dosing without such data.

4 Promotion of Eprex once weekly was a relatively recent event and Roche submitted that this had been done as a response to the introduction of a competitor product, which had a once weekly licence. If there had been no change to the SPC of Eprex in recent years, it would be of interest to know at what point the decision was made to promote once a week if the licence had always permitted this. Roche believed that in fact the company was merely exploiting an ambiguity in the SPC. It recommended that the Authority took steps to check with the appropriate regulatory authority, or at least have Ortho Biotech provide written confirmation from such an authority, that Eprex was licensed for once weekly dosing.

COMMENTS FROM ORTHO BIOTECH

Ortho Biotech stated that its position remained unchanged.

Ortho Biotech noted that Roche had appealed against the Panel's ruling suggesting that it had clearly emphasised that its complaint was with regard to the maintenance phase for patients on haemodialysis and not necessarily for all the other groups of patients mentioned within the SPC. Roche added that the main dispute within the case was with regard to the interpretation of the SPC for Eprex and introduced further support for its view by quoting from the BNF which had stated that the maintenance dose of Eprex in adults suffering from chronic renal failure was that the 'drug is to be given three times per week' and not on a weekly basis.

On two points of accuracy Ortho Biotech firstly noted that the initial complaint from Roche stated clearly that 'the SPC for Eprex did not contain a recommendation for once weekly dosing in any sub group of patients'. Given the broad nature of this statement the Panel appropriately reviewed the Eprex SPC dosing posology section in its entirety and concluded that Roche's statement was not true.

Had Roche's initial complaint been specific to the maintenance phase for patients on haemodialysis (as stated in its appeal), this was not made clear within the initial letter of complaint. Notwithstanding this, the Panel reviewed the implications with regard to the Eprex SPC for adult haemodialysis patients and noted that a recommended total weekly dose of between 75 and 300 IU/kgs was appropriate for these patients and that there was no statement about frequency of dosing for these patients. Therefore it was the Panel's view that it was possible for adult haemodialysis patients to receive a once weekly dose.

On the second point of accuracy, Ortho Biotech noted that the BNF of March 2001 indicated that the maintenance dose was 'usually 25-100 units/kg 3 times weekly'; this was inconsistent with the Eprex SPC which specified for the maintenance phase in adult haemodialysis patients that 'the recommended total weekly dose is between 75 and 300 IU/kg', there being no reference to dosing frequency as also noted by the Panel in its initial ruling. Additionally the use of the word 'usually' by the BNF would imply that the dosing frequency was not always 3 times weekly as indeed it indicated within the disputed leavepiece. Further clouding the robustness of the support to Roche provided by quoting the BNF, Ortho Biotech also noted that the March 2000 edition of the BNF indicated that in patients on haemodialysis the total weekly dose was 600 IU/kg. This was completely inaccurate and recommended a maximum dose at twice that given within the Eprex SPC for this particular patient population.

Ortho Biotech concluded, given these two inaccuracies within the BNF with regard to the dosing of Eprex, that the definitive source of information on dosing of Eprex was the Eprex SPC which contained the correct dosing regimens as approved by the relevant licensing authorities within the UK.

Ortho Biotech noted that Roche had suggested that the word 'total' with the phrase recommended total weekly dose referred to a summation of dosing during the week and also insisted that Eprex was to be given 3 times a week.

Ortho Biotech contested Roche's views on the Eprex SPC on this matter and noted that within the maintenance phase the wording 'total recommended weekly dose' did not relate to Eprex being given 3 times per week or any other dosing frequency (as previously the Panel had ruled upon). Given the specificity of dosing frequency within other sub populations of patients within the SPC (and these included oncology, surgical, paediatric and pre-dialysis renal patients, in addition to adult haemodialysis patients) and the lack of specificity of the dosing frequency during the maintenance phase, clearly clinicians were entitled to define their own dosing frequency based on their own clinical judgement and needs of individual patients. Within this remit they were guided by the recommendations that the weekly dose should not exceed 300 IU/kg. Under such conditions it was possible to give Eprex once a week as some clinicians preferred or twice a week or indeed 3 times a week and here the concept of 'total' implied a maximal dose not exceeding 300 IU/kg per week.

It was also Ortho Biotech's impression that Roche misunderstood its position regarding the Eprex SPC in that it insisted that the dosing frequency for adult renal patients during the maintenance phase was 3 times per week and appeared to suggest that Ortho Biotech advocated the use of Eprex once weekly in all these patients. This was incorrect. The Eprex SPC as previously discussed did not specify a dosing frequency; in addition Ortho Biotech's position was that within the subgroup of adult haemodialysis patients during the maintenance phase, at the discretion of the clinician some of these patients might receive Eprex once weekly within the constraint of a dose not exceeding 300IU/kg per week.

Clearly the reference (within the leavepiece) to the European Survey of Current Practice amongst nephrologists supported this position, in that a proportion of patients did receive once weekly dosing whilst others received twice or three times weekly dosing. The leavepiece, which indicated the availability of new strengths of Eprex, promoted Eprex in accordance with Clause 3.2.

FURTHER COMMENTS FROM ROCHE

Roche stated that its original complaint and subsequent appeal had been based upon its assertion that the SPC for Eprex did not contain a recommendation for once weekly dosing in adult haemodialysis patients.

Whilst the SPC for Eprex referred to a dosage of 50 IU/kg 3 times weekly for treatment in the correction phase, it stated a 'recommended total weekly dose of between 75 and 300 IU/kg' during maintenance. For all other indications, the maintenance doses in the SPC had specific frequencies attached, ranging from 3 times weekly in pre-dialysis to twice weekly in peritoneal dialysis. It was particularly noteworthy that the maintenance dosage specified for paediatric haemodialysis patients was depicted as a table, which stressed thrice-weekly administration.

Roche contended that the absence of specific wording in the SPC relating to frequency of maintenance dosing in adult haemodialysis was simply an ambiguity in the SPC, which was out of kilter with the remainder of the dosing advice in that document, and especially so with respect to the dosing frequency specified for paediatric patients in whom the avoidance of frequent injections would be particularly desirable.

Ortho Biotech was simply attempting to exploit an ambiguity in the SPC in order to promote Eprex 'off-licence', in the face of two competitor products (one of which was Roche's NeoRecormon) for which the requisite data had recently been submitted to the regulatory authorities and marketing authorization obtained, specifically for once-weekly dosing in patients with renal anaenamia.

With regard to the specific wording in the SPC relating to maintenance treatment in adult haemodialysis, this read: 'recommended total weekly dose'. Roche contended that in the context of the advice given in the previous paragraph relating to treatment phase dosing (ie 3 times weekly), no change in dosing frequency was implied.

In everyday medical usage, the word 'total' when referring to dosage implied summation. This was confirmed by the Oxford Dictionary which stated that the word meant: *adjective* 1 complete; comprising the whole (suggested synonyms: complete, comprehensive, entire, full, gross, overall, whole). 2 absolute, unqualified (absolute, downright, out and out, outright, perfect, sheer, thorough, thoroughgoing, unalloyed, unmitigated, unqualified, utter).

It was quite clear that, in the context of a dosing recommendation, the word 'total' did not mean 'maximal' as Ortho Biotech tried to suggest. If that really were so there would be no need to specify a dosing range of 75-300 IU/kg as in the SPC. A 'maximal' dose defined by a range of values (ie a range of doses) was clearly a meaningless concept. Had the SPC truly implied a maximal dose, a single figure would have been listed, and not a range of values.

Roche's final submission was that it believed that Ortho Biotech had not submitted data to the appropriate regulatory authority in support of once weekly administration of Eprex in maintenance for adult patients on haemodialysis. Indeed, the SPC for Eprex was so specific in terms of the dosing frequency for other indications; it was clearly never intended that it should be interpreted liberally for this one indication in isolation. It encouraged the Appeal Board to consider obtaining the views of the regulatory authority as Roche was currently seeking to do.

APPEAL BOARD RULING

The Appeal Board noted that Clause 3.2 of the Code stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC. What the BNF stated about a medicine was not relevant in this regard. The Eprex SPC stated that for adult haemodialysis patients in the maintenance phase the recommended total weekly dose was between 75 and 300 IU/kg. The Appeal Board did not consider that this statement excluded the possibility of using a once weekly dose; reference to such a dosage frequency was thus not inconsistent with the Eprex SPC. The Appeal Board upheld the Panel's ruling of no breach of Clause 3.2 of the Code.

The appeal in this regard was unsuccessful.

2 Leavepiece entitled 'Flexible dosing' (ref A42563 606783)

Pages two and three of this four page leavepiece were headed 'Dose of Epoetin - from ESAM' and presented dosing data from Valderrabano *et al*. A pie chart adapted from Valderrabano *et al* indicated that 26% of patients received a once weekly dose, 36% received a twice weekly dosing and 38% received at least a thrice weekly dose. A bar chart depicted the haemoglobin (Hb) response to one and two doses per week and 3 doses per fortnight at baseline, week 6 and week 12 and was adapted from Kwan and Povey. There was no statistically significant difference between the dosing regimens depicted at any time point. Text above the chart stated that 'Emerging clinical evidence supports a flexible range of dosing regimens for epoetin alfa with total weekly dose remaining unchanged whether receiving once weekly, twice weekly, or three times fortnightly injections'.

COMPLAINT

Roche noted that the data on pages two and three showed comparative haemoglobin responses to Eprex dosing frequencies of one dose/week, 3 doses per fortnight, and 2 doses/week. The supporting text referred to 'emerging clinical evidence' which 'supports a flexible range of dosing regimens'. The statement was not clarified in any way. Unfortunately only one of these dosing regimens (2 doses/week) was covered by the SPC and then only for a limited subset of patients on peritoneal dialysis. Mention of unlicensed dosing regimens was only permissible under the Code if it constituted legitimate exchange of scientific information; however, the item in question was clearly promotional and was clearly being used as such. A breach of Clause 3.2 of the Code was alleged.

RESPONSE

Ortho Biotech stated that this particular item again used the Valderrabano survey which demonstrated that the average maintenance dose for adult haemodialysis patients was within the specifics given within the SPC for Eprex, and also highlighted that within this survey 26% of these patients received epoetin on a once weekly basis, with 36% receiving twice weekly dosing and 38% receiving thrice weekly dosing. This information was presented in a clear, balanced and unambiguous manner as required by Clause 7.2 of the Code, and also as the total weekly dosing did not exceed those specific parameters of the SPC it did not contravene Clause 3.2 of the Code.

Within this piece additional evidence of different dosing regimens, was introduced under a point of 'emerging clinical evidence', again emphasising that these dosing regimens were not established in favour of one generally accepted view, and thus allowed legitimate debate and clinician choice on this issue.

PANEL RULING

The Panel noted the dosing regimens as stated in the Eprex SPC and referred to at point 1 above. The Panel noted that Valderrabano *et al* was a prospective six month follow-up observational survey on anaemia management. Both haemodialysis and peritoneal dialysis patients were included in the survey. Patients were enrolled into an investigation protocol and not studied at random. There was no difference in maintenance doses between iv and sc administration in haemodialysis patients at all dose levels. The maintenance dose administered to the total sample of patients enrolled was 107 ± 80.5 IU/kg/week at month 2 and 109.1 ± 85.2 IU/kg/week at month 6. The Panel noted that the original pie chart (adapted for the leavepiece) showed the distribution of number of sc Eprex injections during the maintenance phase, n = 6365; 25.7%, 36.4%, 37.4% and 0.5% of patients received either 1, 2, 3 or > 3 injections per week respectively during the maintenance phase. The iv chart showed that 11.1%, 22.6%, 65.6% and 0.7% of patients received 1, 2, 3 and > 3 injections per week respectively during the maintenance phase. The survey's authors stated that whether the frequency of administration of a given total weekly dose of epoetin played a significant role in achieving a desired haemoglobin concentration remained debatable, similar responses being reported with once or thrice weekly regimens. The European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure developed as a result of the survey referred to a subcutaneous dose 2 - 3 times a week during the initial administration phase.

The Panel noted that Kwan and Povey, presented as an abstract, was a multicentre open label study designed to evaluate the effects of varying the dose frequency of Eprex on haemoglobin levels in patients receiving continuous ambulatory peritoneal dialysis or haemodialysis. The study authors stated that the results suggested that the dosing frequency of sc Eprex in iron replete patients could be reduced to once a week or three times a fortnight without affecting their haematological response, absolute weekly Eprex dose or safety concerns. The reduction in dose frequency might confer advantages in terms of patient convenience, tolerability and healthcare costs.

The Panel noted the content and heading of the pages at issue. The heading to pages two and three referred

to the ESAM Survey; although the patient population examined was not described. The first bullet point referred to the average maintenance dose for haemodialysis patients. The second bullet point referred to a quarter of patients receiving (sc) one injection of Eprex per week. The third bullet point referred to the new strengths providing the option of fewer injections for more patients. The fourth bullet point referred to emerging clinical evidence supporting a flexible range of dosage regimens for epoetin alpha with total weekly dose remaining unchanged whether receiving once weekly, twice weekly or three times fortnightly injections. The subsequent bar chart referred to the dosage regimens at issue. The Panel considered that the patient population at issue was not made sufficiently clear. Some readers might assume from the first bullet point that the material referred to only haemodialysis patients. Equally the Panel noted that the type size, colour and font of each bullet point was identical; the first was not given undue prominence. The patient population in Valderrabano was not clearly described and the first bullet point merely referred to an average maintenance of 104.7 IU/kg/week rather than an average once weekly dose. The second bullet point referred to a weekly dose. Bearing in mind the visual prominence given to the pie chart and the bar chart which depicted a range of dosing regimens, a reader might assume that the leavepiece referred to all patient subgroups. The data applied to haemodialysis and peritoneal dialysis patients. The Panel noted that whilst it had no allegation on this point the claims would be considered by the reader within the context of the page as a whole.

The Panel noted the dosing regimens as stated in the SPC and set out at point 1 above in relation to each subgroup. The Panel noted the references to the twice and thrice weekly dosing regimen in the SPC and further noted its comments on a once weekly dose at point 1 above. The Panel noted that in relation to adult haemodialysis patients a thrice fortnightly dose was not inconsistent with a recommended total weekly dose of between 75 and 300 IU/kg.

The Panel noted that the 'emerging clinical evidence' claim appeared to relate to haemodialysis patients (ESAM) and patients receiving continuous ambulatory peritoneal dialysis (Kwan and Povey). It did not relate to all patient subgroups. The type of patient and whether the dose was correction or maintenance was not made clear. In some patient subgroups the SPC gave very definite dosing instructions, for example, adult peritoneal dialysis patients were to be dosed twice weekly, subcutaneously, and emerging clinical evidence would not be relevant as promotion must not be inconsistent with the SPC. Given the complexity of the dosing regimens and range of patient subgroups the Panel considered that the mention of once and twice weekly and thrice fortnightly dosing regimens in the leavepiece was misleading and thus inconsistent with the SPC; the emerging clinical evidence did not apply to all subgroups and in some patient subgroups, such as peritoneal dialysis patients, the dosing schedules in the leavepiece were not consistent with the SPC. A breach of Clause 3.2 was ruled.

3 Booklet entitled 'Treatment Guide for Renal Patients' (ref A42141 606439)

The heading on the opening page of the booklet referred to the treatment of anaemia in dialysis patients and patients with renal insufficiency not yet on dialysis.

Page eight of the booklet headed 'Dosage and Administration' discussed response/dose-dependency, pre-treatment checks, initial dose and administration and maintenance. The maintenance section read 'Once target Hb has been reached, the appropriate maintenance dosage can be given as one*, two or three injections per week.' The asterisk referred the reader to a footnote which read 'For adults on haemodialysis'.

COMPLAINT

Roche stated that the SPC for Eprex did not recommend one injection per week for any group of patients. Furthermore, the suggestion made that Eprex could be given twice weekly was only consistent with the SPC recommendations for adult patients on peritoneal dialysis, but no qualifying statement was made to this effect on page 8 or anywhere else in the document. Roche therefore alleged a breach of Clause 3.2 of the Code.

RESPONSE

Ortho Biotech stated that given the strength of its argument at points 1 and 2 it contended that it was not in breach of Clause 3.2, an asterisk being placed to clarify that different dosing regimens might exist at the discretion of the clinician, for adult patients on haemodialysis. This might also help patients understand that different dosing regimens existed in current clinical practice.

PANEL RULING

The Panel noted that the booklet referred to the treatment of anaemia in dialysis patients and in patients with renal insufficiency who were not yet on dialysis who would be given a maintenance dose either once, twice or three times a week. The Panel considered that its comments above at point 1 were relevant. In the Panel's view the once, twice or thrice weekly maintenance dosage regimen for adult and paediatric patients with renal insufficiency was not inconsistent with the SPC for this patient population. No frequency of dosing was given in the relevant section of the SPC. The Panel therefore ruled no breach of Clause 3.2.

4 Ortho Biotech Quiz

The first question read 'Which of the following Eprex dosage regimens can be used during the maintenance phase in adult haemodialysis. Please tick'. The answer options were once, twice or three times per week or 'all of the above'.

COMPLAINT

Roche stated that the only correct answer, consistent with the SPC, was 3 times per week. However,

during a telephone conversation between the companies' medical departments, Ortho Biotech confirmed that the answer judged to be correct by Ortho Biotech was 'all of the above'. Roche therefore alleged a fourth breach of Clause 3.2 of the Code.

RESPONSE

Ortho Biotech regretted that a cordial conversation with a colleague was taken out of context and used to support a complaint to the Authority. The Ortho Biotech medical director had been misquoted, and his contention during the discussion was that it was down to the individual clinician to decide on dosing regimens, as was reflected in clinical practice. Consequently any of the answers to that specific question would be technically correct provided the total weekly dose did not exceed the specific parameters within the SPC for Eprex. Ortho Biotech therefore contended that it was not in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel considered that its rulings at points 1 and 3 were relevant. The question identified the patient population as adults on haemodialysis. No breach of Clause 3.2 was ruled.

Complaint received **6 July 2001**

Case completed **25 October 2001**

CASE AUTH/1205/7/01

GLAXOSMITHKLINE v ASTRAZENECA

Promotion of Symbicort

GlaxoSmithKline complained about the promotion of Symbicort Turbohaler (budesonide/formoterol) for asthma by AstraZeneca. Budesonide was a corticosteroid and formoterol was a long-acting bronchodilator (ß$_2$-agonist). The summary of product characteristics (SPC) for Symbicort 200/6 Turbohaler stated that it delivered the same amount of budesonide and formoterol as the monoproducts, budesonide 160mcg per inhalation and formoterol 4.5mcg per inhalation. The recommended dose was 1-2 inhalations twice daily. When control of symptoms was achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbohaler given once daily. The product was also available as Symbicort 100/6. Symbicort Turbohaler was not intended for the initial management of asthma.

One of the following claims 'The way you look at asthma therapy could be about to change', 'It could change the way you look at asthma therapy' and 'This may change the way you look at asthma therapy' appeared in each of the items. GlaxoSmithKline alleged that they implied that Symbicort was a new class of therapy and very different to those currently available. This was an overstatement. Combination therapy of an inhaled steroid and long-acting ß$_2$-agonist had been available on the market for over two years. Therefore Symbicort was the second agent in this class and did not represent a 'new' class of therapy. GlaxoSmithKline acknowledged that with Symbicort, one was able to adjust the dose relative to patients' symptoms. This however was also not new as patients and clinicians had titrated dose in accordance with guidelines through using single inhaler devices for many years. This was neither a new concept nor one that would be seen as being 'new' in the management of asthma.

The Panel noted that according to its SPC Symbicort was indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta-agonist) was appropriate: in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists or in patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-agonists. The recommended dosage was 1-2 inhalations twice daily. The Panel noted AstraZeneca's submission that prior to Symbicort the only other available long-acting bronchodilator and inhaled steroid combination product licensed for maintenance of asthma was GlaxoSmithKline's Seretide. However the daily dose of Seretide was fixed and could not be titrated up or down without the need for a new strength of inhaler. Symbicort offered flexible dosing during maintenance treatment with one inhaler. The Panel also noted AstraZeneca's submission regarding the clinical relevance of the claims at issue. Nonetheless the Panel considered that the claims at issue were broad and implied a more radical and fundamental change than the introduction of adjustable maintenance therapy in one inhaler. The Panel considered the claims misleading and exaggerated in this regard. Breaches of the Code were ruled.

Upon appeal, the Appeal Board noted there was a difference between Symbicort and Seretide. Symbicort offered flexible dosing during maintenance treatment with one inhaler. The daily dose of Seretide was fixed and could not be titrated up or down without the need for a new strength of inhaler. The Appeal Board considered that the claims at issue were broad and would imply to the audience a more radical and fundamental change than the introduction of adjustable maintenance therapy in one inhaler. The constituent products

were not new, they had been and continued to be available in separate inhalers. The claims were misleading and exaggerated. The Appeal Board upheld the Panel's ruling of breaches of the Code.

The claim 'More effective at improving lung function than double the dose of budesonide in mild asthma*' appeared in a dose leavepiece, immediately above the phrase 'Symbicort 100/6mcg bd vs budesonide Turbohaler 200mcg bd'. The asterisk referred the reader to a footnote which read 'Defined as pre-study inhaled corticosteroid dose 200-500mcg/day'. The claim was referenced to Lalloo *et al* (2000). GlaxoSmithKline alleged that the clinical data in the study did not support this claim. The study measured morning PEF (peak expiratory flow) as the primary endpoint and evening PEF and asthma control as secondary endpoints. In the medical community FEV_1 was also considered to be a measure of lung function but this was not presented in this study. 'More effective' implied a clinically relevant change, as opposed to a statement such as 'statistically significant difference between treatments' which would imply that the claim was based on statistical results. In the Lalloo study, the difference in PEF between the treatment groups was <10L/min. It was commonly accepted that a minimal change or difference between treatments of 15L/min was needed before a clinical effect could be claimed. GlaxoSmithKline accepted that the differences between the treatment groups of 9.2L/min in the primary endpoint of mean morning PEF and 9.4L/min in mean evening PEF were statistically significant. However this difference was not clinically significant and therefore did not support the statement of 'more effective at improving lung function'. AstraZeneca had responded that other markers such as symptom scores, which showed significant differences, supported the claim. GlaxoSmithKline considered that the claim was very specific in stating lung function and that this would be interpreted by health professionals as clinically significant changes in measures of lung function such as PEF and FEV1. GlaxoSmithKline alleged that the claim was not supported by clinical improvement.

The Panel noted that the Symbicort SPC stated that in 'clinical trials the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In a twelve week study the effect on lung function of Symbicort Turbohaler was equal to that of the free combination of budesonide and formoterol and exceeded that of budesonide alone'. No details were given about the doses used. Lalloo *et al* was a 12 week, double blind, randomized parallel group study. The change in PEF was 16.5L/min for Symbicort and 7.3L/min for budesonide (p=0.002). The change in evening PEF was 13.6L/min for Symbicort and 4.2L/min for budesonide (p<0.001). Symbicort increased the time to first mild exacerbation (p=0.02) and decreased relative risk of mild exacerbations by 26% (p=0.02) compared to inhaled corticosteroids alone. Severe exacerbations were too few to detect differences between treatments in this mild population. Symptom free days (days with no asthma symptoms and no night time awakenings) were 55.3% for Symbicort and 48.9% for budesonide (p=0.007). The authors concluded that Symbicort reduced the risk of mild exacerbations and improved asthma control to a significantly greater degree than double the dose of inhaled corticosteroid alone and that Symbicort in a single inhaler was clinically superior to increasing the dose of inhaled corticosteroids in adult patients who were not adequately controlled on low dose inhaled corticosteroid alone.

On balance the Panel considered that the claim was misleading. It gave the impression that there was a clinical difference between the products in relation to lung function. There was a statistically significant difference between the products in relation to PEF in the Lalloo study but the Panel was not convinced on the evidence before it that this alone amounted to a clinical difference in improving lung function. A breach of the Code was ruled.

GlaxoSmithKline stated that the prescribing information for Symbicort on all the items at issue gave no indication of the pack size for either presentation. Previously AstraZeneca's Turbohalers contained 50, 60, 100 or 200 doses. The Symbicort Turbohaler was a significant departure from this with both strengths containing 120 doses. In addition, non-marketed samples contained 60 doses. Clinicians might well therefore be aware of two presentations of Symbicort of different number of doses, 60 and 120. The Panel noted that the Symbicort prescribing information stated that the basic NHS price for Symbicort 100/6 Turbohaler was £33 and Symbicort 200/6 Turbohaler was £38. Both Symbicort 200/6 and 100/6 came in a pack size of 120 doses, no other pack size being marketed in the UK. AstraZeneca had stated that health professionals should always consult the SPC before prescribing but the cost would not appear in the SPC. The Panel considered that the failure to state the number of doses was such that the cost of a specified package or a specified quantity or a recommended daily dose of the medicine had not been stated as required by the Code and a breach was ruled. Upon appeal, the Appeal Board upheld the Panel's ruling of a breach of the Code.

The prescribing information for each item stated 'Adolescents/children: Not recommended'. GlaxoSmithKline noted that the SPC stated 'Adolescents (under 17 years) and Children: Symbicort Turbohaler is not recommended in this group of patients'. The inclusion of the precise limitation in the SPC was important as in the rest of the EU Symbicort was currently licensed for patients over 12 years. GlaxoSmithKline alleged that this omission of the specific age restriction was potentially misleading, not consistent with the SPC and would potentially result in children of less than 17 years of age being treated. The Panel noted the dosage requirement in the SPC and further noted the difference in the European and UK licences in this regard and GlaxoSmithKline's submission that most health professionals were aware that children over the age of 12 were prescribed adult dosages of medicinal products. Nonetheless the Panel considered that the prescribing information made it

sufficiently clear that neither children nor adolescents ought to be prescribed the product and did not consider that it was likely to result in confusion and misunderstanding as alleged. The Panel considered that the prescribing information was a succinct statement of the information in the SPC relating to, *inter alia*, dosage as required. No breach of the Code was ruled.

A bar chart in a Symbicort cost leavepiece compared the monthly cost range (30 days) of branded and generic maintenance treatments with reference to their minimum to maximum licensed doses. Price ranges of £9.50 - £38 and £8.25 - £33 were depicted for Symbicort 200/6 and 100/6 respectively. Price ranges for eight other branded and generic products were also shown. The heading in the top left hand corner read 'Symbicort is a reasonably priced combination for maintenance treatment of adult asthma'. GlaxoSmithKline stated that the table presented the minimum and maximum licensed doses of inhaled steroids and combinations of inhaled steroids and long-acting ß$_2$ agonists, including both Symbicort and Seretide. The Code stated that price comparisons should only be made on the basis of equivalent dosage requirements for the same indication. There was no data supporting that the maximum and minimum doses of the products detailed were equivalent. Therefore the comparison was only on cost and not cost of clinical equivalent treatment options. GlaxoSmithKline alleged that this item was misleading and not capable of substantiation.

The Panel noted that the leavepiece was headed 'cost' and discussed the cost of Symbicort; there was no discussion of clinical issues. AstraZeneca had submitted that the comparison was only on cost and the chart's purpose was to highlight where the price of Symbicort across the full dose range sat in relation to the full dose range of alternative medication for maintenance treatment. The heading to the chart 'Monthly cost (30 days) of branded and generic maintenance treatments' was clear and unambiguous. The Panel considered that the content and purpose of the leavepiece was such that the basis of the comparison was clear; cost range in relation to maintenance treatment. There was no express or implied clinical comparison. The chart was neither misleading nor incapable of substantiation as alleged. The Panel ruled no breach of the Code. Upon appeal, the Appeal Board acknowledged that the information presented was accurate. It was nonetheless possible for accurate information to give a misleading impression. The Appeal Board was concerned that the bar chart implied that the products listed had similar efficacy. The impression was that it was less expensive to use Symbicort than the majority of the other products listed. This was not necessarily so. The Appeal Board decided that the chart was misleading and a breach of the Code was ruled. The Appeal Board considered that the cost ranges were accurate and upheld the Panel's ruling of no breach in that respect.

The statement 'Each inhaler contains either 60 or 120 doses' appeared in a Drug & Therapeutics Committee New Drugs Request booklet. GlaxoSmithKline had been informed that the 60 dose Turbohaler was not marketed in the UK. GlaxoSmithKline alleged that this statement was misleading. The Panel noted that reference to the 60 dose presentation appeared in the SPC which stated 'Each inhaler contains 60 doses or 120 doses' and which concluded 'Not all pack sizes may be marketed'. The Panel noted that the 60 dose pack was available in the UK as a sample only. The Panel considered, as acknowledged by AstraZeneca, that this had not been made sufficiently clear in the booklet in question. A breach of the Code was ruled.

The claim 'Symbicort versus double dose inhaled steroid monotherapy. In mild asthma Symbicort 100/6 has been shown to be significantly more effective than double dose inhaled budesonide (200mcg bd) alone, in increasing morning PEF ($p=0.002$), evening PEF ($p<0.001$) and symptom free days ($p=0.007$) over a 12 week period' appeared in the Drug & Therapeutics Committee New Drugs Request booklet, in a section entitled 'What are the advantages over existing formulary drugs?'. GlaxoSmithKline noted that this claim was referenced to Lalloo *et al*. For the reasons given above the claim as stated, which specifically referred to PEF, was not supported by clinically significant improvement. The Panel noted that the claim at issue was different to that considered above which only referred to Symbicort's benefits with regard to improving lung function compared with double the dose of budesonide. The Panel considered that the claim now at issue was more specific and hence was a fair reflection of the findings of Lalloo *et al*. No breach of the Code was ruled.

The claim 'Symbicort is an effective maintenance treatment, resulting in an improvement in both morning and evening PEF and asthma symptoms' appeared in the Drug & Therapeutics Committee New Drug Request booklet in a section headed 'Does this drug control symptoms effectively?'. GlaxoSmithKline noted that this claim was referenced to Lalloo *et al*. For the reasons stated above GlaxoSmithKline considered that the claim as stated, which specifically referred to PEF, was not supported by clinical improvement. The Panel noted that the claim at issue was different to that considered above, 'more effective at improving lung function than double the dose of budesonide in mild asthma'. The claim at issue was referenced not only to Lalloo *et al* but also Zetterström *et al* (2000). The Panel noted that Zetterström *et al* was a 12 week double blind, randomized, parallel group study which compared the efficacy and safety of Symbicort with the equivalent doses of budesonide administered either alone or with formoterol in asthmatics not adequately controlled on inhaled corticosteroids alone. The primary efficacy variable was morning PEF. The study concluded that PEF increased by 36L/min in the Symbicort group and by 32L/min in the budesonide plus formeterol group; $p<0.001$ versus the budesonide group for both groups. There were no significant differences versus Symbicort and budesonide plus formoterol in this parameter. Both the Symbicort and budesonide plus

formoterol groups increased evening PEF (p<0.001) as against the budesonide only group. The authors further concluded that Symbicort reduced the risk of mild exacerbations and improved asthma control in patients not adequately controlled on inhaled corticosteroids alone. The claim at issue did not refer to lung function; it referred to morning and evening PEF and asthma symptoms. The Panel considered that on balance, given the statement in the SPC, Lalloo *et al* and Zetterström *et al*, the claim was not misleading as alleged. No breach of the Code was ruled.

The claim 'Comparing like with like, does this drug cost more per patient than existing treatment, cost the same as existing treatment, cost less than existing treatment or not compare as there are no existing treatments?', and a table headed 'Typical monthly (30 day) costs for maintenance treatment', appeared in the Drug & Therapeutics Committee New Drug Request booklet in a two page section headed 'Financial Implications'. The first page discussed the costs of Symbicort comparative to current treatment options and a table depicted the community and hospital costs of Symbicort compared to six other combination asthma medications currently available. The claim at issue appeared on the opposite page above a table which set out the typical monthly (30 day) cost range for maintenance treatment with reference to their minimum and maximum licensed doses (mcg) of Symbicort and eight other maintenance treatments. GlaxoSmithKline stated that for reasons stated above, but especially because the statement was made that like was being compared with like, the claim was misleading, and could not be substantiated. The Panel considered that this cost comparison was different to that considered above. The Panel considered that the purpose of the booklet was to compare Symbicort with other products. Whilst the table at issue was clearly labelled 'Typical monthly (30 day) costs for maintenance treatment', the section was introduced by the phrase 'Comparing like with like, …' which the Panel considered implied more than a comparison based upon cost alone. It implied that other variables such as dosage regimens and efficacy had been taken into account and that there was comparative evidence. The Panel noted that limited comparative evidence was presented in the booklet but not in relation to each medicine listed. The Panel considered the page misleading and not capable of substantiation. Breaches of the Code were ruled.

No breaches of the Code were ruled in relation to the claims 'Summary …. In adult patients with mild asthma Symbicort has been shown to be significantly more effective than double the dose of inhaled budesonide in improving morning and evening peak expiratory flow (PEF) …' and 'A clinical trial of 467 mild asthmatics, not optimally controlled on inhaled corticosteroids alone (mean dose 390mcg/day) showed Symbicort (100/6mcg bd) to be significantly more effective than double dose inhaled budesonide (200mcg bd) alone, in increasing morning PEF, evening PEF and symptom free days over a 12 week period', which appeared in the Symbicort Product Profile and which were similar to claims considered above.

GlaxoSmithKline complained about the promotion of Symbicort Turbohaler (budesonide/formoterol) by AstraZeneca UK Limited. Budesonide was a corticosteroid and formoterol was a long-acting bronchodilator ($ß_2$-agonist). Symbicort was indicated for the treatment of asthma. A number of promotional items were at issue.

A Symbicort dose leavepiece (ref SYMB 01 8425)
B Symbicort cost leavepiece (ref SYMB 01 8424)
C Symbicort journal wrapper (ref SYMB 01 8615)
D Symbicort leavepiece (ref SYMB 01 8427)
E Symbicort leavepiece (ref SYMB 01 8495C)
F 'Dear Pharmacist' letter (ref SYMB 01 8597A)
G 'Dear Doctor' letter (ref SYMB 01 8595A)
H Pop-up pen holder (ref SYMB 01 8426)
I Symbicort. A new maintenance treatment for adult asthma leavepiece (ref SYMB 01 8490)
J Symbicort Drug & Therapeutics Committee New Drug Request booklet (ref SYM018719)
K Symbicort product profile (ref SYM018153)

The summary of product characteristics (SPC) for Symbicort 200/6 Turbohaler stated that it delivered the same amount of budesonide and formoterol as the monoproducts, budesonide 160mcg per inhalation and formoterol 4.5mcg per inhalation. The recommended dose was 1-2 inhalations twice daily. When control of symptoms was achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbohaler given once daily. The product was also available as Symbicort 100/6. Symbicort Turbohaler was not intended for the initial management of asthma.

GlaxoSmithKline marketed Seretide, a combination of a corticosteroid (fluticasone) and a long-acting bronchodilator (salmeterol).

1 Claims 'The way you look at asthma therapy could be about to change'
'It could change the way you look at asthma therapy'
'This may change the way you look at asthma therapy'

One or another of these claims appeared in each of the eight items A - H.

COMPLAINT

GlaxoSmithKline alleged that these claims implied that Symbicort was a new class of therapy and very different to those currently available. This was an overstatement. Combination therapy of an inhaled steroid and long-acting $ß_2$ agonist had been available on the market for over 2 years. Therefore Symbicort was the second agent in this class and did not represent a 'new' class of therapy.

GlaxoSmithKline acknowledged that with Symbicort, one was able to adjust the dose relative to patients' symptoms. This however was also not new as patients and clinicians had titrated dose in accordance with guidelines through using single inhaler devices for many years. This was neither a new concept nor

one that would be seen as being 'new' in the management of patients with asthma.

AstraZeneca had responded to its concerns by stating that Symbicort had a number of properties which not only differentiated it from other maintenance therapies but collectively gave it a clear advantage. These properties included the ability to adjust the daily maintenance dose in one single inhaler; a rapid onset of bronchodilation; the efficacy profile; the new improved Turbohaler in which Symbicort was presented.

GlaxoSmithKline commented on these points in turn.

GlaxoSmithKline considered that the ability to adjust the daily maintenance dose in one single inhaler had been present for many years both with the use of corticosteroids and with long-acting ß$_2$ agonists for maintenance therapy.

Seretide also had a rapid onset of bronchodilation, having an effect which was clinically relevant within 30 minutes. Although Symbicort had a more rapid onset of action, GlaxoSmithKline did not consider this was of significant clinical relevance in maintenance therapy where treatments with a greater than 12 hours duration of action were licensed to be taken on a regular once or twice daily basis.

GlaxoSmithKline was unaware of any data which showed Symbicort to have an efficacy profile significantly different from Seretide. The only comparative data between Seretide and Symbicort compared bronchodilation and showed Symbicort to have a more rapid onset of action, achieving a greater increase in FEV_1 at 3 hours. Again this was of questionable clinical relevance in a therapy licensed for regular use.

GlaxoSmithKline was unaware of any data showing that the 'new improved Turbohaler' had any clinical, as opposed to technological, advantages over the 'old' Turbohaler or indeed the Accuhaler. The only differences of which it was aware between the 'old' and 'new' Turbohaler was a new shape of mouthpiece and a dose indicator which indicated doses used in units of 20. GlaxoSmithKline understood there were differences in dose delivered, but these were not different from the comparative data between the 'old' Turbohaler and the Accuhaler.

The Symbicort product profile document (SYM018153) stated that '*in vitro* studies have shown Symbicort to deliver equivalent fine particle fractions with existing products', and that 'In the clinical situation there are no significant differences between Symbicort and concomitant budesonide plus eformoterol'.

GlaxoSmithKline accepted that the dose of Symbicort could be adjusted within the one inhaler and that the Seretide dose was adjusted by prescribing a different strength, but GlaxoSmithKline did not consider that this difference justified the strength of the claim in question.

Although the claim was qualified by the use of the word 'could', GlaxoSmithKline believed that it was an overstatement of what Symbicort offered to the management of patients with asthma both in being different to currently available maintenance therapies and the clinical relevance of this possible difference.

GlaxoSmithKline therefore alleged that the claims were in breach of Clauses 7.2 and 7.10 of the Code.

RESPONSE

AstraZeneca stated that the burden of asthma on patients, carers and on healthcare resources continued to be a problem. A review by Barnes *et al* (1996) stated that 'Underuse of prescribed therapy, which includes poor compliance, significantly contributes towards the poor control of asthma'. Within the remit of asthma management, a large number of medicines had been available. Clearly, for various reasons, they had not adequately addressed the needs of the patient. AstraZeneca submitted that Symbicort was another therapy to be used within overall asthma management, which through its different dosing options, provided a real alternative to further meet patients' needs.

Asthma was a variable disease which necessitated a patient to increase their daily maintenance dose of medication when additional control was required. Likewise a patient might need to reduce their number of doses once control had been achieved. In accordance with current British Thoracic Society (BTS) guidelines, asthma treatment should be matched to patients' symptoms. Such needs for maintenance therapy could be met in a single inhaler by Symbicort in contrast to alternative combination product inhalers.

Symbicort was a new product indicated for the maintenance treatment of asthma where a combination of inhaled steroids and long-acting bronchodilators was appropriate.

The product licence allowed the daily maintenance dose of Symbicort to be adjusted from 1-4 inhalations per day using the same strength inhaler.

Before Symbicort was available, the only other available long-acting bronchodilator and inhaled steroid combination product indicated for the maintenance of asthma was Seretide. However the daily dose for each presentation of Seretide was fixed and could not be titrated up or down without the need for a new strength of inhaler. Patients therefore requiring increased symptom control during maintenance treatment would need a higher strength of medication to be prescribed. In marked contrast, Symbicort offered flexible dosing during maintenance treatment in just one single inhaler.

AstraZeneca acknowledged that long-acting bronchodilators and inhaled steroids had been available for many years; it was not implying that Symbicort, being a combination product of the two, represented a 'new' class of asthma medicine. However the concept of having the flexibility to increase and decrease daily maintenance dosage within one inhaler was a novel one. AstraZeneca believed this could change the way asthma therapy was currently perceived as this new concept carried benefits for both patients and clinicians.

AstraZeneca therefore submitted the claims were both valid and justifiable.

In addition AstraZeneca believed the claims were of clinical relevance. A comparative study had demonstrated that Symbicort had a significantly faster onset of bronchodilation post inhalation (1-3 minutes) than Seretide (30 minutes). The study by Palmqvist *et al* (2001) showed that both 1 and 2 inhalations of Symbicort 200/6mcg significantly improved lung function (percentage increase in FEV1) compared with Seretide 250/50 at 3 and 15 minutes and also over the whole 3 hour study period ($p<0.001$).

AstraZeneca stated that such data was highly suggestive of the clinical relevance of Symbicort from the patient's perspective when additional control was required if breakthrough symptoms arose. A recognised feature of current asthma management was poor compliance with inhaled steroids and this had been extensively studied. Chambers *et al* (1999) found the most common reason for not using inhaled steroids daily was the perception that asthma was an illness of 'wellness intercepted with exacerbations'. AstraZeneca submitted that during these periods of exacerbations/symptom breakthrough, patients needed to feel some benefit from increasing their dose of Symbicort. By increasing the number of doses as part of maintenance treatment, a patient would experience a fast onset of bronchodilation. This might provide valuable reassurance to the patient in the form of perceptible clinical benefit as part of their regular asthma therapy.

AstraZeneca therefore did not agree that the claims constituted an overstatement and did not accept the alleged breach of Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted that according to its SPC Symbicort was indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta-agonist) was appropriate: in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting $beta_2$-agonists or in patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$-agonists. The recommended dosage was 1-2 inhalations twice daily. The Panel noted AstraZeneca's submission that prior to Symbicort the only other available long-acting bronchodilator and inhaled steroid combination product licensed for maintenance of asthma was Seretide. However the daily dose of Seretide was fixed and could not be titrated up or down without the need for a new strength of inhaler. Symbicort offered flexible dosing during maintenance treatment with one inhaler. The Panel also noted AstraZeneca's submission regarding the clinical relevance of the claims at issue. Nonetheless the Panel considered that the claims at issue were broad and implied a more radical and fundamental change than the introduction of adjustable maintenance therapy in one inhaler. The Panel considered the claims misleading and exaggerated in this regard. The Panel ruled breaches of Clauses 7.2 and 7.10 of the Code.

APPEAL BY ASTRAZENECA

AstraZeneca disagreed with the Panel's rulings for the following reasons: the wording was specific with clear intended messages for the reader; there were relevant well-defined standards and issues within current UK asthma management (guidelines, compliance and self-management plans) which related to Symbicort; current therapies had limitations especially during worsening of asthma; there was a clear clinical case for adding a long-acting bronchodilator and delivering this within a combination inhaler; and Symbicort was a combination inhaler that provided adjustable maintenance treatment. This was a significant development for patients practising asthma self-management using the same single inhaler to step up and step down their treatment.

Symbicort was a new product indicated for the maintenance treatment of adult asthma where a combination of inhaled steroid and long-acting bronchodilator was appropriate. The licence recommended a daily maintenance dose of Symbicort to be adjusted from 1-4 inhalations per day using the same strength inhaler.

All three claims contained the words 'could' or 'may' in terms of changing the way asthma therapy was perceived on the introduction of Symbicort. Using the terms 'could' or 'may' did not render the claims as definitive. The impression therefore given was that Symbicort perhaps or may possibly change the way he or she viewed asthma treatment rather than categorically and absolutely.

AstraZeneca stated that the introduction of any new medicine into a well-established therapy area, such as asthma, would inevitably present itself to clinicians as an alternative treatment option if characteristics of the new medicine offered an advantage over existing products. This concept was true in relation to the introduction of Symbicort, which represented a development versus current asthma maintenance treatments for the reasons detailed below. Symbicort therefore offered clinicians a genuine alternative for consideration and consequently had the potential to alter prescribing decisions.

The claims conveyed the message that the way in which clinicians looked at asthma therapy might change, not that asthma therapy *per se* would change. By claiming Symbicort could possibly 'change' clinicians' views on asthma therapy did not infer that such views would necessarily lead to the prescription of Symbicort. Rather that Symbicort was an advancement over alternative asthma treatments and as with all other advances in medicine was likely to modify and alter current practice and thinking.

The following sections outlined AstraZeneca's submission that within the context of current UK asthma management, Symbicort was an important new development providing significant benefits for both clinician and patient.

Asthma was a variable disease with this being recognised in asthma guidelines in relation to its clinical management. Furthermore, literature targeted at patients placed emphasis on the variability of asthma.

Good clinical practice within asthma management in the UK was guided predominantly by the BTS

guidelines. Key points emerging from these guidelines, relevant to the appeal, were: firstly, providing therapy that controlled the symptoms at the minimum dose. This was particularly pertinent in the case of inhaled steroids. And secondly, management of worsening asthma was underlined by increasing the dose of inhaled steroids. Equally important was the manoeuvre to step down the dose once symptoms were under control. The BTS guidelines stated 'stepping down of inhaled steroids once asthma has been controlled is emphasised in current guidelines but is often not implemented, with the result that many well controlled patients are overtreated with inhaled steroids'.

These features were echoed by the Global Initiative in Asthma Management (GINA) guidelines. In addition, these endorsed the need to provide treatment that responded to a patient's level of symptoms.

Clinical management of all chronic conditions, including asthma, was faced with the ongoing problem of poor patient compliance. Individual patients were characterised by their own set of interrelated factors that reduced compliance; for example, impractical treatment regimen, cost of medication, misunderstanding of management plan. The objective measurement of compliance was therefore extremely difficult.

Any therapy that addressed one/some of the underlying cause(s) could reasonably be regarded as making a positive contribution towards improving patient compliance. As discussed later, Symbicort assisted with issues such as fewer inhalers and simpler treatment that remained simple during worsening of asthma.

Providing therapeutic interventions within nationally/internationally agreed guidelines was not all that was required for effective asthma management. There was a wealth of data that supported the need for delivery within patient centred self-management of asthma. At the centre of this growing initiative was the recognition that asthma was a clinically variable disease that demanded therapy to be changed to meet the varying needs of the patient.

Patient involvement appeared to be the key. One survey showed that 68% of respondents would feel comfortable being able to adjust the dose of their inhaler without having to refer to a health professional. This willingness of patients to be actively involved in managing their own asthma might improve the level of compliance.

Given the underlying variability of asthma, a critical period from the patient's perspective was when asthma symptoms increased. Here, the limitations of current therapies were particularly apparent. The role for Symbicort within the context of good clinical practice ('current asthma management') was not only significant but also very different from other therapies available.

Both the BTS and GINA guidelines emphasised that the desired goals/outcomes of therapy included the reduction of symptoms, no limitation of activities and a minimal need for reliever bronchodilators. Despite these clear goals, which translated into realistic needs for the patient, current therapy was clearly failing to meet these needs.

There were features within specific therapy options, as highlighted below, that might explain some of the treatment failures.

Inhaled steroids

Inhaled steroids, although recognised within the medical community as the mainstay of asthma maintenance therapy, were not so well perceived by patients. Compliance with steroids had been demonstrated to be very low. There was a widespread 'steroid phobia' amongst patients that reduced compliance. The practice of increasing inhaled steroids was well recognised and endorsed in the BTS and GINA guidelines. With respect to exacerbations/worsening asthma, patients derived no immediate benefit in symptoms from inhaled steroids. Therefore, they failed to fully comply with the advice of increasing their inhaled steroids during these periods. Stepping up and down through personal asthma management plans (set by the clinician) was an attractive offering for the patient and a feature of good clinical practice.

Long-acting bronchodilators

Both the currently available long-acting bronchodilators (eformoterol and salmeterol) were prescribed as regular maintenance therapy. Eformoterol, in the form of Oxis, could however be prescribed in additional doses, on top of the maintenance dose for 2 days, during the worsening of asthma. This licence was of particular importance to Symbicort because it highlighted the key differentiating pharmacological profile of eformoterol. Eformoterol had been shown to have unique dose response characteristics over a wide range of clinically relevant doses. This supported the clinical benefit of greater bronchodilation at increased doses within the licensed dose range (6-72mcg per day). The onset of action of eformoterol was similar to the short acting relievers (1-3 minutes). From the point of view of patients; during worsening asthma they could take extra doses within the licence from which they would feel a rapid onset of action. These important features were in contrast to salmeterol which did not have the same licence for additional dosing during worsening asthma and a slower onset of bronchodilatory action (20 minutes). These factors were particularly relevant when comparing the clinical use of Symbicort and Seretide during worsening asthma.

The rationale for combination therapy

The clinical case for adding a long-acting bronchodilator

The clinical benefit of adding in a long-acting bronchodilator to an inhaled corticosteroid treatment regimen had been clearly shown in a number of large prospective studies. These studies conclusively demonstrated in a range of clinical outcomes that the addition of a long-acting bronchodilator to an inhaled steroid was clinically superior to increasing the dose of inhaled corticosteroid alone in a target asthmatic

population with a range of disease severity. The results were reflected in the BTS guidelines. The use of a long-acting bronchodilator as an alternative to increasing the dose of inhaled steroid was included at Step 3 in the treatment hierarchy.

Although the clinical case for long-acting bronchodilators was clear, the difficulty remained of patients needing to use multiple separate inhaler devices. This could confuse patients with the potential to adversely affect treatment compliance and hence clinical outcomes. In addition patients were reticent to accept an additional inhaler on account of further adding to prescription charges.

The issue of additional inhaler devices had been approached by the introduction in 1999 of the first combination inhaler device containing both an inhaled steroid and long-acting bronchodilator; Seretide. This combination therapy offered a more convenient way to deliver efficacious asthma treatment using a single inhaler. It did however have limitations in terms of meeting the treatment needs of a variable chronic disease. All the Seretide presentations could only be given as a fixed twice-daily dose. The licence for Seretide did not afford any flexibility in dosing; the dose of salmeterol could not be varied across the range of presentations and all presentations had to be administered twice daily. Therefore the dose of inhaled steroid could not be titrated up or down without the need to prescribe a new strength of inhaler.

Seretide and Symbicort during worsening of asthma

Within the context of self-management, during worsening of asthma the only option for patients taking a particular strength of Seretide was a new strength of Seretide and/or additional steroid inhaler. This was associated with an additional prescription cost for the patient.

The BTS guidelines highlighted as good clinical practice the importance of stepping down the dose of inhaled steroid once asthma was controlled. The same limitations would again apply to Seretide as with stepping up treatment.

Recent patient surveys highlighted the concern that the majority of asthma patients harboured on the potential serious side effects of chronic high dose inhaled steroid use. These concerns could have implications for treatment compliance. Simpler stepping down would therefore be a beneficial feature for Symbicort.

Development in combination therapy provided by Symbicort

Symbicort was the second combination of a long-acting bronchodilator and inhaled steroid available for clinical use and therefore not a new class of therapy.

The clinical efficacy of Symbicort was supported by a study of Zetterstrom (2001) which showed that Symbicort was more effective than the equivalent dose of inhaled steroid alone in terms of improvements in lung function and asthma control. Another study, Lalloo (2000), showed that low dose Symbicort was more effective than a higher dose of inhaled steroid alone in terms of improving symptoms, exacerbation rates and lung function.

Symbicort was very different to currently available Seretide and conferred benefits; the ability to adjust the dose of Symbicort from 1 to 4 inhalations per day relative to patients' symptoms and worsening of asthma using the same inhaler was a feature for combination long-acting bronchodilator and inhaled corticosteroid therapy that was unique to Symbicort; the unique potential for once daily combination therapy; simpler to encourage and implement patient-centred management plans as no need to have a new prescription.

Onset of bronchodilation

Symbicort also had a fast onset of bronchodilation that was superior to Seretide and similar to short-acting bronchodilators such as salbutamol. GlaxoSmithKline disputed the clinical relevance of a fast onset of action of a maintenance treatment. AstraZeneca maintained that this was a clinically relevant feature. A patient experiencing breakthrough symptoms would need to take additional therapy to re-establish control. In the case of Symbicort, it was possible to increase the dose within the licensed range using the same inhaler. The fast onset of bronchodilation would provide valuable reassurance to the patient in terms of symptom improvement. The difference in onset of bronchodilation was clinically significant between Symbicort and Seretide (1-3 minutes compared to 20-30 minutes) and important in the context of a patient increasing adjustable maintenance therapy during worsening of asthma. This was particularly relevant when stepping up from once daily therapy.

Summary

AstraZeneca stated that Symbicort provided clinicians with an alternative treatment option for asthma that, owing to its differential characteristics, had the potential to alter current perception and change the way they saw asthma therapy. The claims were therefore not broad but specific in their intended message.

Symbicort was relevant within good current asthma management, the principles of which were set out in asthma guidelines and met the needs of patients.

Symbicort was a development over other combination inhalers for the maintenance treatment of asthma in that patients could easily adjust the dose according to fluctuating symptoms using the same inhaler. This unique feature was a useful treatment option to assist and encourage the increasing focus on patient-centred management plans. It was a significant and clinically relevant feature because Seretide could only be given as a fixed daily dose and not be titrated according to symptoms without the inconvenience of a new strength of inhaler being prescribed. The claims were therefore not misleading and exaggerated.

AstraZeneca provided a statement from an independent health professional endorsing the claims and stated that further statements would follow.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline considered that the claims were an overstatement of the benefits for Symbicort and broad in their scope. This was centred on the fact that the claims implied that Symbicort could offer a change to clinicians relative to asthma therapy. This was too broad a claim. Other asthma therapies available prior to the launch of Symbicort shared some or all of the features that AstraZeneca implied were particular to Symbicort. GlaxoSmithKline therefore considered that the change Symbicort might offer was not as significant as claimed and did not justify the breadth of the claims.

GlaxoSmithKline stated that in the appeal AstraZeneca had introduced new data and evidence, which had not previously been considered, either in the inter-company discussions prior to this complaint, or by the Panel. The new data supported a potential for Symbicort to offer some benefits. There were no data available evaluating whether these benefits were real and clinically relevant in the management of asthma.

Inhaled steroids had been available for many years as a maintenance therapy in a single inhaler, that asthma patients could titrate in response to asthma symptoms. To address important clinical issues in relation to asthma management and suggest special benefit, it might therefore be important to show not just that the therapy had potentially beneficial features, but that it had a clinical impact in addressing these issues where other therapies were considered to have been 'unsuccessful'.

The data AstraZeneca provided indicated that the potential benefits Symbicort might offer might not be as great or as impactful as implied in improving asthma management. This was highlighted by the fact that for an adjustable maintenance therapy to be of significant clinical benefit, and particularly succeed where other therapies such as inhaled corticosteroids had not, patients needed to be able to perceive their asthma control relative to their asthma symptoms, to adjust their asthma medication without medical consultation and have asthma management plans encouraging them to step down therapy once asthma symptoms had improved. Data provided in the form of the UK AIRE study, a survey of asthma patients, the AIR study (Asthma in real life) and a publication on patient preferences for autonomy in decision making in managing asthma, clearly showed that this 'environment' and these prerequisites were not widespread within the asthma community.

GlaxoSmithKline disagreed with AstraZeneca's view that the claims were specific with clear intended messages for the reader. The claims were not specific. Use of the words 'asthma therapy' implied that Symbicort could change the way one would regard all asthma treatments, not just combination therapy. The ability to adjust the daily maintenance dose in one single inhaler was not new. The use of the broad statement 'asthma therapy' brought into consideration therapies such as inhaled corticosteroids and long-acting bronchodilators, which had been available as asthma therapies one could titrate according to symptoms, for many years. The concept of adjusting a dose of therapy in response to symptoms was also not a new concept and was not only well described, but specifically recommended in asthma guidelines, including the BTS guidelines and the GINA guidelines. The fact that this was not specific to Symbicort, and therefore could not be considered a new concept, was in fact highlighted by AstraZeneca's defence, in citing the wording of the guidelines which was specific to inhaled steroids, under the clinical guidelines section of the appeal.

There were well-defined standards and issues within UK asthma management for the titration of asthma therapies in response to symptoms. The BTS guidelines and the GINA guidelines recommended adjusting a dose of therapy in response to symptoms. However it was important to note that these guidelines did not refer to Symbicort, or to combination therapy. These recommendations were for the use of all asthma therapies, but were principally based on inhaled steroid therapy.

GlaxoSmithKline stated that AstraZeneca's view that current therapies had limitations, especially during worsening of asthma, was a very broad statement. Not all therapies had limitations. Symbicort was not the only medication available that one was able to titrate according to asthma symptoms. In general asthma which was worsening was usually recommended to be managed with the addition of oral steroids to the current or increased dose of the patient's asthma therapy. GlaxoSmithKline agreed that there was a clear case for adding a long-acting bronchodilator and delivering this within a combination inhaler. Symbicort was however not the first medicine in a new class. Seretide had been available as a combination therapy for over 2 years.

GlaxoSmithKline agreed that with Symbicort, one could step up or step down treatment. It did not agree that Symbicort was the only combination to provide adjustable maintenance treatment, or that this was a significant new development. Seretide was available as a number of strengths and therefore a clinician could adjust the dose of maintenance therapy, in relation to symptoms. Although Symbicort could do this with a single inhaler, this again was not a new concept. This was also true for therapies such as inhaled corticosteroids and long-acting bronchodilators, which had been available as asthma therapies one could titrate according to symptoms, for many years.

GlaxoSmithKline's disagreement was not whether one could adjust the dose of Symbicort, in relation to patient symptoms, using a single inhaler, but that this was not something that was a new concept to the clinician. The broad use of the phrase 'the way you look at asthma therapy could be about to change' (emphasis added) brought these other asthma therapies into consideration. GlaxoSmithKline considered that this was an overstatement of Symbicort's benefit.

AstraZeneca stated that the use of the terms 'could' and 'may' did not render the claims as definitive. GlaxoSmithKline considered that it was the use of the phrase 'asthma therapy' which rendered the claim an overstatement as Symbicort did not offer a unique

benefit over all other asthma therapies and therefore GlaxoSmithKline did not consider that Symbicort offered a new or significant change.

GlaxoSmithKline agreed that asthma was a variable disease.

GlaxoSmithKline agreed and endorsed the fundamental principles of the BTS guidelines. These recommended the titration of inhaled steroids, providing therapy that controlled the symptoms at the minimum dose. The guidelines were based on inhaled steroids. Symbicort therefore, although allowing one to adjust the dose of medicine, did not provide a unique characteristic that other 'asthma therapies' did not offer.

GlaxoSmithKline agreed with the need to improve compliance with asthma therapy. However it considered that Seretide also aided compliance in relation to the factors listed.

GlaxoSmithKline agreed with the need for patients to have clear and understandable self-management plans. AstraZeneca cited a survey which showed that 68% of patients would feel comfortable being able to adjust the dose of their inhaler without having to refer to a health professional. GlaxoSmithKline pointed out that the survey was supported by AstraZeneca. The claim was based on market research data, rather than an appropriate cross-over design study, the usual method by which preference was robustly assessed. The statement specific to patients' comfort to adjust the dose of their inhaler was not specific as to which type of medication it referred; reliever medication, preventer medication, or both. The survey data did not question the comfort of adjusting the dose of a new, unfamiliar therapy.

AstraZeneca provided an additional reference, Adams *et al* (2001). This cross sectional observational study assessed patients with moderate to severe asthma managed, at least in part, at two teaching hospitals, over a 12 month period of follow-up. The autonomy preference index used assessed preference associated with 3 hypothetical situations of which the 'moderate' attack most closely represented the clinical situation to which AstraZeneca most commonly referred in its defence, ie an attack of moderate severity requiring increased medications and an unscheduled physician visit. The other hypothetical situations were of 'stable disease' or 'severe attack' (requiring hospitalisation and admission to an intensive care unit). In this publication, patients expressed significantly stronger preferences for self-management autonomy in the 'moderate' scenario with 64% of subjects indicating a preference for more input than their physicians into management decisions. However, it was important to note that there was stronger autonomy about the decision of when to see a physician than for decisions regarding altering medication, with the differences between these 2 scores being significant ($p<0.01$). That was, 'patients regard making changes to their medications in response to increased symptoms to be a negotiable issue to be decided with predominant input from their doctor, and most would not initiate these changes without consultation'. This was the case regardless of whether the patients had been provided with a written action plan outlining when and how to increase medication when symptoms worsen. GlaxoSmithKline therefore disagreed with AstraZeneca that this publication supported that stepping up and stepping down treatment was an attractive option for the patient. GlaxoSmithKline stated that this reference did not support the promotional stance for Symbicort (the stepping up and stepping down of asthma treatment, directed by the patient rather than the clinician) put forward by AstraZeneca.

The rationale for combination therapy

GlaxoSmithKline agreed that there was a clear rationale for adding a long-acting bronchodilator to an inhaled steroid and that there were benefits to a combination device of a long-acting bronchodilator and an inhaled steroid. The benefits of compliance and one prescription charge were true for Seretide. It was true that to increase the strength of Seretide, patients needed to change to a different strength of Seretide inhaler.

GlaxoSmithKline did not agree with the perception raised by AstraZeneca of the inability of Seretide to meet the patient's needs and clinical needs. It had previously provided to AstraZeneca data supporting control with Seretide. Three such studies were referred to.

Kavuru *et al* (2000) compared the efficacy and safety of Seretide 100 Accuhaler bd with salmeterol 50mcg bd, fluticasone 100mcg bd or placebo over 12 weeks in 356 patients aged 12 years and over with a clinical history of asthma. A subanalysis of 240 patients, previously treated with inhaled corticosteroids was available as data on file (SFCA3002). This had been accepted for presentation at the BTS. Shapiro *et al* (2000) compared the efficacy and safety of Seretide 250 Accuhaler bd with salmeterol 50mcg bd, fluticasone 250mcg bd or placebo over 12 weeks in 349 patients aged 12 years and over with a clinical history of asthma. The third study was available as data on file (SAS30003) and had also been accepted for presentation at the BTS. This assessed asthma control and quality of life in 144 patients treated with Seretide 25/50 2 puffs bd via a metered dose inhaler over 12 weeks.

The primary efficacy variables were based on FEV_1 and probability of remaining in the study. Patients were withdrawn from the study for 'lack of efficacy' if their asthma deteriorated during the study; probability of remaining in the study was based on the criteria of good asthma control. Patients who failed to meet any of these criteria were withdrawn from the study:

The results of these studies showed that Seretide provided superior control of asthma to fluticasone or salmeterol alone. Patients receiving Seretide were significantly more likely to remain in the study without being withdrawn due to poor asthma control, compared with those on fluticasone, salmeterol, or placebo ($p\leq0.02$, both trials for Seretide vs all other treatments).

In the study SFCA3002, only 2% of patients on Seretide withdrew from the study due to loss of asthma control over the 12 weeks of the study

compared with 33% on salmeterol, about 11% on fluticasone and 55% on placebo ($p \leq 0.025$ Seretide vs, placebo, salmeterol and fluticasone). Similarly, in the Shapiro study only about 4% of patients on Seretide dropped out due to poor asthma control over the 12 weeks of the study compared with nearly 38% on salmeterol, 22% on fluticasone and 62% on placebo ($p \leq 0.002$). The majority of those patients who were withdrawn had either suffered an exacerbation or showed signs of an impending exacerbation (reduction in PEF or FEV_1 of at least 20%). In the study SAS30003, only 3% of patients treated with Seretide withdrew due to loss of asthma control compared with 9% on fluticasone, 37% on salmeterol and 41% with placebo. These data emphasised the efficacy of Seretide in controlling asthma and suggested that Seretide might help to protect patients from the occurrence of exacerbations.

Based on these data GlaxoSmithKline considered that whether patients were prescribed Seretide 50/100 or 50/250, patients were well controlled. Therefore the requirement for patients to adjust their asthma medication in response to an increase in symptoms or 'poor control' was small.

The need to adjust medication dose with Seretide might not be as great an issue for Seretide, or in comparison with Symbicort, as great a benefit for Symbicort, as AstraZeneca implied.

AstraZeneca purported that Symbicort also offered simpler stepping down of treatment compared with Seretide. GlaxoSmithKline was unaware of any data to support the fact that patients did actually step down treatment with Symbicort, compared with other asthma therapies. It was possible to step down treatment with inhaled steroids, using a single inhaler. However, patients did not often do so. References provided by AstraZeneca (AIRE study, Rabe *et al* 2000, the AIR study and Price *et al*, 1999) highlighted that patients were poor at accurately assessing the severity of their asthma, with perception of asthma control not matching symptom severity.

In the survey provided by AstraZeneca the alteration of asthma therapies by patients was explored. Of the group surveyed, only 37% of patients reported that they adjusted their treatment regimen as a result of changes in symptoms. Of this 37%, only 18% altered their preventer medication dose and 32% altered their preventer and reliever medication dose. Therefore a minority of this group surveyed altered their maintenance medication in response to symptoms. The potential benefit to step down treatment was also not unique as other maintenance therapy, including inhaled steroids, shared this feature. In the survey 80% of patients had not been provided with a plan that showed them how to make changes to medication when asthma improved. GlaxoSmithKline's view was that Symbicort alone would not therefore provide a solution to this clinical issue, which might explain why, despite inhaled steroids sharing this feature, the clinical problem still existed.

APPEAL BOARD RULING

The Appeal Board noted there was a difference between Symbicort and Seretide. Symbicort offered flexible dosing during maintenance treatment with one inhaler. The daily dose of Seretide was fixed and could not be titrated up or down without the need for a new strength of inhaler. The Appeal Board considered that the claims at issue were broad and would imply to the audience a more radical and fundamental change than the introduction of adjustable maintenance therapy in one inhaler. The constituent products were not new, they had been and continued to be available in separate inhalers. The claims were misleading and exaggerated. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.10 of the Code.

The appeal on this point was unsuccessful.

2 Claim 'More effective at improving lung function than double the dose of budesonide in mild asthma*'

This claim appeared in item A, the dose leavepiece, immediately above the phrase 'Symbicort 100/6mcg bd vs budesonide Turbohaler 200mcg bd'. The asterisk referred the reader to a footnote which read 'Defined as pre-study inhaled corticosteroid dose 200-500mcg/day'. The claim was referenced to Lalloo *et al* (2000).

COMPLAINT

GlaxoSmithKline alleged that the clinical data in the Lalloo study did not support this claim.

The study measured morning PEF (peak expiratory flow) as the primary endpoint and evening PEF and asthma control as secondary endpoints. The measure of lung function in this study was therefore PEF, with the study being powered on morning PEF. In the medical community FEV_1 was also considered to be a measure of lung function however this was not presented in this study.

GlaxoSmithKline stated that 'more effective' implied a clinically relevant change, as opposed to a statement such as 'statistically significant difference between treatments' which would imply that the claim was based on statistical results. In the Lalloo study, the difference in PEF between the treatment groups was <10L/min. It was commonly accepted that a minimal change or difference between treatments of 15L/min was needed before a clinical effect could be claimed. Indeed Santanello *et al* (1999) had found a change in PEF of 18.79L/min was the minimum change from baseline needed for patient perceivable improvement. However the general consensus was that 15L/min was a clinically relevant difference, when comparing treatments. GlaxoSmithKline accepted that the differences between the treatment groups shown in Lalloo's study, of 9.2L/min in the primary endpoint of mean morning PEF and 9.4L/min in mean evening PEF were statistically significant. However this difference was not clinically significant and therefore did not support the statement of 'more effective at improving lung function'. AstraZeneca had responded that other markers such as symptom scores, which showed significant differences, supported the claim. GlaxoSmithKline considered that the claim was very specific in stating lung function and that this would be interpreted by health

professionals as clinically significant changes in measures of lung function such as PEF and FEV_1.

GlaxoSmithKline alleged that the claim was not supported by clinical improvement and was in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that the claim was substantiated by the results of Lalloo *et al*. The difference in the primary endpoint; morning PEF (L/min) between Symbicort 100mcg twice daily and budesonide 200mcg twice daily was highly statistically significant (p=0.002) at study-end after 12 weeks' treatment. The claim therefore was correct in that it stated superior effectiveness in this outcome measure for Symbicort as supported by the statistical result.

The word clinical was purposely not included in the claim as this related to a specific statement on lung function. In terms of appraising the wider clinical relevance, the study as referenced, put into context the clinical relevance by assessing together lung function changes, symptom scores and reduction in rescue medication use between the two active treatments.

The author was an internationally renowned opinion leader with over 50 available publications related to asthma. His appraisal from all the study results concluded 'this study shows that Symbicort in a single inhaler is clinically superior to increasing the dose of inhaled corticosteroid in adult patients who are not adequately controlled on low-dose inhaled corticosteroid alone'. Therefore his appraisal incorporated the statistically significant change in lung function between treatments as well as considering symptoms, asthma controlled days and time to exacerbation scores.

The actual clinical significance of just a single outcome measure between two active treatments in asthma studies had not been quantified. Rather the standard methodology to determine actual clinical relevance from the results of asthma clinical studies was to consider changes not just to lung function parameters but equally importantly also to symptom scores and health related quality of life scores.

Neither the current BTS guidelines nor the recent concept paper on the development of a CPMP (Committee for Proprietary Medicinal Products) note for guidance on the clinical investigation of medicinal products in the treatment of asthma, made any reference to a minimal change in lung function required between treatments necessary to demonstrate clinical efficacy. For new asthma medicines to now gain a marketing authorization in the European Union (EU) it was necessary to demonstrate statistically significant changes in both lung function and symptom scores.

AstraZeneca stated that the Santanello study was a placebo controlled study involving a leukotriene antagonist rather than a study comparing two active treatments. This quoted average minimal patient perceivable improvement for PEF of 18.79L/min relative to changes from baseline and not to a difference between two active treatments. In the discussion section of the paper, the author outlined some limitations of using this methodology to provide clinical meaning to changes in clinical measures: 'Therefore, while a level of minimal change in a measure that was defined as clinically relevant by this method might be useful, caution was advised against setting a universal benchmark of what was an important change for a measure based on this method for many reasons including possible differences between treatment groups and other demographic groups'.

AstraZeneca submitted that the claim was factually correct, not misleading in the context of the clinical conclusions in the Lalloo study and was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted Section 5.1 of the Symbicort SPC headed 'Pharmacodynamic Properties' stated with regard to the Symbicort Turbohaler that in 'clinical trials the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In a twelve week study the effect on lung function of Symbicort Turbohaler was equal to that of the free combination of budesonide and formoterol and exceeded that of budesonide alone'. No details were given about the doses used.

The Panel noted that Lalloo *et al* (presented in abstract and poster format) was a 12 week, double blind, randomized parallel group study which evaluated the efficacy and safety of low dose Symbicort (budesonide 80mcg/formoterol 4.5mcg) in a single inhaler twice daily with double the dose of budesonide 200mcg twice daily in adult patients with mild asthma who remained symptomatic on low dose inhaled corticosteroid alone. The primary variable was morning PEF. The change in PEF was 16.5L/min for Symbicort and 7.3L/min for budesonide (p=0.002). The change in evening PEF was 13.6L/min for Symbicort and 4.2L/min for budesonide (p<0.001). Symbicort increased the time to first mild exacerbation (p=0.02) and decreased relative risk of mild exacerbations by 26% (p=0.02) compared to inhaled corticosteroids alone. Severe exacerbations were too few to detect differences between treatments in this mild population. Symptom free days (days with no asthma symptoms and no night time awakenings) were 55.3% for Symbicort and 48.9% for budesonide (p=0.007). The authors concluded that Symbicort reduced the risk of mild exacerbations and improved asthma control to a significantly greater degree than double the dose of inhaled corticosteroid alone.

The poster format concluded that Symbicort in a single inhaler was clinically superior to increasing the dose of inhaled corticosteroids in adult patients who were not adequately controlled on low dose inhaled corticosteroid alone.

The Panel noted GlaxoSmithKline's view in this case was that it was commonly accepted that a minimal change of or difference between treatments of 15L/min was needed before a clinical effect could be claimed. The Panel had no evidence before it in this regard. The Panel also noted AstraZeneca's submission that the actual clinical significance of just

a single outcome between two active treatments in asthma studies had not been quantified and noted its comments on the BTS guidelines and concept paper in this regard. AstraZeneca stated that for new asthma medicines to gain a marketing authorization in the EU it was necessary to demonstrate statistically significant changes in both lung function and symptom scores.

The Panel noted that the CPMP note for guidance in a section headed 'Recommended Primary and Secondary End Points' stated that all endpoints should be chosen depending on the indication. Reference was made to lung function as well as clinical endpoints. Special advice should be given on the appropriateness of different lung function parameters (FEV_1 versus PEFR). The CPMP note for guidance also referred to clinical endpoints being quality of life measurements, exacerbation rates, hospitalisation, etc.

The Panel noted that Santanello *et al* had found a change in PEF of 18.7L/min was the minimum change from baseline needed for patient perceivable improvement but the study authors stated that determining the minimal patient perceivable improvement value for a measure might be helpful to interpret changes. However interpretation should be carried out cautiously when reporting a single value as a clinically important change. The Panel noted that the Santanello *et al* study was to determine the level at which a population of asthmatics in clinical trial perceived change, improvement or deterioration in lung function and other asthma functions after treatment. The study looked at both FEV_1 and PEF.

On balance the Panel considered that the claim was misleading. It gave the impression that there was a clinical difference between the products in relation to lung function. There was a statistically significant difference between the products in relation to PEF in the Lalloo study but the Panel was not convinced on the evidence before it that this alone amounted to a clinical difference in improving lung function. A breach of Clause 7.2 was ruled.

3 Pack size

The prescribing information appeared on all of the items.

COMPLAINT

GlaxoSmithKline stated that the prescribing information for Symbicort 100/6 and 200/6 on all the material at issue did not give an indication of the pack size for either presentation.

Previously AstraZeneca products had been available in Turbohalers containing 50, 60, 100 and 200 doses. However, the Symbicort Turbohaler was a significant departure from this with both strengths containing 120 doses. In addition, the Symbicort Turbohaler currently being sampled to health professionals, but not marketed, contained 60 doses. Clinicians might well therefore be aware of two presentations of Symbicort of different number of doses, 60 and 120.

GlaxoSmithKline alleged that this omission of the pack size from the prescribing information was potentially confusing for health professionals, given that the 120 dose Turbohaler for Symbicort was a new dosage presentation. GlaxoSmithKline alleged that the materials did not meet the requirement of the Code that the cost of either a specified package of the medicine to which the advertisement referred, or a specified quantity or a recommended daily dose, should be presented within the prescribing information as, with the Turbohaler being available in several variations in the number of doses, a Turbohaler was not suitably specific. The omission of the 120 doses would also not allow clinicians to calculate the true cost of the medicine and to make relevant comparisons with other treatment options.

This omission was also in direct contrast to the prescribing information of Pulmicort, available on the dose leavepiece (item A), which stated the three pack sizes (50, 100 and 200) available. A breach of Clause 4.2 of the Code was alleged.

RESPONSE

AstraZeneca stated that in the UK, Symbicort was available in two strengths; 200/6 and 100/6, both of which were only presented in a pack size containing 120 doses. No other pack size was marketed in the UK and therefore a health professional would only be able to prescribe Symbicort in pack sizes of 120 doses.

AstraZeneca acknowledged that Clause 4.2 of the Code stipulated that prescribing information on promotional material should include 'the cost (excluding VAT) of either a specified package of the medicine to which the advertisement relates, …'. All promotional material for Symbicort related to the only marketed presentation of Symbicort ie the 120 dose Turbohaler, which was available in the two strengths. Cost given in the prescribing information would therefore only relate to the 120 dose pack size for each of the two available strengths of Symbicort. AstraZeneca did not believe this would cause confusion amongst prescribers.

It was generally accepted that prescribing information was not intended to give full information about the product, but rather guidance, and health professionals should always consult the SPC before prescribing. This advice was part of the prescribing information for Symbicort.

AstraZeneca provided sample packs of Symbicort Turbohaler that only contained 60 doses; they were clearly marked as sample packs. The rationale for supplying sample packs was to provide prescribers with a small presentation of a particular medicine in order to familiarise themselves with the new product. It did not necessarily imply that the 60 dose presentation was available for prescribing. AstraZeneca did not think that clinicians who were familiar with the concept of pharmaceutical companies supplying sample packs would readily assume the 60 dose pack was available for prescription.

AstraZeneca therefore did not accept a breach of Clause 4.2 of the Code.

PANEL RULING

The Panel noted that Clause 4.2 of the Code required prescribing information to include, *inter alia*, 'the cost (excluding VAT) of either a specified package of the medicine to which the advertisement relates or a specified quantity or recommended daily dose, calculated by reference to any specified package of the product …'. The Panel noted that the Symbicort prescribing information stated that the basic NHS price for Symbicort 100/6 Turbohaler was £33 and Symbicort 200/6 Turbohaler was £38. Some of the promotional material, such as the dose leavepiece (item A) also included the prescribing information for the Pulmicort Turbohaler which gave the number of actuations when stating the cost of each strength of the medicine; 'Basic NHS price: Pulmicort Turbohaler 100 (200 actuations) £18.50, Pulmicort Turbohaler 200 (100 actuations) £18.50 Pulmicort Turbohaler 400 (50 actuations) £18.50. The Panel noted that both strengths of Symbicort 200/6 and 100/6 came in a pack size of 120 doses, no other pack size being marketed in the UK.

The Panel noted AstraZeneca's submission that health professionals should always consult the SPC before prescribing. The Panel noted that the cost would not appear in the product's SPC. The Panel considered that the failure to state the number of doses was such that the cost of a specified package or a specified quantity or a recommended daily dose of the medicine had not been stated as required by Clause 4.2 of the Code.

The Panel noted that Clause 4.2 listed the content of prescribing information and Clause 4.1 required such information to be provided on all promotional material. The Panel thus ruled a breach of Clause 4.1 of the Code.

APPEAL BY ASTRAZENECA

As noted by the Panel, Clause 4.2 listed the requirements for prescribing information that, in accordance with Clause 4.1, must feature on all promotional material. Such requirements included *'… the cost (excluding VAT) of either a specified package of the medicine to which the advertisement relates,* ***or*** *a specified quantity or recommended daily dose …'*.

During preparation of the Symbicort prescribing information *the cost of a specified quantity*' was interpreted as stating the price of each available strength of Symbicort ie 100/6 and 200/6. It was not, as alleged by GlaxoSmithKline, a decision to 'omit' the number of doses per presentation.

This decision was based around the fact that in the UK, Symbicort Turbohaler was available in two strengths; 100/6 and 200/6, both of which were only available for prescription in a pack size of 120 doses. No other pack size was marketed. It therefore followed that all promotional material for Symbicort, including advertisements, only related to this marketed presentation.

The prescribing information for Symbicort made clear reference to the basic NHS price of the two available strengths of Symbicort Turbohaler ie Symbicort 100/6 Turbohaler: £33.00 and Symbicort 200/6 Turbohaler: £38.00.

AstraZeneca submitted that the number of doses contained within each presentation would not necessarily allow a clinician to accurately calculate the cost of Symbicort on a monthly basis because patients who were encouraged to adjust the dose according to asthma fluctuations could in theory make one inhaler last between 30 and 120 days ie from one inhalation per day to two inhalations twice daily.

The prescribing information for Pulmicort Turbohaler, which appeared on a number of Symbicort promotional items, gave the number of doses when stating the cost of each strength. This was on the basis that Pulmicort was available in a number of different pack sizes ie 50, 100 and 200 actuations. In contrast Symbicort was only available in a pack size containing 120 doses with no other pack size marketed in the UK.

The sample size of Symbicort Turbohaler was a 60-dose inhaler. However clinicians would be aware that the rationale behind sample packs was to provide a small example of a medicine and did not necessarily mean a sample size would be a prescribable presentation.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that AstraZeneca had interpreted the wording of Clause 4.2 to mean specified dosage. GlaxoSmithKline did not agree with this interpretation. Such an interpretation did not allow a clinician to accurately assess the true cost of a medicine. GlaxoSmithKline had interpreted the wording of Clause 4.2 to mean the specified number of doses or quantity.

GlaxoSmithKline did not consider that one Turbohaler was a specified quantity. The Turbohaler varied greatly as to the number of doses it contained with the variation in the UK being 50, 60, 100, 120, and 200 doses. If the Turbohaler was only ever available as a fixed number of doses, this would then be specific. Not only did the Turbohaler vary as to the number of doses it contained, the Turbohaler available for Symbicort was a significant departure from that previously available for the Turbohaler, ie it contained 120 doses, not the familiar 100 or 200 doses, in adult asthma.

Not all promotional items for Symbicort mentioned that the Turbohaler was available as 120 doses and therefore the listed cost had no reference and therefore prevented a health professional from making a reasoned judgement as to the accurate cost of prescribing Symbicort.

GlaxoSmithKline also considered that the listing of the relative cost of a medicine was one of the most important elements of the prescribing information as all other information in the prescribing information was presented within the SPC.

APPEAL BOARD RULING

The Appeal Board considered by stating in the prescribing information the costs of Symbicort 100/6 Turbohaler and Symbicort 200/6 Turbohaler and not stating the number of doses meant that the cost of a

specified package or a specified quantity or recommended dose had not been given as mentioned in Clause 4.2 of the Code. The prescribing information as required by Clause 4.1 of the Code had not been provided. The Appeal Board upheld the Panel's ruling of a breach of Clause 4.1 of the Code.

The appeal on this point was unsuccessful.

4 Age limitation in the prescribing information

In relation to Dosage and Administration the prescribing information stated 'Adolescents/children: Not recommended'. This appeared in each promotional item.

COMPLAINT

GlaxoSmithKline stated that for both Symbicort Turbohaler 100/6 and 200/6, under Section 4.2 – Posology and administration – the SPC stated 'Adolescents (under 17 years) and Children: Symbicort Turbohaler is not recommended in this group of patients'.

The inclusion of the precise limitation in the SPC was important as in the rest of the EU Symbicort was currently licensed for patients over 12 years, stating: 'Recommended doses: *Adults and adolescents (12 years and older)* 1-2 inhalations twice daily'.

The product was licensed through the mutual recognition process, however the UK was withdrawn due to concerns by the Medicines Control Agency (MCA). The issue in hand was the use of the product in patients less than 17 years of age. The (under 17) age restriction in the UK SPC reflected the MCA's view of how the product should be used in the UK.

In discussion with AstraZeneca, it had informed GlaxoSmithKline that it believed this was a 'subtle abbreviation'. It had also informed GlaxoSmithKline that the CPMP note for guidance on clinical investigation of medicinal products in children defined adolescent age range as 12 to 17 years.

GlaxoSmithKline did not consider that the abbreviation was subtle, but misleading. It also considered that the average health professional in primary, and indeed in secondary care, was unlikely to be aware of the CPMP notes for guidance on clinical investigation.

Most health professionals were aware that children over the age of 12 were prescribed adult doses of medicinal products, and views of the age of adolescence might vary widely often being viewed as children under 15 or 16.

GlaxoSmithKline stated that AstraZeneca had informed it that the current campaign and the training of its sales representatives was very focussed on the fact that Symbicort was only licensed for adult asthma. However, it did not consider that this removed from AstraZeneca the obligation for the prescribing information to be consistent with the SPC as many promotional items, such as mailing and journal advertisements, would not be delivered by a representative and therefore ensure this clarification.

GlaxoSmithKline alleged that this omission of the specific age restriction was potentially misleading, being not consistent with the SPC. This omission might cause confusion and misunderstanding and would potentially result in children less than 17 years of age being prescribed Symbicort. A breach of Clause 4.2 of the Code was alleged.

RESPONSE

AstraZeneca submitted that it was generally accepted that prescribing was not intended to give full information about the product, but rather guidance.

Although the Code did give some guidance on what should be included in the prescribing information in order for it to be compliant, the responsibility for deciding what constituted a succinct statement of various information on the SPC was for the company.

It was for this reason that AstraZeneca referred to a recent case, Case AUTH/1083/10/00, in which the Panel gave its opinion on whether abbreviating some of the statements on the SPC in the prescribing information would consequently mislead the reader. In this particular case the Panel concluded that although the prescribing information did not include the word 'only' as in 'only in obese patients' and 'only in patients who show an intolerance to metformin' as in the SPC this did not render the prescribing information inconsistent. The Panel considered that there was no real difference between the two statements to cause confusion amongst experienced physicians.

AstraZeneca considered that parallels could be drawn from this case to this current one. The SPC for Symbicort stated that 'Adolescents (under 17 years) and children: Symbicort Turbohaler is not recommended'. AstraZeneca did not consider that abbreviating this advice to 'Adolescents/children: Not recommended' in the PI was different enough to cause confusion amongst prescribers which might lead to Symbicort to be used in an unlicensed age group. The fact that the Symbicort campaign, including training materials, focused only on adult asthma further reinforced this message.

Furthermore, a health professional should always consult the SPC before prescribing. This advice was part of the prescribing information for Symbicort.

AstraZeneca considered the prescribing information included on promotional material for Symbicort reflected regulatory requirements and was sufficiently comprehensive to enable the reader to gauge an opinion on the suitability of use.

AstraZeneca therefore did not agree that the prescribing information was in breach of Clause 4.2 nor did AstraZeneca consider that it was intentionally misleading and in breach of Clause 7.2.

PANEL RULING

The Panel noted the dosage requirement in the Symbicort SPC as stated by the complainant. The Panel further noted the difference in the European and UK licences in this regard and GlaxoSmithKline's submission that most health professionals were aware that children over the age of 12 were prescribed adult

dosages of medicinal products. Nonetheless the Panel considered that the prescribing information made it sufficiently clear that neither children nor adolescents ought to be prescribed the product and did not consider that it was likely to result in confusion and misunderstanding as alleged. The Panel considered that the prescribing information was a succinct statement of the information in the SPC relating to, *inter alia*, dosage as required by Clause 4.2 of the Code. The Panel noted that Clause 4.2 set out the content of prescribing information and Clause 4.1 required it to be provided on all promotional material. No breach of Clause 4.1 was ruled.

The Panel noted that GlaxoSmithKline had not alleged a breach of Clause 7.2, as stated by AstraZeneca, and no ruling on that clause was thus made.

5 Monthly cost (30 days) of branded and generic maintenance treatments

A bar chart in item B, Symbicort cost leavepiece (SYMB 01 8424), compared the monthly cost range (30 days) of branded and generic maintenance treatments with reference to their minimum to maximum licensed doses. Price ranges of £9.50 - £38 and £8.25 - £33 were depicted for Symbicort 200/6 and 100/6 respectively. Price ranges for eight other branded and generic products were also shown. The heading in the top left hand corner read 'Symbicort is a reasonably priced combination for maintenance treatment of adult asthma'.

COMPLAINT

GlaxoSmithKline stated that the table presented the minimum and maximum licensed doses of inhaled steroids and combinations of inhaled steroids and long-acting ß$_2$ agonists, including both Symbicort and Seretide. The Code stated that price comparisons should only be made on the basis of equivalent dosage requirements for the same indication. There was no data supporting that the maximum and minimum doses of the products detailed were equivalent.

For example, no comparative data were available between 2 x 500mcg bd of fluticasone and 2 x 200/6 or 2 x 100/6 of Symbicort Turbohaler, and there was no data to suggest that these treatments were equivalent or that they would be suitable for the same group of patients with asthma. Likewise there were no comparative data between Seretide Accuhaler 500 bd and 2 x 200/6 or 100/6 of Symbicort Turbohaler.

Therefore the comparison was only on cost and not cost of clinical equivalent treatment options. GlaxoSmithKline discussed this with AstraZeneca and it had replied that: 'No claim is made in the material that the price ranges represent therapeutic equivalence'. However GlaxoSmithKline considered that such a dose equivalence was required within the Code, as stated in the supplementary information of Clause 7.2.

GlaxoSmithKline alleged that this item was misleading, not capable of substantiation and was therefore in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

AstraZeneca stated that all therapies displayed were indicated for the maintenance treatment of asthma. Presenting the minimum and maximum licensed dose for each option acknowledged the fact that doses could be adjusted in response to the severity of asthma symptoms. This was in line with existing BTS guidelines with regard to maintenance treatment. Moreover presenting cost associated with each licensed dose for a common indication accorded with current practice seen in renowned publications such as the Drugs and Therapeutics Bulletin.

AstraZeneca acknowledged that the Code stipulated that a price comparison should only be made on the basis of equivalent dosage requirement for the same indication. However the purpose of presenting the information in this format was to highlight to the reader where the price of Symbicort across the full dose range sat in relation to the full dose range of alternative medication for maintenance treatment in asthma. Therefore the comparison was only on cost as indicated from the title of the leavepiece.

It was made clear to the reader that the comparisons in the table were based purely on cost. No claims were made that one treatment was as efficacious as another at a particular dose.

AstraZeneca therefore believed that this cost comparison presented cost information in a fair and comprehensive manner. AstraZeneca did not agree that it was misleading in any way nor a breach of Clause 7.2, 7.3 or 7.4 of the Code.

PANEL RULING

The Panel noted the supplementary information to Clause 7.2, price comparisons, stated, *inter alia*, that 'Price comparisons must be accurate, fair and must not mislead. Valid comparisons can only be made when like is compared with like. It follows therefore that a price comparison should be made on the basis of the equivalent dosage requirement for the same indications'.

The Panel noted that the leavepiece at issue was headed 'cost' and discussed the cost of Symbicort; there was no discussion of clinical issues . The Panel also noted AstraZeneca's submission that the comparison was only on cost and the chart's purpose was to highlight where the price of Symbicort across the full dose range sat in relation to the full dose range of alternative medication for maintenance treatment. The heading to the chart 'Monthly cost (30 days) of branded and generic maintenance treatments' was clear and unambiguous.

The Panel considered that the content and purpose of the leavepiece was such that the basis of the comparison was clear; cost range in relation to maintenance treatment. There was no express or implied clinical comparison. The chart was neither misleading nor incapable of substantiation as alleged. The Panel ruled no breach of Clauses 7.2 and 7.4 of the Code.

The Panel noted that Clause 7.3 was newly introduced to the 2001 Code. Some of the principles were included in Clause 7.2 including the requirement that

comparisons must not be misleading. In the circumstances the Panel decided not to consider the matter in relation to Clause 7.3 of the 2001 Code. The matter was covered by Clauses 7.2 and 7.4 of the 2001 Code which were the same as Clauses 7.2 and 7.3 of the 1998 Code.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that a comparison was both intended and expressly invited was made clear by the statement in large print at the top of the page, 'Symbicort is a reasonably priced combination for maintenance treatment of adult asthma'. The comparison between combination treatments was further highlighted by the table itself, which showed the price ranges for inhaled steroid preparations in pale pink bars, but showed the price ranges for combination of long-acting bronchodilators and inhaled steroids (such as Symbicort and Seretide) in dark pink bars. GlaxoSmithKline considered that this chart was clearly inviting comparison between the price of Symbicort and the alternative combinations of long-acting bronchodilators and inhaled steroids.

The supplementary information to Clause 7.2 stated that 'price comparisons should only be made on the basis of equivalent dosage requirements for the same indication'. GlaxoSmithKline considered that the comparisons could not be made without reference to the equivalent doses of the various preparations and it was unaware of any equivalence studies between regular treatment regimens of Symbicort and Seretide. GlaxoSmithKline also noted that the maximum licensed dose of budesonide in Symbicort was 800mcg bd and the maximum licensed dose of fluticasone in Seretide was 1000mcg bd.

There were available data comparing budesonide (the steroid component of Symbicort) and fluticasone (the steroid component of Seretide). These data showed that fluticasone via the Accuhaler was as potent as budesonide via the Turbohaler at approximately half the microgram dose. This ratio was recognised in current guidelines.

There were no data to support a claim or an implication that the maximum and minimum doses of the products detailed were equivalent.

For example, no comparative data were available between 2 x 500mcg bd of fluticasone and 2 x 200/6 or 2 x 100/6 of Symbicort Turbohaler, and there were no data to suggest that these treatments were equivalent or that they would be suitable for the same group of patients with asthma. Likewise there were no comparative data between Seretide Accuhaler 500 bd and 2 x 200/6 or 100/6 of Symbicort Turbohaler. Therefore the comparison was only on cost and not cost of clinical equivalent treatment options

The chart was introduced by the claim for the 'reasonably priced combination', and therefore other combinations which had different cost ranges were being presented as clinically equivalent choices. Otherwise such a claim could not be made. For example if one presentation had a different potency and range of steroid strengths then Symbicort could be presented as reasonably priced by comparison. Such a comparison should only be made if the other combinations presented were clinically equivalent.

The item was misleading, and could not be substantiated and was therefore in breach of Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM ASTRAZENECA

The heading 'Monthly cost (30 days) of branded and generic maintenance treatments' appeared across the centrefold of the Symbicort cost leavepiece. It introduced a chart illustrating the price bands associated with a number of long-acting bronchodilator and inhaled steroid combinations as well as some inhaled steroids across their full dose range.

All such inhaled long-acting bronchodilator/steroid combinations, whether presented in a single inhaler or available separately as monoproducts, were indicated for the maintenance treatment of adult asthma.

Maintenance treatment was the mainstay of asthma therapy with guidelines such as those issued by the BTS acknowledging that due to fluctuations in symptoms, the dose of maintenance treatment needed to be adjusted from time to time to optimise control.

Presenting the cost of several maintenance treatments over the minimum to maximum licensed dose range not only acknowledged the adjustable nature of maintenance treatment but also allowed the reader to gauge a more realistic estimation of cost per month for each treatment option.

The reader was able to visualise where the cost of Symbicort, across the full dose range, fell in relation to the cost of the full dose range of alternative therapies for maintenance treatment.

For clarity the price bands of the various treatments were presented using different shades of pink and red. This enabled the reader to readily identify those maintenance treatments available as a combination product ie Symbicort and Seretide or as monoproducts.

AstraZeneca acknowledged that in order to comply with Clause 7.2 of the Code 'price comparisons can only be made on the basis of equivalent dosage requirements for the same indication'.

Dosage requirements might apply to individual dose comparisons as well as dose range comparisons. The treatment options presented were therefore equivalent with respect to their common indication ie maintenance treatment in adult asthma. However the table only invited the reader to compare the cost on this basis and not on therapeutic equivalence. Neither the table nor the leavepiece as a whole made any inference that each of the presented dose ranges of maintenance treatments were clinically equivalent. No clinical efficacy claims or claims or comparison were made or implied in the leavepiece.

The heading 'Symbicort is a reasonably priced combination for maintenance treatment of adult asthma' appearing at the top of the page was a literal interpretation of the information being presented in the table ie compared with alternative maintenance

treatment options the cost of Symbicort over the licensed dose range was neither the most expensive nor the cheapest, but reasonably priced.

In summary, the cost comparisons were based upon the price ranges of asthma treatments with a common indication across the full dose range. AstraZeneca did not consider there was a breach of Clauses 7.2 and 7.4 of the Code.

FURTHER COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline noted that AstraZeneca stated that to comply with Clause 7.2 of the Code, 'price comparisons can only be made in the basis of equivalent dosage requirements for the same indication'. AstraZeneca then stated that the treatment options were equivalent with respect to their common indication of maintenance treatment. GlaxoSmithKline disagreed; product licences were authorized by the Medicines Control Agency based on the data submitted. This might be for one or several doses. Licences were granted solely for the product under consideration and no comparisons were made with competitor products. GlaxoSmithKline did not agree that if a product was licensed for the treatment of asthma with a dose range x – y, that this was then equivalent to a product also licensed for the treatment of asthma but with a dose range a – c. An assessment to demonstrate equivalence had not been made by the regulatory authorities.

The purpose of providing monthly cost comparisons to health professionals was for facilitating the choice of different treatment options. For treatments to be compared, clinicians had to be aware of their equivalence based on efficacy and overall effectiveness, that was that dose x of medicine y was equally effective as dose c of medicine a. If there were no data available to demonstrate the equivalence of dose x of medicine y and dose c of medicine a, a comparison of cost could not be made. GlaxoSmithKline considered that this was true for the monthly cost comparison chart as there were insufficient data comparing the treatment options presented.

The fact that a comparison was invited was made clear on two points, the use of the different colours within the bar chart and the use of the heading, 'Symbicort is a reasonable priced combination for the maintenance treatment of adult asthma'.

APPEAL BOARD RULING

The Appeal Board acknowledged that the information presented was accurate. It was nonetheless possible for accurate information to give a misleading impression. The Appeal Board was concerned that the bar chart implied that the products listed had similar efficacy. The impression was that it was less expensive to use Symbicort than the majority of the other products listed. This was not necessarily so. The Appeal Board decided that the chart was misleading and a breach of Clause 7.2 was ruled. The appeal on this point was successful.

The Appeal Board considered that the cost ranges were accurate and therefore it upheld the Panel's ruling of no breach of Clause 7.4 of the Code. The appeal on this point was unsuccessful.

Following its consideration of this case the Appeal Board noted that GlaxoSmithKline wanted clarification on a point raised in the complaint that should breaches be ruled in documents that might have significant impact on locality prescribing, such as the Symbicort Drug and Therapeutics Committee New Drug Request (item J) and the Symbicort Product Profile (item K), that AstraZeneca be required to recover these items in accordance with Paragraph 10.3 of the Constitution and Procedure.

The Appeal Board noted that the documents in question had been ruled in breach of the Code by the Appeal Board in point 3. The Panel had ruled the items in breach of the Code in points 6 and 10.

Paragraph 10.3 of the Constitution and Procedure stated that a company ruled in breach of the Code might also be required by the Appeal Board to take steps to recover items. The Appeal Board noted the circumstances of this case and decided that it was not necessary for AstraZeneca to recover items J and K, such a sanction was not warranted.

6 Statement 'Each inhaler contains either 60 or 120 doses'

This statement appeared on the inside front page of item J, the Drug & Therapeutics Committee New Drugs Request booklet, in a section entitled 'Product Details' which described essential features of Symbicort in relation to its approved and brand name, presentations, therapeutic class, manufacturer and licensed indications.

COMPLAINT

GlaxoSmithKline stated that AstraZeneca had informed it in response to its queries regarding the prescribing information that the 60 dose Turbohaler was not marketed in the UK. GlaxoSmithKline therefore alleged that this statement was misleading and in breach of Clause 7.3 of the Code.

RESPONSE

AstraZeneca stated that for reasons explained at point 3 above, the prescribing information for Symbicort referred to the price of both strengths of Symbicort ie 200/6 and 100/6, both of which were only available in inhalers containing 120 doses.

Although not marketed in the UK, a 60 dose presentation was available as sample pack. Referring to the 60 dose presentation of Symbicort in the above formulary pack did not necessarily mean that it was available on prescription and nor did it imply so.

Information regarding the 60 dose presentation was stated on the SPC for Symbicort as well as a statement ensuring that the reader was aware that not all presentations mentioned were marketed in the UK.

However AstraZeneca acknowledged that this should have been made clearer and it was currently

amending the item to rectify this statement in the formulary pack.

PANEL RULING

The Panel noted that the phrase at issue appeared in a paragraph describing the presentation of Symbicort 200/6 and 100/6.

The Panel noted that reference to the 60 dose presentation appeared in Section 6.5 of the SPC 'Nature and Contents of Container' which stated, *inter alia*, 'Each inhaler contains 60 doses or 120 doses' and which concluded 'Not all pack sizes may be marketed'. The Panel noted that the 60 dose pack was available in the UK as a sample only. The Panel considered, as acknowledged by AstraZeneca, that this had not been made sufficiently clear in the booklet in question. The Panel was curious as to why GlaxoSmithKline had alleged a breach of Clause 7.3 which, in the 2001 Code, related to comparisons and required, *inter alia*, that comparisons should not be misleading. Given that the 2001 Code introduced a new Clause 7.3 and that GlaxoSmithKline had alleged that the material was misleading, AstraZeneca had responded in this regard and had accepted that the statement could have been clearer. The Panel decided that in the circumstances there was a breach of Clause 7.2 of the Code and ruled accordingly.

7 Claim 'Symbicort versus double dose inhaled steroid monotherapy. In mild asthma Symbicort 100/6 has been shown to be significantly more effective than double dose inhaled budesonide (200mcg bd) alone, in increasing morning PEF (p=0.002), evening PEF (p<0.001) and symptom free days (p=0.007) over a 12 week period'

This claim appeared on page 3 of the item J, the Drug & Therapeutics Committee New Drugs Request booklet, in a section entitled 'What are the advantages over existing formulary drugs?'

COMPLAINT

GlaxoSmithKline noted that this claim was referenced, as was the claim at point 2, to Lalloo *et al*. For the reasons given in point 2, the claim as stated which specifically referred to PEF was not supported by clinically significant improvement. GlaxoSmithKline alleged a breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca referred to its response at point 2.

PANEL RULING

The Panel noted that the claim at issue was different to that considered at point 2 which only referred to Symbicort's benefits with regard to improving lung function compared with double the dose of budesonide. The Panel considered that the claim now at issue was more specific and hence was a fair reflection of the findings of Lalloo *et al*. No breach of Clause 7.2 was ruled.

8 Claim 'Symbicort is an effective maintenance treatment, resulting in an improvement in both morning and evening PEF and asthma symptoms'

This claim appeared on page 3 of item J, the Drug & Therapeutics Committee New Drug Request booklet, in a section headed 'Does this drug control symptoms effectively?

COMPLAINT

GlaxoSmithKline noted that this claim was referenced, as was the statement in point 2, to Lalloo *et al*. For the reasons stated in point 2, GlaxoSmithKline considered that the claim as stated which specifically referred to PEF was not supported by clinical improvement. Although the claim was not made against the improvement seen with budesonide, both the improvements, in both morning (16.5L/min) and evening (13.6L/min) PEF, against baseline were below the threshold shown by Santanello of 18.79L/min for patient perceptible changes against baseline, and the change in evening PEF was below the generally agreed threshold of 15L/min. GlaxoSmithKline therefore considered that this statement was in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca referred to its response at point 2 above.

PANEL RULING

The Panel noted that the claim at issue was different to that considered at point 2 above, 'more effective at improving lung function than double the dose of budesonide in mild asthma'. The claim at issue was referenced not only to Lalloo *et al* but also Zetterström *et al* (2000).

The Panel noted that Zetterström *et al* published in abstract and poster format was a 12 week double blind, randomized, parallel group study which compared the efficacy and safety of Symbicort (320/9mcg bd) with the equivalent doses of budesonide administered either alone or with formoterol in asthmatics not adequately controlled on inhaled corticosteroids alone. The primary efficacy variable was morning PEF. The study concluded that PEF increased by 36L/min in the Symbicort group and by 32L/min in the budesonide plus formeterol group; p<0.001 versus the budesonide group for both groups. There were no significant differences versus Symbicort and budesonide plus formoterol in this parameter. Both the Symbicort and budesonide plus formoterol groups increased evening PEF (p<0.001) as against the budesonide only group. The authors further concluded that Symbicort reduced the risk of mild exacerbations and improved asthma control in patients not adequately controlled on inhaled corticosteroids alone.

The claim at issue did not refer to lung function; it referred to morning and evening PEF and asthma symptoms. The Panel noted its ruling in point 7 and considered that on balance, given the statement in the SPC (section 5.1), Lalloo *et al* and Zetterström *et al*, the

claim was not misleading as alleged. No breach of Clause 7.2 was ruled.

9 Claim 'Symbicort has been shown to be significantly more effective than inhaled budesonide alone, in improving morning and evening PEF (p<0.001) over a 12 week period'

GlaxoSmithKline referred to page 4 section 5 of item J, the Drug & Therapeutics Committee New Drug Request booklet, and to the subsection 'Symbicort vs double dose inhaled budesonide monotherapy'.

COMPLAINT

GlaxoSmithKline noted that the claim was referenced, as was the claim in point 2, to Lalloo *et al*. For the reasons stated in point 2, GlaxoSmithKline alleged that the claim as stated which specifically claimed clinical superiority and referred to PEF was not supported by clinically significant improvement. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

AstraZeneca referred to its response at point 2 above.

PANEL RULING

The Panel noted that the subsection of section 5 referred to by GlaxoSmithKline 'Symbicort versus double dose inhaled budesonide monotherapy' did not contain the claim at issue although that subsection did detail the results of Lalloo *et al*. A subsection entitled 'Symbicort vs equivalent dose inhaled budesonide monotherapy' contained a similar claim to that quoted by GlaxoSmithKline although that claim was referenced to Zetterström *et al*. GlaxoSmithKline appeared to have misquoted the subsection, the claim or the reference. In the circumstances it was not possible to proceed. The Director decided on the basis of the complaint as stated that there was no *prima facie* case to answer.

10 Claim 'Comparing like with like, does this drug cost more per patient than existing treatment, cost the same as existing treatment, cost less than existing treatment or not compare as there are no existing treatments?' and table headed 'Typical monthly (30 day) costs for maintenance treatment'

The claim at issue appeared on page 9 of item J, the Drug & Therapeutics Committee New Drug Request booklet, in a two page section headed 'Financial Implications'. The first page (page 8) discussed the costs of Symbicort comparative to current treatment options and a table depicted the community and hospital costs of Symbicort compared to six other combination asthma medications currently available. The claim at issue appeared at the top of page 9 above a table which set out the typical monthly (30 day) cost range for maintenance treatment with reference to their minimum and maximum licensed doses (mcg) of Symbicort and eight other maintenance treatments.

COMPLAINT

GlaxoSmithKline stated that for reasons stated in point 5, but more especially because the statement was made that like was being compared with like, GlaxoSmithKline alleged that the claim was misleading, and could not be substantiated in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

AstraZeneca stated that comparing asthma therapies raised a number of issues including adjusting dosage in line with the variation in disease severity. AstraZeneca considered that this could be sufficiently and comprehensively addressed by presenting the minimum to maximum licensed dosage for all therapies indicated for the maintenance treatment of asthma.

AstraZeneca also referred to its response at point 5.

PANEL RULING

The Panel considered that this cost comparison was different to that previously considered at point 5 above.

The comparison now at issue appeared in a booklet which was designed to place Symbicort on a formulary list. Section 1 of the booklet discussed the advantages of Symbicort over existing formulary drugs, Section 5 discussed the evidence of clinical superiority over similar formulary drugs. The Panel considered that the purpose of the booklet was thus to compare Symbicort with other products. Whilst the table at issue on page 9 was clearly labelled 'Typical monthly (30 day) costs for maintenance treatment' the section was introduced by the phrase 'Comparing like with like, …' which the Panel considered implied more than a comparison based upon cost alone. It implied that other variables such as dosage regimens and efficacy had been taken into account and that there was comparative evidence. The Panel noted that limited comparative evidence was presented in Sections 1, 5 and 7 of the booklet but not in relation to each medicine listed. The Panel considered the page misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel noted that Clause 7.3 was newly introduced to the 2001 Code. Some of the principles were included in Clause 7.2 including the requirement that comparisons must not be misleading. In the circumstances the Panel decided not to consider the matter in relation to Clause 7.3 of the 2001 Code. The matter was covered by Clauses 7.2 and 7.4 of the 2001 Code which were the same as Clauses 7.2 and 7.3 of the 1998 Code.

11 Claim 'Summary …. In adult patients with mild asthma Symbicort has been shown to be significantly more effective than double the dose of inhaled budesonide in improving morning and evening peak expiratory flow (PEF) …'

This claim appeared on page 3 of item K, the Symbicort Product Profile.

COMPLAINT

For the reasons stated in point 2, and as the claim as stated specifically referred to improvements in peak expiratory flow, which were not supported by clinically significant improvement, GlaxoSmithKline alleged that the claim was in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca referred to its response at point 2.

PANEL RULING

The Panel considered that the claim at issue was different to that considered at point 2. The Panel considered however that the claim was similar to those considered at points 7 and 8 and considered that those rulings were relevant here. No breach of Clause 7.2 was ruled.

12 Claim 'A clinical trial of 467 mild asthmatics, not optimally controlled on inhaled corticosteroids alone (mean dose 390mcg/day) showed Symbicort (100/6mcg bd) to be significantly more effective than double dose inhaled budesonide (200mcg bd) alone, in increasing morning PEF, evening PEF and symptom free days over a 12 week period'

This claim appeared on page 7 of item K, the Symbicort Product Profile, in a section headed 'Symbicort vs double dose budesonide monotherapy' and was referenced to Lalloo *et al*.

COMPLAINT

For the reasons stated in point 2, and as the claim as stated specifically referred to improvements in peak expiratory flow, which were not supported by clinically significant improvement, GlaxoSmithKline considered that this statement was in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca referred to its response at point 2.

PANEL RULING

The Panel noted that the claim at issue was different to the considered at point 2. The Panel considered that the claim was similar to that considered at points 7, 8 and 11. No breach of Clause 7.2 was ruled.

Complaint received **9 July 2001**

Case completed **19 November 2001**

CASE AUTH/1207/7/01

ASTRAZENECA v GLAXOSMITHKLINE

Promotion of Seretide

AstraZeneca complained about the promotion of Seretide, a combination of a long-acting bronchodilator (salmeterol) and a corticosteroid (fluticasone), by GlaxoSmithKline. AstraZeneca marketed Symbicort, a combination of a corticosteroid (budesonide) and a long-acting bronchodilator (formoterol).

Seretide Accuhaler was a fixed dose of salmeterol (50mcg) plus 100, 250 or 500mcg of fluticasone. Seretide Evohaler was a fixed dose of salmeterol (25mcg) plus 50, 125 or 250mcg of fluticasone. The products were indicated for the regular treatment of asthma where use of a combination product (long-acting ß2-agonist and inhaled corticosteroid) was appropriate in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting ß2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting ß2-agonist.

The claim 'The moment I stopped feeling like an asthmatic' was the third claim in a journal advertisement beneath the statements 'The moment I caught him looking at me' and 'The first time I went on holiday ... without my parents'. AstraZeneca alleged that the claim was an exaggeration of any benefit Seretide might have by implication. Asthma was a chronic condition and the majority of patients would continually require medication to treat their symptoms especially where maintenance treatment was recommended. However, Seretide was not licensed for acute use and advice for short-acting ß2-agonist usage when patients became uncontrolled on Seretide was given in the summary of product characteristics (SPC). So even when patients were well controlled and symptom free on maintenance doses of Seretide, reliever medication was still recommended. Having rescue medication available and taking medication on a regular basis would continually remind the patient of their condition and they would therefore feel like an asthmatic. AstraZeneca did not agree that adequately controlling symptoms would stop a patient from feeling as if he or she was an asthmatic.

AstraZeneca was concerned that the claim might imply that Seretide had a possible curative effect and it was therefore misleading. This was clearly not so with Seretide, nor with any other asthma medication. GlaxoSmithKline had stated that the claim was based upon personal testimonies from asthmatics who had been treated with Seretide. AstraZeneca did not consider such reports represented robust evidence to support such a major claim, which formed the underlying theme of the current promotional campaign.

The Panel considered that the audience would be very familiar with the nature of asthma and would not think that Seretide had a possible curative effect. In the Panel's view, the advertisement implied that the effect of Seretide on the symptoms of asthma meant that the patient did not feel like an asthmatic. There was no implication that asthma could be cured or that all patients would stop feeling like asthmatics.

The data provided was for the Seretide Accuhaler 100, 250 and Seretide 50 MDI. The asthma quality of life questionnaire (AQLQ) results showed that improvements in all domains from baseline were >0.5 indicating that patients would feel the benefit. Juniper *et al* (1994) stated that a within subject change in score of 0.5 represented the minimal important difference. A change in score of 1 might be considered a moderate change in quality of life. A change in score of more than 1.5 was likely to represent a large change, although it was noted that the current study's estimate of what constituted a large change in score was extremely imprecise. GlaxoSmithKline also referred to four other studies, Kavuru *et al*, data on file, Shapiro *et al* and Jenkins *et al*. All the data showed advantages in some parameters for Seretide compared to fluticasone, beclometasone and budesonide. Patients taking Seretide would need to have their relief medication available at all times. The data indicated that Seretide reduced rescue medication use compared with fluticasone, beclometasone and budesonide. The Panel did not consider that the claim was misleading, exaggerated or all embracing as alleged. The Panel ruled no breach of the Code. The Panel noted the submission that the claim was based on clinical evidence. The patient quotations and testimonies were provided as additional support to the clinical evidence. The Panel considered that the claim was substantiated by the clinical data and the patient testimonies. No breach of the Code was ruled in that regard.

Upon appeal by AstraZeneca, the Appeal Board noted that asthma was a chronic condition; patients whose symptoms were well controlled might experience an exacerbation. There was no implication that asthma could be cured. The Appeal Board considered that the claim 'The moment I stopped feeling like an asthmatic' was not an unreasonable description of how patients with a chronic condition might feel when symptom control was achieved. On this narrow point the Appeal Board upheld the Panel's ruling of no breach of the Code.

The Appeal Board noted the AQLQ data showed that improvement in all domains from baseline was >0.5 indicating that patients would perceive a benefit. Data also indicated that Seretide reduced rescue medication use compared with fluticasone, beclometasone and budesonide. The AQLQ data demonstrated a change from baseline whilst the claim at issue inferred an absolute change in the patient's perception. Further, the data provided did not relate to the entire patient population for whom Seretide was indicated ie those who were already adequately controlled on an inhaled corticosteroid and a long-acting ß2 -agonist. The Appeal Board did not consider that patient testimonies would be sufficient or appropriate evidence to substantiate such a claim and in this regard noted GlaxoSmithKline's submission that they were supplemental to the clinical evidence.

The Appeal Board considered that the claim would be read in the context of the advertisement as a whole. Accompanying text read 'There are some moments when you realize that your life will never be the same again. By changing the way people feel about their asthma, Seretide can change the way they feel about their lives. It's a feeling they'll want to keep'. The Appeal Board considered that in the context of the advertisement the claim implied a continuing effect for the rest of the patient's life. On balance the Appeal Board considered that the claim at issue was a strong one and the data presented was insufficient. The claim was exaggerated and thus could not be substantiated. The Appeal Board ruled breaches of the Code.

The claim 'Great control patients can feel' appeared as a strapline below the product logo at the bottom of a number of pages of the detail aid, some of which were reproduced in the relevant briefing document. AstraZeneca alleged that the word 'great' was a superlative in breach of the Code. The supporting references, Shapiro *et al* and Kavuru *et al*, did not support great control. These studies reported that the number of withdrawals from Seretide due to worsening of asthma was low. Given that patients might often not have absolute control yet remain in the study this did not substantiate 'great control' as a measure of the extent of clinical response. The claim was also based upon the Juniper *et al* (1999) study which determined the level of change in quality of life from baseline, experienced by asthma patients treated with Seretide. For overall asthma-related quality of life and for all individual domains including activities and symptoms the minimum important difference in AQLQ score was 0.5. The change in AQLQ score from baseline for Seretide ranged between 0.45 (activities) and 0.77 (symptoms). None of these values met the criteria for a moderate change with Seretide ie a difference in score of 1. Therefore there was no evidence to support an improvement in quality of life to be regarded as even moderate. Moreover interpreting the level of improvement as 'great' was a gross exaggeration of the data and likely to mislead prescribers.

The Panel did not agree that the word 'great' was a superlative as alleged. The superlative would be 'greatest'. No breach was ruled in that regard. With regard to the claim, the Panel noted its comments above regarding Juniper *et al* 1994. The Panel considered that by using the word 'great', the claim was a strong claim and there was not sufficient supporting data. The quality of life data appeared to indicate a moderate change in quality of life assessment by the patient. The Panel considered that the claim was misleading and a breach of the Code was ruled.

The claim 'Seretide 50 is great value at £19.50' appeared as one of three summary points on the penultimate page of the detail aid. The flow of the detail aid was such that the summary points were designed to be detailed directly after the efficacy profile of high dose Seretide 250 in severe asthma had been discussed. AstraZeneca alleged that reminding a health professional of the price of low dose Seretide 50 when the benefits of high dose Seretide 250 had just been focused upon was misleading. AstraZeneca was concerned that the prescriber might be under the impression that severe asthmatic patients could be adequately controlled with the cheapest presentation of £19.50. This was not so.

AstraZeneca was also concerned that the claim appeared directly under the claim 'Seretide gives great control patients can feel'. This clearly misled the reader as not all patients would get control, whether 'great' or not from using low dose Seretide 50. Many patients with severe asthma might require Seretide 250 to adequately control their symptoms. This was priced at £66.98, a marked increase from £19.50. Furthermore patients treated with Seretide 250 might not necessarily achieve 'great control'. It was for these reasons that the claim inferred that Seretide 50 would provide clinical efficacy and value for money for all patients. AstraZeneca alleged the claim to be an over-statement and consequently misleading.

The Panel noted that the improvement in quality of life scores of Seretide Accuhaler 250 compared to budesonide 800mcg bd was discussed followed by a page showing all the Seretide presentations and suggesting that patients not controlled on various doses of beclometasone be switched to various Seretide doses. The previous claim 'Seretide gives great control patients can feel' had been ruled in breach of the Code above. The claim now at issue was opposite a page showing all the Seretide presentations. The representatives briefing material stated that the 'focus should be on switching beclometasone 100 patients to Seretide 50, whilst showing the range of inhalers to overcome any potential flexibility objection'. With regard to the page at issue, the briefing material linked Seretide 50 with patients not well controlled on beclometasone 100mcg 2 bd. On balance the Panel did not consider that the claim inferred that Seretide 50 would provide clinical efficacy for all patients and ruled no breach of the Code.

Upon appeal by AstraZeneca, the Appeal Board noted that whilst Seretide 50 was the least expensive presentation it was also the least commonly prescribed Seretide presentation. The Appeal Board considered the claim too simplistic; the context in which Seretide 50 represented great value had not been made sufficiently clear. The Appeal Board considered that the claim was misleading and a breach of the Code was ruled.

A support card headed 'Great control from the first dose' included a graph from Shapiro *et al* 2000 showing the mean change from baseline in FEV_1 on day 1 for Seretide 250 Accuhaler bd and fluticasone 250 mcg Accuhaler bd. The graph referred to a clinically significant improvement as being 15% over baseline. This was achieved by Seretide approximately 30 minutes after the first dose until 12 hours after the first dose. Fluticasone did not achieve a clinically significant improvement. AstraZeneca did not consider the graph was capable of substantiating 'great control' for reasons expressed above. An accurate measure of control needed to be based upon a number of clinical

parameters and not just FEV_1 alone. Control was a long-term measure and could not be determined from lung function efficacy observed from the first dose of a medicine.

The Panel's view was that control was a long-term feature and could not be demonstrated in a graph showing the effect of 12 hours post dose. The Panel noted GlaxoSmithKline's submission that clinically significant and relevant improvement was sustained at the first dose level or above for the duration of the 12 week study. There was no reference to this on the material in question. In any event control of asthma was more than showing changes in FEV_1 over 12 hours. The Panel considered the material was misleading as alleged and a breach of the Code was ruled.

A bar chart entitled 'Results: Improvement in quality of life over 24 weeks' appeared in a booklet entitled 'The Role of Seretide in the Management of Asthma in Primary Care'. The chart showed the improvement in AQLQ score for five domains, overall AQLQ score, activity limitation, asthma symptoms, emotional functioning and environmental exposure for Seretide 250 Accuhaler bd compared to budesonide turbo inhaler 800mcg bd. The graph indicated that there were statistically significant and clinically meaningful changes from baseline for all five domains for Seretide. The changes for budesonide were also statistically significant and clinically meaningful changes from baseline with the exception of activity limitation and emotional functioning. GlaxoSmithKline had informed AstraZeneca in June that materials containing this bar chart were no longer in use.

AstraZeneca stated that presenting the treatment bars for Seretide and budesonide adjacent to each other for each of the five measured domains gave the visual impression that Seretide was more effective than budesonide in improving quality of life and was misleading. Firstly, the difference in mean improvement AQLQ scores between the two treatments only reached statistical significance for two of the five domains. This was not indicated on the graph nor in the accompanying text. Secondly, the supporting study (Juniper *et al* 1999) concluded that the magnitude of difference between the two treatments did not reach the minimal important difference of ≥0.5 to imply clinical significance. The heading to the page 'Greater control means improved quality of life' purposely stood as a hanging comparison. This, together with the visual impression given by the bar chart, invited the reader to assume that the heading to the page was a conclusion drawn from comparing Seretide with budesonide. This was misleading.

The Panel considered that the graph gave a visual impression that there was a clinical difference between Seretide and budesonide. The position was complicated as the Juniper abstract gave different results to the Juniper poster. According to the poster the difference in mean change in AQLQ score between the treatments only exceeded 0.5 for the asthma symptoms domain. It appeared from the poster that the difference between Seretide and budesonide was statistically significant for all domains. This was not the same as a clinical difference. The difference shown in the graph was not borne out by the data. The presentation was misleading in relation to the clinical difference between the products and a breach of the Code was ruled. With regard to the heading the Panel considered that it gave the impression of a clinical difference between the products and as above this was not borne out by the data. The heading was misleading and a breach of the Code was ruled.

The claim 'Quick onset of Seretide action that patients can feel from the first dose' appeared in the booklet as a bullet point beneath the heading 'Seretide: Great control you can feel'. AstraZeneca stated that prescribers associated a 'quick' bronchodilatory effect with the relief achieved from using short-acting bronchodilators and formoterol, 1-3 minutes after inhalation. Salmeterol (within Seretide) had a significantly slower onset of action ie 20 minutes. Using the term 'quick' to describe Seretide's onset of action was clearly misleading.

The Panel did not accept that the claim in full would be seen as a comparison between the effects of Seretide and short-acting bronchodilators and formoterol. No breach of the Code was ruled.

AstraZeneca UK Limited complained about the promotion of Seretide (salmeterol and fluticasone) by GlaxoSmithKline. Salmeterol was a long-acting bronchodilator ($ß_2$-agonist) and fluticasone was a corticosteroid. AstraZeneca marketed Symbicort, a combination of a corticosteroid (budesonide) and a long-acting bronchodilator (formoterol).

Seretide Accuhaler was a fixed dose of salmeterol (50mcg) plus 100, 250 or 500mcg of fluticasone. Seretide Evohaler was a fixed dose of salmeterol (25mcg) plus 50, 125 or 250mcg of fluticasone. The products were indicated according to their respective summary of product characteristics (SPCs) for the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) was appropriate in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2-agonist or patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

A Journal Advertisement (ref GEN 26725/B/R1 March 2001)

The advertisement, which appeared in Prescriber, June 2001, featured a photograph of part of a woman's chin and lips.

Claim 'The moment I stopped feeling like an asthmatic'

This was the third claim on the advertisement beneath the statements 'The moment I caught him looking at me' and 'The first time I went on holiday ... without my parents'.

COMPLAINT

AstraZeneca alleged that the claim was an

exaggeration of any benefit Seretide might have by implication.

Asthma was a chronic condition and the majority of patients would continually require medication to treat their symptoms. This was especially true where maintenance treatment was recommended. However, Seretide was not licensed for the acute setting and advice for short-acting ß$_2$-agonist usage when patients became uncontrolled on Seretide was given in the summary of product characteristics (SPC). So even when patients were well controlled on maintenance doses of Seretide and were consequently symptom free, reliever medication was still recommended. Having rescue medication available and taking medication on a regular basis would continually remind the patient of their condition and therefore feel like an asthmatic.

AstraZeneca did not agree that adequately controlling asthma symptoms would stop patients from feeling as if he or she was an asthmatic.

AstraZeneca was concerned that the claim might imply to prescribers that Seretide had a possible curative effect and it was therefore misleading. This was clearly not so with Seretide nor with any other medication involved in the treatment of asthma. Breaches of Clauses 7.2 and 7.10 of the Code were alleged.

AstraZeneca stated that GlaxoSmithKline proposed that the claim was based upon personal testimonies from asthma patients who had been treated with Seretide. However, AstraZeneca did not consider individual reports represented robust evidence to support such a major claim, which formed the underlying theme of the current promotional campaign. AstraZeneca alleged a breach of Clause 7.4 of the Code.

RESPONSE

GlaxoSmithKline submitted that there was no implication that Seretide had a possible curative effect. It was well known that asthma for most patients was a chronic condition for which there was no known cure. However, with any treatment that was successful, there would be a time when the patient became aware of the change in their condition.

The claim was intended to portray the way a patient felt about having successfully treated asthma. With successful treatment the limits that asthma placed on a patient's life were lessened or removed, allowing the patient to do more than they were able to do before.

With asthma, many patients experienced considerable morbidity; it might restrict their ability to exercise or their social interactions. Studies had repeatedly reported that a patient's lifestyle was affected by their asthma. An important goal of asthma management was to control symptoms and thus improve the health-related quality of life of patients.

GlaxoSmithKline submitted that quality of life had been assessed in several Seretide studies, using the disease-specific asthma quality of life questionnaire (AQLQ). The AQLQ had been validated and contained 32 items in four domains: activity limitation, asthma symptoms, emotional function and environmental exposures. Juniper *et al* (1992) determined that a mean change in score of ≥0.5 overall or within an individual domain was clinically meaningful and meaningful to the patient.

The improvements in asthma-related quality of life that had been shown with Seretide had been produced across a range of doses and devices (Reese *et al* 1998, Juniper *et al* 1999 and data on file). The AQLQ results from these studies reported changes in overall quality of life, and specifically in terms of asthma symptoms, activity limitation, emotional function and ability to withstand environmental exposure. The improvements from baseline in quality of life with Seretide were both statistically and clinically significant ($p<0.001$ vs baseline). Improvements in AQLQ score >0.5 were seen across all domains and overall, in the four studies, indicating that patients could feel the benefit; moreover, for most of the domains the improvement in AQLQ score was over 1.0.

The results of the studies showed that the changes were not only statistically significant, but according to the testing applied to the quality of life questionnaire by its designer, Juniper, were well above that level which was noticeable to the patient.

Improvements in asthma-related quality of life from baseline in all domains, for patients on Seretide were demonstrated in these studies. These changes in overall assessment and the individual domains of the four studies detailed were shown to be between 0.72 and 1.32, with a mean over the four studies of 1.02. In none of the studies was the change from baseline for Seretide less than 0.5.

This claim was further supported by the improvements in other efficacy measures that would be perceptible to patients that had been evaluated in studies on Seretide.

Seretide 100 Accuhaler bd significantly increased the number of symptom-free days by 22.6% from baseline compared with a 7.2% change for fluticasone ($p\leq0.025$). Seretide also significantly increased the number of days when no rescue medication was needed and the percentage of nights with no awakenings (Kavuru *et al* 2000).

In a study comparing low dose Seretide MDI with beclometasone MDI, Seretide 50 MDI significantly improved the percentage of ß$_2$-agonist rescue-free days compared with beclometasone 100 MDI (52% v 14%), and also produced a greater change in the percentage of symptom-free 24 hour periods compared with beclometasone (48% v 9%) (data on file).

Seretide 250 Accuhaler bd had been shown to significantly increase the number of symptom-free days by 33.8% from baseline compared with a 15.4% change for fluticasone ($p\leq0.015$). Seretide also significantly reduced rescue medication use compared with fluticasone ($p\leq0.015$) (Shapiro *et al* 2000).

In a study comparing Seretide 250 Accuhaler bd and budesonide Turbohaler 800mcg bd, Seretide 250 Accuhaler bd was significantly more effective at increasing the percentage of days with no asthma

symptoms and reducing daytime use of reliever medication compared with budesonide 800mcg bd ($p \leq 0.001$) (Jenkins *et al* 2000).

GlaxoSmithKline submitted that with regular and effective preventative treatment, such as Seretide, many patients would have days where they were symptom free and therefore did not feel like an asthmatic. That these changes could be experienced and perceived as positive improvements was not only demonstrated in clinical studies, but also supported by feedback from patients.

Patient research and testimonies had reported on the way in which Seretide had impacted upon their life. In these, patients reported that following the prescription of Seretide their lifestyle had changed in a noticeable way.

Formal market research had been carried out on patients prescribed Seretide. Non-directive questions were put to patients asking them to detail how their asthma had been since they had been taking Seretide. Without prompting many patients used words such as 'control' and phrases such as 'I just feel I almost haven't got asthma'. Details were provided.

GlaxoSmithKline stated that these quotations and testimonies were not presented as definitive evidence to support the claim 'The moment I stopped feeling like an asthmatic'. They were provided as additional support to the clinical evidence detailed above. The AQLQ studies clearly demonstrated that patients could feel the difference to their lives when taking Seretide. This was supported by symptomatic improvements in clinical studies. The patient descriptions of lifestyle improvements showed that these improvements were not just a product of clinical research, but reflected the real life impact the prescribing of Seretide had on patients.

GlaxoSmithKline considered that to a patient whose lifestyle had been restricted by asthma, when they appreciated that this lifestyle had improved in a noticeable way, the realisation would be memorable.

A patient would clearly need to continue to take regular medication, and have reliever medication available. The SPC for Seretide stated that patients should have a reliever inhaler available to treat any breakthrough asthma symptoms.

GlaxoSmithKline submitted that it made no suggestion that a patient who was prescribed Seretide would stop being an asthmatic. It suggested that they stop feeling like an asthmatic. It made no suggestion that patients taking Seretide did not need to carry a reliever inhaler. GlaxoSmithKline did not suggest that, as research had shown, they might need to use their rescue medication less often. Studies had demonstrated that patients taking Seretide had a significant increase in the percentage of symptom-fee days and of days where little or no rescue medication was required. If a patient experienced good symptom control and a significant reduction in the need for rescue medication, then they would not constantly be reminded that they were an asthmatic.

GlaxoSmithKline therefore considered that the claim 'The moment I stopped feeling like an asthmatic' was not exaggerated or all-embracing. The claim could be substantiated and was an up-to-date evaluation of the evidence. There was no breach of Clauses 7.2, 7.4 and 7.10 of the Code.

PANEL RULING

The Panel considered that the audience would be very familiar with the nature of asthma and would not think that Seretide had a possible curative effect as alleged by AstraZeneca. In the Panel's view the advertisement implied that the effect of Seretide on the symptoms of asthma meant that the patient did not feel like an asthmatic. There was no implication that asthma could be cured or that all patients would stop feeling like asthmatics.

The data provided was for the Seretide Accuhaler 100, 250 and Seretide 50 MDI. The AQLQ results showed that improvements in all domains from baseline were >0.5 indicating that patients would feel the benefit. Juniper *et al* (1994) stated that a within subject change in score of 0.5 represented the minimal important difference. A change in score of 1.0 might be considered a moderate change in quality of life. A change in score of more than 1.5 was likely to represent a large change although it was noted that the current study's estimate of what constituted a large change in score was extremely imprecise.

The Panel noted that GlaxoSmithKline had also referred to four other studies, Kavuru *et al*, data on file, Shapiro *et al* and Jenkins *et al*. All the data showed advantages in some parameters for Seretide compared to fluticasone, beclometasone and budesonide.

Patients taking Seretide would need to have their relief medication available at all times. The data supplied by GlaxoSmithKline indicated that Seretide reduced rescue medication use compared with fluticasone, beclometasone and budesonide.

The Panel did not consider that the claim was misleading, exaggerated or all embracing as alleged. The Panel ruled no breach of Clauses 7.2 and 7.10 of the Code.

The Panel noted the submission that the claim was based on clinical evidence. The patient quotations and testimonies were provided as additional support to the clinical evidence. The Panel considered that the claim was substantiated by the clinical data and the patient testimonies. No breach of Clause 7.4 of the Code was ruled.

APPEAL BY ASTRAZENECA

AstraZeneca stated that the claim implied that special properties of Seretide could allow patients to stop feeling that they had asthma. The claim represented an extrapolation and exaggeration of the benefits of Seretide, as demonstrated through clinical trials and anecdotal patient reports, in breach of Clause 7.10 of the Code. Furthermore such an exaggeration would inevitably convey a misleading message to those involved in asthma management. Patients who no longer, or to a lesser extent, experienced symptoms were continually and regularly reminded of their condition through other means such as taking medication and doctors' appointments and check ups.

A message which suggested that patients became less aware of their asthma inferred that such patients would also become less concerned about their potentially life-threatening condition. Therefore this claim breached Clause 7.2 of the Code.

Whilst AstraZeneca agreed that there was evidence to support the clinical efficacy of Seretide it did not substantiate the absolute statement that 'patients no longer feel that they have asthma'. This was therefore a breach of Clause 7.4.

AstraZeneca wished to appeal the Panel's decision on each clause in relation to this claim on the basis of the following:

1 The ability of the cited studies to underpin 'The moment I stopped feeling like an asthmatic'

AstraZeneca acknowledged the ability of Seretide to provide clinical benefits (as demonstrated in the cited studies), but not remove the feeling of being an asthmatic.

AstraZeneca had closely reviewed these studies with particular reference to study design, duration, endpoints, results and the appropriateness of their interpretation to add validity to the claim. Particular points that highlighted a clear disparity between features of the studies and the claim were listed below:

Quality of life studies using the AQLQ

Although the validity of the AQLQ as a useful tool within asthma clinical studies was accepted, none of the four domains (activity limitation, asthma symptoms, emotional function and environmental exposure) specifically represented a measurement that equated to a patient's personal perception/ acknowledgement of their individual asthma.

The correct interpretation of the changes in AQLQ was imperative in terms of the conclusions that could be drawn from studies and claims in relation to medicines used in the study:

A change in AQLQ score of 0.5 from baseline was accepted as the minimal change to be clinically important. This meant that a patient would have to achieve this minimum improvement for it to be of clinical significance. It did not mean that in patients achieving a change of 0.5 this was necessarily of clinical relevance in all the individual patients. A moderate change was accepted to be around 1 and a large change considered to be 1.5 or more.

Studies measuring the AQLQ were Reese *et al* 1998, Juniper *et al* 1999 and data on file. Juniper *et al* 1992 was not a Seretide intervention study but a validation of AQLQ.

The AQLQ score in the Reese study was presented as changes from baseline relative to other treatment arms. It was not possible to evaluate the absolute changes from baseline for the Seretide group and therefore comment on the ability to substantiate the claim above.

Both Juniper and data on file presented the changes from baseline for each treatment arm. The ranges of improvements in the score were 0.45 – 0.77 and 0.95 – 1.32 respectively. The figures quoted were relative to pre-randomisation baseline scores. For an individual patient to truly feel relinquished of his/her asthma limitations (and therefore stop feeling like an asthmatic), there would have to be a significantly large change from the baseline value. This would reasonably be expected to be a change of 1.5 or more. There was no evidence for such a significant change with the Seretide group. Indeed in some of the domains, the improvements failed to reach the thresholds for minimally important (0.5) or moderate (1.0) changes.

The studies quoted that used the AQLQ failed to support patients stopping feeling like asthmatics as there were only 3 with Seretide intervention; only 2 presented the data as absolute changes from baseline; the magnitude of change in the AQLQ in these 2 studies ranged from below minimally important to moderate with great inconsistency.

Comparators

Although comparators of inhaled steroid alone, long-acting beta-agonists alone and placebo were present in the studies they had no relevance to this case and supporting the claim. Indeed, salmeterol alone, as a single therapy for asthma, was not licensed in the UK.

The only pertinent feature in the context of the claim was the ability, or otherwise, of the Seretide treatment arm in any/all of the studies to provide outstanding benefits that eliminated symptoms to warrant such a claim.

Compliance

A recurring problem with controlled clinical trials was the ability to extrapolate the results into practice. One of the reasons for this was that compliance in such circumstances was accepted to be far superior to the real life clinical situation. Indeed, in the Kavuru and Shapiro studies the mean compliance rates were 93-100% and 91-95% respectively. This would aid achievement of clinical results that could probably not be repeated in clinical practice. Therefore, in addition to concerns over the results to support the claim, there were also serious doubts that these could be extrapolated into practice.

Duration of studies

All of the cited studies lasted 12 weeks with the exception of Jenkins (24 weeks). The chronic nature of asthma (including well-controlled asthma) could not be reflected in the timeframe of these studies. Patients who experienced better control for three to six months could not be considered to be free of limitations imposed by asthma and the potential to have attacks in the future. The duration of these studies did not allow the extrapolation of the results into the claim above. This extrapolation was seriously flawed as it failed to respect the chronic variable nature of asthma over a period of many years.

Symptom scores

The symptom scores used in Kavuru, Shapiro and

Jenkins were six point scales that were subjectively recorded by patients. There was no indication of a validation for the magnitude of change that was clinically significant. The values recorded reflected the patients' perception of their individual asthma.

At baseline, the patient was subjectively assessing his/her own asthma prior to randomization. The Jenkins paper mentioned the six point symptom score within the 'assessments' section but failed to present any data that specifically presented the pre-randomization and post intervention symptom score. An evaluation of this study and its ability to support the claim, was not possible in the absence of this essential clinical data which was a subjective perception of the patient and his/her asthma.

In the Kavuru study the Seretide group had a baseline score of 1.5. Out of a possible score of 0 to 5, this did not represent significant pre-randomization morbidity (0 = no symptoms, 5 = symptoms that significantly affect daily activities). The reduction was 0.7 which, in the absence of validation, could reasonably be considered to be not outstanding in magnitude. From a low baseline morbidity, the change was not dramatic enough to support the concept of patients no longer feeling like asthmatics.

Similarly in the Shapiro study the baseline symptom score was a modest 1.4 with a reduction of 0.8.

To give credence to the claim it would be reasonable to expect mean reductions in symptom scores to be of a magnitude almost identical to the baseline scores ie symptoms/perception of symptoms eliminated to zero. These changes were not provided by Seretide therapy in any of the studies.

Lung function

The value of lung function improvements to support the claim raised considerable doubt. The perception of feeling like an asthmatic was subjective with very little useful correlation with clinical lung function measurements. A therapy containing a long-acting bronchodilator (Seretide) would be expected to bronchodilate and increase measured lung function without necessarily causing a proportionate improvement in subjective asthma well being.

Number of patients withdrawn from the study due to worsening of asthma

This parameter was used in the three 12 week studies (Kavaru, Data on File and Shapiro). The criteria for withdrawing patients, as attributable to worsening asthma, had been noted.

However, patients on Seretide not being withdrawn from the study, due to these criteria, did not represent a patient on asthma therapy for many years who forgot that they felt as if they still had asthma. More specifically, if a patient was not hospitalised for the duration of the 3 months, it did not imply that they would never be hospitalised throughout their asthma career. Similarly, patients not waking due to asthma over three months, did not imply that they would never be woken by asthma symptoms or correctly felt that this would never happen in the future.

In summary, despite clinical studies showing that Seretide provided clinical benefit and improvement in asthma patients they did not provide substantial evidence to support the claim that patients stopped feeling as though they no longer suffered from asthma. This claim therefore breached Clause 7.4 of the Code.

2 The inconsistency between acknowledging and encouraging good asthma management and 'no longer feeling like an asthmatic'

Asthma was a chronic condition and the majority of diagnosed patients needed treatment (controller, preventer or reliever medication) and avoidance of triggers and allergens, throughout their lives. The patients maintained an awareness of their symptoms.

Asthma was also variable in that patients experienced fluctuations in their symptoms and consequently varied their dosage of medication to achieve and maintain control. This was especially true where maintenance treatment was recommended and as a consequence in the case of Seretide could entail a change in the Seretide inhaler prescribed and used. In addition, as noted in GlaxoSmithKline's original correspondence patients would also continue to carry their rescue medication at all times whilst taking Seretide.

The fact that patients would thus be taking a chronic medication twice daily, which might need to be changed as the condition fluctuated, as well as carrying rescue medication would not therefore stop a patient feeling like an asthmatic.

Indeed, other chronic conditions such as diabetes demanded continual treatment and management and monitoring. Such patients would always be aware that they were diabetic despite the fact that symptoms and potential consequences of poor management were not always experienced.

Asthma treatment guidelines such as British Thoracic Society (BTS), and Global Initiative in Asthma Management (GINA) recognized this characteristic feature of variability in asthma and recommended treatment regimens that could adapt to such disease variability so that optimal control was maintained. For example, the BTS guidelines advocated the stepping up or down of inhaled steroid dose at times when more or less control was required.

A claim which inferred that, owing to a particular product, a patient would stop feeling as though they had a chronic, and potentially serious condition could encourage complacency or bring false hope to those involved in asthma management. Especially in relation to ongoing assessment of patients' asthma so that treatment regimens and dosage could be regularly monitored. Such practice was currently being introduced and encouraged in patient-centred management plans.

In summary, the claim conveyed a misleading and exaggerated message which was inconsistent with currently accepted good asthma management and therefore likely to encourage complacency and raise false hope amongst those involved in its treatment. It therefore contravened Clauses 7.2 and 7.10 of the Code.

3 Individual patient testimonies were not a valid reference

The patient testimonies cited included statements such as: 'I just feel like I almost haven't got asthma anymore' and '… it controls my asthma'.

They were all reports of the improvements patients had noticed and experienced since taking Seretide and the impact this had had on their well being. However none of the testimonies reported a feeling that their asthma had actually improved to the extent that they no longer felt that they had the condition.

In one of the cases a patient commented that '… it's early days … Seem to have control after a month'. This realistic observation took into account that asthma was for the majority of sufferers a chronic condition and therefore a month was a relatively small time to base assumption of symptom cessation upon.

In the claim, the words 'The moment I …' depicted a very poignant and significant point in time which, from then on a patient would never feel like an asthmatic again. It therefore implied the patient would expect to be symptom free for the rest of their lives. This clearly represented an overclaim as every health professional appreciated that asthma was an unpredictable, variable condition. There remained the possibility of an asthmatic experiencing for example an acute asthma attack or breakthrough symptoms at any point in the future. They would therefore continue to feel like an asthmatic during periods of their life to follow.

The claim 'The moment I stopped feeling like an asthmatic' gave an impression that a patient was recalling a memorable moment in his or her life that happened a long time ago. This time period being more than the 12 or 24 weeks' duration of the supporting clinical trials.

In summary, selected anecdotal reports from patients commenting on their asthma improvements whilst taking Seretide could not be used to substantiate a claim which reported a feeling of absolute cessation of their condition. They did not represent what could realistically be expected throughout the remainder of the chronic course of their asthma. Such an exaggeration rendered the claim misleading and in breach of Clauses 7.2 and 7.10 of the Code.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline considered that the overall tone of the appeal was not reflective of the claim in question and was based on a further exaggeration and extrapolation of it by AstraZeneca which stated that the claim represented an extrapolation and exaggeration of the benefits of Seretide and that furthermore, such an exaggeration would inevitably convey a misleading message to those involved in asthma management.

GlaxoSmithKline considered that this was in itself a pejorative statement especially in the use of the word 'inevitably'. It was an inaccurate reflection of the understanding of asthma treatments amongst health professionals. Clinicians were well aware that there were currently no curative treatments for asthma and it considered that given this understanding, the claim would not mislead as to imply that Seretide was possibly curative.

GlaxoSmithKline noted that AstraZeneca further extrapolated its argument to state that 'a message which suggests that patients become less aware of their asthma infers that such patients will also become less concerned about their potentially life-threatening condition'. GlaxoSmithKline considered that this statement was not substantiated by any evidence. It was unaware of any data suggesting that if patients became less aware of their asthma they would also become less concerned about their 'potentially life-threatening condition'. GlaxoSmithKline considered that patients should not have to suffer daily symptoms and limitations of their lifestyles, to be compliant with treatment.

GlaxoSmithKline also considered the use of the phrase 'potentially life-threatening condition' pejorative. Asthma was a condition where over 50% of patients experienced regular symptoms in terms of activity limitation, sleep disturbance and daytime coughing and wheezing. In this context a mortality rate of 0.026% (approximately 1400 per year) should be put into perspective. Most clinicians regarded asthma as life threatening only in relatively few patients at the severe end of the spectrum.

AstraZeneca had interpreted the claim in question to mean that patients prescribed Seretide would be cured of their asthma, that is, 'they no longer suffered from asthma', and experienced a long-term cure from asthma symptoms or exacerbations. GlaxoSmithKline submitted that this was not reflective of the interpretation that was made by health professionals.

The claim in question was intended to reflect a moment in time; to convey to health professionals, who might not be asthmatic and therefore might not have an appreciation of the impact daily symptoms and activity limitation had on an asthmatic's life, the impact that improved asthma control might have. This change could be meaningful to a patient with asthma. An example might be the moment a patient with asthma, who having rushed to catch a bus, realized that they were less breathless than on previous occasions. This might not seem to be a huge achievement, but for the patient it was the moment when they appreciated their improved asthma control. As a healthy and fully active health professional might not appreciate the impact that being able to run for a bus without feeling breathless might have on an asthmatic's life, GlaxoSmithKline tried to convey this impact in other life experiences; 'the moment I caught him looking at me', 'the first time I went on holiday without my parents'. These were all reflective of a moment's experience.

GlaxoSmithKline stated that it had presented data which showed that Seretide had a beneficial clinical treatment effect with an impact on quality of life. The AQLQ was a robust validated questionnaire, which was highly respected at an international level as an evaluation tool. GlaxoSmithKline considered that the data presented on quality of life, using the AQLQ, was appropriate in the assessment of the impact of

asthma and its treatment on a patient's life. AstraZeneca alleged that the AQLQ did not assess a patient's personal perception/acknowledgement of their individual asthma. This was incorrect. The AQLQ was based solely upon how patients perceived the impact of asthma on their lives, and more importantly it measured how specific interventions might change their perception.

All studies which had evaluated quality of life in treatment with Seretide showed a clinically significant improvement compared to baseline. Against an equivalent dose of inhaled steroid, Seretide showed improvement from baseline consistently greater than 1.0, in all domains and overall score. Even against an increased dose of inhaled steroid, improvements above the clinically significant level of 0.5 were shown in all domains and overall score.

In addition to these validated clinical data the individual impact on a patient's life and therefore its personal 'relevance' was supported by the individual patient testimonies.

GlaxoSmithKline did not agree that the claim was exaggerated, an extrapolation of the data or intended to mislead.

1 The ability of the cited studies to underpin 'The moment I stopped feeling like an asthmatic'

Quality of life studies using AQLQ

GlaxoSmithKline noted that AstraZeneca had stated that although the validity of the AQLQ as a useful tool in asthma clinical studies was accepted, none of the four domains specifically represented a measurement that equated to a patient's personal perception/acknowledgement of their individual asthma.

The Juniper AQLQ was based solely upon how patients perceived their asthma to affect their lives. More importantly it could measure a change in this perception with specific therapeutic interventions. The questionnaire consisted of 32 items in four domains: activity limitation, asthma symptoms, emotional function and environmental exposures. GlaxoSmithKline provided a list of items from the questionnaire and stated that these questions clearly set out to evaluate a patient's perception of their individual asthma.

GlaxoSmithKline noted that AstraZeneca alleged that although a change in AQLQ score of 0.5 from baseline was accepted as the minimal change to be clinically important it did not mean that in patients achieving a change of 0.5 this was necessarily of clinical relevance in all the individual patients. The company further stated that a moderate change was accepted to be around 1 and a large change considered to be 1.5 or more.

Juniper defined the change in AQLQ score of 0.5 as the smallest difference in score in the domain of interest which patients perceived as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management. Such a change would be an improvement to the patient's symptoms that they would notice and would perceive.

In its appeal AstraZeneca alleged that the 1992 Juniper study was not a Seretide intervention study but a validation of AQLQ. GlaxoSmithKline agreed and it had made it clear that this study was only referred to as a validation study and not as a Seretide intervention study.

In the same validation paper Juniper stated that a change in score of 1.0 might be considered a moderate change in quality of life with the caveat that, because only a small number of patients (in the validation study) had a large change in health-related quality of life, the current study's estimate of what constituted a large change in score was extremely imprecise.

Therefore a change in AQLQ score of 0.5 did indicate a clinically significant change which patients would perceive. Larger changes in AQLQ scores were more difficult to interpret and thus statements relating to how strongly patients perceived such changes should, in GlaxoSmithKline's opinion, be viewed with caution. However, as shown by the quality of life changes experienced in the studies detailed below, a mean change above 1.0 was experienced across all the studies. Greater improvements were seen where Seretide was compared with an equivalent dose of inhaled steroid rather than an increased dose of inhaled steroid.

There were 4 studies that supported the AQLQ data: Reese *et al* compared Seretide 250mcg Accuhaler with fluticasone 250mcg Accuhaler, salmeterol 50mcg and placebo. SAS30003 (McCarthy *et al* 2001 (in press)) compared Seretide 50mcg MDI with fluticasone 50mcg MDI; Juniper *et al* compared Seretide 250mcg Accuhaler with budesonide Turbohaler 800mcg and SFCA 3002 (McCarthy *et al* 2001 (in press)) compared Seretide 100mcg Accuhaler with fluticasone 100mcg Accuhaler.

GlaxoSmithKline noted that AstraZeneca alleged the AQLQ score in the Reese study was presented as changes from baseline relative to other treatments arms; this allegation was incorrect. The Reese study showed both changes from baseline and within group change in AQLQ. A graph was provided which showed for each treatment group mean changes in AQLQ scores from baseline. It was therefore possible to evaluate changes from baseline for each of the treatment groups.

GlaxoSmithKline noted that AstraZeneca also alleged that in the four studies in some of the domains the improvements failed to reach the thresholds for minimally important (0.5) or moderate (1) changes. This was incorrect. In every study cited the change from baseline was at least at the clinically significant level of 0.5 for all the individual domains and the overall score. These changes in overall assessment and the individual domains of the four studies detailed were shown to be between 0.72 and 1.32, with a mean over the four studies of 1.02. In none of the studies was the change from baseline for Seretide less than 0.5 either in the individual domain or the overall score. AstraZeneca had quoted the figures 0.45-0.77 from the Juniper abstract. GlaxoSmithKline stated that it had pointed out to AstraZeneca that these data in the abstract were incorrect and that correct data could be found in the poster.

GlaxoSmithKline noted that AstraZeneca alleged that not all the studies had Seretide as the intervention. GlaxoSmithKline stated that all four studies used Seretide as a comparator. All four studies presented the data as mean AQLQ changes from baseline, which was entirely appropriate. In all four studies the change from baseline for Seretide was consistently above the score of 0.5 and therefore consistently clinically meaningful.

There were no data to show a direct linear relationship between change in AQLQ score above 0.5 and the size of perceptual change.

GlaxoSmithKline stated that in its initial response it had reproduced the bar charts from the four studies presented as evidence: Reese *et al* (1998), Juniper *et al* and two studies by McCarthy *et al*.

Comparators

Three of the studies quoted above evaluated the effects of Seretide, and its individual components (salmeterol and fluticasone) and placebo. No claim was made in the use of these studies of the effects of Seretide compared to salmeterol. These studies were carried out in the USA, where salmeterol was recommended as monotherapy. Where the data from any of these studies was used in promotional materials in the UK, it was clearly stated that salmeterol was not recommended as monotherapy.

Compliance

AstraZeneca stated that due to the level of compliance associated with clinical trials, the results seen would not be reflective of true clinical practice and it seriously doubted the ability to extrapolate them into real life asthma. This was clearly a fallacious argument, as such a view would seem to invalidate any randomized double-blind clinical study on any medicine. It was accepted that clinical trials were associated with a higher level of compliance than that seen in real life. This was true for all randomized, controlled clinical trials and applied to all medicines, including Seretide or indeed Symbicort. Clinicians were well aware of this fact. Indeed, if one were to concur with AstraZeneca's view, this would invalidate the use of all clinical data except for real life observational data, in the development of best practice in clinical medicine. Current best practice accepted evidence-based medicine (EBM) as the foundation for good clinical care. EBM accepted randomized blinded controlled trials as the most robust form of clinical evidence.

GlaxoSmithKline highlighted that the patient testimonies might be seen as reflective of the impact that Seretide might have on real life asthma.

Duration of studies

GlaxoSmithKline noted that AstraZeneca alleged that the chronic nature of asthma could not be reflected in the timeframe of 12 to 24 weeks studies. The vast majority of studies were of 3-6 months duration and studies of this length were widely accepted by the Medicines Control Agency (MCA) as of sufficient duration to judge the effectiveness of medicines. GlaxoSmithKline accepted that asthma was a chronic disease and patients might experience symptoms for as long as 20 or 30 years. It was clearly unrealistic to expect the efficacy of treatment of a chronic condition only to be validly assessed if the studies covered the duration of the disease from its onset to the end of the patient's life. Extrapolations of normal trial periods to evaluate drug effectiveness were accepted.

The claim 'The moment I stopped feeling like an asthmatic' was intended to reflect a moment in time. GlaxoSmithKline was not claiming that patients would be free of future limitations or would not suffer exacerbations, as it fully understood the chronic and variable nature of the disease. It considered that data of 12 and 24 weeks' duration was sufficient to support a claim reflecting 'a moment'.

Symptom scores

GlaxoSmithKline noted that while AstraZeneca objected (incorrectly) that the AQLQ was invalid because it did not reflect the patient's individual perception of their asthma it now alleged that the use of symptoms scores was invalid because they did reflect the patient's individual perception of their asthma. The symptoms score used in this study was representative of those commonly used in many asthma studies not only those carried out by GlaxoSmithKline, but by other companies and academic centres. Such studies involved the use of diary card measurements, which reflected the severity and duration of the patient's symptoms. These symptoms covered those most commonly experienced in asthma (such as wheeze, shortness of breath, cough, night-time awakening). These symptoms also reflected those used by the National Asthma Campaign in their patients' symptom questionnaires.

GlaxoSmithKline noted that AstraZeneca alleged that the change in symptoms scores in the Kavuru and Shapiro studies were not outstanding in magnitude; no claim had been made that they were. However, in the group of patients in the Kavuru studies who were defined as having mild asthma, a decrease in symptoms score of nearly 50% was clearly clinically significant. This change was not being used to support the concept of patients no longer feeling like asthmatics. This change in perception was being supported by the quality of life data and was further supported by the patients' testimonies. It might also be noted that in the Shapiro study the improvements in symptoms score was greater than 50%.

GlaxoSmithKline noted that AstraZeneca alleged that to give credence to the claims the decrease in symptom score should be greater than 100%. If this were indeed the case it might justifiably claim that Seretide provided a cure for asthma.

Lung function

GlaxoSmithKline noted that AstraZeneca alleged the value of lung function improvements had very little correlation with symptom improvements. GlaxoSmithKline stated that it was generally agreed that a change in peak expiratory flow rate of between

15 and 20L/min was clinically relevant. Santanello claimed that a change in 18.9L/min could be perceived by the patients and was therefore clinically relevant. This would seem to support that changes in lung function did indeed have clinical relevance.

Number of patients withdrawn from the study due to worsening asthma

The exceptionally low withdrawal rates for patients on Seretide in the studies quoted of 3%, 3% and 4% highlighted the effectiveness of Seretide in controlling asthma. There was no assertion that these patients would never experience an exacerbation of asthma or that they would never require hospitalisation. These withdrawal rates did, however, substantiate the claim that Seretide provided good asthma control; that this improved control could be perceived by patients was supported by the AQLQ data.

2 The inconsistency between acknowledging and encouraging good asthma management and 'no longer feeling like an asthmatic'

GlaxoSmithKline considered that there was no inconsistency between encouraging good asthma management and providing medication that might allow patients to stop feeling like an asthmatic.

GlaxoSmithKline noted that AstraZeneca alleged that the need to take a chronic medication twice daily and carry rescue medication would be a constant reminder to the patient of their asthmatic state. GlaxoSmithKline re-iterated that it was not claiming that Seretide could stop patients being asthmatic. It was not suggesting that they could stop taking treatment and stop considering their disease. It was claiming that they could stop feeling like an asthmatic, and could experience a significant improvement in their asthma allowing them to undertake with less restriction various activities. This was supported by the clinically significant improvement in the quality of life as assessed by the AQLQ. It was also further supported by the patient testimonies in which patients themselves described the positive impact improved control had had for them.

The claim was not inconsistent with current treatment guidelines. AstraZeneca referred to the recommendations within the GINA guidelines of the adjustment of asthma treatment in response to patients' level of control – this was a particular interest of AstraZeneca in relation to their promotional campaign for Symbicort.

However, no promotion for Seretide had been contrary to GINA guidelines. GINA guidelines in particular recommended treatment aimed at reducing as far as possible the signs and symptoms of asthma. The GINA guidelines' goals of long term asthma management were minimal or no symptoms, including night-time symptoms; minimal asthma episodes or attacks; no emergency visits to doctors or hospitals; minimal need for as needed (quick relief) ß2-agonist therapy; no limitations on physical activities, including running and other exercise; nearly normal lung function and minimal or no side-effects from medication. GlaxoSmithKline considered that those goals were consistent with the promotion of Seretide.

Further to AstraZeneca's comments regarding adjustment of asthma therapy, although GlaxoSmithKline considered the quoted studies showed that the majority of patients on Seretide would not need adjustment of their therapy as control had been achieved, Seretide's SPC recommended that the dose of Seretide should be titrated to the lowest effective dose that maintained control. This recommendation was consistent with GINA guidelines. It also considered that these aims of the GINA guidelines were consistent with the sentiment of patients no longer having their lives dominated by their asthma, a sentiment endorsed within the promotional campaign for Seretide.

3 Individual testimonies were not a valid reference

GlaxoSmithKline stated that it did not present the individual testimonies as stand alone references; they were only used to support the clinical references and asthma quality of life.

GlaxoSmithKline noted that AstraZeneca alleged that the patient testimonies did not support the positive impact Seretide had on patients' lives, so that they might potentially stop feeling like being an asthmatic. GlaxoSmithKline did not agree. Formal market research had been carried out on patients prescribed Seretide. Non-directive questions were put to patients asking them to detail how their asthma had been since they had been taking Seretide. GlaxoSmithKline provided a list of quotations which it stated were a representative selection of the responses; the full text of the market research showing the questions posed and the patient responses was provided. Without prompting or the use of the leading questions many patients commented on how they had felt since starting Seretide, using words such as 'control', and phrases such as 'I just feel I almost haven't got asthma'.

GlaxoSmithKline stated that it had also received spontaneous reports from patients of the benefit Seretide had produced and reproduced two such reports.

These quotations and testimonies were not presented as definitive evidence to support the statement 'The moment I stopped feeling like an asthmatic'. They were provided as additional support to the clinical evidence supporting the statement. The AQLQ studies clearly demonstrated that patients could feel the difference to their lives when taking Seretide. This was supported by symptomatic improvements in clinical studies. The patient descriptions of lifestyle improvements showed that these improvements were not just a product of clinical research, but reflected the real life impact the prescribing of Seretide had had on patients.

GlaxoSmithKline noted that AstraZeneca also stated that the claim 'The moment I stopped feeling like an asthmatic' gave the impression that a patient was recalling an event that happened a long time ago and

therefore this was not supported by clinical trial data of 12 and 24 weeks. GlaxoSmithKline disagreed. The claim as stated previously also did not imply a long-term treatment effect or an 'absolute cessation of a condition'. It simply reflected a moment when a patient did not have their day limited, in whatever way was meaningful to them, to the same extent that they had prior to treatment with Seretide. This might be something that happened yesterday – it was an individual reflection.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that the claim represented an extrapolation of Seretide's benefits as demonstrated through clinical trials and anecdotal patient report and therefore the use of such an absolute statement to the effect that patients no longer felt as though they suffered from asthma was unjustified.

The clinical studies both individually and collectively did not support the concept of a patient gaining such clinical benefit from Seretide that would dramatically change their perception to no longer feeling like an asthmatic.

There were very clear and significant inconsistencies between generally accepted good clinical management and the perception of no longer feeling like an asthmatic.

Individual personal patient testimonies did not unequivocally support the claim; in some cases they contradicted it.

APPEAL BOARD RULING

The Appeal Board noted that asthma was a chronic condition; patients whose symptoms were well controlled might experience an exacerbation. There was no implication that asthma could be cured. The Appeal Board considered that the claim 'The moment I stopped feeling like an asthmatic' was not an unreasonable description of how patients with a chronic condition might feel when symptom control was achieved. On this narrow point the Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal was unsuccessful on this point.

The Appeal Board noted the AQLQ data provided showed that improvement in all domains from baseline was >0.5 indicating that patients would perceive a benefit. Data also indicated that Seretide reduced rescue medication use compared with fluticasone, beclometasone and budesonide. The Appeal Board noted that the AQLQ data demonstrated a change from baseline whilst the claim at issue inferred an absolute change in the patient's perception. Further, the data provided did not relate to the entire patient population for whom Seretide was indicated ie those who were already adequately controlled on an inhaled corticosteroid and a long-acting ß2 -agonist. The Appeal Board did not consider that patient testimonies would be sufficient or appropriate evidence to substantiate such a claim and in this regard noted GlaxoSmithKline's submission that they were supplemental to the clinical evidence.

The Appeal Board considered that the claim would be read in the context of the advertisement as a whole. Accompanying text read 'There are some moments when you realize that your life will never be the same again. By changing the way people feel about their asthma, Seretide can change the way they feel about their lives. It's a feeling they'll want to keep'. The Appeal Board considered that in the context of the advertisement the claim implied a continuing effect for the rest of the patient's life.

On balance the Appeal Board considered that the claim at issue was a strong one and the data presented was insufficient. The claim was exaggerated and thus could not be substantiated. The Appeal Board ruled breaches of Clauses 7.4 and 7.10 of the Code.

The appeal on these two points was successful.

B Briefing Document for Internal Use (ref GEN 26709/BP) Detail Aid 20238725-BP/January 2001

The material referred to by AstraZeneca was a briefing document for internal use which discussed a detail aid (ref 20238725-BP/January 2001).

1 Claim 'Great control patients can feel'

The claim appeared as a strapline below the product logo at the bottom of a number of pages of the detail aid, some of which were reproduced in the briefing document.

COMPLAINT

AstraZeneca alleged that the word 'great' was a superlative in breach of Clause 7.10 of the Code.

AstraZeneca stated that the supporting references, Shapiro *et al* and Kavuru *et al*, did not support great control. These studies reported that the number of withdrawals associated with Seretide usage due to worsening of asthma was low. Given that patients might often not have absolute control yet remain in the study this did not substantiate 'great control' as a measure of the extent of clinical response.

AstraZeneca stated that the claim was also based upon the Juniper *et al* (1999) study which determined the level of change in quality of life from baseline, experienced by asthma patients treated with Seretide. For overall asthma-related quality of life and for all individual domains including activities and symptoms the minimum important difference in AQLQ score was 0.5. Differences of 1.0 represented a moderate change and differences greater than 1.5 represented large changes (Juniper 1994). The change in AQLQ score from baseline for Seretide ranged between 0.45 (activities) and 0.77 (symptoms). None of these values met the criteria for a moderate change with Seretide ie a difference in score of 1. Therefore there was no evidence from the study to support an improvement in quality of life to be regarded as even moderate. Moreover interpreting the level of improvement as 'great' was a gross exaggeration of the data. This was likely to mislead prescribers about the benefits of Seretide. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline did not accept that the word 'great' was a superlative. Under the supplementary information to Clause 7.10 the word 'greatest' would be classified as a superlative. Great was defined as big; large; or a high degree of magnitude. The comparative was 'greater' and the superlative was 'greatest'.

The claim referred to the fact that Seretide provided highly effective control that resulted in clinically meaningful improvements in quality of life for patients, significant improvements that they could feel. GlaxoSmithKline submitted that the word 'great' was justified. Seretide had been shown to produce clinically significant improvements in four important aspects of asthma control; lung function (the primary endpoint in the majority of asthma clinical studies), overall asthma control (withdrawal from studies due to loss of control), symptom control and quality of life.

Lung Function

An improvement of FEV_1 of ≥15% was accepted as clinically significant in clinical trial design. This was exceeded in all three studies. Where peak expiratory flow (PEF) was the parameter, changes greater than 20L/min were generally taken to be clinically significant.

Santanello *et al* (1999) had shown that a change in PEF of 18.79L/min was the minimum change from baseline needed for a patient to perceive the improvement.

It was important to note that in the studies described below, the improvements in lung function produced with Seretide were over and above those achieved with what might be considered standard therapy for these patients – inhaled corticosteroids.

In three studies (Kavuru *et al*, data on file, Shapiro *et al*), Seretide was significantly more effective at improving lung function than fluticasone alone ($p \leq 0.025$). Both pre-dose FEV_1 and serial FEV_1 measurements were significantly greater with Seretide than with fluticasone alone ($p \leq 0.003$). The improvements in FEV_1 with Seretide were evident quickly from the first dose when starting treatment, with the majority of patients experiencing at least a 15% improvement within 30 minutes, and were maintained over the three-month study periods.

GlaxoSmithKline stated that in both the Kavuru and Shapiro studies, Seretide significantly improved mean morning PEF compared with fluticasone alone, demonstrating differences compared with fluticasone in excess of 35L/min.

Seretide 50 MDI (meter dose inhaler) had been compared with the most commonly prescribed inhaled corticosteroid, beclometasone, in a randomized, double-blind, double-dummy, parallel-group study. Seretide 50 MDI 2 puffs bd produced a statistically and clinically significant improvement in peak expiratory flow, 68L/min, compared with beclometasone 100mcg 2 puffs bd, 30L/min ($p<0.0001$) (SAS 30015 data on file 2001).

In further support of the claim 'great control', a randomized, double-blind and double-dummy study, conducted in patients ≥12 years, compared Seretide with a dose of budesonide greater than the accepted 2:1 fluticasone/budesonide microgram ratio. The study compared the efficacy of Seretide 250 Accuhaler bd with the maximum licensed dose of budesonide, 800mcg bd via the Turbohaler over 24 weeks in 354 patients symptomatic on beclometasone or budesonide at doses of 800-1200mcg/day. Mean morning PEF was the primary efficacy variable (Jenkins *et al* 2000).

Seretide 250 Accuhaler bd gave significantly greater improvements in mean morning PEF than budesonide Turbohaler 800 micrograms bd alone (45 L/min vs 22 L/min over 24 weeks, $p<0.001$). Significant differences in mean evening PEF and clinic FEV1 in favour of Seretide, over budesonide, were also seen ($p<0.001$). A table summarising the results was provided.

GlaxoSmithKline submitted that these results justified the claim as not only were the results highly statistically significant ($p \leq 0.003$), they were also clinically significant.

Overall asthma control

GlaxoSmithKline submitted that three of the studies referenced above (data on file, Kavuru *et al* and Shapiro *et al*) further supported the claim 'great control'. All evaluated the probability of remaining in the study as a measure of asthma control. Control (and thus loss of control) was defined in the study protocols and was a composite measure based on accepted measures of asthma control; lung function, asthma symptoms, use of $ß_2$-agonist reliever therapy and exacerbations.

The efficacy of Seretide 50 MDI, in terms of asthma control, was evaluated in a randomized, double-blind, placebo controlled, 12 week study, comparing Seretide with fluticasone, salmeterol and placebo. Asthma control was monitored throughout the study. Patients were withdrawn if they failed to meet the pre-determined criteria for asthma control. Seretide demonstrated superior control to other treatments with only 3% of patients withdrawing due to loss of control, compared with 41% for placebo, 37% for salmeterol and 9% for fluticasone ($p \leq 0.007$ for Seretide against all comparators) (data on file).

Kavuru *et al* compared the efficacy and safety of Seretide 100 Accuhaler bd with salmeterol 50mcg bd, fluticasone 100mcg bd or placebo over 12 weeks in 356 patients aged 12 years and over with a clinical history of asthma. The primary efficacy variables were based on FEV_1 and probability of remaining in the study. Patients were withdrawn from the study for 'lack of efficacy' if their asthma deteriorated during the study; probability of remaining in the study was based on the criteria of good asthma control. Patients who failed to meet any of these criteria were withdrawn from the study. Only 3% of patients on Seretide withdrew due to poor asthma control over the 12 weeks of the study compared with nearly 50% on placebo, 35% on salmeterol, and 11% on fluticasone ($p \leq 0.02$ for Seretide against all comparators).

Shapiro *et al*, a study of similar design and with similar markers of asthma control, compared the efficacy and safety of Seretide 250 Accuhaler bd with salmeterol 50mcg bd, fluticasone 250mcg bd or placebo over 12 weeks in 349 patients aged 12 years and over with a clinical history of asthma. Like the Kavuru study, the probability of remaining in the study was based on the criteria of good asthma control. Patients who failed to meet these criteria were withdrawn from the study. In this study only 4% of patients on Seretide dropped out due to poor asthma control over the 12 weeks of the study compared with 62% on placebo, 38% on salmeterol and 22% on fluticasone ($p \leq 0.002$ for Seretide against all comparators).

GlaxoSmithKline submitted that these very low withdrawal rates of between 3 and 4% when compared to the drop out rates of the comparator therapies supported the claim 'great control'.

Symptom control

GlaxoSmithKline stated that the claim was further supported by the improvements in other efficacy measures evaluated in studies on Seretide and detailed in response to point A.

Seretide 100 Accuhaler bd significantly increased the number of symptom-free days by 22.6% from baseline compared with a 7.2% change for fluticasone ($p \leq 0.025$). Seretide also significantly increased the number of days when no rescue medication was needed and the percentage of nights with no awakenings (Kavuru *et al*).

In a study comparing low dose Seretide MDI with beclometasone MDI, Seretide 50 MDI significantly improved the percentage of $ß_2$ agonist rescue-free days compared with beclometasone 100 MDI (52% v 14%), and also produced a greater improvement in the percentage of symptom-free 24 hour periods compared with beclometasone (48% v 9%) (data on file).

Seretide 250 Accuhaler bd had been shown to significantly increase the number of symptom-free days by 33.8% from baseline compared with a 15.4% change for fluticasone ($p \leq 0.015$) (Shapiro *et al*) and to be significantly more effective at increasing the percentage of days with no asthma symptoms and reducing daytime use of reliever medication compared with budesonide 800mcg bd ($p \leq 0.001$) (Jenkins *et al*).

GlaxoSmithKline submitted that in the studies detailed above, showing the effects of Seretide on lung function, overall asthma control and symptom control, the level of control achieved was sufficient to justify the claim 'great control'. In these studies Seretide had been evaluated and had shown improvements over and above those achieved with current standard practice for patients not well-controlled on inhaled corticosteroids. The changes were clinically and statistically significant compared to standard asthma treatment with inhaled corticosteroid. Therefore the company considered that this constituted 'great control'. There was no breach of Clause 7.2 of the Code.

Quality of life

GlaxoSmithKline referred to its response in point A above.

GlaxoSmithKline stated that the AQLQ designed and validated by Juniper, evaluated quality of life in patients with asthma. It had been shown that a change from baseline greater than 0.5 could be perceived by the patient.

Four studies evaluating quality of life by use of the AQLQ had shown that Seretide produced improvements from baseline well above the 0.5 change needed for the patient to be able to perceive the change. Improvements in asthma-related quality of life from baseline in all domains for patients on Seretide were demonstrated in these studies. The changes in overall assessment and the individual domains of the four studies detailed were shown to be between 0.72 and 1.32, with a mean over the four studies of 1.02. In none of the studies was the change from baseline for Seretide less than 0.5.

It was clear that these changes were clinically meaningful as determined by the AQLQ.

In response to AstraZeneca's comment that the change in AQLQ score from baseline for Seretide ranged between 0.45 (activities) and 0.77 (symptoms), GlaxoSmithKline pointed out that these data were taken from an abstract and were incorrect. The correct data were within the poster. For this reason the reference to this claim in the detail aid was given as both the abstract (for the study design) and the poster presentation (for the results).

GlaxoSmithKline had detailed AQLQ scores from the four studies evaluating quality of life to demonstrate that these improvements were consistent with and reflected the balance of evidence on asthma-related quality of life for Seretide.

GlaxoSmithKline stated that clinical studies had shown clinically significant improvements in control as determined by lung function, overall asthma control, symptom control and quality of life. Studies particularly assessing quality of life had also shown statistically and clinically significant improvements in quality of life. GlaxoSmithKline submitted that the data in this section supported the claim which was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel did not agree that the word 'great' was a superlative as alleged. The superlative would be 'greatest'. No breach of Clause 7.10 was ruled in that regard.

With regard to the claim the Panel noted its comments in point A regarding Juniper *et al* 1994. The authors stated that assessing the magnitude of change that corresponded to a minimal important difference in a way that was meaningful for health professionals was difficult. Juniper defined the minimal important difference as the smallest difference in score in the domain of interest which patients would perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a

change in the patient's management. The AQLQ referred to a change in quality of life score of 0.5 representing the minimal important difference. A change in score of 1 might be considered a moderate change in quality of life. A change in score of 1.5 was likely to represent a large change.

The Panel noted that there appeared to be a discrepancy between the results in the Juniper abstract 1999 and the poster 1999.

The Panel noted all the data supplied by GlaxoSmithKline. It considered that by using the word 'great', the claim was a strong claim and there was not sufficient supporting data. The quality of life data appeared to indicate a moderate change in quality of life assessment by the patient. The mean change over the four studies was 1.02. A change in score of 1.5 was likely to represent a large change. The Panel considered that the claim was misleading and a breach of Clause 7.2 of the Code was ruled.

B2 Claim 'Seretide 50 is great value at £19.50'

The claim appeared on the penultimate page of the detail aid which was reproduced on page 14 of the briefing document.

COMPLAINT

AstraZeneca stated that the claim at issue was one of three summary points appearing at the end of the detail aid. The flow of the detail aid was such that the summary points were designed to be detailed directly after the efficacy profile of high dose Seretide 250 in severe asthma had been discussed. AstraZeneca alleged that reminding a health professional of the price of low dose Seretide 50 when the benefits of high dose Seretide 250 had just been focused upon was misleading. AstraZeneca was concerned that the prescriber might be under the impression that severe asthmatic patients could be adequately controlled with the cheapest presentation of £19.50. This was not so.

AstraZeneca was also concerned that the claim appeared directly under the claim 'Seretide gives great control patients can feel'. AstraZeneca alleged that this clearly misled the reader as not all patients would get control, whether 'great' or not, from using low dose Seretide 50.

Many patients with severe asthma might require Seretide 250 to adequately control their symptoms. This was priced at £66.98, a marked increase from £19.50. Furthermore patients treated with Seretide 250 might not necessarily achieve 'great control'. It was for these reasons that the claim inferred that Seretide 50 would provide clinical efficacy and value for money for all patients. AstraZeneca alleged the claim to be an over-statement and consequently misleading in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline stated that AstraZeneca's assertion that the flow of the material was such that the summary points were designed to be detailed directly after the efficacy profile of high dose Seretide 250 in severe asthma had been discussed was incorrect.

The study referred to by AstraZeneca was not on high dose Seretide, but on the mid-range dose – 250 bd (high dose was 500 bd) and was not in severe asthma but in moderate to severe asthma. The page describing this study of mid-dose Seretide in moderate to severe asthma occupied only one page of the ten page detail aid.

The summary points did not follow the description of this study. The flow of the material was such that the summary points were detailed directly after a discussion of the full range of Seretide products.

The Seretide product page, which faced the page containing the three summary points, showed the three strengths and two devices in which Seretide was available. It also described the patients for whom Seretide might be considered as appropriate. It showed three strengths of beclometasone, and suggested that if patients were not well controlled that they might be prescribed an increasing dose of Seretide. For example, for patients not well controlled on beclometasone 250mcg 2 puffs bd, Seretide 250 Accuhaler 1 puff bd or Seretide 125 MDI 2 puffs bd were suggested.

The summary page made three claims:

a) 'Seretide is better than increasing the dose of inhaled steroids'

This claim was referenced to two studies, the first of these (Johansson *et al* 1999), compared Seretide 100 Accuhaler 1 puff bd (equivalent to Seretide 50 MDI 2 puffs bd) with budesonide 400mcg bd via Turbohaler. The second study (Jenkins *et al* 2000) compared Seretide 250 Accuhaler 1 puff bd (equivalent to Seretide 125 MDI 2 puffs bd) with budesonide 800mcg bd via a Turbohaler.

The studies showed significant improvements in lung function and symptom control compared with increased doses of inhaled corticosteroids.

b) 'Seretide gives great control patients can feel'

This claim was referenced to six studies. The studies covered the range of Seretide strengths from the lowest to the highest. The data were detailed in point B1.

c) 'Seretide 50 is great value at £19.50'

There was no suggestion that all patients would benefit from Seretide. As with any therapy, some patients would respond better than others. This was the purpose of clinical trials where an evaluation of the clinical relevance of observed changes and the likelihood of the changes occurring by chance was made.

GlaxoSmithKline stated that claims were made by all pharmaceutical companies on the basis of clinical trials where the weight of evidence was such that a doctor could expect on average an improvement for appropriate patients prescribed the therapy. No medicine could claim universal benefit, and certainly no such claim was made for Seretide.

There was no suggestion or implication that patients with asthma of any severity would benefit from the

lowest dose of Seretide. The facing page of the detail aid, which would have been detailed prior to discussion of these points, made it clear that Seretide 50 was recommended for patients whose asthma was not well controlled on low dose beclometasone 100mcg 2 puffs bd.

GlaxoSmithKline provided a monthly cost comparison of some of the alternative ways in which a doctor might prescribe a combination of an inhaled corticosteroid and an inhaled long-acting $ß_2$ agonist for patients with mild to moderate asthma, including Seretide, salmeterol plus generic BDP, Becotide, formoterol plus budesonide and Symbicort Turbohaler.

When evaluating options for prescribing this form of therapy in patients with mild to moderate asthma, GlaxoSmithKline submitted that from the balance of evidence Seretide 50 MDI did offer great value (savings of nearly 60% on all but one of the available options).

It was important to note that the page of the detail aid did not follow directly the page describing the results of the mid-strength study, but faced a description of all the available Seretide formulations.

GlaxoSmithKline submitted that there was no overstatement and no attempt to mislead. It was clearly referenced that the attributes claimed for Seretide in the first two claims were supported by studies evaluating the lowest strength as well as the other strengths.

GlaxoSmithKline therefore submitted that the claim was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted the costs of the various presentations of Seretide. The Accuhaler (60 inhalations) was available as Seretide 100, 250 and 500 costing £33.54, £39.41 and £66.98. The Evohaler (120 inhalations) was available as Seretide 50, 125 and 250 costing £19.50, £39.41 and £66.98.

The Panel noted that the improvement in quality of life scores of Seretide Accuhaler 250 compared to budesonide 800mcg bd was discussed followed by a page showing all the Seretide presentations and suggesting that patients not controlled on various doses of beclometasone be switched to various Seretide doses.

The Panel noted that Seretide 50 cost £19.50. The previous claim 'Seretide gives great control patients can feel' had been ruled in breach of the Code (point B1 above). The claim now at issue was opposite a page showing all the Seretide presentations. The representatives briefing material stated that the 'focus should be on switching beclometasone 100 patients to Seretide 50, whilst showing the range of inhalers to overcome any potential flexibility objection'. With regard to the page at issue the briefing material linked Seretide 50 with patients not well controlled on beclometasone 100mcg 2 bd. On balance the Panel did not consider that the claim inferred that Seretide 50 would provide clinical efficacy for all patients. The Panel therefore ruled no breach of Clause 7.2 of the Code.

APPEAL BY ASTRAZENECA

AstraZeneca considered that the claim was misleading as only the cost of the least prescribed and least expensive presentation was quoted and there was no associated data to substantiate value in the context of efficacy relative to other treatments. The use of the term 'great value' represented an overclaim.

The Seretide range and prescribing data

Stating the cost of the least expensive presentation of Seretide, left an impression that Seretide as a product range was overall good value. This was contrary to the fact that the most commonly prescribed presentation was significantly more expensive than Seretide 50.

Seretide 50 was just 1 of 6 different presentations of Seretide as indicated on the page opposite in the detail aid and was by far the cheapest. The next higher strength, Seretide 250, cost £39.41 (over twice as expensive as Seretide 50).

Prescription data (a copy of which was provided) indicated that Seretide 250 was the most commonly prescribed presentation in the UK. It contributed an average of 36.1% of all Seretide scripts dispensed over the year until July 2001. On the other hand, prescriptions for Seretide 50 only made up on average 5% of all Seretide scripts over the same period and represented the least commonly prescribed Seretide presentation out of the total of six.

The value of Seretide 50 also needed to be considered in the light of data that showed approximately 13% of patients first prescribed Seretide 50 were switched to a higher strength of Seretide within 6 months of starting.

Showing the cost of only the cheapest and least prescribed Seretide presentation in the whole detail aid was very selective about the information presented. In the context of the full Seretide range and associated prices, this was likely to mislead the prescriber.

Value

The term 'value' was generally used to denote cost effectiveness in a valid comparison to another product. It also conveyed that an evaluation or assessment had taken place. Therefore the value of any medication was a measure of the cost effectiveness of that medication compared with other treatments for the same condition (inhaled steroids, long-acting beta agonists and other combination therapies). The term 'value' implied merit that was more than simply cost but rather an overall economic evaluation of that medicine. A claim that Seretide 50 offered great value however was not supported by any specified health economic studies in the detail aid.

In summary, the claim, and the way in which it was presented in the detail aid, did not represent a fair evaluation on account of the significantly higher costs of the other more commonly prescribed presentations of Seretide. Furthermore, in the absence of health economic data a claim for great value, in the context of other less expensive prescribing options, was

neither balanced nor accurate and consequently breached 7.2 of the Code.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that AstraZeneca had introduced data and arguments which had previously not been presented to GlaxoSmithKline or, to its knowledge, to the Authority. It was therefore now appealing this claim based on a new argument. It did not appear to be alleging that the detail aid in question might mislead clinicians to believe that severe asthmatics might achieve control with Seretide 50, the cheapest presentation of Seretide, but that Seretide 50 was not the most commonly used presentation. This argument was therefore not based on the claim made within the detail aid in question.

Range of Seretide and prescribing data

GlaxoSmithKline agreed that Seretide 50 was not the most commonly used presentation. This was why it was promoting this dose in its detail aid. It believed that Seretide 50 was an appropriate strength for use in patients with mild to moderate asthma. Its aim was to encourage clinicians to use this more appropriate dose rather than Seretide 250 in this population.

The claim 'Seretide 50 is great value at £19.50' was based on the monthly cost comparisons of the various ways a doctor might prescribe a combination of an inhaled steroid and an inhaled long-acting ß$_2$-agonist for patients with mild to moderate asthma. GlaxoSmithKline provided a table which detailed the monthly cost of treatment options at equivalent dosage and concluded that based on these comparisons, Seretide 50 offered great value with savings of nearly 60% on all but one of the available options.

That such a promotional campaign was clinically relevant was supported by a study which had shown that the majority of patients at step 2 of the BTS guidelines (as defined by the received dose of beclometasone or equivalent) were uncontrolled.

GlaxoSmithKline's aim was to improve asthma control and to specifically improve the control of patients with mild-moderate asthma. For many of these patients it considered that Seretide 50 might be appropriate and great value in comparison with other ways of prescribing an inhaled steroid and a long-acting ß$_2$-agonist. Seretide 50 could offer savings of nearly 60% on all but one of the available options.

GlaxoSmithKline agreed that currently there was a higher usage of Seretide in patients with more severe asthma (at steps 3 and 4 of the BTS guidelines). This was reflected by the prescription data which showed a greater usage of the higher doses of Seretide, particularly the Seretide 250 Accuhaler. This did not mean that Seretide 50 at step 2 of the guidelines was not an appropriate therapy option to improve control in this patient population.

AstraZeneca also implied that as 13% of patients prescribed Seretide 50 changed dose, patients were not well controlled on this medicine. The reciprocal of this argument was that the great majority of patients (87%) remained on the Seretide 50 dose and therefore might be considered well controlled. Good control had also been seen in the Seretide 50 clinical studies with only 3% of patients being withdrawn due to loss of control of their asthma, Juniper *et al*. In this study the efficacy of Seretide 50 MDI, in terms of asthma control, was evaluated in a randomized, double-blind, placebo-controlled, 12 week study, comparing Seretide with fluticasone, salmeterol and placebo. Control (and thus loss of control) was defined as a composite measure of lung function, asthma symptoms, use of ß$_2$-agonist reliever therapy and exacerbations. Asthma control was monitored throughout the study. Patients were withdrawn if they failed to meet the pre-determined criteria for asthma control. Seretide demonstrated superior control to other treatments with only 3% of patients withdrawing due to loss of control, compared with 41% for placebo, 37% for salmeterol and 9% for fluticasone ($p \leq 0.007$ for Seretide against all comparators).

Value

AstraZeneca considered the term 'value' was generally used to denote cost effectiveness. GlaxoSmithKline disagreed. It considered Seretide 50 offered great value compared to other treatment options that added in a long-acting ß$_2$-agonist to inhaled steroid in the management of mild to moderate asthma patients who were not well controlled. Seretide 50 also offered value to the patient as it only incurred one prescription charge.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that only the cost of the least prescribed and least expensive presentation was quoted. There was no associated data to substantiate value in the context of efficacy relative to other treatments. The use of the term 'great value' represented an overclaim.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Seretide 50 is great value at £19.50' appeared facing a page featuring the six presentations of Seretide. The Appeal Board noted that whilst Seretide 50 was the least expensive presentation it was also the least commonly prescribed Seretide presentation. The Appeal Board considered the claim too simplistic; the context in which Seretide 50 represented great value had not been made sufficiently clear. The Appeal Board considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The appeal on this point was successful.

C GP Campaign and Q&A guidance (ref GEN 26709/BP/January 2001

Support cards – Pack Two (20238729 – BP/January 2001)

Card headed 'Great control from the first dose'

The double sided A4 card included a graph from Shapiro *et al* 2000 showing the mean change from

baseline in FEV_1 on day 1 for Seretide 250 Accuhaler bd and fluticasone 250 mcg Accuhaler bd. The graph referred to a clinically significant improvement as being 15% over baseline. This was achieved by Seretide approximately 30 minutes after the first dose until 12 hours after the first dose. Fluticasone did not achieve a clinically significant improvement.

COMPLAINT

AstraZeneca did not consider the graph was capable of substantiating 'great control' for reasons expressed in point B1. An accurate measure of asthma control, including symptoms, needed to be based upon a number of clinical parameters and not just FEV1 alone. Control was a long-term measure and could not be determined from lung function efficacy observed from the first dose of a medicine. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline stated that in the vast majority of studies on asthma medications, lung function, whether FEV_1 or PEF, was the primary endpoint. Lung function was universally accepted as the first marker of asthma control. There was also a degree of consensus as to the amount of change in lung function which was clinically significant in terms of patient perception and improvement. For FEV_1 this was 15% and a change of or greater than this percentage was usually determined as the level of change needed for a clinically significant result.

As detailed in response to point B1 above it considered that Seretide had been demonstrated to provide control of asthma, which was shown not just in terms of lung function but also in symptom control and improvement in $ß_2$-agonist rescue medication use.

The context wherein this claim and graph were situated made the relevance of and justification for the claim clear.

GlaxoSmithKline stated that inhaled steroids could take 4-7 days before appreciable improvement in lung function took place and patients might stop treatment if they did not feel the benefits quickly. Similarly if patients started to feel well they might stop taking their steroid without noticing any change in asthma control for some time. Clearly neither of these factors encouraged patients to continue taking medication, and might well be a reason why about 50% of asthma patients did not comply with their inhaled steroid therapy.

Seretide, on the other hand, provided clinically significant improvements in lung function which patients should feel quickly from the first dose. The graph showed that there was a rapid (within 30 minutes) improvement in lung function, an accepted measure of asthma control.

This improvement was clinically relevant. However, had it been a short-lived improvement and had lung function improvements returned to non-clinically significant levels after the first dose then this claim would be misleading However, in this study, this clinically significant and relevant improvement was sustained at that level or above for the duration of the 12 week study. Therefore GlaxoSmithKline submitted that the claim was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted the submission from GlaxoSmithKline. The Panel's view was that control was a long-term feature and could not be demonstrated in a graph showing the effect of 12 hours post dose. The Panel noted GlaxoSmithKline's submission that clinically significant and relevant improvement was sustained at the first dose level or above for the duration of the 12 week study. There was no reference to this on the material in question. In any event control of asthma was more than showing changes in FEV_1 over 12 hours. The Panel considered the material was misleading as alleged and a breach of Clause 7.2 was ruled.

D Booklet 'The Role of Seretide in the Management of Asthma in Primary Care' (ref 20222116-BP/August 2000)

GlaxoSmithKline stated that the booklet was no longer in use. The allegations regarding the booklet were considered under the 1998 requirements of the Code as the booklet was withdrawn before July 2001.

1 Bar chart entitled 'Results: Improvement in quality of life over 24 weeks'

The bar chart on page 7 of the booklet showed the improvement in AQLQ score for five domains, overall AQLQ score, activity limitation, asthma symptoms, emotional functioning and environmental exposure for Seretide 250 Accuhaler bd compared to budesonide turbo inhaler 800mcg bd. The graph indicated that there were statistically significant and clinically meaningful changes from baseline for all five domains for Seretide. The changes for budesonide were also statistically significant and clinically meaningful changes from baseline with the exception of activity limitation and emotional functioning.

GlaxoSmithKline informed AstraZeneca in June 2001 that materials containing this bar chart were no longer in use.

COMPLAINT

AstraZeneca stated that presenting the treatment bars for Seretide and budesonide adjacent to each other for each of the five measured domains gave the visual impression that Seretide was more effective than budesonide in improving quality of life.

AstraZeneca alleged that this representation of data was misleading in breach of Clauses 7.2 and 7.3 because the difference in mean improvement AQLQ scores between the two treatments only reached statistical significance for two of the five domains. This was not indicated on the graph nor in the accompanying text. In addition the supporting study

(Juniper *et al* 1999) concluded that the magnitude of difference between the two treatments did not reach the minimal important difference of ≥0.5 to imply clinical significance.

AstraZeneca alleged that the heading to the page 'Greater control means improved quality of life' purposely stood as a hanging comparison and together with the visual impression given by the bar chart, invited the reader to assume that the heading to the page was a conclusion drawn from comparing Seretide with budesonide. However this was misleading as the magnitude of difference in mean improvement AQLQ scores between the two treatments did not reach the minimally important difference of ≥0.5. Reference was made to point B1.

RESPONSE

GlaxoSmithKline stated that no claim was made in the bar chart or accompanying text comparing Seretide and budesonide. However the bar chart did depict the actual study results. The study evaluated Seretide and budesonide and to exclude the budesonide arm might have given the misleading impression that some of the study results were being hidden. The reader might have taken the impression that budesonide was ineffective, or that GlaxoSmithKline was trying to hide a result in favour of budesonide. It had been ruled that a graph which did not show all the study arms could be deemed to show insufficient detail (Case AUTH/1085/10/00 - Promotion of Zyban).

GlaxoSmithKline stated that it had been careful not only to show the full study results, but also highlighted where both the Seretide and budesonide results showed significant changes against baseline. These differences had been highlighted twice in the graph. Once in the form of a dotted line labelled 'clinically meaningful improvement' and also in the form of an asterisk which was labelled 'statistically significant ($p<0.001$) and clinically meaningful change from baseline'.

No claims were made against the difference between the two study arms. However it was made clear where Seretide and budesonide produced changes from baseline greater than the 0.5 necessary for the patient to be able to perceive the change.

GlaxoSmithKline considered that it had made clear the benefits of both treatments and the reader was given all the relevant information on which to make a judgement on the value of the study detailed. The company submitted that the bar chart was not in breach of Clauses 7.2 and 7.3 of the Code.

With regard to the page heading 'Greater control means improved quality of life' GlaxoSmithKline stated that this 'greater' was a comparison with baseline. This was made clear both in the text where the study results were summarised and in the graph. The text stated 'At the end of treatment, Seretide produced clinically meaningful and statistically significant improvements from baseline in overall score and in all four domains'. The bar chart stated in reference to the 'significance*'; 'statistically significant ($p<0.001$) and clinically meaningful change from baseline'. GlaxoSmithKline submitted that it had made it clear to the reader that the claim was against the baseline levels. The page was not in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel considered that the graph gave a visual impression that there was a clinical difference between Seretide and budesonide. The position was complicated as the Juniper abstract gave different results to the Juniper poster. According to the poster the difference in mean change in AQLQ score between the treatments only exceeded the 0.5 threshold for the asthma symptoms domain. It appeared from the poster that the difference between Seretide and budesonide was statistically significant for all domains. This was not the same as a clinical difference.

The difference shown in the graph was not borne out by the data. The presentation was misleading in relation to the clinical difference between the products and a breach of Clause 7.2 of the Code was ruled.

With regard to the heading the Panel considered that it gave the impression of a clinical difference between the products and as above this was not borne out by the data. The heading was misleading and a breach of Clause 7.2 of the Code was ruled.

The Panel noted that Clause 7.3 was a newly introduced requirement to the 2001 Code. Some of the principles were included in Clause 7.2 of both the 1998 Code and the 2001 Code including the requirement that comparisons must not be misleading. In the circumstances the Panel decided not to consider the matter in relation to Clause 7.3 of the 2001 Code. The matter was covered by Clause 7.2.

D2 Claim 'Quick onset of Seretide action that patients can feel from the first dose'

The claim appeared on page 1 of the booklet as a bullet point beneath the heading 'Seretide: Great control you can feel'.

COMPLAINT

AstraZeneca stated that when describing the speed of onset of bronchodilators, prescribers associated 'quick' with the relief achieved from using short-acting bronchodilators and formoterol, ie 1-3 minutes after inhalation (Seberora *et al* 2000). In marked contrast, salmeterol (within Seretide) had a significantly slower onset of bronchodilatory effect, ie 20 minutes, than short-acting bronchodilators and formoterol (Palmqvist).

AstraZeneca alleged that using the term 'quick' to describe the onset of action observed with Seretide was clearly misleading as it implied that the medicine had a bronchodilatory onset comparable with short-acting bronchodilators and formoterol. This was not so. Although the onset of clinical effect was sooner than with inhaled steroids, it was obvious from the claim that it related to bronchodilation, a feature addressed by the bronchodilator element in this combination product, ie salmeterol.

RESPONSE

GlaxoSmithKline pointed out that the bullet point stated 'Quick onset of Seretide action that patients can feel from the first dose – patients should quickly feel clinically significant improvements in lung function, which may encourage them to continue taking their medication'.

Nowhere on the page or anywhere in the material was reference or comparison made to the speed of action of short-acting bronchodilators or formoterol.

GlaxoSmithKline pointed out that Seretide was licensed and promoted as a preventer medication to be used on a regular basis, and was classified as such. The British National Formulary confirmed this, classifying Seretide under corticosteroids. The prescribing information for Seretide stated that it should not be used to relieve acute symptoms. None of the promotional materials suggested that Seretide should be used as other than a regular preventative medication for asthma.

The most commonly prescribed preventer medications, inhaled corticosteroids, had an onset of action of 4 - 7 days, therefore patients would not feel their effects until several days after starting their medication.

Compared to these commonly prescribed preventer medications (in the same drug classification), the onset of action of Seretide – within 30 minutes – was quick. It might not be as quick as short acting bronchodilators such as salbutamol, but no such comparison was made or implied. An improvement in a primary outcome measure within 30 minutes was certainly a considerable advance in treatment response compared to inhaled corticosteroids.

The claim was intended to highlight the fact that patients might experience a response to Seretide within the first day of treatment. In fact they might experience the response within 30 minutes of their first dose in terms of lung function and within the first day of treatment in terms of symptom control.

No comparison with formoterol or short-acting bronchodilators (or indeed Symbicort) was made or implied within the page or the booklet.

GlaxoSmithKline submitted that the claim was not misleading and not in breach of the Code (no specific clause was mentioned by AstraZeneca).

PANEL RULING

The Panel did not accept that the claim in full would be seen as a comparison between the effects of Seretide and short-acting bronchodilators and formoterol. AstraZeneca had alleged that the material was misleading but not cited a clause. GlaxoSmithKline had responded to this allegation. In the circumstances the Panel decided it would make a ruling in relation to Clause 7.2 of the Code. No breach of that clause was ruled.

Complaint received **17 July 2001**

Case completed **18 December 2001**

CASE AUTH/1210/7/01

SCHWARZ PHARMA/DIRECTOR v SCHERING-PLOUGH

Breach of undertaking

Schwarz Pharma, the complainant in Case AUTH/1172/3/01, alleged that following the completion of that case Schering-Plough had continued to use material containing claims about NeoClarityn (desloratadine) that had been ruled in breach of the Code. The material now in question was an eight page newsletter headed 'Allergy Alert'. It had been made available at the Schering-Plough stand at a conference. Schwarz's view was that the newsletter was promotional and not medical information as it was available from the stand to delegates, it was sponsored by Schering-Plough and it dealt exclusively with NeoClarityn, including the prescribing information. Schwarz alleged that the item contained three claims that were found in breach in Case AUTH/1172/3/01.

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 previously given by the Appeal Board.

The Panel considered that the claim in the newsletter that 'desloratadine improves the nasal symptoms of asthma patients who suffer from seasonal allergic rhinitis at the therapeutic dose' was not similar to the claim ruled upon in Case AUTH/1172/3/01. The matter considered in the previous case was a reference to bronchial inflammation and cough as symptoms of seasonal allergic rhinitis which they were not. The Panel thus did not consider that the claim now at issue was covered by the previous ruling and no breach of the Code was ruled in that regard.

The claim that '... desloratadine had anti-inflammatory effects similar to the corticosteroid dexamethasone' was covered by the previous ruling that Schering-Plough had not demonstrated the comparability of the results for desloratadine and dexamethasone. Similarly the Panel considered that the claim in the newsletter that 'desloratadine has been shown to have no effect on wakefulness or psychomotor performance nor does it impair actual driving performance' was covered by its previous ruling with regard to the claim that NeoClarityn had 'no sedation or impairment of performance'.

The Panel considered that Schering-Plough had failed to comply with its undertaking and a breach of Clause 22 was ruled. Schering-Plough's continued use of claims previously ruled in beach of the Code brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel was very concerned that the newsletter had not been withdrawn as a result of its rulings in the previous case. 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 important for the reputation of the industry that companies complied with undertakings. Although Schering-Plough had taken steps to ensure compliance with its undertaking these had not been wholly adequate. Material had been used which should have been withdrawn.

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 in relation to additional sanctions. Failure to comply with an undertaking was a serious matter. It appeared that Schering-Plough had not given sufficient thought to which items needed to be withdrawn as a result of the ruling in the previous cases and that the company's procedures were inadequate. The Panel decided that the circumstances warranted reporting Schering-Plough to the Appeal Board.

The Appeal Board was very concerned that Schering-Plough had failed to comply with its undertaking. It noted the company's response that the newsletter had originally been designed as an educational tool for representatives. In the Appeal Board's view the newsletter should have been withdrawn as a result of the rulings in the previous case. The Appeal Board did not understand the company's position that the newsletter could be used to educate representatives. It appeared that Schering-Plough considered that it was acceptable for representatives to be trained on claims that had been ruled in breach of the Code.

The Appeal Board was concerned about the company's procedures and the implementation of the procedures. It therefore decided that Schering-Plough should be required to undergo an audit of its procedures relating to the Code. This would be carried out by the Authority. The Appeal Board considered that this was a very serious matter and it would decide whether any further action was required once it had received the report on the audit.

Upon receipt of the audit report, the Appeal Board noted that Schering-Plough accepted that it could have been more rapid in completing its review of its practices to take account of the 2001 Code. The company stated that it had tightened its monitoring system to ensure that the error could not happen again. The Appeal Board noted the action taken by Schering-Plough and that it had not implemented some of the recommendations from the previous audit in October 1998.

The Appeal Board did not consider that the circumstances warranted reporting Schering-Plough to the ABPI Board of Management. The Appeal Board decided that Schering-Plough should undergo another audit in six months (May 2002) to check that the recommendations of the recent audit had been implemented. On that basis the Appeal Board decided that no further action was necessary.

Schwarz Pharma Limited, the complainant in Case AUTH/1172/3/01, complained that following the completion of that case on 1 June, Schering-Plough Ltd had continued to make available material

containing claims about NeoClarityn (desloratadine) that had been ruled in breach of the Code. 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

Schwarz Pharma stated that the material now in question was an eight page newsletter dated April 2001 and headed 'Allergy Alert' (ref NCL/01-073 – NCL/01-077). It had been made available at the Schering-Plough stand at the British Society of Allergy and Clinical Immunology conference in July 2001.

Schwarz's view was that the newsletter was promotional and not medical information as it was available from the stand to delegates at the conference, it was sponsored by Schering-Plough and it dealt exclusively with NeoClarityn, including the prescribing information. Further, promotional item identification numbers were included. Schwarz stated that the item contained three claims that were found in breach in Case AUTH/1172/3/01.

Firstly, Schwarz alleged that the claim '... desloratadine had anti-inflammatory effects similar to the corticosteroid dexamethasone' was similar to a ruling of a breach in Case AUTH/1172/3/01 that the anti-inflammatory properties of desloratadine were comparable to dexamethasone (point 6).

Secondly, Schwarz alleged that the claim 'Desloratadine improves the nasal symptoms of asthma patients who suffer from seasonal allergic rhinitis' was an attempt to promote the use of desloratadine in asthma for which it did not have a licence. This was similar to a ruling of a breach in Case AUTH/1172/3/01 (point 3).

Thirdly, Schwarz alleged that the claim 'Desloratadine has been shown to have no effect on wakefulness or psychomotor performance nor does it impair actual driving performance' was similar to a ruling of a breach in Case AUTH/1172/3/01 that desloratadine caused no impairment of performance (point 8).

Schwarz stated that the date of preparation (November 2000) and issue date (April 2001) suggested that the material was in use before Schering-Plough gave its undertaking to withdraw promotional materials containing these claims (June 2001). That it continued to be used after this undertaking was clearly unacceptable. Schwarz alleged that the company had brought discredit upon the pharmaceutical industry in breach of Clause 2.

RESPONSE

Schering-Plough confirmed that the newsletter, originally designed as an educational tool for its representatives, was inadvertently displayed on its stand. To ensure this did not happen again the company had recalled the item from the field. The company sincerely apologised for the error.

PANEL RULING

The Panel was very concerned that the newsletter had not been withdrawn by Schering-Plough as a result of its rulings in the previous case, Case AUTH/1172/3/01. 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 important for the reputation of the industry that companies complied with undertakings. The Panel noted that although Schering-Plough had taken steps to ensure compliance with the undertaking given in Case AUTH/1172/3/01 these had not been wholly adequate. Material had been used which should have been withdrawn.

The Panel considered that the claim in the newsletter that 'desloratadine improves the nasal symptoms of asthma patients who suffer from seasonal allergic rhinitis at the therapeutic dose' was not similar to the claim ruled upon in Case AUTH/1172/3/01 (point 3) as alleged by Schwarz Pharma. The matter considered in the previous case was the reference to bronchial inflammation and cough as symptoms of seasonal allergic rhinitis which they were not; a breach of the Code was ruled. The Panel thus did not consider that the claim now at issue was covered by the previous ruling as such. No breach of Clause 22 was ruled in this regard.

The Panel considered that the claim in the newsletter that '... desloratadine had anti-inflammatory effects similar to the corticosteroid dexamethasone' was covered by its ruling in point 6 in Case AUTH/1172/3/01 that Schering-Plough had not demonstrated the comparability of the results for desloratadine and dexamethasone. Breaches of Clauses 7.2 and 7.8 of the Code had been ruled. Similarly the Panel considered that the claim in the newsletter that 'desloratadine has been shown to have no effect on wakefulness or psychomotor performance nor does it impair actual driving performance' was covered by its ruling in point 8 of Case AUTH/1172/3/01 with regard to the claim that NeoClarityn had 'no sedation or impairment of performance'. The Panel had ruled breaches of Clauses 7.2, 7.3 and 7.8 as the summary of product characteristics (SPC) stated that NeoClarityn had no or negligible influence on the ability to drive or use machines.

The Panel considered that Schering-Plough had failed to comply with its undertaking and a breach of Clause 22 was ruled. The Panel considered that Schering-Plough's continued use of claims previously ruled in breach of the Code brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel was concerned that Schering-Plough's procedures were inadequate.

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

of the Constitution and Procedure. Failure to comply with an undertaking was a serious matter. It appeared that Schering-Plough had not given sufficient thought to which items needed to be withdrawn as a result of the ruling in the previous cases. It appeared that the company's procedures were inadequate. The Panel decided that the circumstances warranted reporting Schering-Plough to the Appeal Board.

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During its consideration of this case, the Panel noted that the declaration of Schering-Plough's sponsorship of the newsletter was not sufficiently prominent. The statement '... this publication is provided by Schering-Plough Ltd as an educational service for health care professionals' appeared on page 8. In the Panel's view the declaration of sponsorship should have appeared on the front page in order to meet the requirements of Clause 9.9 and its supplementary information. The newsletter was more than four pages and should therefore have included a reference to where the prescribing information could be found as required by Clause 4.8 of the Code. The Panel requested that its concerns be drawn to Schering-Plough's attention.

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SCHERING-PLOUGH'S COMMENTS ON THE REPORT TO THE APPEAL BOARD

Schering-Plough stated that it accepted the rulings of the Panel and in no way did it underestimate the gravity of its error in making the newsletter available at the July meeting of the British Society of Allergy and Clinical Immunology. Schering-Plough continued to improve its systems to avoid such mistakes, and had already held an internal, high level review of this occurrence and instituted an even tighter central control of the validation and release of promotional material.

While Schering-Plough realised that this did not necessarily mitigate the offence, it would like to point out that in its efforts to comply with its undertakings to the Authority it recalled and destroyed 16 out of 25 examples of its NeoClarityn promotional material, a total of over 181,500 individual pieces of promotional material. The oversight of retaining the 'Allergy Alert' newsletter which resulted in the Panel's ruling was due to human error and not in any way an attempt to ignore Schering-Plough's previous undertakings. Schering-Plough took very seriously its continued commitment to the Authority.

The Schering-Plough representatives before the Appeal Board apologised for the matter which was due to human error and not due to the company's systems. It had not been made sufficiently clear that the newsletter was only for internal use for educating the representatives although the material would now not pass scrutiny for educational materials.

The company tabled a copy of its policy and procedure. The company had taken action to ensure that educational and promotional materials would not be confused again. It also advised that a team meeting would now take place following notification of rulings under the Code. At these meetings each piece of promotional material would be examined to see if it could be used or had to be withdrawn as a result of the rulings.

An email instructing representatives not to use the newsletter had been sent in July 2001.

APPEAL BOARD CONSIDERATION

The Appeal Board was very concerned that Schering-Plough had failed to comply with its undertaking. It noted the company's response that the newsletter had originally been designed as an educational tool for representatives. It was listed as being approved on an email dated 10 May and was described as a 'Newsletter'.

In the Appeal Board's view the newsletter should have been withdrawn as a result of the rulings in the previous case, Case AUTH/1172/3/01. The Appeal Board did not understand the company's position that the newsletter could be used to educate the representatives. It appeared that Schering-Plough considered that it was acceptable for representatives to be trained on claims that had been ruled in breach of the Code.

The Appeal Board was concerned about the company's procedures and the implementation of the procedures. It therefore decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Schering-Plough should be required to undergo an audit of its procedures relating to the Code. This would be carried out by the Authority. The Appeal Board considered that this was a very serious matter and it would decide whether any further action was required once it had received the report on the audit.

Upon receipt of the Audit report, the Appeal Board noted that the company accepted that it could have been more rapid in completing its review of its policies and procedures to take account of the 2001 Code. The company had tightened its monitoring system to ensure that the error could not happen again. The Appeal Board noted the action taken by Schering-Plough and that it had not implemented some of the recommendations from the previous audit in October 1998.

The Appeal Board did not consider that the circumstances warranted reporting Schering-Plough to the ABPI Board of Management. The Appeal Board decided that Schering-Plough should undergo another audit in six months (May 2002) to check that the recommendations of the recent audit had been implemented. On this basis the Appeal Board decided that no further action was necessary.

Complaint received **23 July 2001**

Case completed **15 November 2001**

HOSPITAL CONSULTANT v AVENTIS PHARMA

Conduct of representative

A hospital consultant complained that a representative from Aventis Pharma had told him that Schering-Plough's product NeoClarityn had been withdrawn over concerns regarding its safety. The complainant had spoken to the Schering-Plough representative who told him that this was not so.

The Panel noted that the parties' accounts of events differed; it was difficult to know when the exchange between the representative and the complainant had taken place. The complainant stated that he had been present at a meeting in July but the representative was reported not to have met him for the first time until several weeks later.

The complainant alleged that he had been told that NeoClarityn had been withdrawn. The representative had referred to the withdrawal of promotional material for NeoClarityn at a meeting in June; she could not remember speaking to the complainant in July. The circumstances were such that it was impossible to determine what had transpired between the parties. No breach of the Code was thus ruled.

A hospital consultant complained about the conduct of a representative from Aventis Pharma Ltd. Aventis marketed Telfast (fexofenadine), a competitor to Schering-Plough Ltd's recently launched product NeoClarityn (desloratadine). Schering-Plough also marketed an older product, Clarityn (loratadine).

COMPLAINT

The complainant stated that he was surprised to learn from the Aventis representative that NeoClarityn had been withdrawn from the UK market over concerns regarding its safety. The complainant had spoken to the Schering-Plough representative who had told him that this was not so.

When writing to Aventis the Authority advised it to consider the requirements of Clauses 2, 8.1, 9.1 and 15.2 of the Code.

RESPONSE

Aventis Pharma stated that in June one of its representatives, and her regional manager, sponsored a lunchtime meeting at the complainant's hospital. In the company's view a simple misunderstanding had occurred. Around the time of the meeting Schwarz Pharma Ltd had sent out a 'Dear Doctor' letter informing the profession that Schering-Plough had withdrawn its promotional material for NeoClarityn. The representative mentioned this in her discussions with several doctors at the meeting. The representative had no recollection of speaking with the complainant. Moreover the company had no record of his attendance although this might be a simple clerical error.

The representative had given her assurance that at no time was it stated or in anyway suggested that NeoClarityn had been withdrawn. It would appear that withdrawal of the promotional material was somehow confused with withdrawal of the product.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the exchange between himself and the Aventis representative took place at a breakfast meeting in July.

FURTHER COMMENTS FROM AVENTIS PHARMA

Aventis apologised for the misunderstanding regarding the date of the meeting; as the complainant was from the ENT department, the company assumed that he had attended the departmental meeting which it had sponsored in June.

Aventis confirmed that its representative had sponsored a breakfast meeting in July. A list of doctors to whom she remembered speaking was provided; the complainant's name was not included. The representative's regional manager stated that it was in fact several weeks later that the representative met the complainant for the first time.

Aventis repeated that there appeared to have been a misunderstanding as a result of the 'Dear Doctor' letter from Schwarz as to whether it was the product or the promotional material that was to be withdrawn.

PANEL RULING

The Panel noted that the parties' accounts of events differed; it was difficult to know when the exchange between the representative and the complainant had taken place. The representative had sponsored a breakfast meeting in July at which the complainant stated he was present although the representative could not remember speaking to him. The letter of complaint was written within two weeks of that meeting. The representative, however, was reported not to have met the complainant for the first time until several weeks after the July breakfast meeting.

The Panel noted that in June Aventis sent its representatives a copy of a letter to GPs from Schwarz Pharma. The letter gave details of adverse rulings made in Case AUTH/1172/3/01 in which Schwarz had complained about the promotion of NeoClarityn by Schering-Plough. Readers were told that promotional material for desloratadine had been considered to be in breach of the Code and that the licence holder was now obliged to replace, amend or qualify all of the relevant claims. Aventis representatives thus clearly knew that there had been problems with the NeoClarityn promotional material. The covering letter from Aventis to its representatives stated that the Schwarz letter was for their information only. The representative, however, was reported to have mentioned the issue in her discussions with doctors at the meeting held in June.

The Panel noted that the complainant alleged that he had learnt from the Aventis representative that NeoClarityn had been withdrawn over concerns regarding its safety. The representative had referred to the withdrawal of promotional material for NeoClarityn at a meeting in June but could not remember speaking to the complainant at the meeting in July. In such circumstances it was impossible to determine what had transpired between the parties. The Panel was thus obliged to rule no breach of Clauses 2, 8.1, 9.1 and 15.2 of the Code.

During its consideration of this case the Panel noted that Schering-Plough had announced the withdrawal of prescription packs of Clarityn tablets for commercial reasons, not because of any adverse safety data (ref The Pharmaceutical Journal, 15 September 2001).

Complaint received **1 August 2001**

Case completed **24 October 2001**

CASE AUTH/1216/8/01

GENERAL PRACTITIONER v WYETH

Representative training exercise

A general practitioner complained about the conduct of a trainee representative from Wyeth. A Wyeth regional trainer had visited the practice with three trainee representatives and provided lunch for the three doctors. The representatives then had approximately twenty minutes with each doctor to promote a particular product, at the end of which time the doctors provided feedback to the trainer.

The first representative spoke to the complainant about venlafaxine (Efexor XL) in light of its new licensed indication for the treatment of generalised anxiety disorder. However, the complainant had not been sent a copy of the summary of product characteristics (SPC) by post and the representative was unable to provide him with one which included that indication. The complainant's understanding was that pharmaceutical companies or their representatives were not allowed to promote medicines unless the doctor had already been provided with an SPC. The complainant suspected that a breach of the Code had occurred.

The Panel noted that the complainant's understanding of the requirements of the Code with regard to the provision of SPCs was incorrect. Representatives had to provide, or have available to provide if requested, a copy of the SPC for each medicine which they were to promote.

The Panel did not accept Wyeth's submission that training exercises were not within the scope of the Code. The Code clearly encompassed written briefing materials and it was the Panel's view that it also encompassed practical training sessions when those sessions involved the detailing of health professionals by representatives.

The Panel noted that, as part of her training, a representative had visited a GP practice and detailed the complainant about the use of Efexor XL in the treatment of generalised anxiety disorder. The SPC given to the complainant referred to the use of the product in depression only. The Panel considered that the conduct of the representative was subject to the Code. The representative had not provided the doctor with an up-to-date SPC and a breach of the Code was ruled.

A general practitioner complained about the conduct of a trainee representative from Wyeth.

COMPLAINT

A regional trainer for Wyeth had visited the practice with three trainee representatives and provided lunch for the three doctors. The representatives then had approximately twenty minutes with each doctor to promote a particular product, at the end of which time the doctors provided feedback to the trainer.

The first representative spoke to the complainant about venlafaxine (Efexor XL) in light of its new licensed indication for the treatment of generalised anxiety disorder. However, the complainant had not been sent a copy of the summary of product characteristics (SPC) by post and the representative was unable to provide him with one which included that indication. She had given the complainant one covering the use of venlafaxine for depression only.

The complainant's understanding was that pharmaceutical companies or their representatives were not allowed to promote medicines for their licensed applications unless the doctor had already been provided with an SPC. The complainant suspected that a breach of the Code had occurred.

Each doctor had been paid a fee by Wyeth but this was not the subject of complaint.

When writing to Wyeth, the Authority drew attention to Clauses 15.2 and 15.8 of the Code.

RESPONSE

Wyeth stated that the incident in question happened during a representative training exercise. These exercises formed an important part of Wyeth's ongoing commitment to ensuring its representatives were trained to an appropriate level.

As was Wyeth's practice with these training exercises, the doctors involved were briefed at the outset by the regional trainer as to the process involved and the feedback required from them on completion of the session. The payment they received for taking part in the training exercise was in line with British Medical Association recommendations.

Given that the incident was clearly a training exercise, it did not fall within the scope of the Code; Clause 15.8 clearly referred to promotion.

In response to a request for further information, Wyeth provided copies of the initial letter used when discussing GP involvement in training days, the reply letter if the doctor agreed to take part in training and the agreement follow up form.

In the initial letter Wyeth stated that it believed that there was no substitute for enabling its representatives to learn by receiving direct feedback from established doctors. Experience had shown that this approach significantly improved the representatives' ability to provide doctors with appropriate information and support relevant to current practice. The letter also stated that during the programme the doctor would be involved for approximately $1^1/2$ hours in listening to and assessing representative presentations and providing open feedback to a training manager. All feedback provided would be reviewed with the aim of further developing Wyeth's representatives and its existing training programmes. An honorarium would be paid in recognition of the time spent.

Wyeth stated that the initial letter was clear about the requirement for feedback and all participants were asked to make the training exercise as realistic as possible.

In this particular instance, however, the training was organised via the practice manager and the relevant letters were not utilised. The trainer completed the briefing verbally, as per the letter provided, before the exercise commenced.

The representatives involved had been with the company for varying lengths of time so the exercise was not part of their initial training course. The GP training days formed an integral part of an initial training course and were also utilised as part of continuous training when new indications were launched.

PANEL RULING

The Panel noted that the complainant's understanding of the requirements of the Code with regard to the provision of SPCs was that companies, or their representatives, were not allowed to promote medicines for their licensed indications unless the doctor had already been provided with an SPC. This was not so. Clause 15.8 stated that representatives must provide, or have available to provide if requested, a copy of the SPC for each medicine which they were to promote.

The Panel noted Wyeth's submission that training exercises were not within the scope of the Code. In this regard the Panel noted that Clause 1.1 stated that the Code applied to the promotion of medicines to members of the health professions. Clause 1.2 defined promotion as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription supply, sale or administration of its medicines. It was specifically stated that promotion included the activities of representatives including detail aids and other printed material used by representatives. Clause 1.2 excluded some activities from the definition of promotion; representative training was not one of the activities so listed. The supplementary information to Clause 15, Representatives, made it clear that the Code applied equally to oral presentations as well as to printed material. Clause 15.9 referred to the need for detailed briefing material for representatives on the technical aspects of each medicine which they would promote. It was stated that briefing material must comply with the relevant requirements of the Code and that it must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The supplementary information to Clause 15.9 stated that the briefing material referred to consisted of both the training material used to instruct representatives about a medicine and the instructions given to them as to how the product should be promoted. Thus, whilst the Code clearly encompassed written briefing material, it was the Panel's view that it also encompassed practical training sessions when those sessions involved the detailing of health professionals by representatives. If it did not it would be a surprising gap and would allow representatives to say and do things during training exercises which would be in breach of the Code if said and done during the course of a normal business call.

The Panel noted that, as part of her training, a representative had visited a GP practice and detailed the complainant about the use of Efexor XL in the treatment of generalised anxiety disorder. The SPC given to the complainant referred to the use of the product in depression only. The Panel considered that the conduct of the representative was subject to the Code. The representative had not provided the doctor with an SPC as required by Clause 15.8 and a breach of that clause was ruled. The company should have ensured that its representative had been given an up-to-date SPC which included the new indication. In the circumstances the Panel ruled no breach of Clause 15.2.

During the consideration of this case the Panel noted Wyeth's submission that the training session in question was arranged with the practice manager and that relevant letters regarding representative training had not been used. The Panel was concerned that in this case there appeared to be no written record that the doctors had agreed that a formal training session could take place in their practice.

The initial letter which was normally used by Wyeth in respect of representative training explained the reasons behind involving established doctors in such training and told the reader that they would be involved for approximately $1^1/2$ hours in listening to and assessing representative presentations. An honorarium would be paid in recognition of the time

spent. Readers were told that if they were interested they should sign and return the attached form. A follow-up letter gave the date and venue of a proposed training programme which would take place in the doctor's local area and stated that the honorarium would be £75. Wyeth's local co-ordinator would contact the doctor to confirm their attendance. The Panel noted that the standard letters supplied by Wyeth implied that doctors would go to a local centre to assist in the training of representatives, not that, as in the case now being considered, representatives would visit a doctor's surgery.

The Panel noted that, accompanied by a regional trainer, three representatives had visited a general practice surgery and promoted a particular product to each of the doctors. The representatives involved had been with Wyeth for varying lengths of time; the exercise was not part of an initial training course. Although not the subject of the complaint, the complainant had stated that each doctor had received a fee of £75. The Panel was concerned that such a payment constituted a fee for the grant of an interview, in breach of Clause 15.3 of the Code, and requested that this matter be taken up in accordance with Paragraph 17 of the Constitution and Procedure for the Authority (Case AUTH/1238/10/01).

Complaint received **8 August 2001**

Case completed **16 October 2001**

CASE AUTH/1217/8/01

YAMANOUCHI PHARMA v PFIZER

Promotion of Cardura XL

Yamanouchi Pharma complained about the promotion of Cardura XL (doxazosin gastrointestinal therapeutic system (GITS)) by Pfizer. The items at issue were a medical press release, a lay press release and a leavepiece. Yamanouchi marketed Flomax MR (tamsulosin). Both products were alpha-blockers for the treatment of the symptoms of benign prostatic hyperplasia (BPH).

Yamanouchi noted that the medical press release, headed 'New data show that not all alpha blockers are the same in the treatment of benign prostatic hyperplasia', stated that the widely held view was that all alpha-blockers had similar efficacy in BPH. Yamanouchi concurred with this – it was tolerability which was considered to differ between products. A meta-analysis by Djavan and Marberger stated that 'All α_1-adrenoceptor antagonists seem to have similar efficacy in improving symptoms and flow. The difference between α_1-adrenoceptor antagonists is related to their side effect profile'. The press release went on to give the results of the study by Kirby *et al* (2001) and made the claim that '[Cardura XL] was significantly more effective than tamsulosin in relieving urinary symptoms (p=0.019)'.

The Kirby study was a crossover design of 47 patients for the efficacy analysis (50 patients entered the study). After a two-week placebo run-in, patients received Cardura XL 4mg/day or tamsulosin 0.4mg/day. Cardura XL was titrated to 8mg/day and tamsulosin was titrated to 0.8mg/day after four weeks if the increase in maximum flow rate (Q_{max}) was <3ml/s and reduction in total International Prostate Symptom Score (IPSS) was <30%. There was then a two-week washout period with placebo, followed by the second treatment phase of tamsulosin or Cardura XL for eight weeks with the same titration requirements at four weeks. The data on file described the results as 'preliminary'. Yamanouchi stated that there were a number of very serious issues with this study which rendered any claim for the UK inappropriate. A crossover design was inappropriate for study end points which were subjective and where the natural course of the disease fluctuated over time. The IPSS was used as the primary variable. This was the subjective scoring system which was used in BPH clinical trials. The score was the total of the severity of seven symptoms recorded 'over the past month'. However, in this study, the baseline IPSS at entry into the second treatment phase could only have been measured over the two-week washout period. The use of an internationally recognised and widely used scoring system which had not been validated for use over a shorter period was unscientific.

Cardura XL was used as licensed in the UK. However tamsulosin could be titrated to twice its UK licensed dose. The summary of product characteristics (SPC) for Flomax MR gave the simple dose regime as 0.4mg daily – no titration, no higher dose allowed. In this study the majority of patients must have been titrated to the higher tamsulosin dose (0.8mg) for the mean study dose to have been 0.7mg. The use by a competitor company of a study which used an unlicensed dose and titration regimen was, in itself, unfair. Yamanouchi alleged that the claim for superior efficacy was neither balanced nor fair and consequently misled. It could not be substantiated.

The Panel noted that the Kirby study was the first direct comparison of Cardura XL with tamsulosin. Pfizer had submitted that it demonstrated differences in side effect profile and efficacy. Results showed that both medicines significantly relieved lower urinary tract symptoms and significantly increased Q_{max} from baseline. Preliminary analysis showed that Cardura XL was significantly more effective than tamsulosin in improving IPSS (p=0.019). The difference between Cardura XL and tamsulosin in improvement of maximum flow rate (Q_{max}) approached significance

in favour of Cardura XL (p=0.089). Cardura XL was significantly more effective in relieving obstructive symptoms (p=0.004). The study also showed that the incidence of treatment-related adverse events was higher in patients receiving tamsulosin (46%) than in patients receiving Cardura XL (40%). Discontinuation due to treatment related adverse events was 4% for tamsulosin patients and none for Cardura XL. The Panel noted that Djavan and Marberger had conducted a meta-analysis on the efficacy and tolerability of alpha$_1$- blockers in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. The study concluded that all alpha$_1$-blockers had similar efficacy in improving symptoms and flow. The difference between them was related to their side effect profile with alfuzosin and tamsulosin appearing to be better tolerated than Cardura, terazosin and prazosin.

The Panel noted that the mean IPSS score at baseline was 18.6±4.98, the score after the washout period (phase III) was 13.9. The change from baseline in maximum flow rate (Q_{max}) returned to baseline value after the washout period. The Panel noted Pfizer's submission that the failure of the IPSS values to return to baseline made no difference as both treatment arms had not returned to baseline. A sequence effect test had been carried out which showed no difference between treatments in the carryover effect. Noting the half-life of the medicines and the submission from Pfizer, the Panel considered that the crossover design was not inappropriate. With regard to the IPSS scoring scheme the Panel noted the submission from Pfizer that some studies used a two week IPSS scoring system. If there were any problem with the score it would apply to both groups as patients were randomised; half receiving doxazosin first and the other half receiving tamsulosin first. The Panel did not consider that it was inappropriate to use the IPSS score for 2 weeks. The mean dose of tamsulosin was 0.7mg per day. The dose given in the SPC was 0.4mg per day. The press release referred in detail to the efficacy results in the Kirby study. No mention was made in the press release of the differences in adverse events in either the Kirby study or the Djavan and Marberger study. The Panel noted that the press release did not refer to the fact that the dose of tamsulosin was inconsistent with its SPC. The Panel considered that the claim that Cardura XL was more effective than tamsulosin in alleviating the symptoms of BPH was unfair and misleading; the dose of tamsulosin used had not been put in the context of the Flomax MR SPC and it was only a preliminary analysis that had shown a significant difference in total IPSS. A strong claim was thus based on preliminary data. Pfizer had failed to substantiate the claim. Breaches of the Code were ruled.

Yamanouchi stated that the medical press release had been misinterpreted. A Chemist & Druggist article stated 'Trial results comparing the two drugs showed that doxazosin GITS was more effective at relieving symptoms and significantly increasing the maximum flow of urine'. The writer had interpreted the ambiguously phrased press release to mean that Cardura XL was significantly more effective than tamsulosin in increasing urine flow as well as symptom relief, whereas the significance shown in the study for urine flow was within the Cardura treated group against baseline. The comparison against tamsulosin was not significant at p=0.089. The Panel considered that the press release was clear that the result for significantly increased maximum flow rate was from baseline and not a comparison between the products. No breach of the Code was ruled.

A lay press release was headed 'Better choice of prostate drugs could ease sleepless nights'. Yamanouchi alleged that the claim that Cardura XL showed 'clear advantages' was in breach of the Code for the reasons outlined above. The Panel considered that the lay press release was misleading and not capable of substantiation for reasons similar to those above. A breach of the Code was ruled.

Yamanouchi alleged that the press release, which had resulted in an article in The Times, also encouraged patients to ask their doctors for a specific, named, superior medicine. This was reinforced by the suggestion that as a result of the good news, men (ie patients, not their doctors) could choose their preferred medication. The Panel noted that the press release made superior claims for Cardura XL compared to tamsulosin. The first paragraph referred to choosing more effective medication. The third paragraph stated 'Now new research is showing clear advantages to one of the products – Cardura XL – meaning that patients on this treatment gain greater relief than those on different drugs'. The press release quoted Kirby as stating that both Cardura XL and tamsulosin were good medicines but that in the study Cardura XL seemed to outperform tamsulosin and would make Kirby lean in the direction of using that agent. The Panel considered that the press release would encourage members of the public to ask their doctors to prescribe a specific medicine. A breach of the Code was ruled.

Page three of the leavepiece compared Cardura XL with tamsulosin referenced to the Kirby study. The page included a bar chart headed 'Cardura XL is more effective than tamsulosin in reducing symptoms' which compared improvements in IPSS for the two products. Details of the study were given beneath the graph including the mean doses of the products, Cardura XL 6.3mg and tamsulosin 0.7mg. Yamanouchi stated that the piece claimed in bold that Cardura XL showed 'Significant improvement against tamsulosin'. The claim was repeated and then it was specified that this was on total IPSS. Yamanouchi alleged that this was in breach of the Code as detailed above. The Panel considered that a ruling above applied to the claim in question and a breach of the Code was ruled.

The leavepiece claimed that Cardura XL was significantly more effective than tamsulosin against total symptom score (IPSS) and obstructive symptoms. Yamanouchi stated that the leavepiece made a further superiority claim on a subset of the IPSS, namely obstructive symptoms. Regardless of whether or not this subset analysis was pre-specified

in the study protocol, this claim was in breach of the Code for the reasons detailed above. The Panel noted that the poster of the Kirby study stated that improvements in obstructive scores with Cardura XL were significantly greater than with tamsulosin (p=0.004). Obstructive score *per se* was not a primary efficacy assessment; the Panel assumed that such a score was a subset of the IPSS. With regard to improvements in IPSS the Kirby study had shown a significant difference in favour of Cardura XL although the analysis was only preliminary. The Panel considered that a ruling above applied to the claims in question and a breach of the Code was ruled.

Yamanouchi stated that the data on file referenced in the leavepiece and sent to it by Pfizer did not mention the subset of obstructive symptoms. Therefore, whilst the data on file was sent promptly from Pfizer, it was not comprehensive and as the data to support this particular claim was not mentioned on the data on file, substantiation had not been provided without delay. The Panel noted that Pfizer had sent by fax the abstract of the Kirby data. This did not include some of the data presented in the leavepiece. The Panel considered that the poster should have been sent in response to the request for the data on file. This should have been sent in the post. It was not acceptable to provide only the abstract. A breach of the Code was ruled.

Yamanouchi stated that the claim for superior efficacy was then shown visually on the leavepiece. Yamanouchi did not consider any visual representation of this study could be balanced or fair as the study design and methodology was inappropriate *per se* and inappropriate for use with UK doctors for the reasons given above. The artwork had an impact which would encourage doctors to prescribe Cardura XL in preference to tamsulosin without the balance of a comparison of the side effect profiles. However, a relevant comparison of side effects could not be made, even if the doctor were to have access to the full study data, due to the tamsulosin dose being twice that licensed in the UK. Doctors would assume that Pfizer would compare only with a licensed dose of a comparator product so that the doctor could make the appropriate benefit/risk assessment. The fact that the dose of tamsulosin used was unlicensed was disregarded in the brief study summary under the artwork. That the actual mean dose of tamsulosin, 0.7mg, was given in small print did not detract from the fact that doctors would not necessarily realise the unlicensed, and therefore inappropriate, nature of the dose. The Panel considered that the artwork was misleading for reasons given above. The reference to the dose given beneath the bar chart did not provide sufficient detail regarding the fact that this was above the SPC dose. The Panel considered that the bar chart was visually misleading and ruled a breach of the Code.

Yamanouchi noted that the claim 'CARDURA XL also had a greater improvement in maximum urinary flow that approached significance (2.6 vs 1.7 ml/s for tamsulosin, p=0.089)' was based on the Kirby study and was therefore in breach of Clauses 7.2 and 7.3 for the reasons detailed above. Yamanouchi considered it disingenuous to use the phrase 'approached significance' for a p value of 0.089. The Panel considered that a ruling above applied here and a breach of the Code was ruled. It was misleading to refer to the improvement in maximum urinary flow as approaching significance. There was an implication that there was a difference between the products and this was not supported by the data. A breach of the Code was ruled.

Yamanouchi alleged that the claim 'CARDURA XL, unlike tamsulosin, has no known adverse drug interactions so is simple to prescribe' implied that tamsulosin was not simple to prescribe, due to its 'known adverse drug interactions'. Although there were two possible interactions listed in the SPC for tamsulosin (diclofenac and warfarin), these were of no known clinical significance and did not require a change in posology. Tamsulosin remained a once-daily treatment for the functional symptoms of BPH for patients on either of these concomitant medications and, as such, it was simple to prescribe. The Panel noted that according to the SPC, Cardura XL had no known interactions with other medicines and other forms of interaction. The Flomax MR SPC stated that diclofenac and warfarin might increase the elimination rate of tamsulosin. The Flomax MR SPC did not refer to any changes in dosing etc as a result of interactions.

The leavepiece was not sufficiently clear about the differences between the products. It implied that because of adverse drug interactions Flomax MR was not simple to prescribe. In the Panel's view this was not so. The claim was misleading and a breach of the Code was ruled.

Yamanouchi Pharma Ltd complained about the promotion of Cardura XL (doxazosin gastrointestinal therapeutic system (GITS)) by Pfizer Limited. The items of which Yamanouchi was aware were a medical press release, a lay press release and a leavepiece (ref 58022 May 2001). Yamanouchi marketed Flomax MR (tamsulosin). Both products were alpha-blockers for the treatment of the symptoms of benign prostatic hyperplasia (BPH).

Yamanouchi stated that Pfizer had started using a comparative study of Cardura XL versus tamsulosin to make claims for superiority of Cardura XL (Kirby *et al* 2001).

Pfizer stated that the Kirby study was the first comparative study of Cardura XL versus tamsulosin in patients with BPH. This was a well conducted and designed study which was ethically approved. It was accepted for presentation at the international meeting of the American Urological Association (AUA) on 7 June 2001 and subsequently accepted for presentation at the British Association of Urological Surgeons (BAUS) meeting in Dublin. Therefore, given that both highly reputable scientific societies had deemed the study suitable for presentation, it would seem reasonable for Pfizer to further communicate the findings of this study to the medical profession.

This case was considered under the provisions of the 1998 Code using the procedures in the 2001 Code.

A Medical press release

This was issued on 28 June 2001 and headed 'New data show that not all alpha blockers are the same in the treatment of benign prostatic hyperplasia'.

A1 Claim for superior efficacy

COMPLAINT

Yamanouchi noted that the press release stated that the widely held view was that all alpha-blockers had similar efficacy in BPH. Yamanouchi concurred with this – it was tolerability which was considered to differ between products. Yamanouchi referred to a meta-analysis by Djavan and Marberger (1999) which stated that 'All α_1-adrenoceptor antagonists seem to have similar efficacy in improving symptoms and flow. The difference between α_1-adrenoceptor antagonists is related to their side effect profile'. The press release went on to give the results of the Kirby study and made the claim that it showed that '[Cardura XL] was significantly more effective than tamsulosin in relieving urinary symptoms (p=0.019)'.

The study was a crossover design of 47 patients for the efficacy analysis (50 patients entered the study). After a two-week placebo run-in, patients received Cardura XL 4mg/day or tamsulosin 0.4mg/day. Cardura XL was titrated to 8mg/day and tamsulosin was titrated to 0.8mg/day after four weeks of therapy if the increase in maximum flow rate (Q_{max}) was <3ml/s and reduction in total International Prostate Symptom Score (IPSS) was <30%. There was then a two-week washout period with placebo, followed by the second treatment phase of tamsulosin or Cardura XL for eight weeks with the same titration requirements at four weeks. The data on file described the results as 'preliminary'.

There were a number of very serious issues with this study which rendered any claim for the UK inappropriate. Similar concerns about the methodology and therefore the interpretation of the study were raised when the study was presented at the BAUS meeting.

a The use of a crossover design for a BPH study

Yamanouchi stated that a crossover design was inappropriate for study end points which were subjective and where the natural course of the disease fluctuated over time. It was a pre-requisite for scientific validity for crossover studies that patients in each treatment arm needed to have comparable baselines and when patients entered the second treatment regimen those baseline characteristics should have returned to their original baseline levels. Firstly, this required patients to lose all benefit of medication during the washout period to avoid any carryover effect. However, the benefit of alpha-blockers might not be completely lost in a two-week period. Secondly, according to the Textbook of Benign Prostatic Hyperplasia (1996) the natural history of BPH showed that symptoms 'wax and wane' over time. In addition, this 'somewhat unpredictable natural history …' meant that '… improvements in symptoms and uroflow are seen in patients treated with placebo', which may 'have been due to a tendency for BPH symptoms to improve spontaneously over the short term'. A review of the natural history of BPH and its implications for clinical trial design stated 'These studies have shown that the clinical course of BPH in individual patients is highly variable over time, whether measured by symptoms or urinary flow rates. An appreciable fraction of patients improve spontaneously without treatment' (Guess1994). This reinforced Yamanouchi's assertion that a crossover design was inappropriate as there could be both a carryover and time effect on the symptom scores at the beginning of the second treatment period.

The International Conference on Harmonisation (ICH) guidelines made the requirements for crossover studies abundantly clear:

'Crossover designs have a number of problems that can invalidate their results. The chief difficulty concerns carryover, that is, the residual influence of treatments in subsequent treatment periods….

When the crossover design is used it is therefore important to avoid carryover …. The disease under study should be chronic and stable…. The washout periods should be sufficiently long for complete reversibility of drug effect. The fact that these conditions are likely to be met should be established in advance of the trial by means of prior information and data.'

Yamanouchi did not believe that the conditions specified in the ICH Guidelines could have been established in advance as this would not be feasible for a disease which was not stable and for such a short washout period.

b The use of the IPSS

Yamanouchi stated that the IPSS was used as the primary variable. This was the well-recognised subjective scoring system which the 'WHO has agreed to use … as the official world-wide symptom assessment tool for patients suffering from prostatism'. This scoring system was used routinely in BPH clinical trials. The score was the total of the severity of seven symptoms recorded 'over the past month'.

However, in this study, the baseline IPSS at entry into the second treatment phase could only have been measured over the two-week washout period. To halve the time over which the patient assessed symptoms was inappropriate (particularly as, in this situation it made a greater proportion of the assessment period more liable to the continuing effects of the treatment the patient had received in the first treatment period). The use of an internationally recognised and widely used scoring system which had not been validated for use over a shorter period was unscientific.

c Dose and titration regimen

Yamanouchi stated that the dose and titration regimen used for Cardura XL was as licensed in the UK. However, for tamsulosin, a titration regimen was also

used with dose escalation to twice the only licensed dose for the UK. The UK summary of product characteristics (SPC) gave the simple dose regime as 0.4mg daily – no titration, no higher dose allowed. In this study the majority of patients must have been titrated to the higher tamsulosin dose for the mean study dose to have been 0.7mg.

The use by a competitor company of a study which used an unlicensed dose and titration regimen was, in itself, unfair, as Yamanouchi would be unable to use it for tolerance or for retaliation as it was outside its licence.

More importantly, its use was totally inappropriate for UK prescribers as the choice of any medication by a doctor should never be based on efficacy alone, but must always be made on the balance of risk/benefit. One side of the equation alone could never be isolated from the other if results were to be interpreted in a balanced manner. Due to the dose used, the side effect profile of tamsulosin from this study was irrelevant for UK physicians and a relevant comparison of the side effect profiles of both medicines could not be made by prescribers. Therefore, risk/benefit assessment appropriate to UK clinical practice could not be made regardless of the efficacy results. The question any prescriber needed to ask was what trade-off there was in terms of side effects for any increased efficacy. This was particularly important when, as the press release stated, it had previously been believed that all alpha-blockers had similar efficacy, but 'the difference between α_1-adrenoceptor antagonists is related to their side effect profile' (Textbook of Benign Prostatic Hyperplasia).

Yamanouchi alleged that the claim for superior efficacy was neither balanced nor fair and consequently misled. It could not be substantiated. A breach of Clauses 7.2 and 7.3 was alleged.

RESPONSE

Pfizer stated that its medical press release referred to the past in that 'It has been widely believed that the alpha-blockers, one of the main classes of therapies to treat BPH, were of more or less similar effectiveness'. Pfizer did not agree that the only difference between this class of agent related to their side effect profile. Yamanouchi pointed to the meta-analysis by Djavan and Marberger which only reviewed data up to October 1998 and hence concluded that all alpha-blockers seemed to have similar efficacy and that the only difference between them related to their side effect profile.

Since the above meta-analysis, the Kirby study was the first direct comparison between Cardura XL and tamsulosin, which had demonstrated that there were differences in not only side effect profile but more importantly in the efficacy between the two agents in the same class.

The Kirby study had been well conducted, the methodology was robust and had been well designed for comparisons between two different agents. It was common practice at scientific meetings for the methodology of any clinical study to be challenged, this did not mean that the study was poorly conducted or badly designed. Pfizer submitted that the study was of high quality and appropriate for use in the UK. Concerns raised regarding the study's design and methodology were addressed.

a The use of a crossover design for a BPH study

The use of a crossover design in this clinical study was appropriate for use in BPH which was a chronic but stable condition. It was also appropriate for use in such a condition where the endpoints reflected symptoms which had been quantified objectively.

Chronic and stable condition Although BPH was a chronic condition, it progressed very slowly over time and could be considered as 'stable'. Data from the Olmsted County Study revealed that urinary flow decreased and prostate size increased with age. A recent review of the natural history of BPH concluded that patients with moderate to severe symptoms should be treated, an alpha-blocker was usually the first treatment of choice, and that only patients in the minimal symptoms group should consider 'watchful waiting' an option. Patients in the Kirby study had moderate/severe symptoms as defined by their IPSS (mean IPSS at baseline = 18.6 ± 4.98, inclusion criteria of IPSS ≥ 12).

Although the symptoms of BPH might 'wax and wane' on a daily basis, the IPSS was designed to assess symptoms over a period of time (usually a few weeks) and not just based on a day. The severity of symptoms was measured over a specified time which eliminated the differences in symptoms caused by day to day variability. In the Kirby study, patients were assessed in total seven times for their IPSS, from baseline visit to their final visit.

Endpoints measuring symptoms It was a widely accepted practice in clinical trials for the treatment of symptomatic BPH to assess improvements such as changes in lower urinary tract symptoms, urinary flow rate and reduction in prostatic volume over time. Some of these 'symptomatic' endpoints were quantified into a scoring system in order to minimise subjectivity, such as the IPSS. In the Kirby study, the primary efficacy endpoints were changes from baseline in lower urinary tract symptoms and urinary flow as measured by IPSS and changes in maximum urinary flow rate (Q_{max}). Both IPSS and Q_{max} were routinely used in efficacy assessments in clinical trials relating to BPH and indeed were necessary endpoints in any study examining efficacy of treatment in this condition. Pfizer therefore disagreed with the suggestion that the endpoints in this study were inappropriate.

Standard crossover ANOVA models were used to analyse the data from this study. Patients in each treatment arm had comparable baselines at the end of phase I (placebo run-in for 2 weeks) with a mean IPSS of 18.6 ± 4.98 and a mean Q_{max} of 10.2 ± 2.93. At the end of phase III (2 week washout period) Q_{max} values did return to their baseline values (10.3 mL/s at initial baseline, 10.5 after washout period, phase III). Although the total IPSS values did not return to baseline (mean baseline of 18.6, mean second baseline after washout at 13.9) this made no difference as both

treatment arms did not return to baseline. In order to ensure that there had been minimal or equal carryover effects, the 'sequence effect' test was carried out. In this study the p-values were not significant for the sequence effects (p=0.672 for total IPSS, and p=0.464 for Q_{max}). Therefore, there was no difference between treatments in the carryover effect. This gave statistical validity to the combined crossover analysis.

The washout period in a crossover study should indeed be sufficiently long in order to minimise carryover effects. A drug was fully eliminated from the body after five elimination half-lives ($T_{1/2}$) of the drug. The elimination half-life of tamsulosin was between 10 and 13 hours and the drug was eliminated from the body after 65 hours (5 x $T_{1/2}$ = 50 to 65 hours). Cardura XL would be fully eliminated from the body after 80.5 hours (maximum), with a half-life of between 15 and 16.1 hours. The two week (336 hours) washout period in this study was, therefore, more than adequate to minimise any carryover effects.

According to the ICH guidelines, 'the chief difficulty (of crossover design) concerns carryover, that is the residual influence of treatments in subsequent treatment periods. In an additive model the effect of unequal carryover will be to bias direct treatment comparisons'. There was minimal but equal carryover in the IPSS endpoint but none for Q_{max}. In addition, the sufficiently long washout period meant that comparisons between tamsulosin and Cardura XL drawn from this study were fair and unbiased.

Pfizer believed, due to changing opinion in urology and current evidence regarding management, coupled with appropriate use of the IPSS, that BPH (especially in patients with moderate/severe symptoms) was indeed a condition for which a crossover study was suitable.

b The use of the IPSS

Pfizer submitted that it was widely accepted practice in clinical trials for the treatment of symptomatic BPH to assess improvements such as changes in lower urinary tract symptoms, urinary flow rate and reduction in prostatic volume over time. Some of these 'symptomatic' endpoints were quantified in an objective scoring system in order to minimise subjectivity such as the IPSS.

The IPSS questionnaire was used seven times in the course of the study. Five of these questionnaires referred to symptoms over the last month, whereas the other two referred to symptoms over the past two weeks. The use of a two week IPSS questionnaire was not unusual practice in urology studies. This was in fact used widely by Yamanouchi in three recently published BPH studies using tamsulosin. The use of a two week IPSS scoring system in no way influenced the outcome of the study nor its interpretation.

c Titration regimen used in the study

Pfizer submitted that the titration criteria in this study were clearly defined for both treatment groups. Patients were initiated on Cardura XL at 4mg/day or tamsulosin at 0.4mg/day. These were subsequently titrated to 8mg/day for Cardura XL or tamsulosin to 0.8mg/day only after 4 weeks, if there were inadequate improvements for Q_{max} and IPSS.

It was common practice in clinical trials to assess effects of a medicine even when the dosage studied had not previously been licensed. The lack of a licensed titration regimen for tamsulosin should not impede clinical research for patients whose symptoms were not adequately controlled. (In fact, Yamanouchi had conducted its own placebo controlled study with tamsulosin using 0.4mg/day and the unlicensed 0.8mg dose). More importantly, UK doctors commonly prescribed higher than licensed doses if they considered that the benefit of doing so outweighed the risks.

The study did not advocate the use of tamsulosin outside the licensed dose. It reported the differences seen in efficacy and tolerability demonstrated in the study based on a mean daily dosage of 6.3mg with Cardura XL and 0.7mg with tamsulosin. Cardura XL was significantly more effective than tamsulosin in improving total IPSS (p=0.019) and relieving obstructive symptoms (p=0.004) in men with BPH. Even though patients tolerated Cardura XL better than tamsulosin, Pfizer had not sought to deliver any information regarding tolerance based on this study.

In conclusion, the Kirby study clearly demonstrated a superiority in efficacy based on validated and well accepted endpoints. The use of a crossover design was perfectly robust for a chronic but stable condition such as BPH. The use of a different dosage regimen to that in the product licence addressed important scientific questions on the doses required for improvement in symptoms.

Therefore, Pfizer believed that its claim for superior efficacy in symptoms improvement for Cardura XL over tamsulosin did not breach Clause 7.2. It had been fully substantiated by the Kirby study and represented the most up-to-date information on this class of agents. Finally, this information was fully substantiated and did not breach Clause 7.3.

PANEL RULING

The Panel noted that the Kirby study was the first direct comparison of Cardura XL with tamsulosin; Pfizer submitted that it demonstrated differences in side effect profile and efficacy. The study was a randomized, double-blind crossover design with patients starting with a two-week placebo run in followed by an eight-week treatment period, a two-week placebo washout and a further eight-week treatment period with whichever medicine was not used during the first treatment period. Primary efficacy assessments were IPSS and Q_{max}. Results showed that both medicines significantly relieved lower urinary tract symptoms and significantly increased Q_{max} from baseline. Preliminary analysis showed that Cardura XL was significantly more effective than tamsulosin in improving IPSS (p=0.019). The difference between Cardura XL and tamsulosin in improvement of maximum flow rate (Q_{max}) approached significance in favour of Cardura XL (p=0.089). Cardura XL was significantly more effective in relieving obstructive symptoms (p=0.004). The study also showed that the incidence of

treatment-related adverse events was higher in patients receiving tamsulosin (46%) than in patients receiving Cardura XL (40%). Discontinuation due to treatment related adverse events was 4% for tamsulosin patients and none for Cardura XL.

The Panel noted that Djavan and Marberger had conducted a meta-analysis on the efficacy and tolerability of alpha$_1$-blockers in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. The study concluded that all alpha$_1$-blockers had similar efficacy in improving symptoms and flow. The difference between them was related to their side effect profile with alfuzosin and tamsulosin appearing to be better tolerated than Cardura, terazosin and prazosin.

The Panel noted that the mean IPSS score at baseline was 18.6±4.98, the score after the washout period (phase III) was 13.9. The change from baseline in maximum flow rate (Q_{max}) returned to baseline value after the washout period. The Panel noted Pfizer's submission that the failure of the IPSS values to return to baseline made no difference as both treatment arms had not returned to baseline. A sequence effect test had been carried out which showed no difference between treatments in the carryover effect. Noting the half-life of the medicines and the submission from Pfizer, the Panel considered that the crossover design was not inappropriate.

With regard to the IPSS scoring scheme the Panel noted the submission from Pfizer that some studies used a two week IPSS scoring system. If there were any problem with the score it would apply to both groups as patients were randomized; half receiving doxazosin first and the other half receiving tamsulosin first. The Panel did not consider that it was inappropriate to use the IPSS score for 2 weeks.

The Panel noted that the mean dose of tamsulosin was 0.7mg per day. The dose given in the SPC was one 0.4mg capsule per day. The starting dose of tamsulosin in the study was 0.4mg/day and increased to 0.8mg per day after 4 weeks if the increase in Q_{max} was <3ml/s and the reduction in total IPSS was <30%.

The Panel noted that the press release referred in detail to the efficacy results in the Kirby study. No mention was made in the press release of the differences in adverse events in either the Kirby study or the Djavan and Marberger study.

Clause 7.2 of the Code required that 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 the evidence clearly. They must not mislead either directly or by implication. The Panel queried whether comparing products using unlicensed doses and/or indications of a competitor product met the requirements of Clause 7.2. Readers might be misled as to the efficacy and tolerability of the competitor product at licensed doses and its approved use. The company with the competitor product could not counter the arguments as it would be open to accusations of promoting an unlicensed indication and/or dose.

The Panel noted that the press release did not refer to the fact that the dose of tamsulosin was inconsistent with its SPC. The Panel considered that the claim that Cardura XL was more effective than tamsulosin in alleviating the symptoms of BPH was unfair and misleading; the dose of tamsulosin used had not been put in the context of the Flomax MR SPC and it was only a preliminary analysis that had shown a significant difference in total IPSS. A strong claim was thus based on preliminary data. The Panel ruled a breach of Clause 7.2 of the Code. Pfizer had failed to substantiate the claim and a breach of Clause 7.3 of the Code (1998 edition) was also ruled.

A2 Interpretation of fourth paragraph

COMPLAINT

Yamanouchi stated that the press release had been very carefully scripted such that, without access to the study results, the fourth paragraph could be misinterpreted. This had in fact happened in a Chemist & Druggist article which stated 'Trial results comparing the two drugs showed that doxazosin GITS was more effective at relieving symptoms and significantly increasing the maximum flow of urine'. Therefore, the writer had interpreted the ambiguously phrased press release to mean that Cardura XL was significantly more effective than tamsulosin in increasing urine flow as well as symptom relief, whereas the significance shown in the study for urine flow was within the Cardura treated group against baseline. The comparison against tamsulosin was not significant at p=0.089.

The Chemist & Druggist article confirmed the ambiguity of the press release and a breach of Clause 7.2 of the Code was alleged.

RESPONSE

Pfizer stated that the press release clearly said 'that doxazosin GITS was significantly more effective than tamsulosin in relieving urinary symptoms (p=0.019), and significantly increased maximum flow rate from baseline (p=0.001)'. This statement was not intended to misrepresent results which proved that Cardura XL relieved urinary symptoms more effectively than tamsulosin and, after a correctly placed comma, went on to state that Cardura XL significantly increased flow rate from baseline. The statement did not indicate nor suggest that Cardura XL increased flow rate more than tamsulosin. The statement was unambiguous.

In addition to sending out the press release, medical journalists could obtain a copy of the results of the study. Pfizer could not be held responsible for any misrepresentation by medical journalists (eg Chemist & Druggist) when it had produced a clear and unambiguous press release. However, Pfizer strongly believed that the information it provided was accurate, balanced, fair, objective and unambiguous and therefore not in breach of Clause 7.2.

PANEL RULING

The Panel considered that the paragraph in the press release was clear that the result for significantly increased maximum flow rate was from baseline and

not a comparison between the products. The Panel therefore ruled no breach of Clause 7.2 of the Code.

B Lay press release

This was dated 28 June 2001 and headed 'Better choice of prostate drugs could ease sleepless nights'.

B1 Claim that Cardura shows 'clear advantages'

COMPLAINT

Yamanouchi alleged the claim that Cardura XL showed 'clear advantages' to be in breach of Clauses 7.2 and 7.3 for the reasons outlined above in A1a, b and c.

RESPONSE

Pfizer stated that the lay press release provided general information on BPH including treatment options such as medical and surgical intervention. The Kirby study clearly demonstrated superior efficacy in terms of total IPSS (p=0.019) and in relieving obstructive symptoms (p=0.004) for Cardura XL over tamsulosin. Therefore, it was fair to state that Cardura XL had a 'clear advantage over tamsulosin'. This advantage was also further qualified to mean relief of symptoms. Furthermore, Kirby (a key opinion leader in the field of urology) believed that 'Both (Cardura XL and tamsulosin) are good drugs, but in this study Cardura XL seemed to outperform tamsulosin'.

This press release reflected the results of the Kirby study in a balanced and fair manner by using accurate, objective data in an unambiguous way. The data was also substantiated. Pfizer did not believe that it breached Clauses 7.2 nor 7.3 (for reasons as outlined in A1a, b and c above).

PANEL RULING

The Panel considered that the lay press release was misleading and not capable of substantiation for reasons similar to those in A1 above. Breaches of Clauses 7.2 and 7.3 (1998 Code) were ruled. In the Panel's view this allegation would have been more appropriately dealt with under Clause 20 as the press release was for the general public. There was no allegation in this regard.

B2 Alleged breach Clause 20.2

COMPLAINT

Yamanouchi alleged that the press release, which resulted in an article in The Times, breached Clause 20.2 as it encouraged patients to ask their doctors for a specific, named, superior medicine. This was reinforced by the suggestion in the first paragraph that as a result of the good news, men (ie patients, not their doctors) could choose their preferred medication.

RESPONSE

Pfizer stated that 'Prostate progress' was the article which appeared in The Times on 12 July, 2001, to mark the then upcoming Sexual Health Week. It highlighted frequent problems suffered by men such as erectile dysfunction and BPH. Clearly, the content of the article might be drawn from many sources and not only from Pfizer's press release. Although the last sentence of the second paragraph stated that 'there is good news for sufferers of both conditions', this did not only refer to treatment with Cardura XL. On reading the article further, the reader would find that the 'good news' related to the fact that symptoms of BPH were generally better recognised, improvements had been made in surgical intervention, the availability of antibiotics and also the availability of effective medical treatments which could be used to postpone surgery and to improve quality of life.

Finally, towards the end of the article, the Kirby study was mentioned. It gave a fair and balanced view of the study by stating that both drugs were effective but that Cardura XL might have a significant advantage. Kirby also mentioned that surgery for BPH was also a common procedure, therefore another possible option.

This article did not actively encourage patients to ask their doctors for a specific medication. Instead it provided a factual and balanced report on two commonly occurring conditions in men (erectile dysfunction and BPH). More importantly, Pfizer did not believe that the article raised unfounded hopes of successful treatment and nor did it raise any safety aspect of the product. Pfizer submitted that neither the press release which contributed to this article, nor the article itself, were in breach of Clause 20.2.

PANEL RULING

The Panel noted that the press release made superior claims for Cardura XL compared to tamsulosin. The first paragraph referred to choosing more effective medication. The third paragraph stated 'Now new research is showing clear advantages to one of the products – Cardura XL – meaning that patients on this treatment gain greater relief than those on different drugs'. The press release quoted Kirby as stating that both Cardura XL and tamsulosin were good medicines but that in the study Cardura XL seemed to outperform tamsulosin and would make Kirby lean in the direction of using that agent. The Panel considered that the press release would encourage members of the public to ask their doctors to prescribe a specific medicine. The Panel therefore ruled a breach of Clause 20.2 of the Code.

C Leavepiece (ref 58022 May 2001)

Page three of the leavepiece compared Cardura XL with tamsulosin referenced to the Kirby study. The page included a bar chart headed 'Cardura XL is more effective than tamsulosin in reducing symptoms' which compared improvements in IPSS for the two products. Details of the study were given beneath the graph including the mean doses of the products, Cardura XL 6.3mg and tamsulosin 0.7mg.

C1 Claim 'Significant improvement against tamsulosin'

COMPLAINT

Yamanouchi stated that the piece claimed in bold that Cardura XL showed 'Significant improvement against tamsulosin'. The claim was repeated and then it was specified that this was on total IPSS. Yamanouchi alleged that this was in breach of Clauses 7.2 and 7.3, as detailed above in A1a, b and c.

RESPONSE

Pfizer stated that the claim appeared at the top of page 3 of the leavepiece and was linked to the claim underneath 'Cardura XL is significantly more effective than tamsulosin against total symptom score (IPSS) and obstructive symptoms'. Any reader could not fail to read the title and the claim jointly. The claim was prominently made.

The Kirby study had demonstrated that Cardura XL was significantly more effective than tamsulosin in improving total IPSS (p=0.019) and obstructive symptoms (p=0.004) in men with BPH. This study, its methodology, results and interpretation had already been discussed in A1a, b and c above.

The claim was therefore accurate, balanced, fair, objective, unambiguous and based on up-to-date information. It was not misleading but could be fully substantiated as discussed above. Therefore the claim was not in breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel considered that its ruling in point A1 above applied to the claim in question. Breaches of Clauses 7.2 and 7.3 (1998 Code) were ruled.

C2 Claim 'CARDURA XL is significantly more effective than tamsulosin against:

– Total symptom score (IPSS)

– Obstructive symptoms'

COMPLAINT

Yamanouchi stated that the leavepiece made a further superiority claim on a subset of the IPSS, namely obstructive symptoms. Regardless of whether or not this subset analysis was pre-specified in the study protocol, this claim, as with any claim based on this study, was in breach of Clauses 7.2 and 7.3 for the reasons detailed above in A1a, b and c.

RESPONSE

Pfizer stated that the claim was fully substantiated by the Kirby study. The endpoints were pre-specified in the study.

The study results showed that irritative and obstructive scores significantly improved from baseline for both doxazosin GITS and tamsulosin (p=0.001). But more importantly, the study also showed that improvements in obstructive scores with doxazosin GITS were significantly greater than with tamsulosin (p=0.004).

The claim was therefore accurate, balanced, fair, objective and unambiguous. It was not misleading and was fully substantiated. Therefore, it did not breach Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the poster of the Kirby study stated that improvements in obstructive scores with Cardura XL were significantly greater than with tamsulosin (p=0.004). Obstructive score *per se* was not a primary efficacy assessment; the Panel assumed that such a score was a subset of the IPSS. With regard to improvements in IPSS the Kirby study had shown a significant difference in favour of Cardura XL although the analysis was only preliminary. The Panel considered that its ruling in point A1 above applied to the claims in question. Breaches of Clauses 7.2 and 7.3 (1998 Code) were ruled.

C3 Provision of data on file

COMPLAINT

Yamanouchi stated that the data on file referenced in the leavepiece and sent to it by Pfizer did not mention the subset of obstructive symptoms. Therefore, whilst the data on file was sent promptly from Pfizer, it was not comprehensive and as the data to support this particular claim was not mentioned on the data on file, substantiation had not been provided without delay. There was, therefore, a breach of Clause 7.4.

RESPONSE

Pfizer stated that it endeavoured, at all times, to handle queries and data inquiries as effectively and quickly as possible.

A telephone request for 'the new Kirby paper' was made by Yamanouchi on 30 July and 1 August. The request was logged and handled by a member of Pfizer's medical information department. Yamanouchi was informed that there were two documents available for the 'Kirby data', namely, an abstract of the study (size A4) and a poster presentation of the data (size A3). Yamanouchi specifically asked for the abstract to be faxed because it needed it urgently as Pfizer was unable to fax an A3 poster. There was no further request for the subsequent A3 poster to be sent on.

Although the A3 poster presentation of the data was more comprehensive and provided the data to support the claim regarding 'obstructive symptoms', this was easily available and was made known to Yamanouchi. Pfizer believed that this misunderstanding could be easily resolved if discussed further.

It appeared that there was some confusion with regard to Yamanouchi's request for data (of which both the abstract and poster were made available to it). Pfizer did not believe as a result of this that it had breached Clause 7.4.

PANEL RULING

The Panel noted that Pfizer had sent by fax the abstract of the Kirby data. This did not include some of the data presented in the leavepiece. The Panel considered that the poster should have been sent in response to the request for the data on file. This should have been sent in the post. It was not acceptable to provide only the A4 abstract. The Panel therefore ruled a breach of Clause 7.4 (1998 Code).

C4 Artwork

COMPLAINT

Yamanouchi stated that the claim for superior efficacy was then shown visually. Yamanouchi did not consider any visual representation of this study could be balanced or fair as the study design and methodology was inappropriate *per se* and inappropriate for use with UK doctors for the reasons given above in A1a, b and c. In particular, the artwork had an impact which would encourage doctors to prescribe Cardura XL in preference to tamsulosin without the balance of a comparison of the side effect profiles. However, a relevant comparison of side effects could not be made, even if the doctor were to have access to the full study data, due to the tamsulosin dose being twice that licensed in the UK. Doctors would assume, not unreasonably, that Pfizer would compare only with a licensed dose of a comparator product in order that the doctor could make the appropriate benefit/risk assessment. The fact that the dose of tamsulosin used was unlicensed was disregarded in the brief study summary under the artwork.

That the actual mean dose of tamsulosin, 0.7mg, was given in small print did not detract from the fact that doctors would not necessarily realise the unlicensed, and therefore inappropriate, nature of the dose.

Yamanouchi alleged that the artwork was in breach of Clause 7.6.

RESPONSE

Pfizer stated that based on the information provided in A1a, b and c above, it believed that the study design and methodology used in its detail was acceptable. The graph in question was clear and limited to the claim that 'CARDURA XL (doxazosin GITS) is more effective than tamsulosin in reducing symptoms'. It showed graphically the improvements in IPSS seen in both treatment arms and included the relevant p-value (p=0.019). Beneath the graph, a brief study description was included along with mean dosages used in the study for both medicines. Pfizer was willing to consider including a claim to highlight that the 0.8mg dose for tamsulosin was not currently licensed, if this was felt to be appropriate by the Authority.

The bar chart in question gave a fair representation of one of the study outcomes, it was relevant to the claim and, as all relevant information was supplied, was balanced. Therefore, it was not in breach of Clause 7.6.

PANEL RULING

The Panel considered that the artwork was misleading for reasons given in point A1 above. The reference to the dose given beneath the bar chart did not provide sufficient detail regarding the fact that this was above the SPC dose. The Panel considered that the bar chart was visually misleading and ruled a breach of Clause 7.6 (1998 Code).

C5 Claim 'CARDURA XL also had a greater improvement in maximum urinary flow that approached significance (2.6 vs 1.7 ml/s for tamsulosin, p=0.089)'

COMPLAINT

Yamanouchi noted that the claim was based on the Kirby study and was therefore in breach of Clauses 7.2 and 7.3 for the reasons detailed above in A1a, b and c.

Yamanouchi considered it disingenuous to use the phrase 'approached significance' for a p value of 0.089. In its data on file, Pfizer described this difference in flow rate as 'marginal.' 'Marginal' and 'approached significance' were not synonymous and gave very different impressions. The use of the words 'approached significance' in a piece of promotional material to describe a p-value well removed from the accepted 0.05 was unacceptable. Clinicians might or might not be familiar with the (lack of) significance of 0.089, but the implication was that the difference between products was real. With this p-value, it was not possible to know whether the difference was or was not real. Yamanouchi considered the use of the word 'approached' in this context to be misleading and in breach of Clause 7.2.

RESPONSE

Pfizer stated that maximum urinary flow rates were compared in both treatment groups. The difference was marginal in favour of Cardura XL but not statistically significant (p=0.089). It was clear from the word 'approached' that statistical significance was not achieved as also denoted by the p-value. This claim was taken directly from the poster.

Pfizer did not believe that there had been a breach of Clause 7.2. However, it would be willing to consider re-phrasing the claim without the words 'approached significance' if this was felt by the Authority to be appropriate.

PANEL RULING

The Panel considered that its ruling in point A1 above applied here and breaches of Clauses 7.2 and 7.3 (1998 Code) were ruled. The Panel considered that it was misleading to refer to the improvement in maximum urinary flow as approaching significance. There was an implication that there was a difference between the products and this was not supported by the data. A breach of Clause 7.2 of the Code was ruled.

C6 Claim 'CARDURA XL, unlike tamsulosin, has no known adverse drug interactions so is simple to prescribe'

COMPLAINT

Yamanouchi alleged that the claim implied that tamsulosin was not simple to prescribe, due to its 'known adverse drug interactions'. Although there were two possible interactions listed in the SPC for tamsulosin (diclofenac and warfarin), these were of no known clinical significance and did not require a change in posology. Tamsulosin remained a once-daily treatment for the functional symptoms of BPH for patients on either of these concomitant medications and, as such, it was simple to prescribe.

Yamanouchi alleged that the claim was in breach of Clause 7.2.

RESPONSE

Pfizer stated that the claim was representative of the two products' SPCs. Cardura XL had no known adverse drug interactions and as such was simple to prescribe as it avoided the problem of interaction with concomitant medication. However, this was different in the Flomax MR SPC. It was stated under Section 4.5 that warfarin and diclofenac might interact with tamsulosin resulting in an increase in elimination rate of tamsulosin. This could lead to hypotensive effects. Pfizer had made no reference to the fact that tamsulosin was not simple to prescribe.

The claim was accurate and not misleading, and based on the up-to-date information in the SPCs for both products. Pfizer therefore believed that this claim was not in breach of Clause 7.2.

PANEL RULING

The Panel noted that according to the SPC Cardura XL had no known interactions with other medicines and other forms of interaction. The Flomax MR SPC stated that diclofenac and warfarin might increase the elimination rate of tamsulosin. The Flomax MR SPC did not refer to any changes in dosing etc as a result of interactions.

The leavepiece was not sufficiently clear about the differences between the products. It implied that because of adverse drug interactions Flomax MR was not simple to prescribe. In the Panel's view this was not so. The claim was misleading as alleged and a breach of Clause 7.2 of the Code was ruled.

Complaint received **8 August 2001**

Case completed **1 November 2001**

CASE AUTH/1218/8/01

ASTRAZENECA/DIRECTOR v GLAXOSMITHKLINE

Promotion of Seretide and breach of undertaking

AstraZeneca complained about a fieldforce guidance document produced by GlaxoSmithKline and that company's use of the In-Check Dial.

The latter aspect involved an allegation of a breach of undertaking and was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

AstraZeneca believed the fieldforce guidance document, which was about AstraZeneca's product Symbicort and produced prior to the launch of that product, was an internal briefing document for the GlaxoSmithKline sales teams. AstraZeneca was concerned firstly that, at initial inter-company discussions, it was led to believe that this document had not been subjected to the certification requirements of the Code.

Secondly, throughout the document there was explicit reference to 'yo-yo asthma', a term used to describe how Symbicort might be used as an adjustable maintenance treatment. This term was not recognised by the British Thoracic Society, UK health professionals or included in any global asthma management guidelines. This was the first time AstraZeneca had heard the use of this term and it had also attracted health professional comment which was how the matter came to AstraZeneca's attention. The document clearly expected the sales teams to refer to stepping up and stepping down as 'yo-yo asthma'. The tone of the document was such that it appeared to disparage both the medically accepted practice of adjusting asthma treatment to the patient's level of asthma control and the use of Symbicort in this context. AstraZeneca alleged that the contents and intended messages were disparaging.

The Panel noted the submission that the document was subjected to the normal certification process and fully approved before its distribution to the field force. The Panel therefore ruled no breach of the Code.

The Panel did not accept that the term 'yo-yo asthma' and the tone of the document disparaged the accepted practice of adjusting asthma treatment to the patient's level of control. Nor was it disparaging about the use of Symbicort in this regard. No breach of the Code was ruled.

On appeal by AstraZeneca, the Appeal Board noted that the document had been subjected to the normal certification process and fully approved before its distribution to the salesforce. The Appeal Board thus upheld the Panel's ruling of no breach of the Code.

The Appeal Board noted that the term 'yo-yo asthma' was used by GlaxoSmithKline in a briefing document which attempted to pre-position Symbicort prior to its launch. As soon as Symbicort became available GlaxoSmithKline realised that its anticipated positioning of the product had been wrong and the document at issue had been replaced by another which did not refer to 'yo-yo asthma'. Nonetheless the Appeal Board did not consider that the use of the term in the original document had either disparaged Symbicort or the clinical opinion of health professionals as alleged. The Appeal Board upheld the Panel's ruling of no breach of the Code.

AstraZeneca referred to Case AUTH/1096/11/00 which involved GlaxoSmithKline's use of the In-Check Dial as a prize in a promotional competition. Although the In-Check Dial was a device and not a medicine, the Panel had considered that the provision of the In-Check Dial by GlaxoSmithKline in such circumstances came within the scope of the Code.

It was recently brought to AstraZeneca's attention that at a meeting in Leicester in July the same In-Check Dial was being used promotionally on a GlaxoSmithKline exhibition stand. AstraZeneca had also been made aware of continuing distribution of the same device to clinicians. In one particular case the In-Check Dial was given to a physician in the Midlands in July. These were two examples that clearly indicated that GlaxoSmithKline was continuing to use this In-Check Dial, which had been the subject of the recent case, within promotional activity. AstraZeneca viewed these events as serious and alleged a breach of undertaking and a breach of Clause 2 of the Code.

The Panel noted that it had to decide whether the demonstration of the In-Check Dial at the hospital was subject to the Code. The circumstances were different to the previous case. The Panel noted that a respiratory care associate (RCA) ran the stand. GlaxoSmithKline submitted that the materials on it were not promotional. The stand had also included an In-Check Dial for demonstration purposes.

The Panel noted the submission regarding the activities of the RCAs. It was not necessarily unacceptable for companies to have employees who focussed on audit, training and education. The arrangements, activities and materials had to comply with the Code. Companies needed to ensure that the arrangements and activities were very carefully controlled and managed. Guidance on the provision of medical and education goods and services had been issued by the Authority in the November 1999 issue of the Code of Practice Review. This had been added to the supplementary information to Clause 18.1 in the 2001 Code. There was no allegation about the role of the RCAs.

The Panel noted that the In-Check Dial had been inadequately labelled in that it implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use AstraZeneca's Turbohaler device and that was not so.

The Panel considered that the nature of the meeting, or who was demonstrating the In-Check Dial, were not relevant factors. It was inappropriate to use misleading material whether it was for an educational purpose or for a promotional purpose. The Panel considered that the effect of GlaxoSmithKline demonstrating the inadequately labelled In-Check Dial was to give misleading information about one of its competitors, AstraZeneca's Turbohaler. In the Panel's view, this amounted to promotion and was thus subject to the Code. The Panel considered that the continued use of the inadequately labelled In-Check Dial for a promotional purpose meant that GlaxoSmithKline had failed to comply with the undertaking given in Case AUTH/1096/11/00. The Panel ruled a breach of Clause 22 of the Code.

With regard to the allegation concerning the distribution of the In-Check Dial to a physician in the Midlands, the Panel noted that AstraZeneca was unable to provide any information other than that it was given to a physician in the Leicestershire area in early July 2001. The Panel noted that it was not possible for GlaxoSmithKline to investigate the matter due to insufficient information. The Panel therefore ruled no breach of Clause 22 of the Code in that regard.

The Panel considered that failure to comply with an undertaking was a serious matter. GlaxoSmithKline had withdrawn the In-Check Dial from the representatives who had been informed that the RCAs were not promotional in their activities and would be able to continue to use and supply the item as an educational tool. A memorandum dated 26 July stated that the In-Check Dials were to be returned for re-labelling.

The Panel noted that there was no evidence that the In-Check Dial had been used again by the representatives. It had not been used with promotional materials. It had been available for the RCAs to use with what GlaxoSmithKline submitted were educational materials. GlaxoSmithKline had attempted to comply with the undertaking but its actions had been insufficient. On balance, the Panel did not consider that the use of the In-Check Dial brought discredit upon and reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled. This ruling was appealed by AstraZeneca.

Following its consideration of this case the Panel noted that GlaxoSmithKline had discussed the undertaking in the previous case with members of the Authority. The company had been told that the undertaking prevented the promotional use of the In-Check Dial. The use of the In-Check Dial for an educational purpose had not been considered in the previous case. It may have been that the Authority's informal advice was inadequate and that it should have advised against any use of the misleadingly

labeled In-Check Dial by a pharmaceutical company. It may have been as a result of the Authority misunderstanding the information from GlaxoSmithKline or being given insufficient detail. This matter highlighted the difficulties that could arise from informal requests for advice.

The Appeal Board 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. GlaxoSmithKline had withdrawn the original In-Check Dial from its fieldforce in April 2001 but had continued to allow its respiratory care team to demonstrate the device eg at the meeting in Leicester. The company had accepted the Panel's ruling that such use had been in breach of its undertaking in Case AUTH/1096/11/00. The Appeal Board noted that there was no evidence to substantiate the further allegations of GlaxoSmithKline's continued use of the original In-Check Dial as cited by AstraZeneca. There were no details from either party as to what had been supplied to the doctor in the Midlands in July. AstraZeneca had not revealed the identity of the doctor and GlaxoSmithKline had thus had not been able to fully investigate the matter. Other meetings held in the South West in October and cited by AstraZeneca in its appeal as further examples of the continued use of the In-Check Dial, were held almost a month after newly labelled versions of the In-Check Dial had been made available to the fieldforce. At the appeal hearing itself AstraZeneca's representatives produced an In-Check Dial which had allegedly been distributed by GlaxoSmithKline at the first of these meetings. Other companies had been represented at this meeting. GlaxoSmithKline confirmed that the labelling on the device produced by the AstraZeneca representatives was not the same as the original labelling on the In-Check Dial at issue in Case AUTH/1096/11/00 and nor was it the same as the newly labelled device used by the company. It thus appeared that the device brought to the appeal hearing by AstraZeneca had been obtained from a company other than GlaxoSmithKline. The Appeal Board considered that it had no evidence before it to show that GlaxoSmithKline had demonstrated the original In-Check Dial at either of these meetings.

In the Appeal Board's view GlaxoSmithKline had taken steps to comply with its undertaking although these had not been wholly adequate. It was unfortunate that the device had not been withdrawn from all GlaxoSmithKline employees. On balance the Appeal Board considered that the company's actions in this regard had not been such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel's ruling of no breach of Clause 2 was upheld.

AstraZeneca complained about a fieldforce guidance document produced by GlaxoSmithKline and the company's use of the In-Check Dial.

The latter aspect involved an allegation of a breach of undertaking and was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

AstraZeneca had launched Symbicort (eformoterol with budesonide) in June 2001 for the treatment of asthma. GlaxoSmithKline also had a combination product for the treatment of asthma, Seretide (salmeterol with fluticasone).

1 Fieldforce guidance document (May 2001) The AZ combination defence

COMPLAINT

AstraZeneca had two concerns about what it believed to be an internal briefing document for the GlaxoSmithKline sales teams produced prior to the launch of Symbicort.

Firstly, at initial inter-company discussions AstraZeneca was led to believe that this document had not been subjected to the full rigour of the complete internal sign off process. This was particularly important in terms of the clear messages it was designed to deliver through the sales teams. AstraZeneca was also assured that it had not been distributed to the fieldforce as a briefing tool. However, AstraZeneca's information indicated that this document had been made available to the fieldforce in various parts of the UK and had been in use to deliver the messages contained. AstraZeneca alleged breaches of Clauses 14.1 and 15.9 of the Code.

Secondly, throughout the document there was explicit reference to 'yo-yo asthma', a term used to describe how Symbicort might be used as an adjustable maintenance treatment. This term was not recognised by the British Thoracic Society, UK health professionals or included in any global asthma management guidelines. This was the first time AstraZeneca had heard the use of this term and it had also attracted health professional comment which was how the matter came to AstraZeneca's attention. The document clearly expected the sales teams to refer to stepping up and stepping down as 'yo-yo asthma'. The tone of the document created the impression that it was meant to disparage both the medically accepted practice of adjusting asthma treatment to the patient's level of asthma control and the use of Symbicort in this context. AstraZeneca alleged breaches of Clauses 8.1 and 8.2 of the Code.

RESPONSE

GlaxoSmithKline stated that AstraZeneca alleged that 'yo-yo asthma' was a term used to disparage the medically accepted practice of adjusting asthma treatment to the patient's level of asthma control and the use of Symbicort in this context. AstraZeneca alleged that this term appeared throughout the document. This was incorrect; 'yo-yo asthma' appeared three times in total, once on page six and twice on page eight of this eleven-page document.

The document in question was an internal briefing document drawn up prior to the launch of Symbicort. It was intended to be a comprehensive educational and briefing document about the product.

AstraZeneca mentioned that through inter-company discussions it was led to believe that the document had not been subjected to the full approval process. The production and approval of this document followed the circulation of a draft document on the subject which was circulated to senior managers within GlaxoSmithKline for comment. GlaxoSmithKline initially thought through inter-company discussions that AstraZeneca was referring to this draft version, as it had made GlaxoSmithKline aware that it had possession of other confidential GlaxoSmithKline documents which had been circulated with this draft. GlaxoSmithKline could confirm that the document enclosed by AstraZeneca with its complaint was not the draft version but the final version, subjected to the normal sign-off process and hence fully approved prior to its distribution to the fieldforce.

In addition, the document was clearly designated for internal use only and included clear and explicit instructions that it was only to be used reactively to respond to specific questions raised by customers about Symbicort.

The term 'yo-yo asthma' was introduced into the sales force briefing documents prior to the launch of Symbicort to make them aware of the kind of asthma management that GlaxoSmithKline considered would be promoted by AstraZeneca. GlaxoSmithKline's belief at this time was that AstraZeneca's strategy would be to recommend a patient-led management based on the flexible dosing of Symbicort. GlaxoSmithKline's view was that it was likely that the recommendations from AstraZeneca would suggest that patients could step up and step down their treatment according to their level of symptom control and that this could be on a regular basis (ie monthly, weekly or even daily), depending on symptoms. This potentially rapid change, up and down, in treatment dosage seemed appropriately reflected in the term 'yo-yo'. GlaxoSmithKline considered at that time that 'yo-yo asthma' was an appropriately simple term to describe this stepping up and down of asthma treatment.

The assessment of the launch strategy of a competitor was a normal practice in the industry. Prior to the launch of a new product, companies had to assess the positioning a competitor might seek for that product and the claims it might make in order that a context might be placed around the position of such a product and its relation to the products of other companies. These assessments were necessary so that representatives could respond to questions that might be raised by customers.

However, at the launch of Symbicort GlaxoSmithKline assessed the product claims and promotional strategy as being significantly different from those it had predicted. AstraZeneca's campaigns did not seem to recommend as rapid a change in Symbicort dosing as GlaxoSmithKline had first thought, and there were additional changes in the licence and product positioning that it had not anticipated. GlaxoSmithKline was also concerned that a comprehensive briefing document might create, for the fieldforce, too much emphasis on the competitor's product. Accordingly, a new, abbreviated, much more simple document was produced. Among other changes, this new version contained no reference to 'yo-yo asthma' as it was considered that such a term was not appropriate in view of the promotional materials that had been produced for Symbicort. This new briefing document was sent to all members of the field force on 8 June, four days after the launch of Symbicort, with an instruction that this document should replace all previous Symbicort briefing documents.

GlaxoSmithKline provided a copy of the current document together with the copy of the communication to the field force instructing them that the document replaced all previous materials relating to Symbicort.

In communication with AstraZeneca prior to the initiation of this complaint GlaxoSmithKline had assured it that no documents containing this claim had been circulated since the launch of Symbicort, and that the current documents had replaced all previous materials on Symbicort defence.

AstraZeneca alleged that members of the field force were using the term 'yo-yo asthma' with customers and that customers had raised this issue with AstraZeneca. In GlaxoSmithKline's communications with AstraZeneca prior to the submission of this complaint, its issue was solely with the content of the document. AstraZeneca had made no allegations in any communication with GlaxoSmithKline that it had received comments from health professionals on any GlaxoSmithKline representative activity on this issue. GlaxoSmithKline had no evidence that any members of the field force had used the term 'yo-yo asthma' when responding to questions from customers. Indeed, such activity would cause GlaxoSmithKline concern, as it was not within its current strategy and did not appear in any current briefing documents or promotional materials.

GlaxoSmithKline certainly had no intention to cause discord with health professionals or to disparage the tone or content of the British Guidelines on Asthma Management, both of which it held in high regard. On a point of note, AstraZeneca had stated that it was through the comments of health professionals that it became aware of the use of this term. As far as GlaxoSmithKline could determine, AstraZeneca was aware of this term 'yo-yo asthma' only from its possession of the internal briefing document which it had enclosed with its complaint. The methods by which these materials might have been acquired were currently under investigation.

Furthermore, GlaxoSmithKline would be pleased to act on any evidence that members of its fieldforce were using this term contrary to briefing documents current since the launch of Symbicort.

Accordingly GlaxoSmithKline considered that the use of the term 'yo-yo asthma' was a simple descriptive term used as an analogy to explain its prediction of the AstraZeneca promotional strategy for Symbicort and used to differentiate this product from Seretide. GlaxoSmithKline considered that its use was not in breach of the Code and, furthermore, such a term was not in current use by members of the GlaxoSmithKline fieldforce.

PANEL RULING

The Panel noted the submission that the document complained about by AstraZeneca was subjected to the normal certification process and fully approved before its distribution to the field force. The Panel therefore ruled no breach of Clauses 14.1 and 15.9 of the Code.

The Panel noted that the document at issue did refer to 'yo-yo asthma'. Representatives were instructed to refer to the regular stepping up and stepping down as 'yo-yo asthma'. It was stated that symptom driven dosing encouraged 'yo-yo asthma'. The document had been replaced with a two page document 'Post Launch Update – AZ combination' dated 7 June 2001 which had been sent with an email stating that the updated reference document replaced all previous documents. The Panel noted the submission that GlaxoSmithKline considered that the term 'yo-yo asthma' was not appropriate in view of the promotional materials produced for Symbicort. The new material did not categorically state that the term was not to be used. It was stressed that the new document replaced all previous documents.

The Panel noted that there was a general allegation that representatives were using the term 'yo-yo asthma'. No specific evidence was provided. GlaxoSmithKline stated that it would be pleased to act on any evidence that its fieldforce were using the term contrary to briefing documents current since the launch of Symbicort.

The Panel did not accept that the term 'yo-yo asthma' and the tone of the document disparaged the accepted practice of adjusting asthma treatment to the patient's level of control. Nor was it disparaging about the use of Symbicort in this regard. No breach of Clauses 8.1 and 8.2 of the Code was ruled.

APPEAL BY ASTRAZENECA

AstraZeneca stated that its decision to appeal the rulings of no breach of the Code was two fold.

Inconsistencies within GlaxoSmithKline's account

AstraZeneca stated that there were a number of inconsistencies between accounts described in GlaxoSmithKline's response to the Authority and those recorded in previous inter-company discussions between the two companies.

GlaxoSmithKline maintained that there were three versions of the document: a draft version sent only to senior managers for comment prior to the launch of Symbicort; a version which had been subjected to a full approval process and then disseminated to GlaxoSmithKline representatives prior to the launch of Symbicort and an amended version sent to the fieldforce after the launch of Symbicort.

GlaxoSmithKline maintained that the first two documents contained the term 'yo-yo asthma'.

During inter-company discussions between AstraZeneca and GlaxoSmithKline in July, AstraZeneca raised concerns over a representative briefing document that had come into its possession after the UK launch of Symbicort. This document was the subject of this case. The document was clearly described to GlaxoSmithKline in terms of the title ie Fieldforce guidance document 'The AZ combination', and referred to the fact that the document contained the term 'yo-yo asthma'. The date of the document, May 2001, was not mentioned initially; however, from the descriptions used, both AstraZeneca and GlaxoSmithKline felt confident of the document's identity.

GlaxoSmithKline's response was one of great concern which was reiterated in subsequent inter-company discussions. Firstly, GlaxoSmithKline was concerned with how AstraZeneca had access to a document that GlaxoSmithKline said was only in draft form with a limited circulation. GlaxoSmithKline was so concerned as to how the document had been obtained that taking the matter up at a senior level between the two companies was considered. The response from GlaxoSmithKline gave a very strong indication that the document being discussed had not been finally signed off. At no point was the existence of the two documents, one draft and one approved, mentioned by GlaxoSmithKline.

Secondly, GlaxoSmithKline expressed concern over the use of the term 'yo-yo asthma' with customers to describe the concept of stepping up and down of asthma treatments. Both parties were in verbal agreement over the inappropriateness and lack of medical validity such term carried.

On 26 July, AstraZeneca received written assurance from GlaxoSmithKline that the term 'yo-yo asthma' was not used in any documents currently distributed to the fieldforce or head office staff within GlaxoSmithKline.

On 7 August, AstraZeneca responded to this letter with its record of the discussion which documented that there were specific assurances from GlaxoSmithKline that the documents **had not been** distributed to the fieldforce and that the term 'yo-yo asthma' was not endorsed/supported as a term to be used for discussion with customers.

The response GlaxoSmithKline submitted to the Authority in which it confirmed that the above document was in fact a final version that had been subjected to normal sign off processes before being distributed to the fieldforce prior to the launch of Symbicort was not consistent with its previous account to AstraZeneca. GlaxoSmithKline also commented that the term 'yo-yo asthma', as referred to on several occasions in the document, was to brief its fieldforce as to how it thought AstraZeneca would position Symbicort in the market.

Another example of an inconsistency between GlaxoSmithKline and AstraZeneca inter-company dialogue and the response submitted by GlaxoSmithKline to the Authority was that when the fieldforce briefing document was first discussed, GlaxoSmithKline confirmed that the document was only ever distributed as a draft to a limited audience prior to the launch of Symbicort. However as part of GlaxoSmithKline's response to the Authority it enclosed a memorandum sent at the time of the UK launch of Symbicort notifying the recipients that previous documents should be replaced with the one

attached which had a very wide distribution list, indicating that previous documents had been received by the same audience pre-launch and not a limited one as AstraZeneca was led to believe. Not all of the sales teams who received both documents were specialists in discussing respiratory medicine, eg the SmithKline Beecham anti-infectives team and diabetes area sales managers. Such representatives were not in a position to discuss the concept of 'yo-yo asthma' in the context of carefully managed and appropriate stepping up and down of asthma medication.

The fact that GlaxoSmithKline's response to the Authority was so different to the account given in inter-company dialogue was a serious concern. It called into question the integrity of such dialogue and undermined confidence in a process which was endorsed by the Authority and the Appeal Board and was viewed as an essential part of how companies attempted to address Code issues without recourse to formal complaint.

The only way to investigate these inconsistencies and determine whether there had been breaches of Clauses 14.1 and 15.9 was for the Appeal Board to have a copy of the full signature sheet, with dates, for the approval of the briefing document issued prior to the launch of Symbicort.

'Yo-yo asthma' used to intentionally disparage an accepted clinical practice

AstraZeneca stated that in the document, GlaxoSmithKline deliberately and artificially differentiated between long-term and regular stepping up and down of asthma therapy as an artificial anticipation of Symbicort's product position, which proved to be an incorrect assumption.

AstraZeneca fully acknowledged that within the pharmaceutical industry companies were likely to assess launch strategies of others prior to the launch of competitor products and therefore engage in activities that might protect current market share or position. However, AstraZeneca did not believe that inventing disparaging terms such as 'yo-yo asthma' to intentionally weaken a competitor's predicted product strategy whilst undermining accepted clinical practice was in the true spirit of the Code. The document itself encouraged representatives to coin the phrase 'yo-yo asthma' when discussing with customers the concept of regular stepping up or down of asthma treatment in response to symptoms breakthrough through the specific instruction: 'Regular stepping up and down – please refer to as Yo-Yo asthma'. AstraZeneca did not regard this as responsible behaviour.

Symbicort was indicated for the maintenance treatment of adult asthma which was specific to neither long-term nor regular stepping up or down of doses. The product licence allowed doses to be adjusted from one inhalation once a day to two inhalations twice daily in response to symptom fluctuation.

Using the term 'yo-yo asthma' to describe the stepping up and down of asthma medication did not, in AstraZeneca's opinion, accurately or fairly describe the well established concept of adjusting asthma treatment from time to time to optimise control in asthma patients and similarly how Symbicort could be used in maintenance treatment. These dose adjustments should be monitored by a clinician as part of a carefully organised management plan and should occur over periods of time. They should not occur frequently and rapidly. The phrase 'yo-yo asthma' did not convey this image of how asthma should be managed effectively, instead it gave an impression that stepping up and down treatment occurred only as an extreme, with little control and rapidly.

AstraZeneca noted that the memorandum to the fieldforce dated 8 June notifying it of the replacement document made no mention that the term 'yo-yo asthma' should not be used with customers any more.

AstraZeneca considered the term 'yo-yo asthma' derogatory and disparaging not only in relation to how the product licence for Symbicort allowed doses to be adjusted either up or down in response to breakthrough symptoms of asthma, but also in terms of its intention to belittle the concept of stepping up and down of asthma medication, namely inhaled steroids, which was well recognised as good clinical practice and documented in the British Guidelines on Asthma Management. AstraZeneca therefore considered such an intentionally disparaging and invented term constituted breaches of Clauses 8.1 and 8.2 of the Code.

COMMENTS FROM GLAXOSMITHKLINE

Inconsistencies within GlaxoSmithKline's account

GlaxoSmithKline stated that it wished to clarify the events and the order in which they occurred.

The document referred to by AstraZeneca in its original complaint was an internal briefing document drawn up prior to the launch of Symbicort. It was intended to be a comprehensive educational and briefing document about the product. This document had a wide distribution to a number of sales forces that were involved with promotion in asthma.

AstraZeneca mentioned that through inter-company discussions it was led to believe that the document had not been subjected to the full approval process. GlaxoSmithKline initially believed that AstraZeneca was referring to a draft version of the briefing document. This was because it also complained about an internal PowerPoint presentation which it had acquired along with the briefing document. The PowerPoint presentation and the draft briefing document together had only been made available to area sales managers at an internal briefing. These documents had therefore been acquired by AstraZeneca either through people who at that time were working for GlaxoSmithKline or somebody who had joined AstraZeneca from GlaxoSmithKline had taken this confidential information and passed it to AstraZeneca, thereby breaching terms and conditions within their company contract. There had been cases of such individuals passing between the two companies at this time, making such a concern a possibility. This was the reason for considering high level discussions between both companies as a result of this issue.

There was clearly some dispute regarding the discussions which had taken place between AstraZeneca and GlaxoSmithKline prior to the complaint to the Authority.

GlaxoSmithKline rebutted the allegations that it had given specific assurances that the documents had not been distributed to the fieldforce. GlaxoSmithKline informed AstraZeneca that the PowerPoint presentation had had a limited circulation and that it would not have been available to the fieldforce as it was limited to senior managers (head office and area sales managers). A record of the discussions stated 'this PowerPoint presentation was not in general distribution among the fieldforce and therefore could not have been available for a fieldforce representative to pass on to a competitor's representative either directly or indirectly'. This PowerPoint presentation was not referred to in the complaint from AstraZeneca.

The production and approval of the document about which AstraZeneca had complained followed the circulation of a draft document on the subject for comment. GlaxoSmithKline again confirmed that the document enclosed by AstraZeneca with its complaint was not the draft version sent to senior managers but the final version, subjected to the normal sign-off process and hence fully approved prior to its distribution to the fieldforce.

GlaxoSmithKline's account of these inter-company discussions was not inconsistent with its response to the Authority following the complaint from AstraZeneca. It was however inconsistent with AstraZeneca's reporting of these discussions.

GlaxoSmithKline reiterated that the assessment of the launch strategy of a competitor was usual in the industry. Prior to the launch of a new product, companies had to assess the positioning a competitor might seek for that product and the claims it might make in order that a context might be placed around the position of such a product and its relation to the products of other companies. These assessments were necessary so that representatives could respond to questions that might be raised by customers.

Following the launch of Symbicort GlaxoSmithKline assessed its product claims and promotional strategy as being significantly different from those the company had predicted. AstraZeneca's campaigns did not seem to recommend as rapid a change in Symbicort dosing as GlaxoSmithKline had first thought. There were also changes to the licence for Symbicort.

Accordingly, a new, abbreviated, much simpler document was produced. This new version contained no reference to 'yo-yo asthma' as it was considered that such a term was no longer appropriate in view of the promotional materials that had been produced for Symbicort. This new briefing document was released to all members of the fieldforce immediately following the launch of Symbicort, with an instruction that this documentation should replace all previous Symbicort briefing documents.

At no time did GlaxoSmithKline agree that the term 'yo-yo asthma' was inappropriate or lacked medical validity, as alleged by AstraZeneca. GlaxoSmithKline did agree, however, following its assessment of AstraZeneca's promotional stance for Symbicort, that the document it had produced required a number of changes. These were not only to reflect AstraZeneca's promotional stance regarding the rapidity of up and down dosing of Symbicort but also to reflect differences in the licence for Symbicort, which GlaxoSmithKline had also not anticipated. An example of such a difference was that in the UK Symbicort was not licensed for use in children from 12 years of age, but only for adults and adolescents aged 17 years or above. GlaxoSmithKline had initially anticipated that the licence for Symbicort would be the same as that in Europe, for children aged 12 years and above. This was seen not to be the case, once the summary of product characteristics (SPC) for Symbicort was available publicly.

Minutes of these inter-company discussions on 24 July detailing these agreements were taken by GlaxoSmithKline and sent to AstraZeneca on 26 July. AstraZeneca amended these minutes, adding statements and returned them to GlaxoSmithKline on 7 August.

Within the GlaxoSmithKline version of the minutes, it had been recorded that 'the term 'yo-yo asthma' was not in use in any documents currently distributed to the fieldforce or head office staff within GlaxoSmithKline'. AstraZeneca reviewed these minutes and added further statements/amendments to them. The statement that AstraZeneca had quoted within its complaint the 'term 'yo-yo asthma' was/will not be endorsed/supported by GlaxoSmithKline as a term to be used for discussions with customers had been added.

GlaxoSmithKline did not agree with the amendments made by AstraZeneca and further comments were made on the original minutes sent from GlaxoSmithKline to AstraZeneca. In these minutes the following statements was added 'He confirmed that the use of the term 'yo-yo asthma' was not part of GlaxoSmithKline's current strategy, and was not included in any documents produced following the launch of Symbicort'. Therefore GlaxoSmithKline disagreed that there was an agreement between the two companies that 'yo-yo asthma' was an inappropriate term or lacked medical validity. It was also not agreed that 'yo-yo asthma' was/will not be endorsed/supported by GlaxoSmithKline as a term to be used.

There were obvious discrepancies between the understanding of agreements made at these inter-company meetings. These discrepancies were supported by the inter-company minutes of these discussions. These had not been provided, however if it was deemed necessary to submit these minutes to support its statements, GlaxoSmithKline would do so.

GlaxoSmithKline re-iterated its assurance that no documents containing the term 'yo-yo asthma' had been circulated since the launch of Symbicort, and that the current documents had replaced all previous materials on Symbicort defence.

GlaxoSmithKline provided a copy of the internal certificate of approval of the briefing document in

question which confirmed that the briefing document was approved for circulation to the sales force on 21 May 2001, in advance of the launch of Symbicort. GlaxoSmithKline also provided the certificate of approval of the amended briefing document, approved on 8 June, following the launch of Symbicort and GlaxoSmithKline's reassessment of the promotional strategy.

GlaxoSmithKline therefore considered that the briefing document was not in breach of Clauses 14.1 and 15.9 of the Code.

'Yo-yo' asthma used to intentionally disparage an accepted clinical practice

GlaxoSmithKline stated that AstraZeneca alleged that 'yo-yo asthma' was a term used to disparage the medically accepted practice of adjusting asthma treatment to the patient's level of asthma control and the use of Symbicort in this context, constituted breaches of Clauses 8.1 and 8.2 of the Code.

GlaxoSmithKline reiterated that, the term 'yo-yo asthma' was introduced into the sales force briefing documents prior to the launch of Symbicort to make the representatives aware of the kind of asthma management that GlaxoSmithKline considered would be promoted by AstraZeneca.

Prior to the launch of Symbicort GlaxoSmithKline believed that AstraZeneca's strategy would be to suggest that patients could step up and step down their treatment according to their level of symptom control and that this could be on a rapid and regular basis (ie monthly, weekly or even daily), depending on symptoms. This potentially rapid change, up and down, in treatment dosage, seemed appropriately reflected in the term 'yo-yo asthma'. GlaxoSmithKline considered at that time that 'yo-yo asthma' was an appropriately simple term, to describe this stepping up and down of asthma treatment.

The practice of adjusting a patient's therapy in accordance with their symptoms was an approach to asthma management that GlaxoSmithKline wholly supported. It certainly had no intention to cause discord with health professionals, or to disparage the tone or content of the British Guidelines on Asthma Management which supported this practice.

Accordingly GlaxoSmithKline considered that the use of the term 'yo-yo asthma' in this document was a simple descriptive term used as an analogy to explain its prediction of the AstraZeneca promotional strategy for Symbicort, and used to differentiate this product from Seretide.

At the launch of Symbicort AstraZeneca's claims and promotional strategy were significantly different from those GlaxoSmithKline had predicted. It therefore changed and reissued briefing documents as previously discussed.

GlaxoSmithKline reiterated that no documents containing this claim had been circulated since the launch of Symbicort, and that the current documents had replaced all previous materials on Symbicort defence.

GlaxoSmithKline therefore believed that the use of the term 'yo-yo asthma' did not disparage the accepted practice of adjusting the level of a patient's treatment and was not in breach of Clauses 8.1 and 8.2 of the Code.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that its reasons for appealing against the ruling of no breach of Clauses 8.1, 8.2, 14.1 and 15.9 of the Code remained as detailed in its letter of appeal. However, it would like to take the opportunity to reiterate the main points that underpinned these reasons.

The document brought to the attention of AstraZeneca raised concerns that it felt needed to be addressed:

Content

The term 'yo-yo asthma' was deliberately created by GlaxoSmithKline to describe stepping up and stepping down of asthma therapy using the 'AZ Combination' (Symbicort). This was not a recognized medical term nor one that was referred to in the UK asthma guidelines. AstraZeneca was concerned that encouraging the term 'yo-yo asthma' amongst clinicians would create confusion about the appropriate use of Symbicort as an adjustable maintenance treatment.

AstraZeneca representatives stated at the appeal that the company had not received one of GlaxoSmithKline's letters (17 August) in relation to the minutes of the intercompany discussions.

Development of the document

In the true spirit of inter-company dialogue, AstraZeneca looked to resolve the issues contained within this document. However, the responses from GlaxoSmithKline were unsatisfactory with subsequent obvious disparity between the account presented to AstraZeneca with that given to the Authority. This cast serious doubts over the approval process in relation to this distributed document.

APPEAL BOARD RULING

The Appeal Board noted that it had been provided with the approval certificates for the fieldforce guidance document (May 2001) and for the subsequent two page briefing document issued after the launch of Symbicort and dated 7 June 2001. The document at issue therefore, the one dated May 2001, had been subjected to the normal certification process and fully approved before its distribution to the salesforce. The Appeal Board thus upheld the Panel's rulings of no breach of Clauses 14.1 and 15.9 of the Code. The appeal on this point was thus unsuccessful.

The Appeal Board noted that the requisite certificate had only been provided by GlaxoSmithKline in response to the appeal. AstraZeneca made no indication that it wished to withdraw the appeal. In any event the Appeal Board noted that this was not possible under Paragraph 15.2 of the Constitution and Procedure as notice of appeal could only be withdrawn by a complainant up to the time the respondent's comments on the appeal had been received but not thereafter.

The Appeal Board noted that the term 'yo-yo asthma' was used by GlaxoSmithKline in a briefing document which attempted to pre-position Symbicort prior to its launch. As soon as Symbicort became available GlaxoSmithKline realised that its anticipated positioning of the product had been wrong and the document at issue had been replaced by another which did not refer to 'yo-yo asthma'. Nonetheless the Appeal Board did not consider that the use of the term in the original document had either disparaged Symbicort or the clinical opinion of health professionals as alleged. The Appeal Board upheld the Panel's rulings of no breach of Clauses 8.1 and 8.2 of the Code. The appeal on this point was unsuccessful.

During consideration of the appeal, the Appeal Board was concerned that neither the document in question nor the certificate included a reference number so there could be no doubt as to what had been certified. This was a recommendation in the Guidelines on company procedures relating to the Code which appeared on pages 40 and 41 of the Code of Practice booklet. The Appeal Board requested that its concern be drawn to GlaxoSmithKline's attention.

2 Use of the In-Check Dial within promotional activity

The In-Check Dial was a device which comprised a low range inspiratory flow meter (15 to 120L/min) that had a selectable resistance, calibrated to enable the measurement of airflow as if the patient was using the various inhalers; Turbohaler, Accuhaler/Diskus, Autohaler and the Easi-Breathe/Surehaler.

A table which appeared on a card accompanying the In-Check Dial, headed 'Optimum Inspiratory Flow', showed the inspiratory flow rates for the various inhalers. Similar information appeared on the In-Check Dial itself without the reference to 'Optimum Inspiratory Flow' and using symbols for the different types of inhalers.

COMPLAINT

AstraZeneca referred to Case AUTH/1096/11/00 which involved a 'Dear Doctor' letter sent by Allen & Hanburys Limited. In addition to the content of the letter, the Panel also considered the use of the In-Check Dial by GlaxoSmithKline within promotional activity. In that case promotional activity took the form of the In-Check Dial being a prize within a competition. Although the In-Check Dial was a device and not a medicine, the Panel had considered that the provision of the In-Check Dial by GlaxoSmithKline in such circumstances came within the scope of the Code. The report of the case stated:

'The Appeal Board considered that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. The range for the maximum effect was 60-90L/min. The Appeal Board considered that the inadequate labelling on the device itself was such that its use for a promotional purpose was misleading.'

AstraZeneca was not privy to the specific undertakings made and rectifying actions taken by GlaxoSmithKline. However, it would be reasonable to expect that the particular version of the device would not be used again at all by GlaxoSmithKline as part of promotional activities. AstraZeneca expected the GlaxoSmithKline sales force to have been notified of the ruling and for the inadequately labelled In-Check Dial to have been recalled.

It was recently brought to AstraZeneca's attention that at a meeting in Leicester in July the same In-Check Dial was being used promotionally on a GlaxoSmithKline exhibition stand. AstraZeneca had also been made aware of continuing distribution of the same device to clinicians. In one particular case the In-Check Dial was given to a physician in the Midlands in July. These were two examples that clearly indicated that GlaxoSmithKline was continuing to use this In-Check Dial, which had been the subject of the recent case, within promotional activity. AstraZeneca viewed these events as serious deviations from undertakings made after a ruling.

AstraZeneca alleged breaches of Clauses 22 and 2.

RESPONSE

GlaxoSmithKline stated that a notice was sent to all members of the fieldforce informing them of the ruling in Case AUTH/1096/11/00, instructing them that the In-Check Dial should not be used in any promotional activity and withdrawing the In-Check Dial from the promotional fieldforce.

During one of a series of regular teleconferences between medical advisers at AstraZeneca and GlaxoSmithKline, it was reported that a member of the GlaxoSmithKline fieldforce had been seen to promote the In-Check Dial at a meeting in Leicester, in breach of the ruling.

Following this teleconference, although GlaxoSmithKline had no knowledge or evidence of the promotional use of the In-Check Dial, it sent a notice to all members of staff working in the field, reinforcing the instructions that had been circulated following the ruling in this case. They were re-informed that use of the device for promotional purposes after GlaxoSmithKline had given an undertaking to the Authority was regarded as a major breach of the Code.

GlaxoSmithKline had not received any independent evidence of the promotional use of the In-Check Dial following the undertaking. Taking in turn the issues raised by AstraZeneca, it would appear that the alleged supply of an In-Check Dial to a physician in the Midlands was a general allegation, supported with no specific details either in relation to the time and place of the customer contact or the individual customer. Without these details, GlaxoSmithKline was unable to investigate this allegation. However, if such an allegation could be made with support from the health professional involved, GlaxoSmithKline would wish to investigate, clearly taking such activity by a member of its field force extremely seriously.

With regard to a meeting in Leicester, GlaxoSmithKline confirmed that a meeting was held

at a local hospital. This was one of a series of regular educational meetings organised not by any pharmaceutical company but by the nursing staff at the hospital. The delegates who attended the one day event were practice nurses, hospital nurses, health visitors and school nurses. No GlaxoSmithKline sales representative attended the local hospital on that date and there was no promotional stand and nor were any GlaxoSmithKline promotional materials available. However, this meeting was attended by a GlaxoSmithKline Respiratory Care Associate (RCA).

The RCA was a member of a team which did not have a promotional role and did not take part in any promotional activity. Not only did members of this team have no promotional materials, but they were not permitted to take part in promotional activities. They were involved only in education, training and audit.

GlaxoSmithKline stated that guidance on the provision of medical and educational goods and services had been issued in November 1998. At that time, the company ensured that the roles of the respiratory care team met this guidance. Clear distinctions were made from representatives both in roles and provision of services. Examples of this were that representatives were not allowed to use an audit service with a customer, as this might result in a blurring of the roles of the representative and the RCA in the eyes of the customer. Similarly, although a representative and an RCA might hold a joint educational practice meeting, if the representative delivered a product based presentation as part of this educational meeting, the RCA was not allowed to be present in the same room, whilst this promotional activity was occurring. Furthermore, the RCA's materials for use with customers were all non-promotional and they did not give out promotional aids. They received copies of promotional materials and briefing documents but these were for their own information only. In compliance with the Code, the RCAs were also not included in any local sales incentive schemes or received sales related bonuses. The RCAs were not allowed to respond to questions about specific products. They were briefed that any such questions must be passed to the local representative who then responded directly to the health professional concerned.

At the meeting in question the RCA had a stand which displayed non-promotional materials such as audit record cards, peak flow diaries, peak flow mouthpieces, Desmond Dragon books, etc, plus one In-Check Dial for demonstration purposes. The In-Check Dial was the same as that at issue in Case AUTH/1096/11/00. Copies of the items available on the stand were provided.

The In-Check Dial was demonstrated by the RCA solely to educate delegates on the relevance of inspiratory flow resistance, not to show advantages of one inhaler over another. The device was not used promotionally. The In-Check Dial was kept in the plastic case with the laminated instruction leaflet at all times, except when being demonstrated. It was not given to any delegate at the meeting, and there was no possibility of the device becoming separated from the laminated instruction sheet (this was a concern of the Appeal Board – that the device might become separated and a health professional misinterpret the green bars).

Among four other stands at this meeting, there was an AstraZeneca stand and a stand from Clement Clarke International (makers of the In-Check Dial). The In-Check Dial was being demonstrated at the Clement Clarke International stand.

It was GlaxoSmithKline's understanding that the ruling of a breach of the Code in Case AUTH/1096/11/00, and the reason that the use of this device came within the remit of the Code, was because it had been used within a promotional context as part of a promotional mailing. Following this ruling there were communications between the Authority and GlaxoSmithKline on this specific issue. It was explained that GlaxoSmithKline had RCAs working in the field who had no promotional remit, and did not engage in promotional activities. Any use of the In-Check Dial by an RCA would not have been in a promotional activity, but in education and training of health professionals in the evaluation of respiratory function. The purpose of these discussions was to raise the awareness of these RCAs to the Authority and that GlaxoSmithKline's interpretation of the undertaking of not to use the In-Check Dial promotionally would not extend to these non-promotional roles.

As the RCAs were non-promotional, coupled with the educational use of the In-Check Dial at the meeting to demonstrate the principle of measuring peak inspiratory flow, GlaxoSmithKline did not accept that it had breached the undertaking given in Case AUTH/1096/11/00. It was therefore not in breach of Clauses 22 and 2 of the Code.

PANEL RULING

First the Panel noted the relevant ruling in Case AUTH/1096/11/00 in which it had been decided that the offer of an In-Check Dial on a letter promoting Ventolin Accuhaler meant that the provision of the device was within the scope of the Code. The case went to appeal. The Appeal Board noted that the In-Check Dial itself had a label which ran along its length. The top edge of the label was marked from 15-120L/min with graduations at every 5L/min. Beneath this scale symbols depicting four different inhalation devices were shown (Accuhaler, Turbohaler, Autohaler and Easi-Breathe) and for each device a green band was shown. The green band for Turbohaler started at 60L/min and finished at 90L/min. There was no explanation on the label as to what the symbols for each inhaler device represented or how the green bars for each inhaler device should be interpreted.

The In-Check Dial was accompanied by a booklet which gave instructions as to its use in English and twelve other languages. A laminated card headed 'Optimum Inspiratory Flow' was also provided. Beneath the heading on the card, in similar but not identical format, was a copy of the label which was on the In-Check Dial itself. The card had more information than the labelling on the In-Check Dial.

It was only by reference to the instruction booklet and the laminated card that the labelling of the In-Check Dial itself was explained. The Appeal Board noted that in practice the In-Check Dial would eventually become separated from any accompanying explanatory item. GlaxoSmithKline had stated that the use of the word optimum was critical in the application of the In-Check Dial.

The Appeal Board considered that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. The range for the maximum effect was 60-90L/min. The Appeal Board considered that the inadequate labelling on the device itself was such that its use for a promotional purpose was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

Turning to the case now before it, Case AUTH/1218/8/01, the Panel noted GlaxoSmithKline's submission that it had communicated the arrangements for RCAs to the Authority. The Authority was not in a position to approve any activity in relation to the Code and could only give informal guidance. In any event it would not have advised that what had been ruled to be an inadequately labelled device with regard to a competitor product could be used by a pharmaceutical company for a promotional purpose.

The Panel noted that in the undertaking given in Case AUTH/1096/11/00 GlaxoSmithKline had accepted the decisions of the Panel and Appeal Board and stated that the date on which the In-Check Dial in question was last used promotionally was 23 April 2001. The accompanying letter made no mention of use of the In-Check Dial by RCAs.

In the present case, Case AUTH/1218/8/01, the Panel noted that it had to decide whether the demonstration of the In-Check Dial at the hospital was subject to the Code. The circumstances were different to the previous case. The Panel noted that an RCA ran the stand. GlaxoSmithKline submitted that the materials on it, the audit record cards, peak flow diaries and mouthpieces, Desmond Dragon books and accompanying posters were not promotional. The stand had also included an In-Check Dial for demonstration purposes.

The Panel noted the submission regarding the activities of the RCAs. It was not necessarily unacceptable for companies to have employees who focussed on audit, training and education. The arrangements, activities and materials had to comply with the Code. Companies needed to ensure that the arrangements and activities were very carefully controlled and managed. Guidance on the provision of medical and education goods and services had been issued by the Authority in the November 1999 issue of the Code of Practice Review. This had been added to the supplementary information to Clause 18.1 of the 2001 Code. There was no allegation about the role of the RCAs.

The Panel noted that the In-Check Dial had been inadequately labelled in that it implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use AstraZeneca's Turbohaler device and that was not so.

The Panel considered that the nature of the meeting, or who was demonstrating the In-Check Dial, were not relevant factors. It was inappropriate to use misleading material whether it was for an educational purpose or for a promotional purpose. The Panel considered that the effect of GlaxoSmithKline demonstrating the inadequately labelled In-Check Dial was to give misleading information about one of its competitors, AstraZeneca's Turbohaler. In the Panel's view, this amounted to promotion and was thus subject to the Code. The Panel considered that the continued use of the inadequately labelled In-Check Dial for a promotional purpose meant that GlaxoSmithKline had failed to comply with the undertaking given in Case AUTH/1096/11/00. The Panel ruled a breach of Clause 22 of the Code.

With regard to the allegation concerning the distribution of the In-Check Dial to a physician in the Midlands, the Panel noted that AstraZeneca was unable to provide any information other than that it was given to a physician in the Leicestershire area in early July 2001. The Panel noted that it was not possible for GlaxoSmithKline to investigate the matter due to insufficient information. The Panel therefore ruled no breach of Clause 22 of the Code in that regard.

The Panel considered that failure to comply with an undertaking was a serious matter. GlaxoSmithKline had withdrawn the In-Check Dial from the representatives who had been informed that the RCAs were not promotional in their activities and would be able to continue to use and supply the item as an educational tool. A memorandum dated 26 July stated that the In-Check Dials were to be returned for re-labelling.

The Panel noted that there was no evidence that the In-Check Dial had been used again by the representatives. It had not been used with promotional materials. It had been available for the RCAs to use with what GlaxoSmithKline submitted were educational materials. GlaxoSmithKline had attempted to comply with the undertaking but its actions had been insufficient. On balance, the Panel did not consider that the use of the In-Check Dial brought discredit upon and reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled. This ruling was appealed.

Following its consideration of this case the Panel noted that GlaxoSmithKline had discussed the undertaking in the previous case with members of the Authority. It appeared that the company had been told that the undertaking prevented the promotional use of the In-Check Dial. The use of the In-Check Dial for an educational purpose had not been considered in the previous case. It may have been that the Authority's informal advice was inadequate and that it should have advised against any use of the misleadingly labelled In-Check Dial by a pharmaceutical company. It may have been as a result of the Authority misunderstanding the information from GlaxoSmithKline or being given

insufficient detail. This matter highlighted the difficulties that could arise from informal requests for advice.

APPEAL BY ASTRAZENECA

AstraZeneca appealed the ruling of no breach of Clause 2 of the Code. AstraZeneca acknowledged that the Panel had found GlaxoSmithKline in breach of Clause 22 of the Code on the basis that the In-Check device had continued to be used under the instruction of the company bearing the same labelling that had been ruled in breach of Case AUTH/1096/11/00. GlaxoSmithKline had therefore failed to comply with the undertaking given in that case.

However AstraZeneca had further conclusive evidence demonstrating that GlaxoSmithKline had continued to use the In-Check Dial, with the unmodified labelling, in promotional activities since the undertaking, and considered such activity to be a serious breach of the Code.

GlaxoSmithKline co-sponsored chest specialist registrar training days for specialist registrars from the west country in October. The meetings were both held at a hospital postgraduate centre during which named GlaxoSmithKline representatives manned an exhibition panel which displayed the In-Check Dial which was freely available to those attending the meeting.

In addition, in October GlaxoSmithKline co-sponsored a paediatric meeting held at a hotel in the South West where again a named GlaxoSmithKline representative manned an exhibition panel which displayed the In-Check Dial.

These meetings were held almost six months since the Authority had received from GlaxoSmithKline its signed letter of undertaking in relation to Case AUTH/1096/11/00, assuring cessation of the In-Check Dial being used promotionally.

Such activities constituted an action that brought the whole of the industry into disrepute and therefore AstraZeneca considered a ruling of a breach of Clause 2 justifiable.

AstraZeneca was also concerned that GlaxoSmithKline did not provide the letter of undertaking in the true spirit of the Code. GlaxoSmithKline sought informal advice prior to making the undertaking in relation to using the device in a non-promotional role ie as part of a medical and educational service delivered by its respiratory care team. The Panel was not in a position to approve an activity being conducted by a company in relation to Code compliance and could only give informal guidance. Furthermore, as the Panel subsequently ruled that the use of the In-Check Dial by the respiratory care team did fall within the scope of the Code, it was therefore very unlikely to have given contrary advice to GlaxoSmithKline on this subject.

However it would seem that GlaxoSmithKline had interpreted the informal advice in a creative manner, in that it only instructed sales teams to discontinue using the In-Check Dial and allowed its nursing teams to carry on using the device with no modification to the labelling at educational meetings.

AstraZeneca did not consider that a Clause 2 allegation should be weakened by the fact that informal advice had been interpreted wrongly.

Health professionals would not necessarily make the distinction between a sales representative working for GlaxoSmithKline and those that had a non-promotional role and were working under the remit of an educational nursing team for the same company. This was especially true if identical messages were being communicated in terms of the In-Check Dial and inspiratory flow rates needed for a variety of asthma inhalers. Moreover, a health professional was likely to consider information regarding products and devices from a fellow health professional working with a pharmaceutical company more credible than from a sales representative working for that same company.

AstraZeneca believed that these points contributed to a ruling of Clause 2.

Furthermore, AstraZeneca had recently received a copy of a GlaxoSmithKline document titled 'In-Check Dial Briefing document for Respiratory Representatives' dated July 2001 and marked for internal use only. This document contained a picture of the In-Check Dial with no apparent modifications from the device ruled to be inadequately labelled in Case AUTH/1096/11/00. The document referred to the provision of a sticker stating 'The Optimum Inspiratory Flow Range for each device is shown by the green bars. Full details can be found in the Instruction Booklet or at www.inspiratory.com'. The instruction to the representatives was that 'With this sticker attached, the In-Check Dial may be used for promotional purposes'.

The Appeal Board noted in the previous case that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. In the July fieldforce briefing the misleading visual impression on the In-Check Dial remained despite the use of the sticker and the wording contained therein. Furthermore the wording of the sticker did not provide adequate explanation for the interpretation of the In-Check Dial markings.

Any illustration of the inspiratory flow required to use the Turbohaler effectively should start at 30L/min. The use of the term 'Optimum' with the use of the bars to compare different devices did not take into account the effective performance of those devices below the so called optimum range. This was oversimplistic and therefore still misleading. Furthermore reference to the instruction booklet or the website did not address the Appeal Board's concern that in practice the In-Check Dial would eventually become separated from any accompanying explanatory item.

This was further evidence of the inadequacy of GlaxoSmithKline's response to the ruling in Case AUTH/1096/11/00. This contributed to a breach of

Clause 2 and AstraZeneca requested that the Appeal Board make a ruling on this new use of the In-Check Dial as a related matter.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that it considered that in its appeal, AstraZeneca had raised new issues relating to new materials, which were not part of the case considered by the Panel. It considered the new issues raised by AstraZeneca to be the labelling of the In-Check Dial and the representative In-Check briefing document.

GlaxoSmithKline did not consider that these new issues came within the scope of this appeal as AstraZeneca was appealing the ruling of the Panel on Case AUTH/1218/8/01 with respect to a possible breach of undertaking in Case AUTH/1096/11/00. The new issues were not in relation to a breach of undertaking, but concerns it had regarding actions made by GlaxoSmithKline as a result of the rulings by the Panel and the Appeal Board in Case AUTH/1096/11/00. One of the steps made by GlaxoSmithKline was to communicate to Clement Clarke International reasons why GlaxoSmithKline could no longer continue to purchase the In-Check Dial. Clement Clarke International re-developed the In-Check Dial, with amended labelling, to address the concerns of the Appeal Board. The issues raised by AstraZeneca related to this new version of the In-Check Dial and therefore not the same device as that considered in Cases AUTH/1096/11/00 and AUTH/1218/8/01. It was for this reason that GlaxoSmithKline considered that if AstraZeneca had concerns regarding the amended In-Check Dial, this should be the subject of a new complaint and consideration by the Panel.

GlaxoSmithKline noted the preliminary view of the Chairman of the Appeal Board that the issues outlined above did not in his opinion come within the remit of the appeal. GlaxoSmithKline also noted that a formal view of the Appeal Board would be taken as part of the appeal process. It understood that if the Appeal Board considered that these issues did not fall within the scope of the appeal, then the appeal would proceed as planned, without consideration of these matters. If however the opinion of the Appeal Board was contrary to the preliminary view of the Chairman, then this particular point of the appeal would be deferred to a later appeal meeting.

Case AUTH/1096/11/00 and its relevance to this case

Firstly, GlaxoSmithKline considered that it was important to review the original complaint regarding the In-Check Dial (Case AUTH/1096/11/00 – Accuhaler 'Dear Doctor' letter). In this case the In-Check Dial was made available to general practitioners as a prize in a competition associated with the Accuhaler mailing. The Panel and the Appeal Board both considered whether the In-Check Dial fell within the remit of the Code, being a device. It was considered that it was the promotional use of the In-Check Dial, making it available as a prize, that brought the device within the scope of the Code. The case of the In-Check Dial was subject to an appeal and thereby considered by the Appeal Board. A breach of Clause 7.2 was ruled as the Appeal Board considered that the In-Check Dial might become separated from the accompanying card over time. Should this happen, the green bars on the In-Check Dial were not clearly labelled, in the absence of the accompanying card, as depicting optimum inspiratory flow. It was important to note that the Appeal Board did not rule the device in breach regarding the green bars and any concern that they were erroneous in depicting optimum inspiratory flow for the devices represented on the In-Check Dial. The issue was discussed at length at the appeal.

Following the consideration of the case by the Panel and prior to the decision to take the case to appeal, GlaxoSmithKline received a written review of the case along with a form for a declaration of undertaking. This original declaration was specific in its wording, relating to the promotional use of the In-Check Dial.

Following the appeal by GlaxoSmithKline, the Authority telephoned GlaxoSmithKline to inform it that the appeal had been unsuccessful. Soon after this, and prior to receiving the written summary of the case and a new declaration of undertaking, GlaxoSmithKline contacted the Authority. GlaxoSmithKline mentioned that the In-Check Dial had only come within the remit of the Code through its promotional use. GlaxoSmithKline had noted that the original declaration of undertaking had been specific in its wording regarding agreeing to no longer use the current In-Check Dial promotionally.

GlaxoSmithKline informed the Authority that if the new declaration was also specific in its wording, it would consider that it was only the promotional use that could not be continued. GlaxoSmithKline informed the Authority that it had certain employees that were non-promotional in their role, the respiratory care team. The respiratory care team did not have a promotional purpose and did not carry promotional materials. There was a clear distinction between promotional representatives and non-promotional staff. This was the reason for seeking clarification and advice.

As these individuals were entirely non-promotional, GlaxoSmithKline considered that the use of the In-Check Dial by these individuals in training, education and audit would not be covered by the declaration of undertaking if it was specific in its wording to promotional use. The new declaration of undertaking was specific to the promotional use only and therefore GlaxoSmithKline continued to allow the respiratory care team to use the device in training, education and audit.

AstraZeneca had alleged that GlaxoSmithKline wrongly interpreted any informal advice from the Authority. This was factually incorrect. This discussion with the Authority was in good faith. GlaxoSmithKline was fully aware that the guidance was informal and that if a further complaint were to be made, the Panel would have to act on it. However, GlaxoSmithKline rejected the charge that it interpreted the Panel's advice in a creative manner. It acted after careful consideration of the Panel's advice, interpretation of the Appeal Board's ruling and its knowledge of the non-promotional role of the respiratory care team.

AstraZeneca alleged that the subsequent ruling of the Panel was testimony to the fact that GlaxoSmithKline might have purposefully misinterpreted the advice from the Panel. The subsequent ruling of a breach of Clause 22 did not represent the fact that it had purposefully misinterpreted any informal advice which AstraZeneca considered the Authority might have given, but in fact reflected a possible misunderstanding between GlaxoSmithKline and the Authority. GlaxoSmithKline submitted that there was no intention to breach this undertaking, but that its discussions led it to believe that it was acting within the spirit of the ruling and the Code. Unfortunately, GlaxoSmithKline did not follow-up the discussion with the Authority with a letter reiterating the issues that were discussed.

Although the Panel considered that the use of the In-Check Dial by the respiratory care team could be considered to be promotional, GlaxoSmithKline did not agree.

The respiratory care team was entirely non-promotional. The Code recognised the role of non-promotional, educational advisers. Clause 18.1 on the provision of medical and educational goods and services covered in detail the requirements to ensure that pharmaceutical companies made a clear distinction between promotional and non-promotional roles. A previous employee was a member of the working party involved in devising this amendment to the Code. Glaxo Wellcome and subsequently GlaxoSmithKline ensured that it complied with these changes and enforced such changes as a result of the issuing of guidance in November 1999.

AstraZeneca had stated that health professionals did not differentiate between sales teams and medical educational services provided by non-promotional staff. GlaxoSmithKline disagreed. Health professionals did differentiate between the sales teams and the respiratory care team. The respiratory care team was recognised as offering unbiased educational and audit advice. They carried no promotional materials and did not have access to such materials. Their role was primarily educational. They conducted educational meetings with no promotional content and met with nurses to advise them on audit procedures. Such audit procedures were very strictly regulated by GlaxoSmithKline to ensure that there was no promotional content within audit materials and that no product messages could be derived as a result of such audits.

GlaxoSmithKline therefore considered there was no issue to answer with respect to the respiratory care team and did not consider that the team's use of the In-Check Dial supported a ruling of Clause 2. Although the Panel considered that the use of the In-Check Dial by the respiratory care team could be considered to be promotional, GlaxoSmithKline did not agree. It did not wish to appeal this issue however as it saw no benefit to be gained, as the In-Check Dial had by this time already been amended and therefore the issue had some degree of irrelevance, due to the passage of time. Although GlaxoSmithKline had accepted a ruling of a breach of Clause 22, it strongly considered that a ruling of a breach of Clause 2 would be unfair and wholly inappropriate.

Case AUTH/1218/8/01 – Promotional activities of GlaxoSmithKline

In turning to this case, Case AUTH/1218/8/01 – promotional activities of GlaxoSmithKline, AstraZeneca had alleged that GlaxoSmithKline had continued to use the In-Check Dial with the unmodified labelling in promotional activities. It made this allegation in relation to meetings that took place in the South West in October.

Following the original ruling of breach in Case AUTH/1096/11/00, all promotional activity in relation to the In-Check Dial ceased, as in GlaxoSmithKline's undertaking.

The In-Check Dial was not manufactured by GlaxoSmithKline. It was the property of Clement Clarke International. GlaxoSmithKline simply purchased this device as an item of relevance to the practice of medicine and made it available to health professionals as it did with other devices such as the Wright mini peak flow meter. Following the ruling of the Panel and the Appeal Board, the inability of GlaxoSmithKline to continue to use the device in its promotional activities was communicated to Clement Clarke. As this ruling would apply to the use of the device by other pharmaceutical companies in addition to GlaxoSmithKline, Clement Clarke decided to amend the In-Check Dial and address the concerns of the Appeal Board.

Following this amendment to the device, GlaxoSmithKline purchased new versions of the In-Check Dial and made them available to the field force on 10 September.

AstraZeneca had alleged that the unmodified In-Check Dial was made available at meetings held in October. GlaxoSmithKline stated that any devices displayed at the meetings were the amended devices and provided communications from the representatives named by AstraZeneca, confirming this. Therefore, GlaxoSmithKline denied any breach of its undertaking signed in April 2001. Furthermore, it considered that it had not acted in breach of Clause 2 of the Code in relation to this matter.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that its final comments remained as detailed in its initial letter of appeal but it would like to take the opportunity to highlight the main area of concern it wished the Appeal Board to consider.

AstraZeneca had noted GlaxoSmithKline's views regarding what it considered to be within the remit of the forthcoming appeal. AstraZeneca maintained that in the interests of bringing all issues around the In-Check Dial to a satisfactory closure, all new relevant items (internal GlaxoSmithKline briefing document – July 2001) should be considered, especially given the timelines since the matter was first brought to the Authority's attention. AstraZeneca believed it was important to consider the continued promotion of the new In-Check Dial as this provided further evidence of GlaxoSmithKline's failure to implement the proper undertaking following a ruling.

AstraZeneca had the following comments in reply to

those made by GlaxoSmithKline: the Appeal Board ruling made in May 2001 in Case AUTH/1096/11/00 was very clear and required unambiguous remedial action from GlaxoSmithKline within the true spirit of the undertaking made; informal advice obtained from the Authority should not attenuate the response to a breach ruling in any way; and the distribution of the In-Check Dial through the respiratory care team was not immune from consideration within the context of the alleged breach of Clause 2. It should be viewed alongside the continued promotional use by the sales team (examples of which had been submitted).

SCOPE OF THE APPEAL

The Chairman stated that his preliminary view was that the new labelling on the In-Check Dial and the briefing material for the newly labelled device were not within the scope of the current complaint. These matters could be the subject of a separate complaint. The further examples of the alleged use of the original labelled In-Check Dial were, in his view, covered by the complaint now under consideration. The Appeal Board agreed with the Chairman.

APPEAL BOARD RULING

The Appeal Board 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. GlaxoSmithKline had withdrawn the original In-Check Dial from its fieldforce in April 2001 but had continued to allow its respiratory care team to demonstrate the device eg at the meeting at Leicester. The company had accepted the Panel's ruling that such use had been in breach of its undertaking in Case AUTH/1096/11/00. The Appeal Board noted that there was no evidence to substantiate the further allegations of GlaxoSmithKline's continued use of the original In-Check Dial as cited by AstraZeneca. There were no details from either party as to what had been supplied to the doctor in the Midlands in July. AstraZeneca had not revealed the identity of the doctor and GlaxoSmithKline had thus had not been able to fully investigate the matter. The meetings held in the South West in October were almost a month after newly labelled versions of the In-Check Dial had been made available to the fieldforce. At the appeal hearing itself AstraZeneca's representatives produced an In-Check Dial which had allegedly been distributed by GlaxoSmithKline at the first of these meetings. Other companies had been represented at this meeting. GlaxoSmithKline confirmed that the labelling on the device produced by the AstraZeneca representatives was not the same as the original labelling on the In-Check Dial at issue in Case AUTH/1096/11/00 and nor was it the same as the newly labelled device used by the company. It thus appeared that the device brought to the appeal hearing by AstraZeneca had been obtained from a company other than GlaxoSmithKline. The Appeal Board considered that it had no evidence before it to show that GlaxoSmithKline had demonstrated the original In-Check Dial at either of these meetings.

In the Appeal Board's view GlaxoSmithKline had taken steps to comply with its undertaking although these had not been wholly adequate. It was unfortunate that the device had not been withdrawn from all GlaxoSmithKline employees. On balance the Appeal Board considered that the company's actions in this regard had not been such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel's ruling of no breach of Clause 2 was upheld. The appeal was thus unsuccessful.

Complaint received **8 August 2001**

Case completed **13 December 2001**

CASE AUTH/1224/8/01

AVENTIS PHARMA v PHARMACIA

Fragmin leavepiece

Aventis Pharma complained about a Fragmin (dalteparin sodium) leavepiece entitled 'Antithrombotic efficacy made simple' and issued by Pharmacia & Upjohn. The leavepiece was spiral bound and opened in landscape format with each upper and lower page forming a double page spread. Fragmin was a low molecular weight heparin.

The claim 'No need to monitor anticoagulant effect with Fragmin therapy' appeared on a double page spread headed 'Low Molecular Weight Heparins vs Unfractionated Heparins – The Rationale'. Aventis alleged that the claim was inaccurate and misleading as the prescribing information and the summary of product characteristics (SPC) stated that 'anticoagulant monitoring is generally not necessary', which implied it was required in some situations. This unqualified all-embracing claim would compromise patient safety.

The Panel noted that each presentation of Fragmin had its own SPC. According to presentation, indication and dose there appeared to be some inconsistencies with regard to the need to monitor the anticoagulant effect. The claim appeared on the lower page of a double page spread which compared Fragmin with unfractionated heparins and immediately beneath a claim which referred to 'all indications'. Other data on the double page made specific reference to surgical prophylaxis, DVT (deep vein thrombosis) treatment and unstable angina. The Panel considered that the context of the claim was such that a reader would assume that it related to all presentations, indications and dosages. The claim implied that there was never any need to monitor the anticoagulant effect of Fragmin therapy and this was not so. The claim was misleading in this regard and a breach of the Code was ruled.

The claim 'In a two-phase study of total hip arthroplasty, the risk of post-operative DVT was significantly (p=0.039) reduced by 63% through prolonged Fragmin prophylaxis' appeared as the third bullet point on a double page headed 'Fragmin and Thromboprophylaxis' and subheaded 'If post-surgical DVT could be prevented, most cases of pulmonary embolism could be avoided'. It was referenced to Lassen *et al* (1998). Aventis alleged that this claim was misleading, as the risk reduction of 63% quoted was against placebo in the long-term phase of the study, which was not stated and was therefore a hanging comparison. The previous two bullet points and the adjoining graph were all in comparison with unfractionated heparin (UFH), making the misleading implication that the results on this page were compared with UFH. Moreover, it was also not stated in either the bullet point or the table on the following page that all patients in this trial (including those in the placebo group) were given dalteparin.

The Panel noted that the claim appeared on the upper page of a double page spread beneath two bullet points which compared Fragmin with unfractionated heparin and adjacent to two bar charts which depicted the comparative incidence of thrombosis between patients receiving Fragmin (5%) and those receiving low dose heparin (9.2%) (p<0.02) and the percentage of those patients with pulmonary embolism (Fragmin 0; low dose heparin 1.2; p=ns). The lower facing page featured a table which depicted data from Lassen *et al* (1998) in relation to the comparative efficacy of prolonged (35 days) thromboprophylaxis with Fragmin versus standard (7 days) prophylaxis with Fragmin in DVT prevention during total hip arthroplasty. Following 7 days on Fragmin once daily, patients were randomized to continue the prophylaxis with either Fragmin or placebo for a further 28 days. The analysis revealed a statistically significant between group difference in the occurrence of total DVT in favour of prolonged prophylaxis with Fragmin with a relative reduction rate of 63%. The Panel considered that the design of the top half of the double page spread was such that the claim at issue would be read in light of the preceding comparative claims and the adjacent data. A reader would assume that the risk reduction of 63% was similarly against unfractionated/low dose heparin which was not so. The claim was misleading and a breach of the Code was ruled.

A bar chart entitled 'Recurrent PE [pulmonary embolism] and deaths' appeared on the top half of a double page spread headed 'Fragmin and Pulmonary Embolism', referenced to Kovacs *et al* (2000). It depicted the number of patients with recurrent PE (5) who had died (4) and total number of patients (108). Three adjacent bullet points discussed the association between DVT and PE and stated that Fragmin was now indicated for the treatment of PE. The lower half of the double page spread featured three bullet points, two of which were referenced to Kovacs *et al* and stated 'In a recent study using Fragmin in the outpatient treatment of PE, none of the 4 deaths (3.7%) was attributable to PE or major bleeds' and 'PE recurred in 5 (4.6%) of 108 patients treated with Fragmin'. Aventis alleged that the bar chart was not clearly labelled and misled due to incompleteness as only data from dalteparin treated patients managed at least partially as outpatients was shown, whereas there were 158 patients identified in the study with PE; fifty of these were managed as inpatients and no data was collected on their outcomes. The fact that over 10% of patients (11) received unfractionated heparin for a mean of 2.1 days was also omitted. As the graph did not appear in the Kovacs paper, it should also be clearly labelled as 'adapted from' rather than directly referenced. Also, it was not made clear that this was not a comparative efficacy study, but a prospective cohort study that could only draw conclusions about the epidemiology of dalteparin treated patients with pulmonary embolism. The graph implied this was efficacy data by omitting this fact.

The Panel noted that Kovacs *et al* was a prospective cohort study of eligible patients with PE managed as outpatients using dalteparin (200 IU/kg subcutaneously daily) for a minimum of 5 days and

warfarin for 3 months. Outpatients included those managed exclusively out of hospital and those managed initially for 1-3 days as inpatients who then completed therapy out of hospital. Inpatients were managed either with unfractionated heparin or dalteparin. There was a total of 158 patients; 108 patients were managed as outpatients of whom 27 were managed for an average of 2.5 days as inpatients of whom 11 received a mean of 2.1 days of unfractionated heparin and then completed dalteparin therapy as outpatients. Patients managed exclusively as inpatients were not followed. For all outpatients the overall symptom recurrence rate of venous thromboembolism was 5.6% (6/108). The bar chart was labelled 'Recurrent PE and deaths'; the y axis depicted the number of patients, the x axis total patients, recurrent PE and death. Claims referenced to Kovacs *et al* appeared as bullet points diagonally opposite the bar chart on the lower half of the double page spread. The Panel considered that the positioning of the barchart and text was such that the barchart would not necessarily be read in light of the bullet points. Given the methodology of the study the labelling was inadequate; the data had not been sufficiently explained. It had not been stated that 11 patients had received unfractionated heparin for a mean of 2.1 days. The bar chart was misleading in this regard and a breach of the Code was ruled. The Panel did not consider that the bar chart need be labelled as having been adapted as it had not been taken from a published paper and no breach was ruled in that regard. The Panel did not consider that the failure to mention that the study was a prospective cohort study implied that the data presented was efficacy data and no breach was ruled in that regard.

The claim 'Fragmin reduced death and MI by 63% (p=0.001)' referenced to Wallentin *et al* (1996) (the FRISC study), appeared as the first bullet point on a double page headed 'Fragmin and Unstable Coronary Artery Disease (UCAD)' with the sub-heading 'The protective effects of [Fragmin twice daily] were most pronounced for severe initial manifestation of instability and other indicators of high risk'. Aventis noted that the claim was on a page where the next bullet point and adjoining graph were in comparison to UFH. The result quoted in the claim at issue was in comparison to placebo and this was not stated – Aventis alleged that it was thus a hanging comparison, misleading in both omitting the comparator and by implying that the result was compared to UFH. This implication made the claim exaggerated – as dalteparin was only equivalent to UFH, not superior.

The Panel noted that Wallentin *et al* (the FRISC study) was a prospective, multicentre double-blind, randomized placebo controlled parallel group trial designed to compare the difference in the rate of death or new myocardial infarction during the first six days of treatment with Fragmin or placebo in patients with unstable coronary artery disease. During the first 6 days the absolute difference in the rate of death or new myocardial infarction was 3%, the relative reduction was 63%. The Panel noted that the claim at issue appeared on a double page spread where other claims and graphs compared Fragmin with UFH. In the Panel's view readers would assume that the claim was similarly a comparison with UFH which was not so. The claim was misleading in that regard and a breach of the Code was ruled.

The claim 'Fragmin matches the 'gold standard' of heparinisation in composite outcomes of death and MI in the acute phase' appeared as the second bullet point on the same page as the claim above. It was accompanied by a graph headed 'Fragmin matches the 'gold standard''. Both were referenced to Klein *et al* (1997). Aventis alleged that the title of this graph was not an accurate representation of the results of the study quoted. In the paper the authors stated 'It should be noted that the trial was not powered to detect a difference between heparin and dalteparin in the acute phase'. Therefore the comparative claim could not be made as the study was not powered to detect a difference. Pharmacia itself had acknowledged that it was not appropriate to use the word 'equivalent'. Neither therefore was it appropriate to use the word 'match', as it had an identical meaning. The claim of matching a 'gold standard' could not be supported.

The Panel noted that Klein *et al* (FRIC study) was a prospective, randomized multinational and parallel group study designed to compare the efficacy and safety of weight adjusted subcutaneous dalteparin twice daily with intravenous unfractionated heparin in the acute treatment of unstable angina or non Q wave myocardial infarction and to investigate the value of prolonged treatment with dalteparin at a lower dose in comparison with placebo in patients initially anticoagulated for a period of 5 to 8 days. All patients received aspirin throughout the study. In the acute phase patients with unstable coronary heart disease received open treatment with either Fragmin or unfractionated heparin. In the double-blinded prolonged treatment phase Fragmin was compared to placebo. The primary outcomes of the study were death, myocardial infarction and recurrence of angina during the double-blinded phase of the study. The secondary outcome was death, MI and recurrence of angina in the acute open phase of the study. The authors stated that the trial did not have sufficient power to show equivalence of heparin and Fragmin in the acute open phase. The study showed that in the acute phase comparable rates of individual or combined outcomes were observed in the two treatment groups. The authors noted that in view of the relatively small number of deaths in either group the marginally significant excess early mortality with Fragmin was, in their view, a chance finding. The study supported the evidence suggesting that body weight adjusted low molecular weight heparin administered subcutaneously twice daily could be used as a alternative to intravenous unfractionated heparin in this indication. The authors considered that the data presented in relation to the acute phase strongly suggested equivalence of both treatment regimens. The claim at issue related to treatment during the acute phase and referred to Fragmin matching the 'gold standard' of treatment of heparin. In the Panel's view a reader would assume that Fragmin was equivalent to heparin in the acute

phase and there was insufficient evidence in this regard. The claim was misleading and a breach of the Code was ruled.

Aventis Pharma Ltd complained about a 22 page Fragmin (dalteparin sodium) leavepiece (ref 160-0201/05/00 (P5373)) entitled 'Antithrombotic efficacy made simple' and issued by Pharmacia & Upjohn Limited. The leavepiece was spiral bound and opened in landscape format with each upper and lower page forming a double page spread. Dalteparin was a low molecular weight heparin.

1 Claim 'No need to monitor anticoagulant effect with Fragmin therapy'

This claim appeared on a double page headed 'Low Molecular Weight Heparins vs Unfractionated Heparins – The Rationale'. It was the second bullet point under a sub-heading 'Efficacy and ease of use'.

COMPLAINT

Aventis Pharma alleged that the claim was inaccurate as the prescribing information and the summary of product characteristics (SPC) stated that 'anticoagulant monitoring is generally not necessary', which implied it was required in some situations. This unqualified all-embracing statement would compromise patient safety when using dalteparin as it was inaccurate and misleading. A breach of Clause 7.2 was alleged.

RESPONSE

Pharmacia Limited quoted the relevant part of the SPC, adding emphasis to the key points:

'Treatment of venous thromboembolism (VTE).

Fragmin can be administered subcutaneously either as a single daily injection or as twice daily injections.

(a) Once daily administration

200 IU/kg body weight is administered s.c once daily. **Monitoring of the anticoagulant effect is not necessary.** The single daily dose should not exceed 18,000 IU.

(b) Twice daily administration

A dose of 100 IU/kg body weight administered s.c twice daily can be used for patients with increased risk of bleeding. **Monitoring of the treatment is generally not necessary but can be performed with a functional anti-Factor Xa assay.** Maximum plasma levels are obtained 3-4 hours after s.c injection, when samples should be taken. Recommended plasma levels are between 0.5-1.0 IU(anti-Factor Xa)/ml.'

Pharmacia stated that the claim at issue was a succinct summary of the SPC. It was on the page entitled 'Low Molecular Weight Heparins vs Unfractionated Heparins – The Rationale' and merely highlighted the main advantage of all low molecular weight heparins (LMWHs) over unfractionated heparin, for which monitoring was mandatory.

The statement 'No need to monitor anticoagulant effect with Fragmin therapy' neither stated nor implied that there was never any need to monitor anticoagulant effect, which appeared to be the basis of the Aventis complaint.

Aventis quoted from a previous case initiated by Rhône-Poulenc Rorer (now Aventis), Case AUTH/760/8/98, 'The Panel noted the main theme was the convenience of Fragmin ... and patients did not require monitoring. No breach was ruled'.

PANEL RULING

The Panel noted that in Case AUTH/760/8/98 Rhône-Poulenc Rorer had alleged that the claim 'Reduces cardiovascular morbidity and mortality in [unstable coronary artery disease] by up to 63%', in an advertisement for Fragmin, was a hanging comparison. The Panel noted that the main theme of the advertisement was the convenience of Fragmin and in that regard referred to one of the other claims about the product ie that it did not require monitoring. The ruling of no breach of Clause 7.2, however, was in respect of the allegation of a hanging comparison. There had been no complaint about there being no requirement to monitor therapy and no ruling had been made about that aspect of the advertisement.

A banner on the front page of the leavepiece announced that it applied to all presentations. The leavepiece was dated May 2000 when Fragmin was available as syringes (2,500IU, 5,000IU, 10,000IU, 12,500IU,15000IU and 18000IU), ampoules (10,000IU/1ml and 4ml), a graduated syringe and a multi-dose vial.

Each presentation of Fragmin had its own SPC. The Panel noted that there appeared to be some inconsistencies with regard to the need to monitor the anticoagulant effect. In the once daily treatment of thromboembolism the SPCs for the syringes (10,000-18,000IU) stated that such monitoring was not usually necessary whereas for the same indication the SPCs for the 1ml ampoule and the multidose vial both stated that such monitoring was not necessary. Where thromboembolism was to be treated with twice daily injections of Fragmin, monitoring of therapy was 'generally not necessary' (1ml ampoule and 4ml vial). With regard to thromboprophylaxis using the 2500 or 5000IU syringes, both SPCs stated that Fragmin, when administered in a dose of 2500-5000IU/day, did not generally accumulate and therefore monitoring of the effect was not usually required. In the prevention of clotting during haemodialysis or haemofiltration, the SPCs for the 1ml and 4ml ampoules both referred to the antithrombotic effect of Fragmin being monitored when necessary. The Fragmin graduated syringe was for use in patients with unstable coronary heart disease; the only reference to monitoring of therapy was with regard to patients with severely disturbed hepatic function in whom a reduction in dosage might be necessary.

The Panel noted that the claim appeared on the lower page of a double-page spread which compared Fragmin with unfractionated heparins and immediately beneath a claim which referred to 'all indications'. Other data on the double-page made specific reference to surgical prophylaxis, DVT

treatment and unstable angina. The Panel considered that the context of the claim was such that a reader would assume that it related to all presentations, indications and dosages. The claim implied that there was never any need to monitor the anticoagulant effect of Fragmin therapy and this was not so. The claim was misleading in this regard. A breach of Clause 7.2 was ruled.

2 Claim 'In a two-phase study of total hip arthroplasty, the risk of post-operative DVT [deep vein thrombosis] was significantly (p=0.039) reduced by 63% through prolonged Fragmin prophylaxis'

This claim appeared as the third bullet point on a double page headed 'Fragmin and Thromboprophylaxis' and subheaded 'If post-surgical DVT could be prevented, most cases of pulmonary embolism could be avoided'. The claim was referenced to Lassen *et al* (1998).

COMPLAINT

Aventis alleged that this claim was misleading, as the risk reduction of 63% quoted was against placebo in the long-term phase of the study, which was not stated and was therefore a hanging comparison. The previous two bullet points and the adjoining graph were all in comparison with unfractionated heparin (UFH), making the misleading implication that the results on this page were compared with UFH. Moreover, it was also not stated in either the bullet point or the table on the following page that all patients in this trial (including those in the placebo group) were given dalteparin. A breach of Clause 7.2 was alleged.

RESPONSE

Pharmacia stated that this was effectively the same complaint made by Rhône-Poulenc Rorer in 1998 (Case AUTH/760/8/98) when it claimed that the statement 'reduces cardiovascular morbidity and mortality in UCAD by up to 63%' was a hanging comparison because placebo was not mentioned. The ruling on that occasion was in Pharmacia's favour.

The term used was 'risk ... reduced' not 'relative risk'.

The fact that the other studies on this page were comparisons with unfractionated heparin – and clearly stated this – in no way implied that the third bullet, which quite clearly referred to a separate study, was an unfractionated heparin comparison.

The fact that all patients received dalteparin in the first phase of the study was not relevant to the conclusion regarding the efficacy of dalteparin in the prolonged prophylaxis phase which was reported here.

PANEL RULING

In the Panel's view this was not the same complaint as in the previous case, Case AUTH/760/8/98. The Panel noted that the claim appeared on the upper page of a double page spread beneath two bullet points which compared Fragmin with unfractionated heparin and adjacent to two bar charts which depicted the comparative incidence of thrombosis between patients receiving Fragmin (5%) and those receiving low dose heparin (9.2%) ($p<0.02$) and the percentage of those patients with pulmonary embolism (Fragmin 0; low dose heparin 1.2; p=ns). The lower facing page featured a table which depicted data from Lassen *et al* (1998) in relation to the comparative efficacy of prolonged (35 days) thromboprophylaxis with Fragmin versus standard (7 days) prophylaxis with Fragmin in DVT prevention during total hip arthroplasty.

The Panel noted that Lassen *et al*, a multicentre, randomized, double-blind prospective study, compared the efficacy and safety of prolonged 35 days' thromboprophylaxis with a standard length (7 days) regimen in patients undergoing total hip arthroplasty. Following 7 days on Fragmin once daily, patients were randomized to continue the prophylaxis with either Fragmin or placebo for a further 28 days. The analysis revealed a statistically significant between group difference in the occurrence of total DVT in favour of prolonged prophylaxis with Fragmin with a relative reduction rate of 63%.

The Panel considered that the design of the top half of the double page spread was such that the claim at issue would be read in light of the preceding comparative claims and the adjacent data. A reader would assume that the risk reduction of 63% was similarly against unfractionated/low dose heparin which was not so. The Panel considered the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

3 Bar chart entitled 'Recurrent PE [pulmonary embolism] and deaths'

This bar chart appeared on the top half of a double page spread headed 'Fragmin and Pulmonary Embolism', referenced to Kovacs *et al* (2000). It depicted the number of patients with recurrent PE (5) who had died (4) and total number of patients (108). Three adjacent bullet points discussed the association between DVT and PE and stated that Fragmin was now indicated for the treatment of PE. The lower half of the double page spread featured three bullet points, two of which were referenced to Kovacs *et al* and stated 'In a recent study using Fragmin in the outpatient treatment of PE, none of the 4 deaths (3.7%) was attributable to PE or major bleeds' and 'PE recurred in 5 (4.6%) of 108 patients treated with Fragmin'.

COMPLAINT

Aventis alleged that the bar chart was not clearly labelled as to what the data referred to. The bar chart misled due to incompleteness as only data from dalteparin treated patients managed at least partially as outpatients was shown, whereas there were 158 patients identified in the study with pulmonary embolus. Fifty of these were managed as inpatients and no data was collected on their outcomes. The fact that over 10% of patients (11) received unfractionated heparin for a mean of 2.1 days was also omitted. As

the graph did not appear in the Kovacs paper, it should also be clearly labelled as 'adapted from' rather than directly referenced. In addition to this it was not made clear that this study was not a comparative efficacy study, but a prospective cohort study that could only draw conclusions about the epidemiology of dalteparin treated patients with pulmonary embolism. The graph implied this was efficacy data by omitting this fact. Breaches of Clauses 7.2 and 7.8 were alleged.

RESPONSE

With regard to the allegation that the bar chart was not clearly labelled, Pharmacia stated that the three bullet points below the graph clearly explained the graph. The numbers of deaths and PEs corresponded with the numbers in the graph and were taken from the paper by Kovacs, which was referenced correctly from both.

With regard to the point that only patients treated as outpatients were included, Pharmacia stated that the title of the paper by Kovacs referenced from the graph and bullet points was 'Outpatient Treatment of Pulmonary Embolism with Dalteparin'. As explained in the paper, the main eligibility criterion for the study was that patients received out-patient treatment for PE, either exclusively or following hospital discharge. There seemed little need to mention patients who were not eligible for the trial.

With regard to not stating that 10% received UFH, Pharmacia reiterated, as explained in the paper, the UFH was administered prior to the patient being admitted to the study.

As a general clinical comment, the short duration of action of UFH meant a carry-over effect was extremely unlikely in a study of a minimum duration of 5 days.

The use of UFH before the study began had no effect on the conclusion of the study and there was consequently no necessity to mention it.

Pharmacia stated that the graph had been drawn de novo from data in the paper. The supplementary information to Clause 7.8 of the Code stated that 'If a graph ... is taken from a published paper but has not been reproduced in its entirety ... it must be clearly labelled as 'adapted from'. In this case the graph did not appear in the original publication so nothing had been 'adapted'.

Pharmacia stated that it was difficult to see how this could be confused with a comparative study. There was no mention of a comparator anywhere on the double page spread.

PANEL RULING

The Panel noted that Kovacs *et al* was a prospective cohort study of eligible patients with pulmonary embolism managed as outpatients using dalteparin (200 IU/kg subcutaneously daily) for a minimum of 5 days and warfarin for 3 months. Outpatients included those managed exclusively out of hospital and those managed initially for 1-3 days as inpatients who then completed therapy out of hospital. Inpatients were managed either with unfractionated heparin or dalteparin. There was a total of 158 patients; 108 patients were managed as outpatients of whom 27 were managed for an average of 2.5 days as inpatients of whom 11 received a mean of 2.1 days of unfractionated heparin and then completed dalteparin therapy as outpatients. Patients managed exclusively as inpatients were not followed. For all outpatients the overall symptom recurrence rate of venous thromboembolism was 5.6% (6/108).

The Panel noted that the bar chart was labelled 'Recurrent PE and deaths'; the y axis depicted the number of patients, the x axis total patients, recurrent PE and death. Claims referenced to Kovacs *et al* appeared as bullet points diagonally opposite the bar chart on the lower half of the double page spread. The Panel considered that the positioning of the barchart and text was such that the barchart would not necessarily be read in light of the bullet points. The Panel considered that given the methodology of the study the labelling was inadequate; the data had not been sufficiently explained. It had not been stated that 11 patients had received unfractionated heparin for a mean of 2.1 days. The bar chart was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that the requirements of Clause 7.8 and the supplementary information thereto as cited were those of the 2001 Code. These requirements and supplementary information were identical to those of Clause 7.6 in the 1998 edition of the Code which applied in this case. The supplementary information to Clause 7.6 stated, *inter alia*, that 'If a graph, table or suchlike is taken from a published paper but has not been reproduced in its entirety, the graph must clearly be labelled as having been adapted from the paper in question'. The Panel did not consider that the bar chart should be so labelled; it had not been taken from a published paper as mentioned in the supplementary information to Clause 7.6 of the Code. No breach of that clause was ruled in this regard.

The Panel did not consider that the failure to mention that the study was a prospective cohort study implied that the data presented was efficacy data. No breach of Clause 7.2 was ruled on this point.

4 Claim 'Fragmin reduced death and MI by 63% (p=0.001)'

This claim, referenced to Wallentin *et al* (1996) (the FRISC study), appeared as the first bullet point on a double page headed 'Fragmin and Unstable Coronary Artery Disease (UCAD)' with the sub-heading 'The protective effects of [Fragmin twice daily] were most pronounced for severe initial manifestation of instability and other indicators of high risk'. The second bullet point began 'Fragmin matches the 'gold standard' of heparinisation …'. An adjacent graph compared the occurrence of the composite outcome of death and MI in the acute phase of patients receiving heparin and Fragmin, beneath the heading 'Fragmin matches the 'gold standard''. The second bullet point and graph were referenced to Klein *et al* (1997). The lower half of the double page spread featured a bar chart comparing treatment costs and time savings of therapy with Fragmin versus unfractionated heparin.

COMPLAINT

Aventis alleged that the claim was misleading, and because of this, also exaggerated. It was on a page where the next point and adjoining graph were in comparison to UFH. The result quoted in the claim at issue was in comparison to placebo and this was not stated – thus it was a hanging comparison, misleading in both omitting the comparator and by implying that the result was compared to UFH. This implication made the claim exaggerated – as dalteparin was only equivalent to UFH, not superior. This was essentially a repetition of the breach of Clause 7.2 of the Code as was ruled in favour of Rhône-Poulenc Rorer under point 2 in Case AUTH/614/9/97. A breach of Clause 7.2 was alleged.

RESPONSE

Pharmacia stated that a better precedent was the later case, AUTH/760/8/98, which examined this precise statement. The Panel ruling on that occasion was 'no breach' ie in favour of Pharmacia. Pharmacia had reminded Aventis of this later ruling and noted that it chose not to appeal at the time.

On this occasion there was even less potential for confusing this statement with UFH since the statement and graph showing equivalence to UFH were juxtaposed.

The breach of Clause 7.2 in Case AUTH/614/9/97, to which Aventis referred, related to use of the term 'standard' treatment. Interpretation in the UK was different from that in Sweden where the study was conducted. In the current material the term 'standard treatment' had not been used and there was no breach of undertaking.

PANEL RULING

The Panel noted that Wallentin *et al* (the FRISC study) was a prospective, multicentre double-blind, randomized placebo controlled parallel group trial designed to compare the difference in the rate of death or new myocardial infarction during the first six days of treatment with Fragmin or placebo in patients with unstable coronary artery disease. Secondary aims were to compare the difference in rate of death or new myocardial infarction after 40 and 150 days and to assess long-term treatment with Fragmin and placebo for another 35-45 days. All patients without contraindications received aspirin daily and as needed calcium antagonists and organic nitrates. During the first 6 days the absolute difference in the rate of death or new myocardial infarction was 3.0%, the relative reduction was 63%.

The Panel noted that Case AUTH/614/9/97 concerned the use of the FRISC data in a Fragmin detail aid. Rhône-Poulenc Rorer alleged, *inter alia*, that the layout of the heading on two facing pages of the detail aid implied that the data presented on the two pages was a comparison with heparin. This was not the case. The Panel had considered that the impression given by the heading was that the data presented all compared Fragmin with standard heparin. The Panel noted that the graph on the second page was from the FRISC study which had compared Fragmin with 'standard medication'. The explanation of standard medication was in small print below the graph and did not include heparin. The Panel considered that given the headline most readers would assume that standard medication had included standard heparin which was not so. The fact that this was explained in the small print was not acceptable under the Code. The Panel had considered that the headline together with the presentation of the FRISC data was misleading in breach of Clause 7.2 of the Code.

Case AUTH/760/8/98 referred to by Pharmacia concerned a Fragmin journal advertisement. It was alleged that the claim 'Reduces cardiovascular morbidity and mortality in UCAD [unstable coronary artery disease] by up to 63% (p=0.001)' which was referenced to the FRISC study, was a hanging comparison in breach of Clause 7.2. The Panel noted the main theme of the advertisement was the convenience of Fragmin, it could be administered in a convenient regimen by simple subcutaneous injection and was not as complicated to administer as standard heparin and patients did not require monitoring. The claim in question addressed the efficacy of Fragmin. The Panel considered that, given the theme of the advertisement and the fact that there was no mention of the efficacy of Fragmin in comparison with other agents, the claim would be taken to be versus placebo which was the case. No breach of Clause 7.2 was ruled.

Turning to the present case the Panel considered that there were differences between the present case and those previously considered; the material at issue was different.

The Panel noted that the claim at issue appeared on a double page spread where other claims and graphs compared Fragmin with UFH. In the Panel's view readers would assume that the claim was similarly a comparison with UFH which was not so. The claim was misleading in that regard and a breach of Clause 7.2 was ruled.

5 Claim 'Fragmin matches the 'gold standard' of heparinisation in composite outcomes of death and MI in the acute phase'

This claim appeared as the second bullet point on the same page as the claim in point 4 above. It was accompanied by a graph headed 'Fragmin matches the 'gold standard''. Both were referenced to Klein *et al* (1997).

COMPLAINT

Aventis alleged that the title of this graph was not an accurate representation of the results of the study quoted. In the paper the authors stated 'It should be noted that the trial was not powered to detect a difference between heparin and dalteparin in the acute phase'. Therefore the comparative claim could not be made as the study was not powered to detect a difference. In its response to Aventis' letter, Pharmacia itself acknowledged that it was not appropriate to use the word 'equivalent'. Neither therefore was it appropriate to use the word match, as

it had an identical meaning. The claim of matching a 'gold standard' could not be supported. A breach of Clause 7.2 was alleged.

RESPONSE

Pharmacia stated that the authors of the paper had said that the trial was not powered to detect a difference between heparin and dalteparin. However they concluded that 'Fragmin and LMWH are equivalent or comparable' and that the data 'strongly suggest equivalence of both treatment regimens'.

Because 'equivalence' had a statistical definition which was not achieved in this study, Pharmacia had not used that term but the less precise term 'match'.

Pharmacia did not accept that 'match' had an identical meaning to 'equivalent'. (A tie could match a shirt but would never be described as being equivalent to a shirt.)

PANEL RULING

The Panel noted that Klein *et al* (FRIC study) was a prospective, randomized multinational and parallel group study designed to compare the efficacy and safety of weight adjusted subcutaneous dalteparin twice daily with intravenous unfractionated heparin in the acute treatment of unstable angina or non Q wave myocardial infarction and to investigate the value of prolonged treatment with dalteparin at a lower dose in comparison with placebo in patients initially anticoagulated for a period of 5 to 8 days. All patients received aspirin throughout the study. In the acute phase patients with unstable coronary heart disease received open treatment with either Fragmin or unfractionated heparin. In the double-blinded prolonged treatment phase Fragmin was compared to placebo. The primary outcomes of the study were death, myocardial infarction and recurrence of angina during the double-blinded phase of the study. The secondary outcome was death, MI and recurrence of angina in the acute open phase of the study. The authors stated that the trial did not have sufficient power to show equivalence of heparin and Fragmin in the acute open phase. The study showed that in the acute phase comparable rates of individual or combined outcomes were observed in the two treatment groups. The authors noted that in view of the relatively small number of deaths in either group the marginally significant excess early mortality with Fragmin was, in their view, a chance finding. The study supported the evidence suggesting that body weight adjusted low molecular weight heparin administered subcutaneously twice daily could be used as a alternative to intravenous unfractionated heparin in this indication. The authors considered that the data presented in relation to the acute phase strongly suggested equivalence of both treatment regimens.

The Panel noted that the claim at issue related to treatment during the acute phase and referred to Fragmin matching the 'gold standard' of treatment of heparin. In the Panel's view a reader would assume that Fragmin was equivalent to heparin in the acute phase and there was insufficient evidence in this regard. The claim was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received	**28 August 2001**
Case completed	**30 October 2001**

CASE AUTH/1228/9/01

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Medical information letter

A general practitioner complained about a letter from GlaxoSmithKline's medical information department, which compared the company's product Seroxat (paroxetine) with Lundbeck's product Cipramil (citalopram). The complainant was upset at what seemed to be an attempt to undermine his confidence in citalopram, a product he had used for a number of years. He had successfully treated the vast majority of his depressed patients with 20mg citalopram although the letter asserted that this was an ineffective dose.

The letter highlighted the theoretical effects of citalopram on heart rhythm, with details of citalopram overdose case reports. The same level of information on Seroxat was not given. The complainant found this unbalanced and almost scaremongering.

The letter stated 'The Seroxat SPC states that Seroxat does not produce clinically significant changes in blood pressure, heart rate and ECG'. The complainant could not find this statement in the summary of product characteristics (SPC). The letter also stated that no randomised comparative trials between Seroxat and Cipramil had been conducted. On contacting Lundbeck the complainant had been sent three papers.

The complainant was disappointed that such a letter had come from the scientific department of a reputable company.

The Panel noted that one of the three papers sent to the complainant by Lundbeck discussed the use of Seroxat and Cipramil in a condition for which Cipramil had no licence. A poster and paper, however, discussed the use of the products in conditions for which both were licensed; both had been published in 2001. Although the publication date of the paper was unknown the poster had been presented two months before the letter to the complainant had been written. It was thus not true to state that there had been no comparative trials of Seroxat and Cipramil. The letter was not accurate and was misleading. A breach of the Code was ruled.

The letter discussed the dosage of Seroxat and Cipramil and gave comparable information for both. The dosage recommendations for both were noted together with the high percentage of prescriptions written for the starting dose of 20mg. It was stated that Seroxat 20mg had been found to be an optimal dose in most patients while with Cipramil doses higher than 20mg were associated with a better response. The Panel did not consider that the information given was unfair or disparaging of Cipramil. No breach of the Code was ruled.

The letter drew attention to the warning in the Cipramil SPC regarding the theoretical possibility of an adverse effect on heart rhythm but added, as did the SPC, that in extensive ECG monitoring of patients, including some with pre-existing cardiac conditions, no clinically significant changes were noted. The supplementary information to Clause 8.1 stated that provided critical references to another company's products were accurate, balanced, fair etc, and could be substantiated, they were acceptable under the Code. The Panel considered that the theoretical cardiovascular effects of Cipramil had been put into a clinical context. The information given was not misleading or disparaging; no breach of the Code was ruled.

The letter continued by stating 'In comparison, the Seroxat SPC states that Seroxat does not produce clinically significant changes in blood pressure, heart rate and ECG'. The Panel could not find such a statement in the Seroxat SPC. On the contrary the SPC stated that there had been spontaneous reports of postural hypotension. The statement in the letter was thus not true and a breach of the Code was ruled.

The 'Overdose' section of the letter stated that the major difference between Seroxat and Cipramil was the reporting of ECG abnormalities following Cipramil overdose. The letter referred to patients who had survived a Cipramil overdose, but who had exhibited QTc prolongation, and to six fatalities where it was proposed that one possible mechanism of death was prolongation of the QTc interval leading to ventricular arrhythmia. Reference was also made to the widespread use and safety of Cipramil in almost 8 million patients. A report of a case of Cipramil overdose associated with long-lasting sinus bradycardia with severe hypotension and intermittent syncopes that required a temporary pacemaker was cited. In contrast, the letter stated that reports of cardiac events had rarely been received following Seroxat overdose. Those that had been received included cardiac arrest and atrial fibrillation but were usually milder symptoms of bradycardia and tachycardia. In all of these reports events were confounded by other medications or alcohol being taken in excess. The Panel considered that the overdose information was not inconsistent with that given in their SPCs. The information was not unbalanced nor disparaging of Cipramil. No breach of the Code was ruled.

A general practitioner complained about a letter which he had received from GlaxoSmithKline's medical information department. The writer thanked the recipient for seeing the company's representative and understood that the doctor had requested further information about Seroxat (paroxetine), a GlaxoSmithKline product, and citalopram. Citalopram was Lundbeck Ltd's product Cipramil.

COMPLAINT

The complainant stated that he was rather upset to have received the letter which seemed to be an attempt to undermine his confidence in the use of citalopram, a product that colleagues and he had used successfully and safely for a number of years. In the vast majority of patients the complainant had successfully treated their depression with a dose of 20mg of citalopram and the assertion in the letter was

that somehow he was mismanaging his patients, as this was an ineffective dose.

The comparison and contrasts between Seroxat and Cipramil in the letter highlighted theoretical effects of citalopram on heart rhythm, with detailed descriptions of citalopram overdose case reports. The same level of information on Seroxat cardiac arrest and arrhythmias was not provided. The complainant found this all rather unbalanced and almost scaremongering.

Furthermore, the 'Adverse Events' section of the letter stated 'the Seroxat SPC states that Seroxat does not produce clinically significant changes in blood pressure, heart rate and ECG'. The complainant could not find such a statement in the Seroxat summary of product characteristics (SPC).

Subsequent to receiving the letter from GlaxoSmithKline, the complainant had contacted Lundbeck, the manufacturers of Cipramil, to see if any comparative trials had been done of Seroxat versus citalopram. He was sent copies of such trials. Lundbeck's succinct reply differed from the letter by GlaxoSmithKline, which stated, in the introduction and summary sections, that no randomised comparative trials had been conducted between Seroxat and citalopram.

The complainant had brought this to the Authority's attention as he neither expected, nor appreciated, receiving mailings containing unbalanced information. He was very disappointed that this had come from the scientific department of a reputable pharmaceutical company.

When writing to GlaxoSmithKline, the Authority drew attention to Clauses 7.2 and 8.1 of the Code.

RESPONSE

GlaxoSmithKline stated that it had carefully reviewed the issues raised and it would like to offer its apologies to the GP for the upset caused by the information contained within the letter.

GlaxoSmithKline's medical information department updated its letters on a regular basis. This particular outdated medical information letter should have been withdrawn. The situation had been fully investigated; the person responsible for reviewing this letter was no longer a GlaxoSmithKline employee and the company had ensured that their work had been reviewed.

Regarding the comparative trial data sent by Lundbeck to the complainant, the poster presentation and the clinical paper had only recently been made available for public review and the third (1997) publication referred to obsessive compulsive disorder for which citalopram did not have a licence and so was not included in the letter.

GlaxoSmithKline fully endorsed the Code but, on this occasion, it acknowledged that breaches of Clauses 7.2 and 8.1 of the Code had inadvertently occurred.

PANEL RULING

The Panel noted that the letter began by thanking the addressee for seeing the representative and noting that he would like 'further information on Seroxat and citalopram'. The letter had been 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. The Panel noted that the original enquiry was stated to be a request for 'further information on Seroxat and citalopram', and that in terms of its content the letter related solely to the subject of the enquiry. The letter compared the licensed indications of the two medicines, discussed dosage, adverse events, overdose and use in the elderly. In order to be exempt from the Code under Clause 1.2 the letter had to be accurate, not misleading and not promotional.

After first discussing the licensed indications the letter stated that there had been no randomised comparative trials conducted between Seroxat and Cipramil. On contacting Lundbeck, the manufacturers of Cipramil, the complainant was sent three papers one of which, Mundo *et al* (1997), compared the efficacy of Seroxat and Cipramil in the treatment of obsessive compulsive disorder, an indication for which Cipramil did not have a licence. Within the licensed indications for both medicines there was a poster presentation comparing their use in depressed patients with associated anxiety (Jefferson *et al* 2001) and a paper comparing their use in the treatment of panic disorder (Perna *et al* 2001). The Panel did not know the publication date of the latter but noted that the poster had been presented at the Annual Meeting of the American Psychiatric Association in May 2001, two months before the letter to the complainant had been written. At the time the letter was written it was thus not true to state that there had been no randomised comparative trials conducted between Seroxat and Cipramil. The Panel noted GlaxoSmithKline's submission that the letter at issue was outdated and should have been withdrawn. The letter was not accurate and was misleading. It was therefore not in accordance with the exemption in Clause 1.2 of the Code. The letter was subject to the Code and the Panel ruled a breach of Clause 7.2.

The letter went on to discuss 'Dosage' and gave comparable information for both Seroxat and Cipramil. The dosage recommendations for both were noted together with the high percentage of UK prescriptions which were for the starting doses of 20mg (78% and 86% respectively). It was stated that Seroxat 20mg had been found to be the optimal dose for most patients. With regard to Cipramil the letter discussed studies wherein doses higher than 20mg were associated with a better response. The Panel did not consider that the information comparing the doses of Cipramil and Seroxat was unfair or disparaging of Cipramil. No breach of Clauses 7.2 and 8.1 was ruled.

Under a heading of 'Adverse Events' the letter drew readers' attention to the warning in the Cipramil SPC

regarding the theoretical possibility of an adverse effect on heart rhythm (prolongation of QTc interval). The letter added however, as did the SPC, that in ECG monitoring of 2500 patients in clinical trials, including 277 with pre-existing cardiac conditions, no clinically significant changes were noted. The Panel noted that the supplementary information to Clause 8.1 stated that provided that critical references to another company's products were accurate, balanced, fair etc, and could be substantiated, they were acceptable under the Code. The Panel considered that the theoretical cardiovascular effects of Cipramil had been put into a clinical context. The information given was not misleading or disparaging and no breach of Clauses 7.2 and 8.1 was ruled.

Under the same heading the letter continued by stating 'In comparison, the Seroxat SPC states that Seroxat does not produce clinically significant changes in blood pressure, heart rate and ECG'. The Panel could not find such a statement in the Seroxat SPC. On the contrary the SPC stated that there had been spontaneous reports of postural hypotension. The statement in the letter was thus not true and a breach of Clause 7.2 was ruled.

The 'Overdose' section of the letter stated that the major difference between Seroxat and Cipramil was the reporting of ECG abnormalities following Cipramil overdose. The letter referred to patients who had survived a Cipramil overdose, but who had exhibited QTc prolongation, and to six fatalities where it was proposed that one possible mechanism of death was prolongation of the QTc interval leading to ventricular arrhythmia (Ostrom *et al* 1996). Reference was also made to the widespread use and safety of Cipramil in almost 8 million patients (Hale 1998). A paper by Rothenhausler *et al* (2000) was cited which reported a case of Cipramil overdose associated with long-lasting sinus bradycardia with severe hypotension and intermittent syncopes that required a temporary pacemaker. In contrast, the letter stated that reports of cardiac events had rarely been received following Seroxat overdose. Those that had been received included cardiac arrest and atrial fibrillation but were usually milder symptoms of bradycardia and tachycardia. In all of these reports events were confounded by other medications or alcohol being taken in excess. The Panel considered that the overdose information given for Cipramil and Seroxat was not inconsistent with that given in their respective SPCs. The information was not unbalanced nor disparaging of Cipramil. No breach of Clauses 7.2 and 8.1 was ruled.

Complaint received **10 September 2001**

Case completed **24 October 2001**

CASE AUTH/1229/9/01

MERCK SHARP & DOHME v PFIZER

Lipitor abbreviated journal advertisement

Merck Sharp & Dohme complained about an abbreviated advertisement for Lipitor (atorvastatin) issued by Pfizer. The advertisement featured the photograph of a helicopter about to touch down onto a rooftop heliport. The headline read 'Going down' below which was the Lipitor 10mg product logo together with the strapline 'In most cases, the starting dose is all you need'. The claim '77% of patients reach their LDL-C targets with 10mg starting dose' appeared to have been 'stamped' onto the advertisement.

Merck Sharp & Dohme alleged that this claim was all embracing as it implied that 77% of all different types of hyperlipidaemic patients would reach their desired LDL-C targets with the 10mg starting dose. It was also unclear what LDL-C target these 77% of patients actually achieved. In intercompany correspondence Pfizer had commented that this claim and the target LDL-C that the patients achieved was clarified by reference to Neil *et al* (1999), 'which should help readers to obtain further information should they need to'. References should not be included in an abbreviated advertisement and so the claim should stand alone. This advertisement required clinicians to read the Neil *et al* study for clarification so the claim was ambiguous.

The Panel noted that abbreviated advertisements were exempt from the need to include prescribing information provided that they met the requirements set out in the Code. The amount of information allowed to be given was restricted. If the information in an advertisement went beyond that allowed, then the advertisement would not be an abbreviated advertisement and would not be exempt from the requirement to include prescribing information. The claim was referenced to Neil *et al* but the supplementary information to the Code stated that references should not normally be included in abbreviated advertisements. The advertisement had provided information beyond that allowed in abbreviated advertisements and was therefore not exempt from the requirements to include prescribing information. No prescribing information for Lipitor had been provided and a breach of the Code was ruled.

The Panel noted that the claim did not specify the patient population to which it referred. Lipitor was indicated as an adjunct to diet for reduction of elevated plasma lipids in patients with a variety of lipid disorders. The particular group of dyslipidaemic patients included in the Neil study were those with CHD. The Panel considered that

the omission of this fact was misleading; by not stating the specific patient population to which it referred the claim implied that 77% of all dyslipidaemic patients would reach LDL-C targets with the 10mg starting dose which was not so. The claim did not define what was meant by 'LDL-C targets'. The Panel considered that the claim was ambiguous as alleged and a breach of the Code was ruled.

Merck Sharp & Dohme was concerned that dosage particulars were being mentioned without due merit in an abbreviated advertisement. The claims were based on LDL-C targets being achieved with the 'starting dose' and the associated prescribing information clearly stated the starting dose for Lipitor to be 10mg. Merck Sharp & Dohme therefore did not understand why dosage particulars were mentioned and alleged a breach of the Code.

The Panel noted that the supplementary information to the Code stated that, *inter alia*, dosage particulars should not be included unless such information was given as the reason why the medicine was recommended for the indication or indications referred to in the advertisement. The Panel considered that the 10mg starting dose was the reason why the medicine was recommended. The advertisement informed prescribers of the expected effect with the 10mg starting dose of Lipitor so obviating the need to increase the dose in the majority of patients. The Panel considered that in this regard the advertisement met the requirements of an abbreviated advertisement and no breach of the Code was ruled on this particular point.

Merck Sharp & Dohme Limited complained about an abbreviated advertisement (ref 90986/h) for Lipitor (atorvastatin) issued by Pfizer Limited. The advertisement featured the photograph of a helicopter about to touch down onto a rooftop heliport. The headline read 'Going down' below which was the Lipitor 10mg product logo together with the strapline 'In most cases, the starting dose is all you need'. The claim '77% of patients reach their LDL-C targets with 10mg starting dose' appeared to have been 'stamped' onto the advertisement.

1 Claim '77% of patients reach their LDL-C target with 10mg starting dose'

COMPLAINT

Merck Sharp & Dohme alleged that this claim was all embracing as it implied that 77% of all different types of hyperlipidaemic patients would reach their desired LDL-C targets with the 10mg starting dose. It was also very unclear what LDL-C target these 77% of patients actually achieved. In intercompany correspondence Pfizer had commented that this claim and the target LDL-C that the patients achieved was clarified by reference to Neil *et al* (1999), 'which should help readers to obtain further information should they need to'. Merck Sharp & Dohme stated that in an abbreviated advertisement this claim should be 'stand alone', since the contents of abbreviated advertisements were restricted under the Code and references should not be included. This advertisement required clinicians to read the Neil *et al* study for clarification so the claim was ambiguous and in breach of Clauses 7.2 and 5 of the Code.

RESPONSE

Pfizer did not agree that the claim was all embracing and unclear. The claim was substantiated by reference to the GP Matrix Study (Neil *et al*). This study showed that in accordance with guidelines recommending a lower LDL-C treatment goal of ≤3mmol/l in patients with coronary heart disease (CHD), 77% of patients achieved this target when put on the 10mg starting dose of Lipitor.

The 3mmol/l target for LDL-C was a well established target in the CHD National Service Framework, Joint British Recommendations, Clinical Resource Efficiency Support Team and Scottish Intercollegiate Guidelines Network. These bodies were well known and their guidelines accepted for the treatment of hypercholesterolaemia and/or prevention of CHD. Pfizer did not, therefore, feel it necessary to expressly refer to the 3mmol/l level.

Lipitor had been demonstrated in this study to get 77% of patients to an LDL-C target of ≤3mmol/l. The study was based on patients whose hyperlipidaemia conditions were commonly seen in general practice – those with hyperlipidaemia (also known as dyslipidaemia) and with existing CHD. These were the patients which doctors were advised to treat according to the various guidelines as priority. The claim did not state 'all types of hyperlipidaemic patients'.

Given the well recognised nature of the 3mmol/l target for LDL-cholesterol and the supporting study, Pfizer did not believe that the claim was in any way all embracing or misleading. In consideration of the types of patients, Pfizer would be happy to consider re-phrasing the claim to reflect that these were CHD patients. However, Pfizer did not consider that the claim breached Clause 7.2 of the Code.

Pfizer referred to an earlier ruling on the same claim in Case AUTH/1095/11/00 where the Panel had ruled no breach of Clause 7.2

Under Clause 5.4 of the Code, abbreviated advertisements must provide a list of information which included 'at least one indication for use consistent with the summary of product characteristics' (SPC). Also, abbreviated advertisements might contain an additional concise statement consistent with the SPC, giving the reason why the medicine was recommended for the indication(s) given.

The claim was consistent with Lipitor's indications for use as outlined in its SPC. Lipitor was indicated for reduction of elevated lipids (including total cholesterol, LDL-C and triglycerides) in patients with different types of hypercholesterolaemia or hyperlipidaemia. It was also indicated for the elevation of HDL-C, lowering of LDL-HDL and total cholesterol/HDL ratios. By lowering LDL-C, Lipitor would aid patients to reach their LDL-C targets. Therefore, Pfizer believed that the claim of '77% of patients reach their LDL-C target with 10mg starting

dose' was a relevant reason as to why Lipitor was recommended for use as per its licensed indication(s).

Pfizer did not believe that the claim breached Clause 5.

PANEL RULING

The Panel noted that the advertisement was an abbreviated advertisement. Clause 5.1 stated that such advertisements were exempt from the requirement to include prescribing information provided that they met the requirements set out in Clause 5 of the Code. The amount of information allowed to be given in an abbreviated advertisement was restricted. If the information in an advertisement went beyond that allowed then the advertisement would not be exempt from the requirement to include prescribing information. Clause 4.2 of the Code listed the component parts of the prescribing information and Clause 4.1 stated that the information listed in Clause 4.2 must be provided.

The Panel noted that the claim was referenced to Neil *et al*. The supplementary information to Clauses 5.4 and 5.5 of the 1998 Code, which applied in this case, Abbreviated Advertisements – Permitted Information, stated that marketing authorization numbers, references, dosage particulars, details of pack sizes, cost and quantitative particulars should not be included in abbreviated advertisements. The supplementary information stated that there may be exceptions to the above if the information was given as the reason why the medicine was recommended for the indication or indications referred to in the advertisement. The Panel did not consider that the provision of the reference met such a criterion. The advertisement had thus provided information beyond that allowed in abbreviated advertisements and therefore was not exempt from the requirements to include prescribing information. No prescribing information for Lipitor had been provided and a breach of Clause 4.1 was ruled.

The Panel noted that the claim did not specify the patient population to which it referred. Lipitor was indicated as an adjunct to diet for reduction of elevated plasma lipids in patients with a variety of lipid disorders. The particular group of dyslipidaemic patients included in the Neil study were those with CHD. The Panel considered that the omission of this fact was misleading; by not stating the specific patient population to which it referred the claim implied that 77% of all dyslipidaemic patients would reach LDL-C targets with the 10mg starting dose which was not so.

The claim did not define what was meant by 'LDL-C targets'. The Panel noted that in Case AUTH/1095/11/00 the complaint had also been that, in the same claim as at issue now, the LDL-C target had not been stated; there had been no complaint that the patient population had not been stated. The advertisement in which the claim had appeared in Case AUTH/1095/11/00 had included prescribing information. The Panel's ruling of no breach of Clause 7.2 had not been appealed by the complainant. The advertisement now at issue was an abbreviated advertisement and although it also included the claim '77% of patients reach their LDL-C target with 10mg starting dose' the advertisements were different.

The Panel noted that the complaint that the LDL-C targets had not been defined had been made in conjunction with a complaint that the patient population had not been specified. The Panel considered that the advertisement was ambiguous as alleged. A breach of Clause 7.2 of the Code was ruled.

During its consideration of this case the Panel queried whether the abbreviated advertisement included at least one indication as required by Clause 5.4 of the Code. It requested that its concerns be drawn to the company's attention.

2 Inclusion of dosage particulars

COMPLAINT

Merck Sharp & Dohme stated that the advertisement contained three references to the 10mg dose. Its concern was that dosage particulars were being mentioned without due merit in an abbreviated advertisement. The advertisement was basing its claims on LDL-C targets being achieved with the 'starting dose' and the associated prescribing information clearly stated the starting dose for Lipitor to be 10mg. Merck Sharp & Dohme therefore did not understand why dosage particulars were mentioned and believed this to breach Clauses 5.4 and 5.5 since this did not appear to fall within the exceptions mentioned in the supplementary information to such clauses.

RESPONSE

Pfizer stated that the supplementary information clearly stated that dosage particulars could be provided if it was the reason why the medicine was recommended for the indication(s) referred to in the advertisement.

In the Lipitor abbreviated advertisement, 10mg was referred to and depicted in the artwork because it was relevant to the claim of '77% of patients reach their LDL-C target with 10mg starting dose'. The starting dose of Lipitor was 10mg and it was this starting dose which allowed 77% of patients to reach their LDL-C targets.

Pfizer sought further clarification from the Authority regarding the definition of the term 'dosage particulars'. In the advertisement, only 10mg was used with no further information provided on the frequency of usage, nor how the medicine should be taken nor anything else related to the dosing.

Pfizer did not believe that the 10mg dose referred to in the advertisement constituted a breach of the Code.

PANEL RULING

The Panel noted that the supplementary information to Clauses 5.4 and 5.5 in the 1998 Code, Abbreviated Advertisements – Permitted Information, stated that, i*nter alia*, dosage particulars should not be included unless such information was given as the reason why

the medicine was recommended for the indication or indications referred to in the advertisement. The Panel considered that the 10mg starting dose was the reason why the medicine was recommended. The advertisement informed prescribers of the expected effect with the 10mg starting dose of Lipitor so obviating the need to increase the dose in the majority of patients. The Panel considered that in this regard the advertisement met the requirements of an abbreviated advertisement. No breach of Clause 5.1 was ruled on this particular point.

Complaint received **17 September 2001**

Case completed **1 November 2001**

CASE AUTH/1230/9/01

PROCTER & GAMBLE and AVENTIS PHARMA/DIRECTOR v MERCK SHARP & DOHME

Fosamax journal advertisement

Procter & Gamble and Aventis Pharma complained jointly about a journal advertisement for Fosamax (alendronate) 70mg issued by Merck Sharp & Dohme. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

Procter & Gamble and Aventis noted that in Case AUTH/1178/4/01 the Panel had ruled that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' was misleading and in breach of the Code. The Panel had considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The wording in the advertisement now at issue was 'Well tolerated. Even in the upper GI tract of patients exposed to NSAIDs/aspirin'. This revised claim was not substantially different from the original and the complainants alleged that Merck Sharp & Dohme had thus failed to comply with its undertaking.

The complainants alleged that the revised claim was still exaggerated The emphasis of the claim was now on good tolerability in the GI tract. However, the summary of product characteristics (SPC) for Fosamax 70mg stated that 'Alendronate can cause local irritation of the upper gastro-intestinal mucosa' and the special warnings and precautions section referred to both upper GI and oesophageal reactions. Such statements were inconsistent with an unqualified 'well tolerated' claim. Although limited safety data were available on this specific group of patients, the claim being made was broad; the use of the word 'even' sought to reassure that 'well tolerated' applied not just to the upper GI tract, but also to other areas and to overall tolerability in this group of patients. The claim did not reflect that patients with a history of major upper GI tract disease were excluded from the study. It was therefore exaggerated because it was not qualified by these GI exclusion criteria.

Once again, the complainants alleged that this claim misled as to the suggested safety profile of alendronate 70mg in this vulnerable population and this constituted a failure to comply with an undertaking.

The Panel noted that Case AUTH/1178/4/01 similarly concerned a journal advertisement for Fosamax 70mg issued by Merck Sharp & Dohme. It was alleged, *inter alia*, that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' misled as to the overall safety profile of alendronate 70mg in this population as conflicting data in combination with limited clinical trial data were available on the safety of concurrent use of NSAIDs and/or aspirin with Fosamax; overall tolerability data were not provided for this group of patients and data that were provided for this group were inadequate to support the claim. The claim at issue in Case AUTH/1178/4/01 was referenced to Schnitzer *et al* (2000). The relevant patient population in Schnitzer had taken NSAIDs or aspirin at some point in the study. In the Panel's view not all of these patients would have been on a regimen; some would have used NSAIDs once or occasionally. There was little data in the Schnitzer study in this regard. The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The claim was misleading and a breach of the Code had been ruled.

In the present case, Case AUTH/1230/9/01, the Panel noted that the claim at issue and the promotional material were different to that previously considered and in the Panel's view sufficiently different not to be covered by the undertaking given in Case AUTH/1178/4/01. No breach of the Code was ruled in that regard.

The claim was referenced to Schnitzer and data on file. The data on file in relation to Schnitzer stated that approximately 50% of patients used NSAIDs or aspirin at some point during the study. Approximately 68% of these patients were on NSAIDs/aspirin for more than one month (or 30 days). The average duration of exposure to NSAIDs/aspirin was 174.8 days (SE=6.3). The data

showed that 12.9% (23/178) of patients taking alendronate 10mg daily and aspirin-containing therapies and/or NSAIDs experienced an upper GI adverse event. Of those patients taking alendronate 70mg and aspirin-containing therapies and/or NSAIDs, 14.1% (38/269) experienced an upper GI adverse event. The data on file referred to the absence of a placebo group in the Schnitzer study and to the fracture intervention trial (FIT) data. The Panel noted that the FIT trial compared alendronate and placebo with regard to upper GI tract events. The doses of alendronate were 5mg per day for 2 years and 10mg per day during years 3 through to 4.5. FIT stated that the proportion of women reporting any upper GI tract event was similar in the alendronate and the placebo groups during treatment with both 5mg per day and 10mg per day as was the proportion of women with serious upper GI tract events. FIT did not investigate the effects of alendronate at 70mg per week.

The Panel noted that the FIT study showed that daily doses of Fosamax, 5 or 10mg, caused no more upper GI events than placebo even in patients exposed to NSAIDs. The Schnitzer study showed that in terms of upper GI adverse experiences a high weekly dose of Fosamax (70mg) was as well tolerated as small daily doses (5 or 10mg) even in patients exposed to NSAIDs. The Fosamax 70mg SPC, however, stated that Fosamax 'can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty'.

The Panel considered that the claim in question gave the impression that prescribers did not need to worry about upper GI side effects when prescribing Fosamax 70mg even to patients who had been exposed to aspirin/NSAIDs; given the advice in the SPC that caution should be used when the product was given to patients with active upper gastrointestinal problems that was not so. The Panel considered that the claim was misleading and a breach of the Code was ruled.

Procter & Gamble Pharmaceuticals, UK Ltd and Aventis Pharma Ltd complained about an advertisement for Fosamax (alendronate) 70mg issued by Merck Sharp & Dohme Limited and published in GP on 22 June. The licensed dose of Fosamax 70mg was one tablet once a week. The complainants co-promoted Actonel (risedronate).

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

When writing to Merck Sharp & Dohme the Authority asked it to bear in mind the provisions of Clause 2 of the Code as well as Clauses 7.2 and 22 which had been referred to by the complainants.

COMPLAINT

Procter & Gamble and Aventis noted that in Case AUTH/1178/4/01 the Panel ruled that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' was in breach of the Code. The ruling stated that: 'The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The claim was misleading and a breach of Clause 7.2 was ruled'. This identical claim had recently been withdrawn from Merck Sharp & Dohme's advertising in Germany.

The wording in the advertisement now at issue was 'Well tolerated. Even in the upper GI tract of patients exposed to NSAIDs/aspirin'. The complainants alleged that this revised claim was not substantially different from the original and that Merck Sharp & Dohme had therefore failed to comply with its undertaking, so breaching Clause 22.

The claim was misleading for the reasons explained in detail in Case AUTH/1178/4/01. The complainants considered that the revised claim was still exaggerated because:

i) The emphasis of the claim was now on good tolerability in the GI tract. However, the summary of product characteristics (SPC) for Fosamax 70mg stated that 'Alendronate can cause local irritation of the upper gastro-intestinal mucosa' and the special warnings and precautions section referred to both upper GI and oesophageal reactions. Such statements were inconsistent with an unqualified 'well tolerated' claim.

ii) Although limited safety data were available on this specific group of patients, the claim being made was broad; the use of the word 'even' sought to reassure that 'well tolerated' applied not just to the upper GI tract, but also to other areas and to overall tolerability in this group of patients. The word 'even' could be interpreted in several ways, however, one dictionary definition was 'even – used as an intensive to emphasise the comparative degree < [even] better than last time >'. Given this meaning of the word, it was not unreasonable that a doctor could interpret the claim to apply more broadly than the data supported.

iii) The claim did not reflect that patients were excluded from the study. The FDA had recently issued a notice of violation letter to Merck Sharp & Dohme for Fosamax claims on its US website, including a claim of 'proven tolerability'. The website also included information about tolerability in a group of patients vulnerable to GI disease; the FDA letter noted that the claim 'Up to 54% of patients with a history of GI disorders at baseline' was misleading because it did not 'convey the material information that patients who had a history of major upper GI tract disease were excluded from the studies'. Similarly, the claim in question referred to a population vulnerable to GI disease. It was therefore exaggerated because it was not qualified by these GI exclusion criteria.

Once again, the complainants alleged that this claim misled as to the suggested safety profile of alendronate 70mg in this vulnerable population, in breach of Clause 7.2. Further, they alleged that this constituted a failure to comply with an undertaking within a reasonable time, in breach of Clause 22.

RESPONSE

Merck Sharp & Dohme stated that it had paid great attention to the ruling in Case AUTH/1178/4/01 and believed that it had taken it fully into account in formulating a new claim regarding NSAIDs/aspirin and thus had complied with its undertaking in line with Clause 22. Merck Sharp & Dohme believed the revised claim was substantiated by the available data, did not mislead and was not in breach of Clause 7.2.

Merck Sharp & Dohme believed the key elements of the ruling from Case AUTH/1178/4/01 to be: the claim 'well tolerated' was acceptable and not in breach; single or occasional use of an NSAID or aspirin did not constitute a 'regimen'; the reference provided did not provide adequate information to make a judgement with regard to whether NSAID/aspirin usage constituted 'regimens' and the Panel had not been provided with sufficient evidence to support the claim 'Even in patients on concurrent NSAID/aspirin regimens' [in the context of well tolerated].

As 'Well tolerated' was deemed acceptable under the ruling this claim was not revised. As such Merck Sharp & Dohme did not propose to discuss it further. However, should the Panel wish to revise its previous ruling, Merck Sharp & Dohme noted that further Fosamax 70mg studies had been completed which it would submit, in conjunction with further argument, to further defend this claim.

In light of the Panel's ruling with regard to the NSAID/aspirin claim at issue in Case AUTH/1178/4/01 in the context of the heading 'Well tolerated', a new claim was developed and references provided with regard to detail of NSAIDs/aspirin exposure and event rates. The claim was now related to upper GI tolerability in patients exposed to NSAIDs/aspirin, rather than overall tolerability in patients taking NSAID/aspirin regimens. Merck Sharp & Dohme believed this new claim represented a considerable change from the original and was substantiated by the available data.

In the past Procter & Gamble and Aventis had criticised Merck Sharp & Dohme for quoting FDA regulatory documents in letters to the Authority (Case AUTH/1074/9/00). Given this position Merck Sharp & Dohme was somewhat surprised to see the quotation of both German and FDA material regarding promotion in this complaint. It believed its past quotation of objective clinical trial data from the US label for risedronate was markedly different in this respect. The judgements involved in considering promotional claims differed from state to state, according to the jurisdiction involved. This was especially the case where the US and Europe were concerned. The German case was with reference to a German translation of the original NSAIDs/aspirin claim used in the UK and was withdrawn following an objection to the claim not being restricted to the upper GI tolerability. The revised NSAIDs/aspirin claim now at issue would seem to satisfy the objections raised in Germany to the original claim.

Clause 22: New claim following Case AUTH/1178/4/01

With regard to Case AUTH/1178/4/01, the Panel found a number of issues related to the claim used in relation to NSAIDs/aspirin. Merck Sharp & Dohme studied these carefully and believed that it had endeavoured to take all of the concerns into account in developing new material for Fosamax 70mg. In the original ruling 'The Panel noted that the claim at issue referred to an NSAID regimen. The relevant population in Schnitzer had taken NSAIDs or aspirin at some point in the study. In the Panel's view not all of these patients would have been on a regimen; some would have used NSAIDs once or occasionally.' The word 'exposed' was consistent with the wording used by Schnitzer when discussing upper GI adverse events in relation to NSAIDs/aspirin ('... during periods of exposure to NSAIDs/aspirin'), and conveyed no implication regarding duration of dosing, which seemed to be the main issue with 'regimen'.

The Panel had also noted that 'There was little data in the Schnitzer study in this regard [in relation to NSAID/aspirin use].' To address this element of the Panel's comments an additional data on file reference was provided to give further detail on the degree of NSAIDs/aspirin exposure that was lacking in Schnitzer, the only reference for the original claim. As stated in Schnitzer approximately 50% of patients in the study had taken NSAIDs/aspirin at some point. The data on file provided further detail: 'Approximately 68% (402/591) of these patients were on NSAIDs/aspirin for more than one month (or 30 days). The average duration of exposure to NSAIDs/aspirin was 174.8 days (SE=6.3).' The consistency and relevance of this to the UK situation data was confirmed when drawing up the new claim eg NICE in its recent review of COX II inhibitors found average treatment duration on NSAIDs to be 180 days a year. P-values were not quoted as the differences were not significant.

Merck Sharp & Dohme further noted that 'The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a population on an NSAIDs/aspirin regimen.' The issue of 'regimen' had been discussed above. The claim referred to in this statement was 'well tolerated' ie general or overall tolerability. The Schnitzer paper used to reference that claim in promotional material referred only to upper GI adverse events, and further data provided to the Authority in the context of the complaint similarly dealt only with upper GI adverse events. As this data had been found to be inadequate to support the broad claim on well tolerated, the claim was revised so that it only referred to the upper GI tract.

In light of the above, Merck Sharp & Dohme believed that: it had given due consideration to the judgement of the Panel; the new claim was different and

supported by the available evidence; it had complied with its undertaking under Clause 22; a breach of Clause 2 did not thereby arise.

Clause 7.2 and bullet points of complaint

i) Emphasis of the claim

The general claim 'Well tolerated' was found not to be in breach in Case AUTH/1178/4/01. To summarise the arguments used in the defence and findings in that case, Schnitzer's paper stated repeatedly that Fosamax once weekly was found to be well tolerated. The Panel considered this claim acceptable in the general osteoporotic population when administered in accordance with the SPC and ruled no breach of Clause 7.2. In addition to the data submitted previously there were other data that Merck Sharp & Dohme would be happy to provide should the Panel wish to consider the issue again (as examples abstracts from a forthcoming American Society for Bone and Mineral Research meeting were provided). Merck Sharp & Dohme could not agree that the bullet point emphasised upper GI tolerability in the general postmenopausal osteoporotic population in the manner alleged.

ii) Use of word 'Even'

Merck Sharp & Dohme was surprised to see the data on this NSAIDs/adverse events aspirin group described as 'limited' when claims had been made with risedronate and concurrent NSAIDs in promotional material with apparently lower numbers of patients exposed to active treatment (whilst these studies were of longer duration than Schnitzer some had high drop out rates, and also experience in FIT suggested almost 2/3 of upper GI adverse events occurred in the first 12 months of average 3.8 year follow up in any case). Also, the study by Graham and Malaty referred to in the previous complaint was much smaller than Schnitzer's, and had a design completely inappropriate for the question that was studied. However, the numbers exposed to Fosamax 70mg and concurrent NSAID/aspirin were not insubstantial, and were sufficient, Merck Sharp & Dohme believed, to draw reasonable conclusions. These conclusions had been published in the peer reviewed paper by Schnitzer *et al*.

Some physicians might have concerns about using bisphosphonates with concurrent NSAIDs/aspirin (indeed the complainants acknowledged these concerns in risedronate promotional material). In order to address such concerns the statement with this patient group had been included in promotional materials for alendronate. The complainants seemed to interpret the use of the word 'even' in this context in a somewhat perverse fashion. 'Even' as used in this context did not imply anything with regard to the general tolerability in the group of patients exposed to NSAIDs/aspirin as alleged. Fosamax 70mg was generally well tolerated in the general postmenopausal osteoporotic population when taken according to the recommendations in the SPC, and also in an area where the prescriber might express some unease, the upper GI tract of those who were taking NSAID/aspirin concurrently.

iii) Patient exclusion from studies

With regard to the FDA notice of violation letter, Merck Sharp & Dohme believed the issue of exclusion criteria was considered by the Panel in Case AUTH/1178/4/01, and the Panel seemed to concur with Merck Sharp & Dohme's view that the exclusion criteria broadly reflected the contra-indications and warnings/precautions of the SPC ie Fosamax 70mg was well tolerated when taken in accordance with the SPC.

Merck Sharp & Dohme also provided detailed information which it stated supported the claim 'Even in the upper GI tract of patients exposed to NSAIDs/aspirin'. As it had taken into account the findings of the Panel in Case AUTH/1178/4/01 Merck Sharp & Dohme did not believe that this new claim was in breach of Clauses 7.2 or 22.

PANEL RULING

The Panel noted that Case AUTH/1178/4/01 similarly concerned a journal advertisement for Fosamax 70mg issued by Merck Sharp & Dohme. It was alleged, *inter alia*, that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' misled as to the overall safety profile of alendronate 70mg in this population as conflicting data in combination with limited clinical trial data were available on the safety of concurrent use of NSAIDs and/or aspirin with Fosamax; overall tolerability data were not provided for this group of patients and data that were provided for this group were inadequate to support the claim. The Panel had noted that the claim at issue in Case AUTH/1178/4/01 was referenced to Schnitzer *et al* (2000) which was a one year, randomized, double blind, multicentre study designed to evaluate the efficacy and safety of oral Fosamax 10mg od, 35mg twice weekly and 70mg once weekly in postmenopausal women with osteoporosis. Women were not excluded because of previous or active gastrointestinal disease but were excluded if there was a history of major upper gastrointestinal mucosal erosive disease defined as a) significant upper gastrointestinal bleeding within the last year requiring hospitalisation or transfusion, b) recurrent peptic ulcer disease documented by radiographic or endoscopic means, c) dyspepsia that was uncontrolled by medication and d) oesophageal stricture or dysmotility. Patients were not excluded if, *inter alia*, there was concomitant use of aspirin or non-steroidal anti-inflammatory medications. The study authors stated that the assessment of the safety profiles for the three treatment regimens focussed primarily on the analysis of upper gastrointestinal adverse experiences. In general the three dosing regimens were well tolerated, the study did not have a placebo comparison group, the incidences of adverse experiences were low and similar to those observed in the placebo arms of previous alendronate studies after one year. There were no significant differences among the three treatment groups in the proportion of patients with upper gastrointestinal adverse experiences or in those discontinuing due to upper gastrointestinal experiences. Further analysis showed that there was no temporal relationship between the

onset of upper gastrointestinal adverse experiences and dosing with the once weekly tablet. Serious upper gastrointestinal experiences were also analysed; there were no serious upper gastrointestinal adverse experiences reported in the once or twice weekly treatment groups; the incidence of serious upper gastrointestinal adverse experiences was significantly lower in the 70mg once weekly compared to the 10mg daily group. The study authors noted that approximately 50% of patients used NSAIDs and/or aspirin at some point during the study. There were no between-group differences in the incidence of upper gastrointestinal adverse events in these patients during the periods of exposure to NSAIDs/aspirin.

The Panel noted the placebo controlled studies with 70mg once weekly referred to by Merck Sharp & Dohme; Van Dyke *et al* (2000) and Lanza *et al* (2000). Van Dyke *et al*, an abstract, was a placebo controlled multicentre 2 year study which assessed the safety of Fosamax 70mg once weekly in periodontal disease in men and women. The abstract stated that one year data showed that the overall and upper gastrointestinal safety and tolerability profile of Fosamax was very favourable compared to placebo. P values were not provided. Lanza *et al* concluded that Fosamax 70mg once weekly was not associated with endoscopic upper gastrointestinal mucosal lesions compared to placebo in men and women. The mean gastric erosion scores in both treatment groups (Fosamax and placebo) were significantly lower than in those given aspirin.

The Panel noted Merck Sharp & Dohme's submission that in general the precautions and contraindications in the SPC reflected the exclusion criteria for Schnitzer *et al*. The Panel noted the exclusion criteria in Watts 1999, Bauer 2000 and Schnitzer 2000 and the allegation that relatively few patients in the alendronate clinical trials (10mg and 70mg) were those in the high risk population. The Panel noted the submission that the level of NSAID/aspirin use and rate of peptic ulcers in Schnitzer *et al* was consistent with the osteoporotic control group in van Staa (1997).

The Panel noted that interaction with NSAIDs/aspirin was not mentioned in the Fosamax SPC.

The Panel noted that Graham and Malaty (2001) was a blind crossover randomized single centre endoscopic study in healthy volunteers designed to assess whether Fosamax and naproxen were synergistic as causes of gastric ulcers. The study authors concluded that the combination regimen resulted in a significantly higher degree of gastric damage than either medicine alone ($P<0.05$). In addition, treatment with naproxen alone was significantly more injurious than alendronate alone ($P<0.05$). No oesophageal injury was seen in any group. Duodenal injury was mild but was significantly more common in the alendronate-alone group ($P<0.05$). The authors recommended that until epidemiological studies clearly showed that Fosamax use was not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving Fosamax, and vice versa.

The Panel noted that in the fracture intervention trial (FIT) which examined the upper gastrointestinal tract safety profile of Fosamax 5 and 10mg, approximately 88% of all participants reported at least one day of NSAID or aspirin use during the study. Event rates were higher during NSAID use compared with non use in both placebo and Fosamax treatment groups. In each case sensitivity analysis showed that there was no evidence that concurrent use of Fosamax and NSAIDs resulted in an excess of gastroduodenal or oesophageal events compared with concurrent use of NSAIDs and placebo. The 70mg dose was not examined. The Panel noted its comments above on the relevant data in Schnitzer *et al*.

The Panel noted that in Case AUTH/1178/4/01 the claim at issue referred to an NSAID regimen. The relevant patient population in Schnitzer had taken NSAIDs or aspirin at some point in the study. In the Panel's view not all of these patients would have been on a regimen; some would have used NSAIDs once or occasionally. There was little data in the Schnitzer study in this regard. The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The claim was misleading and a breach of Clause 7.2 was ruled.

Turning to the present case, Case AUTH/1230/9/01, the Panel noted that the claim at issue and the promotional material were different to that previously considered and in the Panel's view were sufficiently different not to be covered by the undertaking given in Case AUTH/1178/4/01. No breach of Clauses 22 and 2 of the Code was ruled.

The Panel noted that the claim was referenced to Schnitzer *et al* (2000) and data on file. The Panel considered that its comments on Schnitzer *et al* at Case AUTH/1178/4/01 were relevant here. The data on file in relation to Schnitzer *et al* stated that approximately 50% of patients used NSAIDs or aspirin at some point during the study. Approximately 68% of these patients were on NSAIDs/aspirin for more than one month (or 30 days). The average duration of exposure to NSAIDs/aspirin was 174.8 days (SE=6.3). The data showed that 12.9% (23/178) of patients taking alendronate 10mg daily and aspirin-containing therapies and/or NSAIDs experienced an upper GI adverse event. Of those patients taking alendronate 70mg and aspirin-containing therapies and/or NSAIDs, 14.1% (38/269) experienced an upper GI adverse event. The data on file referred to the absence of a placebo group in the Schnitzer study and to the FIT data. The Panel noted that the FIT trial compared alendronate and placebo with regard to upper GI tract events. The doses of alendronate were 5mg per day for 2 years and 10mg per day during years 3 through to 4.5. FIT stated that the proportion of women reporting any upper GI tract event was similar in the alendronate and the placebo groups during treatment with both 5mg per day and 10mg per day as was the proportion of women with serious upper GI tract events. FIT did not investigate the effects of alendronate at 70mg per week.

The Panel noted that the FIT study showed that daily doses of Fosamax, 5 or 10mg, caused no more upper

GI events than placebo even in patients exposed to NSAIDs. The Schnitzer *et al* study showed that in terms of upper GI adverse experiences a high weekly dose of Fosamax (70mg) was as well tolerated as small daily doses (5 or 10mg) even in patients exposed to NSAIDs. Section 4.4 of the Fosamax 70mg SPC, however, stated that Fosamax 'can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty'.

The Panel considered that the claim in question gave the impression that prescribers did not need to worry about upper GI side effects when prescribing Fosamax 70mg even to patients who had been exposed to aspirin/NSAIDs; given the advice in the SPC that caution should be used when the product was given to patients with active upper gastrointestinal problems that was not so. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

Complaint received **21 September 2001**

Case completed **21 November 2001**

CASE AUTH/1232/9/01

ALCON LABORATORIES v ALLERGAN

Promotion of Lumigan

Alcon Laboratories complained about a lecture given by an Allergan scientist at a symposium on 'Current Medical and Surgical Treatments for Glaucoma' for ophthalmologists and eye care doctors. The title of the lecture as listed in the programme was 'Mechanisms of Action of Prostaglandins and Prostanoids' but in the event the lecture was entitled 'Lumigan Ophthalmic Solution represents a new class of intraocular pressure lowering agents'. The presentation discussed the mechanism of action of Lumigan (bimatoprost), a clinical review of Lumigan versus Xalatan (a commercially available glaucoma treatment), benefits of Lumigan and details of side effect profile, dosage, storage and pack size. Many of the slides clearly referred to 'Lumigan', with no attempt to use the generic name. The presentation was commercial, it was given by an Allergan employee and it promoted Lumigan. Lumigan did not have a marketing authorization in the UK or elsewhere in Europe. It did have a licence in America where it was commercially available.

The Panel noted that the presentation was given by an American based employee of Allergan at a UK meeting. Allergan had not reviewed the presentation for use in the UK prior to the meeting. It was an established principle under the Code that in relation to matters which came within the Code the UK based company was responsible for the acts or omissions of its overseas divisions.

Firstly, the Panel had to decide whether the presentation was promotional. According to the agenda the Allergan scientist gave a 20 minute talk entitled 'Mechanisms of Action of Prostaglandins and Prostanoids'. The first slide of the actual presentation was headed 'Lumigan Ophthalmic Solution represents a New Class of IOP-Lowering Agents'. The presentation initially discussed prostamides as a class and compared the biosynthetic pathways and mechanisms of action of prostamides and prostaglandins. A slide headed 'Clinical Evaluation of Lumigan (bimatoprost) for Glaucoma', featuring a product pack shot, introduced a series of slides showing comparative efficacy data, each of which showed advantages for Lumigan. The Panel considered that the style and content of the presentation meant that it was promotional. It had the appearance of promotional material and could not be described as the legitimate exchange of medical and scientific information. Lumigan did not have a UK marketing authorization. The Panel considered that Lumigan was being promoted prior to the grant of its licence and a breach of the Code was ruled.

Alcon Laboratories (UK) Limited complained about a talk given by an Allergan scientist at a one day symposium on 'Current Medical and Surgical Treatments for Glaucoma' with an audience of ophthalmologists and eye care doctors.

COMPLAINT

Alcon stated that during the morning session a lecture was given by a scientist employed by Allergan. The title of the lecture as listed in the programme was 'Mechanisms of Action of Prostaglandins and Prostanoids' but he actually gave a presentation on a different topic, the title of which, and wording of the introductory slide on the day, being 'Lumigan Ophthalmic Solution represents a new class of intraocular pressure lowering agents'.

The presentation then discussed the mechanism of action of Lumigan (bimatoprost), a clinical review of Lumigan versus Xalatan (a commercially available glaucoma treatment), benefits of Lumigan and details of side effect profile, dosage, storage and pack size. Many of the slides very clearly mentioned the word

'Lumigan', with no attempt to use the generic name. The presentation was commercial, it was given by an Allergan employee and was promoting Lumigan.

Lumigan did not have a marketing authorization in the UK or elsewhere in Europe. It did have a licence in America where it was commercially available.

Alcon noted that Clause 3.1 prohibited the promotion of a medicine prior to the grant of the marketing authorization which permitted its sale or supply. Alcon alleged a breach of Clause 3.1 of the Code.

RESPONSE

Allergan Limited stated that the speaker, a research and development (R&D) scientist with Allergan, had had extensive preclinical experience with the synthetic prostamide analogue, bimatoprost, which was now licensed in the USA for the treatment of glaucoma. Lumigan was not licensed in the UK.

Given this background, it was understandable that in discussing the pharmacology and mechanisms of action of these agents, the speaker discussed the pharmacology and mechanism of action of Lumigan. He presented some clinical data to demonstrate how differences in pharmacology and mechanism of action translated into differences in clinical effects, thus differentiating and establishing Lumigan as a new class of intraocular pressure lowering agent. During the presentation, he referred to Lumigan by its brand name rather than by generic name, as he was accustomed to presenting on this subject in the USA, where use of brand names was acceptable.

The presentation was not reviewed by Allergan for use in the UK prior to the meeting. The speaker mistakenly believed that, as he was making a presentation as an R&D scientist at a scientific meeting, such review was not necessary. He did not at any time believe that his presentation was promotional.

Allergan was fully committed to abiding by the Code, investing considerable time and resource to ensure that all promotional activities complied with all Code requirements. Although not intended as a promotional presentation, Allergan accepted that within the context of the Code, the presentation constituted a violation of Clause 3.1, for which it apologised. Allergan stated that it had taken steps to reinforce to its global R&D colleagues that any activity within the UK, whether of a scientific or promotional nature, must be fully reviewed in advance to ensure that it complied with all requirements of the Code.

PANEL RULING

The Panel noted that the presentation was given by an American based employee of Allergan at a UK meeting. Allergan had not reviewed the presentation for use in the UK prior to the meeting. The Panel noted that it was an established principle under the Code that in relation to matters which came within the Code the UK based company was responsible for the acts or omissions of its overseas divisions. In this regard the Panel noted that Allergan had subsequently reminded its global R&D colleagues that any activity within the UK must be fully reviewed in advance to ensure that it complied with all the requirements of the Code.

Firstly, the Panel had to decide whether the presentation was promotional or not. It was not as straightforward as whether the brand name or the generic name was used as implied by Allergan's response.

The Panel noted that according to the agenda the Allergan scientist gave a 20 minute talk entitled 'Mechanisms of Action of Prostaglandins and Prostanoids'. The first slide of the actual presentation was headed 'Lumigan Ophthalmic Solution represents a New Class of IOP-Lowering Agents'. The presentation initially discussed prostamides as a class and compared the biosynthetic pathways and mechanisms of action of prostamides and prostaglandins. A slide headed 'Clinical Evaluation of Lumigan (bimatoprost) for Glaucoma', featuring a product pack shot, introduced a series of slides showing comparative efficacy data, each of which showed advantages for Lumigan. The Panel considered that the style and content of the presentation meant that it was promotional. It had the appearance of promotional material and could not be described as the legitimate exchange of medical and scientific information as referred to in the supplementary information to Clause 3 of the Code. Lumigan did not have a UK marketing authorization. The Panel considered that Lumigan was being promoted prior to the grant of its licence contrary to the requirements of Clause 3.1 of the Code, a breach of which was accordingly ruled.

Complaint received **28 September 2001**

Case completed **4 December 2001**

MERCK SHARP & DOHME v NOVARTIS

Promotion of Lescol

Merck Sharp & Dohme complained about the promotion of Lescol (fluvastatin) by Novartis. There were two items at issue, an advertisement in the medical and pharmaceutical press and a 'Dear Health Professional' letter; each referred to the withdrawal of cerivastatin, which had occurred as a result of a high reported incidence of rhabdomyolysis. The advertisement referred to a practice-based management solution to transfer patients to alternative therapy. The letter referred to a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol. Merck Sharp & Dohme marketed Zocor (simvastatin).

The advertisement was headed 'Advertisement Feature Important Announcement'. The subheading read 'Continuity of treatment following cerivastatin world-wide withdrawal'. Merck Sharp & Dohme noted that although the advertisement referred to the 'smooth transfer of cerivastatin patients to the alternative therapy of your choice', this was preceded by a paragraph detailing the calls made 'on conversion of cerivastatin patients to Lescol (fluvastatin)'. The benefits of the switch were then elucidated by describing the Novartis programme. Merck Sharp & Dohme alleged that the provision of this programme was offered as an inducement to buy or prescribe Lescol.

The Panel noted that in a previous complaint, concerning a 'Dear Health Professional' letter, Case AUTH/1221/8/01, Merck Sharp & Dohme had similarly alleged that the provision of the Patient Continuity Support Programme constituted an inducement to prescribe Lescol. In that case, the Panel had decided, on balance, that the support programme was part of the promotion of Lescol. It was not described as anything else in the letter in question. The Panel considered that neither the benefits nor the description of the support programme amounted to a gift, benefit in kind or pecuniary advantage given as an inducement to prescribe Lescol. The Panel had therefore ruled no breach of the Code. The Panel considered that that ruling similarly applied to the advertisement at issue in the present case and no breach of the Code was ruled.

Although the 'Dear Health Professional' letter now at issue dated 10 August was different to that considered in Case AUTH/1221/8/01 the paragraph describing the support programme was the same in each. Merck Sharp & Dohme stated that its concerns about the inducement to prescribe Lescol being used by Novartis were heightened on review of the 'Dear Health Professional' letter at issue, which was similar in many ways to the letter considered in Case AUTH/1221/8/01. Unlike the advertisement considered above which referred to 'therapy of your choice', the letter specifically addressed the Lescol: Novartis Patient Continuity Support Programme and stated that 'Novartis has developed a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol'. A breach of the Code was alleged.

The Panel considered that its ruling in Case AUTH/1221/8/01 with regard to the Patient Support Programme similarly applied to the 'Dear Health Professional' letter at issue in the present case and no breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about the promotion of Lescol (fluvastatin) by Novartis Pharmaceuticals UK Limited. There were two items at issue, an advertisement (ref LES 01/58) and a 'Dear Health Professional' letter (A308681(11)79131). Both items referred to the withdrawal of cerivastatin, which had occurred as a result of a high reported incidence of rhabdomyolysis. The advertisement referred to a practice-based management solution to transfer patients to alternative therapy. The 'Dear Doctor' letter referred to a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol. Merck Sharp & Dohme marketed Zocor (simvastatin).

A Advertisement

The advertisement was headed 'Advertisement Feature Important Announcement'. The subheading read 'Continuity of treatment following cerivastatin world-wide withdrawal'. The advertisement appeared in the medical and pharmaceutical press (The Pharmaceutical Journal, 18 August).

COMPLAINT

Merck Sharp & Dohme noted that although the advertisement referred to the 'smooth transfer of cerivastatin patients to the alternative therapy of your choice' this was preceded by a paragraph detailing the calls made 'on conversion of cerivastatin patients to Lescol (fluvastatin)'. The benefits of the switch were then elucidated by describing the Novartis programme. Merck Sharp & Dohme alleged that the provision of this programme was offered as an inducement to buy or prescribe Lescol and was in breach of Clause 18.1 of the Code.

RESPONSE

Novartis stated that the Novartis Patient Continuity Support Programme consisted of a set of IT guidance notes relating to a number of GP prescribing systems. It provided the health professional with a step-by-step guide by which they were able to select from their systems patients currently receiving cerivastatin who required review. It also provided draft templates for surgery letters to local pharmacies and a set of draft template letters for patients and reception support.

The guidance notes were devised originally to assist health professionals requesting specific assistance from the company in transferring patients from other statins to Lescol, and had been available for some time. However, following the withdrawal of cerivastatin the company received an increased number of requests for assistance both in relation to the logistics of identifying patients for review and the suitability of Lescol as an alternative therapy. In the

light of these requests it was quickly realised that materials offering practical advice on the logistics of the audit process such as this had a broader value than originally anticipated and the decision was taken to make them more widely available. To support this broader usage, a number of additional generic template patient letters were added to the original programme.

Having decided to make these materials more widely available the advertisement at issue was placed in The Pharmaceutical Journal where the free availability of the programme would be appreciated by the broadest audience of health professionals requiring urgent support for their own cerivastatin review process.

As the advertisement clearly identified, these guidance notes were available directly from the company via the medical information department and their provision was not linked in any way to the prescription of Lescol. The materials were provided to the requesting health professional both as hard copy and also on disk so that they could be adjusted to their specific needs. The materials were sent to interested health professionals regardless of their prescribing intention and their ultimate prescribing decision. There was no requirement for the health professional to see a representative or give the medical information department any more information than an address for delivery. Novartis therefore strongly refuted Merck Sharp & Dohme's suggestion that these materials were in breach of Clause 18.1 of the Code. Novartis emphasised that health professionals found these support materials to be of considerable value during the patient review process.

PANEL RULING

The Panel noted that in Case AUTH/1221/8/01 Merck Sharp & Dohme had similarly alleged that the provision of the Patient Continuity Support Programme constituted an inducement to prescribe Lescol. The Panel referred to its ruling in the previous case which concerned a 'Dear Health Professional' letter dated 9 August.

Panel ruling in Case AUTH/1221/8/01

The Panel noted that, in the introduction to the Patient Continuity Support Programme, the penultimate paragraph referred to the programme having been developed to support the smooth transfer of cerivastatin patients to alternative therapies. The Patient Continuity Support Programme gave a medical information number for further details. The IT guidance notes provided technical instructions for eight different software systems to enable the user to identify patients receiving cerivastatin and effect a switch. The technical instructions merely referred to a switch to alternative therapy, Lescol was not mentioned. Sample letters to patients who were having their medication changed were provided together with sample notices to practice staff to keep them informed of the initiative and letters to pharmacists. Each sample letter and notice stated that it was an example which could be modified as appropriate. Each example was provided in both a draft format with the name of the new medication to be inserted by the doctor and a completed format whereby fluvastatin 40mg was inserted as the new medication. The statement 'After careful review fluvastatin has been chosen as one of a small selection of drugs which the practice believe to be in line with current best thinking. Fluvastatin works to produce the same benefits as your existing medication' also appeared in the completed format letters.

The Panel noted that as a result of the withdrawal of cerivastatin GPs would have to identify and transfer patients to suitable alternative medication. The Panel considered that technical instructions enabling practices to identify and switch patients using their existing software would be helpful to practices. It could be argued that such a service would enhance patient care and benefit the NHS as required by the supplementary information to Clause 18.1 of the Code. However, the supply of such goods and services must not be done in such a way as to amount to an inducement to prescribe, supply, administer, recommend or buy any medicine contrary to the requirements of Clause 18.1 of the Code and its supplementary information. The supplementary information also stated that goods and services must not bear the name of any medicine but may bear a corporate name.

The Panel noted that, in contrast to the introduction to the Patient Continuity Support Programme which stated that the programme would 'support the smooth transfer of cerivastatin patients to alternative therapies', the 'Dear Health Professional' letter at issue stated that it would 'support the smooth transfer of cerivastatin patients to Lescol'. The reader was referred to the Novartis medical information department for further details. In the Panel's view it could be argued that the support programme was being offered to doctors who had decided to transfer patients from cerivastatin to Lescol. Doctors who were considering changing patients from cerivastatin to Lescol could also obtain details although this was not mentioned in the letter in question. The Panel noted Novartis' submission that the materials were sent to health professionals regardless of their prescribing intention and their ultimate prescribing decision.

The Panel was unsure whether the arrangements amounted to an inducement to prescribe. The benefit to the doctor was a document, akin to a computer manual, which gave instructions about how to search their computers for patients on cerivastatin and how to change these patients to other medication. In addition to the 'computer manual' example letters to send to patients were provided. It appeared that practices would have to carry out the changes. The Panel considered that the position was somewhat unusual in that changes would have to be carried out regardless of whether the practice used the support programme or not, although patients on cerivastatin would not necessarily have to be changed to Lescol.

The inducement might be the simplification of changing patients although in that regard the Panel noted that it was a practice run support programme; Novartis was not providing IT staff to change the practice's computer records etc. There was no

inherent value in the documents provided. It was perfectly possible for the support programme to be used in changing patients to a treatment other than Lescol. This would not be apparent from the 'Dear Health Professional' letter which clearly linked the support programme to Lescol.

It could be argued that the support programme was part of the promotion of Lescol and was not a medical and educational good or service as described in the supplementary information to Clause 18.1 of the Code.

On balance the Panel decided that the support programme was part of the promotion of Lescol. It was not described as anything else in the letter in question. The Panel considered that neither the benefits nor the description of the support programme amounted to a gift, benefit in kind or pecuniary advantage given as an inducement to prescribe Lescol. The Panel therefore ruled no breach of Clause 18.1 of the Code.

Panel ruling in Case AUTH/1233/9/01

The Panel considered that its ruling in Case AUTH/1221/8/01 similarly applied to the advertisement at issue in Case AUTH/1233/9/01. Although the second paragraph of the advertisement referred to the conversion of cerivastatin patients to Lescol the next paragraph went on to state that the Novartis practice-based management solution would enable the smooth transfer of cerivastatin patients to the alternative therapy of choice. No breach of Clause 18.1 of the Code was ruled.

B 'Dear Health Professional' letter

The 'Dear Health Professional' letter now at issue was different to that considered in Case AUTH/1221/8/01. The previous letter had been dated 9 August. The letter now at issue was dated 10 August. The paragraph describing the support programme was however the same in each letter.

COMPLAINT

Merck Sharp & Dohme stated that its concerns about the inducement to prescribe Lescol being used by Novartis were heightened on review of the 'Dear Health Professional' (10 August) letter, which was similar in many ways to the 'Dear Health Professional' (9 August) letter considered in Case AUTH/1221/8/01. Unlike the advertisement considered above which referred to 'therapy of your choice', the letter specifically addressed the Lescol: Novartis Patient Continuity Support Programme and stated that 'Novartis has developed a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol'. Again this appeared to breach Clause 18.1 of the Code.

* * * * *

The previous complaint, Case AUTH/1221/8/01, was not completed when the current complaint was received. Subsequently both parties had accepted the Panel's rulings of no breach of the Code.

Paragraph 5.1 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication, it might be allowed to proceed at the discretion of the Director if new evidence was adduced by the complainant or if the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which was not the subject of appeal to the Code of Practice Appeal Board.

The Director thus decided that as Case AUTH/1233/9/01 covered matters similar to those in Case AUTH/1221/8/01, and as Case AUTH/1221/8/01 had not been the subject of an appeal, the allegations about the 'Dear Health Professional' (10 August) letter in Case AUTH/1233/9/01 should proceed. The case was a little unusual as Paragraph 5.1 of the Constitution and Procedure rather assumed that the party making a complaint about a matter closely similar to a previous complaint would be different to the original complainant. In this instance they were the same. Nonetheless, the Director decided that Case AUTH/1233/9/01 was to proceed.

RESPONSE

Novartis stated that its response to this allegation was largely a repetition of its response to Case AUTH/1221/8/01 and that in point A above.

PANEL RULING

The Panel considered that its ruling in Case AUTH/1221/8/01 with regard to the Patient Support Programme similarly applied to the 'Dear Health Professional' (10 August) letter at issue in Case AUTH/1233/9/01. No breach of Clause 18.1 of the Code was ruled.

Complaint received **28 September 2001**

Case completed **10 December 2001**

WYETH v NOVO NORDISK

Kilovance leavepiece

Wyeth complained about a Kliovance (estradiol/norethisterone) leavepiece issued by Novo Nordisk.

Wyeth noted that the heading to page 2 was 'Rapid bleed control' followed by the claim '73% of women can expect to be amenorrhoeic as early as 8 weeks from start of treatment' which was referenced to Archer *et al* (1999). Wyeth considered that this claim implied that Kliovance rapidly induced a state of amenorrhoea. In fact, data in the Archer paper showed the incidence of bleeding as 0% at 0 months, rising rapidly to just under 30% by 1 month. Thus, the claim was inaccurate and ambiguous.

The Panel noted that Kliovance was a continuous-combined HRT indicated for oestrogen deficiency symptoms in women who were more than one year past the menopause. Such women would have no bleeding before starting Kliovance therapy. In the intended patient population it seemed a paradox to claim that Kliovance had rapid bleed control. The Panel considered, however, that prescribers would know that although continuous-combined HRT did not cause monthly withdrawal bleeding, unanticipated bleeding episodes could occur, particularly in the first few months of therapy. Archer *et al*, however, showed that at cycle 2, 72.7% of women on Kliovance reported no incidence of bleeding. The Panel considered that within the context of the therapy area Kliovance did demonstrate rapid bleed control and that the claim was thus not inaccurate or ambiguous as alleged. No breach of the Code was ruled.

The claim '73% of women can expect to be amenorrhoeic as early as 8 weeks from the start of treatment', and the figure beneath it which showed the percentage of women amenorrhoeic at 2 months (73%), 6 months (83%) and 11 months (90%), were both referenced to Archer *et al* (1999). In addition, the figure was also referenced to Archer *et al* (1998) which was the original abstract of the 1999 publication.

Wyeth noted that Archer *et al* (1999) used the term 'no bleeding' and not 'amenorrhoea'. Moreover, the 'no bleeding incidence' was not defined in the paper, and it was unclear whether 'no bleeding' meant 'no bleeding (with or without spotting)' or 'amenorrhoea (ie no bleeding and no spotting)'. The level of ambiguity and lack of clarity generally in the Archer paper was such that the use of the term 'amenorrhoea' as opposed to 'no bleeding' could not be justified.

The Panel noted that Archer *et al* recorded vaginal bleeding data as no bleeding or spotting, bleeding, or spotting. Bleeding was defined as release of uterine blood that required sanitary protection, while spotting was defined as release of uterine blood that did not require sanitary protection. All months were classified into one of three categories; month with no bleeding, month with bleeding (with or without spotting) or month with spotting only (no bleeding). The Panel considered it was clear from the definitions given by Archer *et al* that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The term no bleeding, as used by Archer *et al*, was thus effectively amenorrhoea. The Panel noted that the original abstract of the Archer paper used the term amenorrhoea to define a state of no spotting or bleeding. The Panel considered that use of the term amenorrhoea could be justified and was thus not misleading as alleged. No breach of the Code was ruled.

The claim 'A side effect profile to aid compliance' appeared as the second bullet point on page 3 of the leavepiece, beneath the heading 'What does Kliovance mean for your patients'. The claim was referenced to data on file, Stadberg *et al* (1996) and Borrego *et al* (1999). Wyeth stated that HRT side effects did not aid compliance. Stadberg *et al* reported less severe mastalgia with Kliovance vs Kliofem ($p<0.05$). This should be made clear in the leavepiece, together with the fact that Kliovance might aid compliance, as there was no proof of a compliance benefit. Wyeth thus considered the claim ambiguous, inaccurate and misleading.

The Panel noted that the data on file which reported Kliovance discontinuation rates showed that of 442 patients 38 (9%) discontinued therapy because of adverse events. Stadberg *et al* showed that Kliovance was less likely to cause severe mastalgia than Kliofem ($p<0.05$). Of the 20 patients randomized to Kliovance two reported urinary tract infections and withdrew for that reason. In Borrengo *et al*, which demonstrated that treatment with Kliovance did not lead to significant changes in body weight, 21% of the 295 patients randomized to Kliovance withdrew from the study. Another claim in the leavepiece was 'Low dose, high compliance', referenced to the data on file as discussed above and also DIN-LINK data which showed how patients discontinued HRT therapy over time. For oral continuous-combined HRT as a whole, 45% of patients remained on therapy after a year. This figure was reported to be as low as 25% for one particular product. For Kliovance the figure was 43.2% which compared well with the overall figure. On balance the Panel considered that the claim 'A side effect profile to aid compliance' was not unreasonable. No breach of the Code was ruled.

Wyeth complained about a Kliovance (estradiol/norethisterone) leavepiece (ref KG/01/05) issued by Novo Nordisk Limited.

1 Claim 'Rapid bleed control'

COMPLAINT

Wyeth noted that the heading to page 2 was 'Rapid bleed control' followed by the claim '73% of women can expect to be amenorrhoeic as early as 8 weeks from start of treatment' which was referenced to Archer *et al* (1999). Wyeth considered that this claim implied that Kliovance rapidly induced a state of

amenorrhoea. In fact, data in the Archer paper showed the incidence of bleeding as 0% at 0 months, rising rapidly to just under 30% by 1 month. Thus, the claim was inaccurate and ambiguous. Wyeth alleged a breach of Clause 7.2.

RESPONSE

Novo Nordisk agreed that the claim 'Rapid bleed control' implied that Kliovance rapidly induced a state of amenorrhoea. Archer *et al* showed clearly that 73% of women were free of bleeding or spotting by the end of the 8th week of therapy. Kliovance was a continuous-combined hormone replacement therapy (HRT) intended for the treatment of menopausal symptoms and the prevention of osteoporosis in postmenopausal women. These women were by definition period free at the start of therapy, and continuous-combined HRT was intended to provide the benefits of HRT without a monthly bleed. However bleeding problems were a recognised side effect of continuous-combined HRT, with irregular bleeding or spotting a common complaint in the first few months of treatment. Archer *et al* demonstrated that Kliovance rapidly returned 73% of women to a bleed-free state by the end of month 2. Wyeth's statement that the incidence of bleeding rose from 0% to 30% by one month indicated some misunderstanding of the issues surrounding continuous-combined HRT and bleeding. In the discussion section of the paper, Archer *et al* stated 'Our results show that continuous-combined formulations of E2 1mg with norethindrone acetate 0.1, 0.25 or 0.5mg are associated with a low incidence of bleeding during the initial 3 months of treatment and beyond'. Novo Nordisk considered this claim therefore to be fair, accurate and unambiguous and not in breach of Clause 7.2 of the Code.

PANEL RULING

Kliovance was a continuous-combined HRT indicated for oestrogen deficiency symptoms in women who were more than one year past the menopause. Such women would have no bleeding before starting Kliovance therapy. In the intended patient population it seemed a paradox to claim that Kliovance had rapid bleed control. The Panel considered, however, that prescribers would know that although continuous-combined HRT did not cause monthly withdrawal bleeding, unanticipated bleeding episodes could occur particularly in the first few months of therapy. Archer *et al*, however, showed that at cycle 2, 72.7% of women on Kliovance reported no incidence of bleeding. The Panel considered that within the context of the therapy area Kliovance did demonstrate rapid bleed control and that the claim was thus not inaccurate or ambiguous as alleged. No breach of Clause 7.2 was ruled.

2 Claim '73% of women can expect to be amenorrhoeic as early as 8 weeks from start of treatment' and the figure beneath it which showed the percentage of women amenorrhoeic at 2 months (73%) 6 months (83%) and 11 months (90%)

The claim and the figure were both referenced to Archer *et al* (1999); in addition the figure was also referenced to Archer *et al* (1998) which was the original abstract of the 1999 publication.

COMPLAINT

Wyeth noted that Archer *et al* (1999) used the term 'no bleeding' and not 'amenorrhoea'. Moreover, the 'no bleeding incidence' was not defined in the paper, and it was unclear whether 'no bleeding' meant 'no bleeding (with or without spotting)' or 'amenorrhoea (ie no bleeding and no spotting)'. A figure in the Archer paper contained line graphs for the incidence of bleeding (with or without spotting). The Kliovance line for months 10, 11 and 12 was horizontal at 10%. It would therefore be expected that the incidence of no bleeding (with or without spotting) would be approximately 90%, and indeed a table of data in Archer *et al* (1999) listed no bleeding incidence at cycle 11 as 89.7%. This suggested that the data was not amenorrhoea. The level of ambiguity and lack of clarity generally in the Archer paper was such that the use of the term 'amenorrhoea' as opposed to 'no bleeding' could not be justified, and therefore breached Clause 7.2.

RESPONSE

Novo Nordisk stated that with respect to the term 'amenorrhoea', examination of the data made it clear that 'no bleeding' in this capacity was intended to mean 'no bleeding or spotting'. 'No bleeding incidence (% mo)' referred to the percentage of observed months (woman-months) in which no bleeding or spotting was reported. This was clarified in the 'Materials and Methods' section of the Archer paper with the sentence 'All months (cycles) were classified into one of the following categories: month with no bleeding, month with bleeding (with or without spotting), or month with spotting only (no bleeding). It was therefore obvious that 'no bleeding' referred to women who were neither bleeding nor spotting, as women who were spotting only were classified as such.

Novo Nordisk stated that this was clearly demonstrated in the table of data referred to by Wyeth, where the final column of Table 2 gave the results for Kliovance. The overall 'No bleeding incidence (% mo)' was 81.9%, the 'Bleeding incidence (with or without spotting) (% mo)' was 8.7%, and the 'Spotting incidence (without bleeding) (% mo)' was 9.4%. These numbers added up to 100%. If 'no bleeding incidence (with or without spotting)' included women who were only spotting, then the figures would add up to more than 100%, as the woman-months of spotting only would have been counted twice.

Novo Nordisk considered that the substitution of the term amenorrhoea was acceptable and that it added clarity. Furthermore the abstract of this study, published in 1998 defined the term 'no spotting or bleeding' as 'amenorrhoea'.

PANEL RULING

Archer *et al* recorded vaginal bleeding data as no bleeding or spotting, bleeding, or spotting. Bleeding

was defined as release of uterine blood that required sanitary protection, while spotting was defined as release of uterine blood that did not require sanitary protection. All months were classified into one of three categories; month with no bleeding, month with bleeding (with or without spotting) or month with spotting only (no bleeding). The Panel considered it was clear from the definitions given by Archer *et al* that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The term no bleeding, as used by Archer *et al*, was thus effectively amenorrhoea. The Panel noted that the original abstract of the Archer paper used the term amenorrhoea to define a state of no spotting or bleeding. The Panel considered that use of the term amenorrhoea could be justified and was thus not misleading as alleged. No breach of Clause 7.2 was ruled.

3 Claim 'A side effect profile to aid compliance'

This claim appeared as the second bullet point on page 3 of the leavepiece, beneath the heading 'What does Kliovance mean for your patients'. The claim was referenced to data on file, Stadberg *et al* (1996) and Borrego *et al* (1999).

COMPLAINT

Wyeth stated that HRT side effects did not aid compliance. Stadberg *et al* reported less severe mastalgia with Kliovance vs Kliofem ($p<0.05$). This should be made clear in the leavepiece, together with the fact that Kliovance might aid compliance, as there was no proof of a compliance benefit. Wyeth thus considered the claim ambiguous, inaccurate and misleading in breach of Clause 7.2.

RESPONSE

Novo Nordisk stated that 'A side effect profile to aid compliance' implied that Kliovance had been developed to have a favourable side effect profile, and that this fact was intended to help patients comply with their therapy. This had been shown to be true. The references showed that Kliovance had a low incidence of side effects in all the clinical trials of up to two years' duration, similar to placebo apart from breast tenderness (data on file). The Stadberg study showed that Kliovance was less likely to cause severe breast pain than Kliofem, the higher dose product of the same hormone combination. Borrego demonstrated that a year's therapy with Kliovance did not lead to significant changes in body weight.

Novo Nordisk noted that side effects certainly affected compliance. This could be seen from the data on file supplied. Although 9% was a small number of trial subjects to withdraw from a study due to adverse events it followed that a good side effect profile would aid compliance, as fewer patients would experience side effects that might cause them to discontinue their treatment. Novo Nordisk stated that it was not stating that the side effects of Kliovance would help patients to comply with their treatment, rather that the side effect profile of Kliovance was an aid to compliance. Given that Kliovance had high compliance, as already shown, and an excellent side effect profile as demonstrated, Novo Nordisk considered that the claim, 'A side effect profile to aid compliance' was far from ambiguous, was fair and accurate, and was not misleading.

PANEL RULING

The Panel noted that the data on file which reported Kliovance discontinuation rates showed that of 442 patients 38 (9%) discontinued therapy because of adverse events. Stadberg *et al* showed that Kliovance was less likely to cause severe mastalgia than Kliofem ($p<0.05$). Of the 20 patients randomized to Kliovance two reported urinary tract infections and withdrew for that reason. In the trial by Borrengo *et al*, which demonstrated that treatment with Kliovance did not lead to significant changes in body weight, 21% of the 295 patients randomized to Kliovance withdrew from the study.

The Panel noted that another claim in the leavepiece was 'Low dose, high compliance'. This claim was referenced to the data on file as discussed above and also DIN-LINK data which showed how patients discontinued HRT therapy over time. For oral continuous-combined HRT as a whole, 45% of patients remained on therapy after a year. This figure was reported to be as low as 25% for one particular product. For Kliovance the figure was 43.2% which compared well with the overall figure.

On balance the Panel considered that the claim 'A side effect profile to aid compliance' was not unreasonable. No breach of Clause 7.2 was ruled.

Complaint received **10 October 2001**

Case completed **20 November 2001**

CASE AUTH/1236/10/01

LILLY v JANSSEN-CILAG

Misleading claims about Zyprexa

Lilly alleged that misleading claims about its product Zyprexa (olanzapine) were being made by representatives from Janssen-Cilag, the manufacturer of Risperdal (risperidone), a competitor antipsychotic medicine.

Lilly had received a letter from a consultant psychiatrist requesting further information because he had been concerned to be told by a Risperdal representative that olanzapine could 'directly affect glucose metabolism leading to diabetes'. He was also warned that 'within a month or two it would probably become mandatory for all patients on olanzapine to need monthly glucose monitoring'. Lilly stated that it had subsequently received reports of similar conversations Janssen-Cilag representatives had had with health professionals.

Lilly stated that there was no credible evidence that Zyprexa directly affected glucose metabolism leading to diabetes. There was no requirement in the Zyprexa summary of product characteristics (SPC) for blood glucose testing, nor would the upcoming revised SPC contain such a stipulation.

Two claims in particular were being made by Janssen-Cilag representatives, namely that around one in three patients taking Zyprexa would develop diabetes, and that blood monitoring of patients on olanzapine would soon become mandatory. Both of these 'facts' were blatantly false, and seemed designed to frighten health professionals into prescribing alternative treatments. Lilly alleged that Janssen-Cilag representatives had been briefed to make such statements. Janssen-Cilag denied this, but its position was wholly incompatible with the evidence that Lilly had received. Lilly could not stress strongly enough the negative impact that this campaign of misinformation was having on mental health professionals and their patients.

The Panel noted that Section 4.4 of the Zyprexa SPC stated that 'Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus'. There was no mention of mandatory monthly glucose monitoring. Section 4.8 stated that hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma had been spontaneously reported very rarely, including some fatal cases. This information also appeared in Section 4.4 of the SPC.

Mir and Taylor, a review of published literature on atypical antipsychotics and hyperglycaemia, stated that blood glucose monitoring was essential for all patients starting clozapine or olanzapine. The authors summarised 15 case reports seemingly associated with olanzapine therapy. The discussion referred to the incidence of impaired glucose tolerance noting that diabetes was prevalent in the general population and more prevalent in schizophrenia regardless of drug therapy. The paper also referred to the difficulty of establishing a relationship between atypical antipsychotics and the emergence of hyperglycaemia. One reason being the inherent unreliability of spontaneous reporting of adverse effects. It was also noted that Zyprexa and clozapine were the most widely prescribed atypicals in the UK.

Mir and Taylor was provided to Janssen-Cilag representatives to give to customers as appropriate. The representatives briefing material gave detailed information about antipsychotic medicines and effects on glucose metabolism. The relevant sections of the SPCs for Zyprexa and Clozaril (clozapine) were reproduced. Reference was made to the Mir and Taylor paper pointing out that the conclusion that blood glucose monitoring was essential for all patients starting clozapine or olanzapine was at variance with the relevant SPCs. The caveats in the Mir and Taylor paper were not reproduced in the briefing material.

The briefing material instructed representatives not to state that glucose testing was mandatory for clozapine or olanzapine and told them not to speculate about possible changes to competitor SPCs. The briefing material also included a list of nine questions to ask customers which the Panel considered, in conjunction with the provision of the Mir and Taylor paper, would encourage the initiation of discussions on blood glucose monitoring.

With regard to the letter to Lilly from the consultant psychiatrist, the Panel noted Janssen-Cilag's submission that the representative was having a scientific discussion on emerging data with the psychiatrist.

The Panel considered that the representative had misled the psychiatrist about the data relating to glucose metabolism. Mir and Taylor stated that 'Blood glucose monitoring is essential for all patients starting clozapine or olanzapine'. This was not consistent with the particulars given in the Zyprexa SPC. Although the briefing material reminded representatives that they must not state that glucose testing was mandatory for clozapine or olanzapine, they had been given a clinical paper which appeared to suggest the opposite. The SPC information did not appear to have been mentioned to the psychiatrist. With regard to the other correspondence provided by Lilly, the Panel considered that the Janssen-Cilag representatives were misleading health professionals about the data in relation to glucose metabolism. The representatives were following the briefing material which the Panel considered was inadequate. There was however no specific allegation in this regard. All the available evidence had not been reflected and Zyprexa had been disparaged; breaches of the Code were ruled. The representatives had failed to comply with all the requirements of the Code and a further breach of the Code was ruled.

The Panel considered that on balance the circumstances did not warrant a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Eli Lilly and Company Limited alleged that misleading claims about its product Zyprexa (olanzapine) were being made by representatives from Janssen-Cilag Ltd, the manufacturer of Risperdal (risperidone), a competitor antipsychotic medicine.

COMPLAINT

Lilly stated that it wished to complain in the strongest possible terms about a national campaign of misinformation about Zyprexa by Janssen-Cilag.

Lilly was initially made aware that the Janssen-Cilag sales force was making grossly misleading claims about Zyprexa by a consultant psychiatrist in May. The psychiatrist wrote to Lilly requesting further information because he had been concerned to be informed by the Risperdal representative that olanzapine could 'directly affect glucose metabolism leading to diabetes'. Furthermore, the representative also warned him that 'within a month or two it would probably become mandatory for all patients on olanzapine to need monthly glucose monitoring'. A copy of the consultant's letter was provided. Breaches of Clauses 7.2 and 7.9 of the Code were alleged.

There was no credible evidence that Zyprexa directly affected glucose metabolism leading to diabetes. Furthermore, there was no requirement in the Zyprexa summary of product characteristics (SPC) for blood glucose testing, nor would the upcoming revised SPC contain such a stipulation.

Lilly presented the medical director of Janssen-Cilag with a copy of the letter and was assured that the false claims described were the actions of a 'rogue' representative and not evidence of anything more widespread. However, following this initial discussion Lily had received a number of similar communications from mental health professionals all around the UK, either directly or by e-mail via its sales force. Such communications continued to arrive. Copies were provided. Some were from health professionals and some were e-mail reports of conversations Lilly representatives had had with health professionals.

Analysis of these communications revealed that two claims in particular were being made by Janssen-Cilag representatives, namely that around one in three patients taking Zyprexa would develop diabetes, and that blood monitoring of patients on olanzapine would soon become mandatory. Both of these 'facts' were blatantly false, and seemed designed to frighten health professionals into prescribing alternative treatments. Breaches of Clauses 2 and 8.1 were alleged. It was no coincidence that Risperdal was Zyprexa's main competitor in this area and most likely therefore to benefit from such a situation.

Lilly stated that it was inconceivable that all instances of these untrue statements being made could be explained away as the actions of 'rogue' representatives – the false claims were too consistent, they were being delivered by too many individuals, and being made in too many geographical locations. What seemed clear was that Janssen-Cilag representatives had been briefed to make such statements. Janssen-Cilag denied this, but its position was wholly incompatible with the evidence that Lilly had received, and continued to receive, from health professionals all over the UK. A breach of Clause 15.2 was alleged.

Lilly could not stress strongly enough the negative impact that this campaign of misinformation was having on mental health professionals and their patients. There was evidence that patients were having to undergo unnecessary blood testing, that it was driving doctors to switch their patients from Zyprexa to other medicines (with the inherent risk of relapse that this carried) and that overall, clinicians were experiencing considerable anxiety and confusion as a result of the misleading information that they were being given.

Lilly subsequently met with Janssen-Cilag with the evidence described above. Lilly's view was that the only way to satisfactorily resolve this situation would be for Janssen-Cilag to send a mutually agreed communication to all mental health professionals in the UK acknowledging that an unknown but significant number of them had been misled by Janssen-Cilag representatives on this issue and clearly stating the facts as they stood, namely that there was no conclusive evidence that any atypical antipsychotic caused diabetes, and that no atypical antipsychotic SPC carried a recommendation for routine blood glucose testing. A breach of Clause 15.10 was alleged.

Lilly stated that Janssen-Cilag acknowledged its concerns and agreed a few days after the meeting to the sending of a corrective letter. Unfortunately, despite the fact that more than four weeks had passed since this undertaking was given, no such letter had been agreed upon and sent despite Lilly's best efforts to drive the process.

Lilly had been negotiating in good faith with Janssen-Cilag since May in order to bring this matter to an amicable and professional conclusion, and had refrained from making a formal complaint to the Authority in the hope that Janssen-Cilag would realise the gravity of the accusations being made and take suitably strong and timely corrective action. Instead, more than four months since Lilly's original complaint to Janssen-Cilag, there was still no corrective letter. In addition, it appeared that the Janssen-Cilag sales force had continued to, and were continuing to, mislead customers by making the false claims outlined above (the most recent report of this occurring came in from the field last week).

Lilly's contention was that Janssen-Cilag had breached Clauses 2, 7.2, 7.9, 8.1, 15.2 and 15.10 of the Code, with the behaviour described, and most seriously Clause 2.

RESPONSE

Janssen-Cilag stated that the issues raised by Lilly pertaining to antipsychotics and glucose dysregulation were complex. In order to put Lilly's allegations into context, Janssen-Cilag had provided background information on these matters before addressing Lilly's specific concerns. Additionally, it was important to delineate the differences in the SPCs for Risperdal and Zyprexa with respect to glucose

dysregulation, the chronology of changes to the SPC of Zyprexa, the timing of Janssen-Cilag becoming aware of these changes, the timing of an important scientific meeting at which these matters were discussed (the American Psychiatric Association (APA) meeting in May) and the timings of changes to the briefing materials Janssen-Cilag supplied to its representatives. Despite the important differences in the SPCs of Zyprexa and Risperdal with respect to references to glucose dysregulation, Lilly had tried to defend its product by saying that any adverse comment against it with respect to glucose dysregulation related not only to Lilly's product but to all members of the class of atypical antipsychotics.

The emerging debate about glucose dysregulation and antipsychotic medication and olanzapine in particular

Historically, researchers had shown that patients with schizophrenia had a higher incidence of diabetes than the general population. The precise mechanism for this was unclear. The introduction of the first antipsychotic, chlorpromazine, in the 1950s also led to an increase in the number of schizophrenia patients with diabetes. More recently, the debate had centred on the newer atypical antipsychotics and clozapine and olanzapine, which were chemically related, in particular.

Such was the evidence available up to the end of 2000 that the Maudsley Hospital, recognised as a centre of excellence in psychiatry, included in the 6th edition of its Prescribing Guidelines a recommendation for blood glucose monitoring at baseline and 3-6 monthly thereafter for olanzapine and some other antipsychotics, but not for Risperdal. In March 2001 the Chief Pharmacist at the Maudsley Hospital co-authored a review article on atypical antipsychotics and hyperglycaemia (Mir and Taylor 2001). The paper concluded 'Blood glucose monitoring is **essential** for all patients starting clozapine or olanzapine' (Janssen-Cilag's emphasis). Taylor's and the Maudsley Guidelines' authors' conclusions from the then existing scientific literature were compelling evidence that Lilly's contention that 'There is no credible evidence that Zyprexa directly affects glucose metabolism leading to diabetes' was erroneous (see also, below, the comment on the Medicine Control Agency's (MCA) interpretation of the evidence on this aspect of olanzapine).

This year's APA meeting was attended by psychiatrists from all over the world, including approximately 300 from the UK. There were several posters and presentations about antipsychotics and glucose metabolism, which resulted in increasing awareness of this issue. The most discussed data concerned olanzapine's effects on glucose metabolism and diabetes. A presentation by Dr Newcomer estimated the incidence of diabetes with olanzapine to be in the range 6-30%, and a presentation by Dr Meyer included reference to a study by Casey (2000) with a three-year cumulative incidence figure of 35%. One well-conducted randomized controlled double-blinded study in 268 patients by Glick *et al* (2001) comparing olanzapine to ziprasidone examined in great detail the propensity of these agents to affect glucose metabolism even when given in a short-term (6 week) study and showed that olanzapine did indeed increase insulin resistance, a known precursor to the development of Type II diabetes.

Not all publications examining the effect of olanzapine on glucose dysregulation had concluded that olanzapine did importantly and negatively impact on glucose metabolism differentially from other agents. Cavazzoni *et al* (2001) used a large US prescription claims database to analyse the incidence of diabetes as assessed by new prescriptions for antidiabetic drugs and concluded that there was no statistically significant difference in the risks of diabetes with olanzapine and risperidone. However, Gianfrancesco *et al* (2001), a study of claims data from a similarly large US database, concluded that risperidone was not associated with a higher risk of developing diabetes but that the risk for olanzapine-treated patients was 3.3 times that of untreated patients.

Separate from direct consideration of glucose metabolism, it should also be borne in mind that large weight gains occurred in greater than 10% of olanzapine-treated patients (Zyprexa SPC). It had been postulated that the weight gain that was seen with Zyprexa, which was far in excess of that seen with other unrestricted atypical antipsychotics, was linked to the propensity of olanzapine to adversely impact glucose metabolism, since it was well-recognised that excess weight was an independent risk factor for the development of Type II diabetes.

There were no warnings or precautions or undesirable effects listed on the Risperdal SPC that related to glucose dysregulation.

The SPC for Zyprexa at launch contained little by way of specific comment in this regard. By December 2000, when the SPC was updated, the following statements had been added:

'Section 4.4. Special warnings and special precautions for use

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.

Section 4.8. Undesirable effects

Common (1-10%): Non-fasting plasma glucose levels 11mmol/l (suggestive of diabetes), as well as non-fasting levels 8.9mmol/l but <11mmol/l (suggestive of hyperglycaemia) in patients with baseline non-fasting glucose levels 7.8mmol/l, have been seen occasionally in clinical trials. Hyperglycaemia or exacerbation of pre-existing diabetes, occasionally associated with ketoacidosis or coma, has been spontaneously reported very rarely, including some fatal cases.'

The SPC for Zyprexa was further updated in June 2001 and changes were made to the commentary on 'glucose metabolism' in the 'Undesirable effects' part of the SPC as follows:

'Section 4.8. Undesirable effects

Common (1-10%): In clinical trials with olanzapine, in over 5,000 patients with baseline nonfasting glucose levels 7.8mmol/l, the incidence of nonfasting plasma glucose levels 11mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of nonfasting plasma glucose levels 8.9mmol/l but <11mmol/l (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo. For further information see section 'Very rare (<0.01%)' below.

Very rare (<0.01%): Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also section 4.4, 'Special warnings and special precautions for use').'

The effect of the June 2001 changes to Lilly's SPC was to put into context the finding in clinical trials that non-fasting blood glucose levels suggestive of diabetes had been seen commonly (1-10%) with Zyprexa. However, the warning that 'appropriate clinical monitoring is advisable … in patients with risk factors for the development of diabetes mellitus' was retained.

The addition of these warnings relating to glucose metabolism concerns to the Zyprexa SPC since its first introduction were further evidence that Lilly's contention that 'There is no credible evidence that Zyprexa directly affects glucose metabolism leading to diabetes' was erroneous.

The June 2001 update of the Lilly SPC was first publicised to Janssen-Cilag's knowledge in mid-August when this revised version appeared on the eMC website. Hence, Janssen-Cilag could not have known about this important change before this date. As soon as Janssen-Cilag became aware of this change, it updated its representatives' briefing materials.

Representatives' briefing materials

Janssen-Cilag had no specific representatives' briefing material referring to glucose dysregulation available for its representatives prior to June of this year; the company's promotional messages had concentrated on Risperdal's efficacy and relative cost-effectiveness.

In June, following contact from Lilly (see letter from psychiatrist below), through being aware of the controversy on glucose dysregulation and olanzapine aired at the May APA and having heard from customers that Lilly was defending its product by saying that these issues pertained to all atypical antipsychotics including Risperdal, Janssen-Cilag considered that it was necessary to provide its representatives with detailed briefing materials which were issued in early July.

Janssen-Cilag's main aims with these briefing materials were to educate its representatives about the issues, to supply them with information on the lack of glucose dysregulation issues with Risperdal and to aid them in having a fair scientific dialogue with their customers about an emerging area of scientific debate (ie the propensity of certain atypical antipsychotics to increase the risk of diabetes) and important related elements in the SPCs of competitors' products.

In mid-August, Janssen-Cilag became aware through examination of the literature that olanzapine's SPC had had important revisions made. This and the discussions between Janssen-Cilag and Lilly led Janssen-Cilag to revise its briefing materials and the revised materials were issued on 20 September. Copies were provided.

Responses to Lilly's allegations

The psychiatrist

From discussion with the medical director at Lilly, Janssen-Cilag was able to identify the psychiatrist who wrote to Lilly. The representative who had seen this psychiatrist was aware of data presented at the then very recent APA regarding olanzapine and glucose dysregulation. This particular psychiatrist had an especial interest in the matter and questioned the Janssen-Cilag representative who was able to discuss emerging scientific data with him. Janssen-Cilag's representative had referred to the Mir and Taylor review, which stated that routine blood glucose monitoring was essential with olanzapine. Janssen-Cilag denied any breach of Clauses 7.2 and 7.9. Its representative was simply having a scientific discourse on emerging publications from respected scientists.

That this psychiatrist should feel compelled to write for clarification to Lilly was, Janssen-Cilag contended, more a problem of Lilly's own making in that it had not kept its customers abreast of the emerging scientific information and opinions on olanzapine and 'diabetes'.

Letters from customers to Lilly contained the common theme, objected to by Lilly, that 'diabetes' occurred more commonly with olanzapine than customers had thought.

Lilly, in its letter of complaint, misrepresented the letters' authors' enquiries. Lilly's complaint stated that these letters claimed that around one in three patients would develop diabetes. In fact letter 2 stated '… A very high rate of …diabetes' and '… this ***risk*** (Janssen-Cilag's emphasis) may be as high as 30%'. Janssen-Cilag did not know what numerical value the author considered to be 'very high' for the development of diabetes. But the author had heard that data presented at the APA indicated that the ***risk*** (Janssen-Cilag's emphasis) of developing diabetes might be as high as 30%. In letter 3, the author's enquiry concerned the possibility of 'a higher incidence of hyperglycaemia/type II diabetes … than previously indicated … by … Lilly'. This author did not specify any specific incidence or risk percentage. The author of letter 4 was concerned about the '… very real risk of the increase in diabetes (with olanzapine)' with 'Figures … suggest(ing) a one in three ***chance*** (Janssen-Cilag's emphasis) of developing diabetes (on olanzapine)'.

Janssen-Cilag contended that its representatives were fairly representing their briefing materials, were using published information derived from the APA and were not telling customers that 'around one in three of patients on olanzapine ***will*** develop diabetes', or words to that effect, and accordingly Janssen-Cilag denied any breach of Clause 8.1. In Janssen-Cilag's

view, Lilly had confused its customers' request for information on the ***risks*** of developing diabetes as implying that Janssen-Cilag representatives were saying the ***incidence*** of diabetes was 'one in three'. (Janssen-Cilag's emphasis.)

'Incidence' had a specific meaning in medicine. It meant the number of new cases of a particular condition occurring in one year. Sometimes commentators used the term 'incidence' to refer to the numbers of new cases occurring in a timeframe longer than one year but forgot to state the timeframe. Strictly such commentators should qualify their use of 'incidence' by saying eg '3-year incidence' or 'life-time incidence', depending on the particular circumstances.

Detailed comments were made by Janssen-Cilag about e-mails from Lilly representatives. One e-mail simply stated that Janssen-Cilag representatives were using Mir and Taylor and were referring to the recommendation that blood glucose testing should be done regularly. This was inconsistent with Janssen-Cilag's representatives' briefing materials.

Another e-mail alleged that the Janssen-Cilag's representative had said, 'Lilly were withholding the fact (of induction of diabetes) from the medical profession'. What Janssen-Cilag's representatives told it was that despite important changes in December 2000 and earlier to olanzapine's SPC with respect to glucose dysregulation, there was little evidence of Lilly having brought these important changes to the attention of its customers. On the contrary, Janssen-Cilag's representatives were communicating the glucose dysregulation elements of olanzapine's SPC to health professionals, the health professionals were commonly unaware of these elements, thanked Janssen-Cilag's staff for bringing them to their attention and expressed disquiet that Lilly had not made these elements known to them.

With regard to one e-mail Janssen-Cilag stated that this Lilly representative seemed more concerned at the 'damage' done to Lilly than possible harm caused by inappropriate use of olanzapine in some patients and was alarmed at what the Maudsley hospital's recommendations were. Janssen-Cilag suggested that Lilly should take this concern to the Maudsley itself.

Janssen-Cilag referred to its response above in relation to comments about the incidence of diabetes in the e-mails from Lilly representatives.

Janssen-Cilag denied any breach of Clause 8.1 that Lilly was inferring from any aforementioned e-mails.

As shown in Janssen-Cilag's detailed rebuttals above, it considered that its representatives had always acted with a high standard of ethical conduct and consequently Janssen-Cilag denied any breach of Clause 15.2.

The alleged breach of Clause 15.10 was contained in a paragraph of Lilly's letter relating to dialogue and meetings between the companies. It seemed to be misplaced. Irrespective of this, as a company Janssen-Cilag denied any breach of any part of Clause 15.

Lilly alleged that Janssen-Cilag had brought the industry into disrepute, in breach of Clause 2, by entering into fair scientific dialogue on an emerging scientific issue. Janssen-Cilag's representatives had fairly and in a balanced manner represented this scientific issue to health professionals. The surprise and disappointment had been that most health professionals had not been made aware by Lilly of important changes to the SPC of olanzapine with respect to glucose dysregulation over the recent past. Additionally, Janssen-Cilag representatives were not only making health professionals aware of the emerging scientific debate but were also making them aware of the conclusions of a highly respected institute and its staff. It was disingenuous of Lilly to argue that Janssen-Cilag should have a breach of Clause 2 ruled against it in these circumstances. Janssen-Cilag denied any breach of Clause 2.

Janssen-Cilag would additionally like to refer to that part of Lilly's complaint which stated that following a meeting between Janssen-Cilag and Lilly, Janssen-Cilag 'agreed … to the sending of a corrective letter'. This was not agreed to. Janssen-Cilag had agreed to try and find a mutually acceptable letter to health professionals but attempts to negotiate this broke down because Lilly refused to have elements of olanzapine's SPC, specifically 'Appropriate clinical monitoring is advisable … in patients with risk factors for the development of diabetes mellitus', included in the letter.

PANEL RULING

The Panel noted that Section 4.4 of the Zyprexa SPC, headed 'Special warnings and special precautions for use', stated that 'Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus'. There was no mention of mandatory monthly glucose monitoring.

Section 4.8 of the Zyprexa SPC 'Undesirable effects' (Very rare <0.01%) referred to hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma having been spontaneously reported very rarely, including some fatal cases. This information also appeared in Section 4.4 of the SPC.

Mir and Taylor, a review of published literature, stated that blood glucose monitoring was essential for all patients starting clozapine or olanzapine. The authors summarised case reports for 15 patients (10 cases of hyperglycaemia and 5 cases of ketoacidosis) seemingly associated with olanzapine therapy. The discussion referred to the incidence of impaired glucose tolerance noting that diabetes was prevalent in the general population and more common in those with schizophrenia regardless of drug treatment. The paper also referred to the difficulty of establishing a relationship between atypical antipsychotics and the emergence of hyperglycaemia. One reason being the inherent unreliability of spontaneous reporting of adverse effects. It was also noted that Zyprexa and clozapine were the most widely prescribed atypicals in the UK.

Mir and Taylor was provided to Janssen-Cilag representatives to give to customers as appropriate according to a memorandum dated 4 July. Another memorandum dated 20 September which replaced the

memorandum of 4 July stated that the paper, in response to a customer enquiry, could be requested via e-mail and that prescribing guidance should be taken from the SPC rather than a published review article. The Panel noted that the briefing material supplied to Janssen-Cilag representatives gave detailed information about antipsychotic medicines and effects on glucose metabolism. The relevant sections of the SPCs for Zyprexa and Clozaril (clozapine) were reproduced. Reference was made in a section headed 'Key information that customers may refer to', to the Mir and Taylor paper pointing out that the conclusion that blood glucose monitoring was essential for all patients starting clozapine or olanzapine was at variance with the relevant SPCs. The caveats in Mir and Taylor were not reproduced in the briefing material. The briefing material reproduced part of the Lilly press release on the topic which stated that there were essentially no significant differences among the types of antipsychotic medicines in terms of diabetes risk. The incidence of diabetes identified by new prescriptions for insulin or oral hypoglycaemic agents was comparable in patients taking older antipsychotics like haloperidol and those taking newer ones like olanzapine and risperdone.

The briefing material instructed representatives not to state that glucose testing was mandatory for clozapine or olanzapine and stated that representatives should not speculate about possible changes to competitor SPCs. The briefing material also included a list of nine questions to ask customers. These related to diabetes including 'Do you routinely measure glucose levels?' and 'Are you aware of recent changes to the clozapine or olanzapine SPC with regard to glucose metabolism?' The Panel considered that these questions, in conjunction with the provision of Mir and Taylor, would encourage representatives to initiate discussions on blood glucose monitoring and emerging data and noted the difference between the Zyprexa SPC and the Mir and Taylor paper on blood glucose monitoring.

With regard to the letter to Lilly from the consultant psychiatrist, the Panel noted Janssen-Cilag's submission that the representative was having a scientific discussion on emerging data with the psychiatrist.

The Panel considered that the representative had misled the psychiatrist about the data relating to glucose metabolism. Mir and Taylor gave data from 15 olanzapine case studies and referred to the difficulties in establishing a definitive relationship between atypical antipsychotics and the emergence of hyperglycaemia through spontaneous reports of adverse events and the higher incidence of diabetes in schizophrenia regardless of any treatment. The abstract of the paper ended with 'Blood glucose monitoring is essential for all patients starting clozapine or olanzapine'. This was not consistent with the particulars given in the Zyprexa SPC. Although the briefing material reminded representatives that they must not state that glucose testing was mandatory for clozapine or olanzapine, they had been given a clinical paper which appeared to suggest the opposite. The SPC information did not appear to have been mentioned to the psychiatrist. With regard to the other correspondence provided by Lilly, the Panel considered that the Janssen-Cilag representatives were misleading health professionals about the data in relation to glucose metabolism. The representatives were following the briefing material which the Panel considered was inadequate. There was however no specific allegation in this regard. All the available evidence had not been reflected. Breaches of Clauses 7.2 and 7.9 were ruled. Zyprexa had been disparaged and a breach of Clause 8.1 was ruled. The representatives had failed to comply with all the requirements of the Code and a breach of Clause 15.2 of the Code was ruled.

The Panel noted that Lilly had alleged a breach of Clause 15.10 which stated that companies were responsible for the conduct of their representatives if these are within the scope of their employment even if they were acting contrary to the instructions which they have been given. It was not possible to breach Clause 15.10 which simply set out the company's responsibility. The Director decided there was thus no *prima facie* case to answer on this point.

The Panel considered that on balance the circumstances did not warrant a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **11 October 2001**

Case completed **15 January 2002**

CASE AUTH/1237/10/01

WYETH v ASTRAZENECA

Nexium journal advertisements

Wyeth complained about journal advertisements for Nexium (esomeprazole) issued by AstraZeneca. There were a number of variations in the layout of the advertisements but all featured a high jumper with the impression of wings added and the ground appearing hundreds of feet below. Each advertisement was headed 'Expect more. Achieve more' with text lower down stating 'Nexium heals more reflux oesophagitis patients than lansoprazole'. Wyeth marketed Zoton (lansoprazole).

Wyeth alleged that AstraZeneca had used a hanging comparison in the heading 'Expect more. Achieve more' and presented a misleading and ambiguous claim. The advertisement suggested superior healing rates for all patients with reflux oesophagitis whereas the data clearly showed that only in the minority of patients with more severe reflux disease was the healing for Nexium significantly better than for lansoprazole. Data taken from the cited study (Castell *et al* 2001) showed that 76% of patients had milder grades of erosive oesophagitis (Los Angeles Grades A,B). In these grades the response rates seen with Nexium and lansoprazole were practically identical (Grade A: 91.7 v 91.3%; Grade B: 86.3 v 86% respectively). The vast majority of patients treated for reflux disease in the UK were within Grades A and B.

The Panel did not consider that the heading 'Expect more. Achieve more' was a hanging comparison. It was clear from the only claim in the advertisement, 'Nexium heals more reflux oesophagitis patients than lansoprazole', that Nexium was being compared with lansoprazole.

In the Panel's view the combination of the visual, the heading and the claim gave the impression that the healing rates achieved with Nexium, compared with lansoprazole, were outstanding. The claim 'Nexium heals more reflux oesophagitis patients than lansoprazole' was referenced to (Castell *et al*) a study of over 5000 patients which compared the healing rates of esomeprazole and lansoprazole in erosive oesophagitis. Both treatment groups were well matched with regard to severity (grade) of erosive oesophagitis at baseline. Healing rates in those patients with Grade A or B erosive oesophagitis were similar in both treatment groups. The poster stated that esomeprazole produced consistently higher healing rates across all grades of disease severity, while the efficacy of lansoprazole tended to decline to a greater extent with increasing grade of severity of oesophagitis. There was no subgroup analysis. Overall esomeprazole was significantly more effective than lansoprazole (P<0.001) for healing erosive oesophagitis over the eight week treatment period. This was the primary efficacy endpoint for the study. Crude healing rates stratified for baseline severity showed significantly higher healing rates for esomeprazole than for lansoprazole at week 4 (75.7% vs 71.7%) and week 8 (87.6% vs 84.2%) (p<0.01).

The Panel considered that although the claim 'Nexium heals more reflux oesophagitis patients than lansoprazole' accurately reflected the overall findings of the study, the fact that there was very little difference in healing rates in the majority of patients, ie those with Grade A or B erosive oesophagitis, was not apparent. Assuming that the demographics of the study were similar to the general population of patients with erosive oesophagitis, those classified with Grade A or B would represent the largest group of patients treated. The reported overall advantage for esomeprazole appeared to be due to its superior efficacy, compared to that of lansoprazole, in those patients with Grade C or D erosive oesophagitis ie approximately 25% of patients. The Panel considered that the advertisement as a whole gave the impression that the healing rates for Nexium were outstanding compared to lansoprazole. This was a strong message. The Castell study provided some data to support that impression but lacked data showing advantage for Nexium at each grade of the disease. The Panel considered that doctors reading the advertisement would assume that there was data to support the message that the healing rate for any patient with reflux oesophagitis would be vastly superior if Nexium was used as opposed to lansoprazole. This was not so. The Panel considered that the advertisement was misleading and a breach of the Code was ruled.

Wyeth alleged that AstraZeneca had used an image that strongly suggested that Nexium had vastly superior performance to lansoprazole when in reality the data did not support this. The lone athlete image, in depicting super-human performance, unfairly suggested the product too had vastly superior performance compared to lansoprazole. Further, AstraZeneca had sought to take unfair advantage of the reputation of Zoton in plagiarizing the successful long running and well-established UK Zoton promotional campaign based on the sole athlete theme. That theme had been in existence since November 1998 and in its current format featuring photographs of an athlete since March 2000.

The Panel noted its ruling above. The Panel considered that the comparison was misleading and a breach of the Code was ruled. The Zoton and Nexium advertisements both featured a lone high jumper. The Zoton advertisement was a literal interpretation with a photograph of a high jumper set against a plain dark blue background. The Nexium advertisement was more mythical with a winged figure clearing a bar set hundreds of feet above the ground. The Panel considered that the execution of the advertisements was so different that it was unlikely that prescribers would be misled or confused and no breach of the Code was ruled in that regard.

The Panel did not consider that lansoprazole had been disparaged or that the advertisements brought the industry into disrepute.

Wyeth complained about journal advertisements for Nexium (esomeprazole) issued by AstraZeneca UK

Limited. There were a number of variations in the layout of the advertisements (refs NEX AD 9383, NEX AD 9385 and NEX AD 9401) but all featured a high jumper with the impression of wings added; the ground appeared hundreds of feet below. Each advertisement was headed 'Expect more. Achieve more' with text lower down stating 'Nexium heals more reflux oesophagitis patients than lansoprazole'. Wyeth marketed Zoton (lansoprazole). AstraZeneca stated that it was disappointed that Wyeth had not first raised the matters on an intercompany basis.

1 Alleged breach of Clause 7.2

COMPLAINT

Wyeth alleged that AstraZeneca had breached Clause 7.2 of the Code by the use of a hanging comparison in the heading 'Expect more. Achieve more' and by presenting a misleading and ambiguous claim as to the significance of the referenced data.

The advertisement suggested superior healing rates across the whole reflux oesophagitis patient population whereas the data clearly showed that only in the minority of patients ie those with more severe reflux disease, was the healing for Nexium significantly better.

Wyeth provided a table of data taken from the referenced abstract and poster presentation (Castell *et al*, 2001). Wyeth stated that this showed that the majority of patients studied (76%) had milder grades of erosive oesophagitis (Los Angeles [LA] Grades A,B). In these grades the response rates seen with Nexium and lansoprazole were practically identical (Grade A: 91.7 v 91.3%; Grade B: 86.3 v 86% respectively). The vast majority of patients treated for reflux disease in the UK were within Grades A and B.

RESPONSE

AstraZeneca noted that the supplementary information to Clause 7.2 stated that hanging comparisons were defined as those comparisons whereby that with which a medicine was being compared was not stated. This was clearly not the case with AstraZeneca's advertisements, since it had qualified the claim with the strapline with reference to the healing of reflux oesophagitis by Nexium compared to lansoprazole. AstraZeneca did not believe that the heading represented a hanging comparison.

In relation to the allegation that the advertisements were misleading and ambiguous with respect to the referenced data, AstraZeneca stated that the study to which the advertisements referred was a very large (n = 5241), extremely robust clinical trial. It was the only study to date to have undertaken a direct clinical comparison of the healing doses of esomeprazole (40mg once daily) and lansoprazole (30mg once daily) in a population of patients with reflux oesophagitis. The study comprised a randomized double-blind comparison of esomeprazole and lansoprazole in patients with endoscopically verified erosive reflux oesophagitis. The severity grade of the oesophagitis was classified according to the Los Angeles (LA) Classification (A to D). This classification method was explained in further detail in Kahrilas *et al* (2000). Essentially the severity of oesophagitis was determined by the appearance of the oesophageal mucosa on endoscopy. Grade A represented the mildest degree of mucosal damage and Grade D the most severe. The primary endpoint of the study was endoscopically verified healing across the entire study population at week 8.

Intention to treat (ITT) data were plotted using Kaplan-Meier life table estimates of healing and statistically analysed via the log-rank test. This analysis showed a highly significant difference in favour of esomeprazole across the whole treated population over the eight week period (92.6% v 88.8% $P<0.001$). AstraZeneca noted that Wyeth had failed to acknowledge this primary endpoint in its letter of complaint. Furthermore, crude healing rates for patients stratified for baseline severity of oesophagitis and analysed at both weeks 4 and 8 showed statistically significant differences in overall healing in favour of esomeprazole, using the Cochran-Mantel-Haenszel (CMH) test.

It was important to note that in primary care, patients with reflux oesophagitis might frequently be diagnosed according to clinical symptoms alone and symptom control was often the main management strategy in this setting. It was also well recognized that symptoms did not necessarily equate to the degree of mucosal damage and, indeed, this fact was illustrated by the demographic data from the study (tabulated in table 1 of the poster). Severity of heartburn (a primary symptom of oesophagitis) was rated as moderate or severe in almost 90% of the study population, whereas approximately 25% were found to have oesophagitis of LA Grade C or D on endoscopy. This proportion was similar to that observed in previous studies that also looked at healing of reflux oesophagitis; Kahrilas and Richter *et al* (2001).

Practitioners might initiate therapy for suspected reflux oesophagitis without endoscopic confirmation of its degree of severity. It therefore followed that in practice a prescriber might not know where a patient's disease severity fell on the scale of LA Grade A to D, based on symptoms alone. The primary endpoint of the study therefore, ie healing across all grades of disease, was highly relevant to clinical practice.

The figures quoted by Wyeth did not appear as such in the poster, as the information was depicted graphically. Wyeth had chosen to tabulate and compare data on the crude healing rates within the differing grades of disease severity, whilst ignoring the primary study endpoint, of healing across the entire study population. The study was specifically designed to compare healing of reflux oesophagitis across all grades of disease severity. AstraZeneca considered that Wyeth's citation of stratified data was not relevant in this case.

AstraZeneca noted that Wyeth, in support of its position, asserted, without citing any evidence, that the vast majority of patients treated for reflux disease in the UK were within Grades A and B. AstraZeneca

was unaware of any data to support this statement and none had been provided by Wyeth.

AstraZeneca pointed out that the claim related to reflux oesophagitis. It did not relate to reflux disease in its entirety, which included patients with endoscopy-negative disease.

AstraZeneca noted that Wyeth implied that, assuming a majority of UK patients might fall within Grades A and B, the overall statistically significant difference between the two products at 8 weeks could, for practical purposes, be ignored. In AstraZeneca's view, the study showed a statistically significant difference between the two products in a population of reflux oesophagitis patients, representative of the spectrum of disease severity encountered in clinical practice. The claim was, therefore, both clinically relevant and substantiable.

PANEL RULING

The Panel did not consider that the heading 'Expect more. Achieve more' was a hanging comparison. It was clear from the only claim in the advertisement, 'Nexium heals more reflux oesophagitis patients than lansoprazole', that Nexium was being compared with lansoprazole. No breach of Clause 7.2 was ruled in that regard.

The advertisement featured the photograph of a high jumper, with the impression of wings added, clearing a bar which appeared to be set hundreds of feet above the ground. In the Panel's view the combination of the visual, the heading and the claim gave the impression that the healing rates achieved with Nexium, compared with lansoprazole, were outstanding.

The claim 'Nexium heals more reflux oesophagitis patients than lansoprazole' was referenced to a study by Castell *et al* (2001) which compared the efficacy of standard doses of esomeprazole and lansoprazole in healing of erosive oesophagitis and symptom resolution. The study included over 5000 patients. Both treatment groups were well matched with regard to severity (grade) of erosive oesophagitis at baseline; the majority (approximately 75% in each group) had Grade A or B; 18% in each group were classified with Grade C and approximately 6% in each group were classified with Grade D. The study was only available in a poster format which gave no details of recruitment methods. The Panel assumed that the distribution of erosive oesophagitis grades seen in the study was similar to that which would be seen in the general population of such patients. Healing rates for the various grades of erosive oesophagitis were presented in a graph. Healing rates in those patients with Grade A or B erosive oesophagitis were similar in both treatment groups. The poster stated that esomeprazole produced consistently higher healing rates across all grades of disease severity, while the efficacy of lansoprazole tended to decline to a greater extent with increasing grade of severity of oesophagitis. There was no subgroup analysis. Overall esomeprazole was significantly more effective than lansoprazole (P<0.001) for healing erosive oesophagitis over the eight week treatment period. This was the primary efficacy endpoint for the study. Crude healing rates stratified for baseline severity showed significantly higher healing rates for esomeprazole than for lansoprazole at week 4 (75.7% vs 71.7%) and week 8 (87.6% vs 84.2%) (p<0.01).

The Panel considered that although the claim 'Nexium heals more reflux oesophagitis patients than lansoprazole' accurately reflected the overall findings of the study, the fact that there was very little difference in healing rates in the majority of patients ie those with Grade A or B erosive oesophagitis, was not apparent. Assuming that the demographics of the Castell study were similar to the general population of patients with erosive oesophagitis, those classified with Grade A or B would represent the largest group of patients treated. The reported overall advantage for esomeprazole appeared to be due to its superior efficacy, compared to that of lansoprazole, in those patients with Grade C or D erosive oesophagitis ie approximately 25% of patients. The Panel also noted AstraZeneca's submission that in practice symptom control was often the main management strategy and that the severity of a patient's oesophagitis in terms of grade might not be known. The claim in question, however, referred to healing and so was clearly linked to endoscopically verified erosive oesophagitis and its improvement with therapy.

The Panel considered that the advertisement as a whole gave the impression that the healing rates for Nexium were outstanding compared to lansoprazole. This was a strong message. The Castell study provided some data to support that impression but lacked data showing advantage for Nexium at each grade of the disease. The Panel considered that doctors reading the advertisement would assume that there was data to support the message that the healing rate for any patient with reflux oesophagitis would be vastly superior if Nexium was used as opposed to lansoprazole. This was not so. The Panel considered that the advertisement was misleading. A breach of Clause 7.2 was ruled.

2 Alleged breach of Clauses 7.3 and 9

COMPLAINT

Wyeth alleged that AstraZeneca had breached Clause 7.3 of the Code by:

- using an image that strongly suggested that Nexium had vastly superior performance to lansoprazole when in reality the data did not support this; the lone athlete image was taken from a long running lansoprazole campaign and, in depicting super-human performance, unfairly suggested the product too had vastly superior performance compared to lansoprazole;
- seeking to take unfair advantage of the reputation of Zoton in plagiarizing the successful long running and well-established UK Zoton promotional campaign based on the sole athlete theme; the theme had been in existence since November 1998 and in its current format featuring photographs of an athlete since March 2000; recent examples of the Zoton campaign were provided; Wyeth considered that Clause 9.3 was also relevant here.

RESPONSE

AstraZeneca stated that the image used in its advertisement depicted a winged figure, approximating in appearance to a high jumper. This was clearly an imaginary figure, intended to provide a light-hearted visual representation of the strapline 'Expect More, Achieve More'. Furthermore the winged figure was alone in the picture and not obviously being compared to any others.

AstraZeneca did not receive any feedback during the extensive market research conducted on this campaign that health professionals interpreted the image as denigrating other proton pump inhibitors (PPIs) in any way, and no direct comparisons were drawn by health professionals, to lansoprazole or to any other PPIs.

The accusation by Wyeth of plagiarizm was unacceptable; Wyeth could not assert ownership over the appearance of a lone athlete image in pharmaceutical advertising. A quick perusal of the advertisements in journals such as Pulse and Prescriber would reveal this to be a commonly recurring theme and examples were enclosed for the Panel to review. Indeed, the athlete theme was one that AstraZeneca's predecessor company itself employed in 1991 and 1992 in a Losec campaign (copies were provided) and this predated the use by Wyeth of athletic imagery in Zoton promotion. It hardly needed stating that athletic imagery was also ubiquitous in other commercial advertising and this merely reflected the effectiveness of such images to signify achievement and physical prowess and to associate products with positive aspirations.

AstraZeneca noted that Wyeth's advertisement featuring a high jumper did not appear in the medical press until at least a week after the first appearance of AstraZeneca's new advertisement featuring a winged figure. Any perceived similarity, therefore, could not be considered to be plagiarizm by AstraZeneca. Notwithstanding the above, AstraZeneca was not aware that use of such common imagery constituted a breach of the Code. No attempt was made to unfairly take advantage of Zoton's image, an athlete being, as AstraZeneca had shown, in no way uniquely identified with Zoton.

For the above reasons, AstraZeneca considered that Clause 9.3 was irrelevant here and was unable to accept the suggestion that prescribers would be misled or confused by the advertisement, so as to believe that it was, in fact, advertising Zoton. The only common element of the imagery was a man dressed in a sporting singlet. The realistic treatment of the figure of the athlete by Wyeth was in marked contrast to the more imaginary figure employed by AstraZeneca. Colours, lay out, background, model used and use of fantasy elements in the AstraZeneca advertisement all contributed to clearly differentiating AstraZeneca's advertising from that of Wyeth. In view of the fact AstraZeneca put a considerable amount of resource into researching, developing and placing advertisements, to develop an advertisement that could be perceived as a competitor's would clearly be very counterproductive.

AstraZeneca reiterated that the AstraZeneca advertisement preceded the appearance of the high jumper version of Wyeth's advertisement.

PANEL RULING

The Panel noted its comments above that, in its view, the combination of the heading, the visual of the winged high jumper and the claim, gave the impression that the healing rates achieved with Nexium, compared with those seen with lansoprazole, were outstanding. The Castell *et al* study showed overall esomeprazole was significantly more effective than lansoprazole for healing erosive oesophagitis over the eight week treatment period, however in the majority of patients, those with Grade A or B erosive oesophagitis, there was little difference in healing rates. The Panel considered that the comparison was misleading and a breach of Clause 7.3 was ruled.

Both the Zoton (lansoprazole) advertisement and the Nexium advertisement featured a lone high jumper. The Zoton advertisement was a literal interpretation with a photograph of a high jumper set against a plain dark blue background. The Nexium advertisement was more mythical with a winged figure clearing a bar set hundreds of feet above the ground. The Panel thus considered that the execution of the advertisements was so different that it was unlikely that prescribers would be misled or confused. No breach of Clause 9.3 was ruled.

3 Alleged breach of Clause 8.1

COMPLAINT

Wyeth alleged that AstraZeneca had breached Clause 8.1 by disparaging lansoprazole – as indicated above, the unqualified reference made to Nexium healing more reflux oesophagitis patients than lansoprazole was neither balanced nor fair.

RESPONSE

AstraZeneca stated that as it had shown above in point 1, the claim that Nexium healed more reflux oesophagitis patients than lansoprazole was fully substantiable and represented the balance of the evidence, therefore AstraZeneca felt there were no grounds for implying that it had disparaged lansoprazole. The statement was factual and verifiable and was thus fair.

PANEL RULING

In point 1 above the claim 'Nexium heals more reflux oesophagitis patients than lansoprazole' was ruled to be in breach of Clause 7.2 of the Code as it was misleading with regard to the comparative efficacy of esomeprazole and lansoprazole. The advertisement was too positive for the healing effects of Nexium. The Panel did not consider that the claim disparaged lansoprazole. No breach of Clause 8.1 was ruled.

4 Alleged breach of Clause 2

COMPLAINT

In view of the above, and the obviousness of the Code infringements, Wyeth asked the Panel to consider whether AstraZeneca had also breached Clause 2 of the Code.

RESPONSE

AstraZeneca denied any breach of Clauses 7.2, 7.3, 8.1 or 9.3 of the Code of Practice and from this it followed that it had done nothing, in its opinion, to bring the industry into disrepute. AstraZeneca refuted the implication that it had been guilty of breaching Clause 2 of the Code.

PANEL RULING

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.

Complaint received **15 October 2001**

Case completed **20 December 2001**

CASE AUTH/1238/10/01

PARAGRAPH 17 v WYETH

Representative training exercise

During its consideration of Case AUTH/1216/8/01, which involved a complaint from a general practitioner about a Wyeth representative training exercise, the Panel noted that the payment of a fee to each of the doctors, which had not been the subject of complaint, might constitute a breach of the Code and asked that the matter be taken up in accordance with Paragraph 17 of the Constitution and Procedure for the Authority.

The initial letter which was normally used by Wyeth in respect of representative training explained the reasons behind involving established doctors in such training and told the reader that they would be involved for approximately 1 1/2 hours in listening to, and assessing, representative presentations. An honorarium would be paid in recognition of the time spent. Readers were told that if they were interested they should sign and return the attached form. A follow-up letter gave the date and venue of a proposed training programme which would take place in the doctor's local area and stated that the honorarium would be £75. Wyeth's local co-ordinator would contact the doctor to confirm their attendance. The standard letters supplied by Wyeth implied that doctors would go to a local centre to assist in the training of representatives and not that, as in the case then being considered, representatives would visit a doctor's surgery.

Accompanied by a regional trainer, three representatives had visited the surgery and promoted a particular product to each of the doctors. The exercise was not part of an initial training course. Although not the subject of the complaint, the complainant had stated that each doctor had received a fee of £75. The Panel noted that no copy of the correspondence between Wyeth and the practice had been provided by either party. The feedback forms and other documentation from the event had been destroyed once the information from them had been collated; a copy of the information collated from the feedback forms had not been submitted to the Panel. Wyeth thus had no documentation regarding the arrangements for the event. The Panel noted that contrary to Wyeth's submission that all parties involved in the event were aware that this was a training exercise and took part on that basis, the practice manager had stated that the proceedings were poorly managed and that on the day the doctors were uncertain as to their role.

The training event had taken place with actual GPs in the surgery. This was not necessarily unacceptable but the arrangements had to comply with the Code such that it amounted to a *bona fide* training exercise rather than a promotional event. It was not necessarily unacceptable in such circumstances to provide an honorarium The GPs were uncertain as to their role. The practice manager stated that the proceedings were poorly managed. This was unacceptable. Overall the Panel considered that the arrangements did not amount to a *bona fide* training exercise and thus the payment amounted to a fee for the grant of an interview. A breach of the Code was ruled.

During its consideration of Case AUTH/1216/8/01, which involved a complaint from a general practitioner about a Wyeth representative training exercise, the Code of Practice Panel noted that the payment of a fee to each of the doctors, which had not been the subject of complaint, might constitute a breach of Clause 15.3 of the Code of Practice and asked that the matter be taken up in accordance with Paragraph 17 of the Constitution and Procedure for the Authority.

COMPLAINT

The Panel noted that the initial letter which was normally used by Wyeth in respect of representative training explained the reasons behind involving established doctors in such training and told the reader that they would be involved for approximately 1 1/2 hours in listening to, and assessing, representative presentations. An honorarium would be paid in recognition of the time spent. Readers were told that if they were interested they should sign and return the attached form. A follow-up letter gave

the date and venue of a proposed training programme which would take place in the doctor's local area and stated that the honorarium would be £75. Wyeth's local co-ordinator would contact the doctor to confirm their attendance. The standard letters supplied by Wyeth implied that doctors would go to a local centre to assist in the training of representatives and not that, as in the case then being considered, representatives would visit a doctor's surgery.

Accompanied by a regional trainer, three representatives had visited a general practice surgery and promoted a particular product to each of the doctors. The representatives involved had been with Wyeth for varying lengths of time; the exercise was not part of an initial training course. Although not the subject of the complaint, the complainant had stated that each doctor had received a fee of £75. The Panel was concerned that such a payment constituted a fee for the grant of an interview, in breach of Clause 15.3 of the Code, and requested that this matter be taken up in accordance with Paragraph 17 of the Constitution and Procedure of the Authority.

RESPONSE

Wyeth strongly refuted any suggestion that the £75 honorarium paid to the doctors involved in the representative training session constituted a payment made for the purposes of gaining an interview or was in breach of any other requirement of the Code. A detailed investigation of the process used in this particular session showed that all parties involved were aware that this was a training exercise and took part on that basis.

Following a verbal discussion between Wyeth's local regional business manager and the practice manager a letter was sent to the practice manager approximately one month before the training exercise. The training exercise was then co-ordinated by one of the representatives involved. On the actual day the GPs arrived singly but each was fully briefed by the regional trainer prior to commencing. Details of the brief were provided.

The trainer then explained the process, showing them the feedback forms they would be required to complete either during the discussion or at the end. The logistics of the exercise were then explained ie the GPs would see each representative in turn; the GPs should treat the discussion as a normal call; the GPs could ask questions as necessary.

Once the exercise had been completed the feedback forms were collected and a face to face discussion between the regional trainer and the GP took place. The questions posed were along the lines of: What were your general impressions of the representative? What did you learn new as a result of the conversation? What, if anything, would you now do differently following the discussion? Would you be prepared to carry out a similar exercise in the future?

Wyeth stated that GPs were generally chosen to participate in representative training days based on their location and an established working relationship with the practice.

At some point all representatives would be involved in similar training sessions because Wyeth saw them as a key part of a continuous personal development programme. Generally the training sessions would be used as part of an initial training course, following a launch or change in campaign materials, where there was an obvious training need or to ensure that established representatives were continuing to meet their customers' needs. Each training session would have a regional trainer or regional business manager facilitating the meeting and taking feedback.

The representatives involved had been with the company for between one and four years. They detailed Efexor, Zoton and, where time allowed, the Prem range. Efexor was licensed for the treatment of generalized anxiety disorder in June. Initial training had already taken place, follow up training and launch was in early July.

In response to a request by the Authority for clarification, Wyeth stated that the information it had provided regarding the setting up of the training exercise was a true and accurate representation of the sequence of events. Wyeth did not hold a copy of the actual letter sent to the practice, the content would have been as per the letters the Authority had seen.

There were no specific guidelines regarding the number of training exercises that should be held, they would always form part of an initial training course or launch of a new product or indication. Additional sessions would be held on an as needed basis, as determined by the regional business manager and field based trainer. The current rate was four per year.

The training day in question took place in August and was located in the practice. The feedback forms in question were destroyed once the information from them had been collated.

In response to a request by the Authority for further clarification Wyeth stated that the information given above regarding the setting up of the training exercise was a true and accurate representation of the sequence of events. In its earlier investigation of Case AUTH/1216/8/01 it had spoken to the trainer and representative involved in the exercise, and not to the regional business manager who had instigated the exercise – it was the latter that sent the letter to the practice manager.

Wyeth explained that whilst it did not have a copy of the letter on file it had spoken to the practice manager who had confirmed verbally that a letter was sent and that all those involved were aware of the event. A letter from the practice manager, confirming that a letter was sent to the practice prior to the training exercise taking place, was provided.

Wyeth stated that once the feedback from the training exercise had been given all the documentation was destroyed and therefore it had no documentation regarding this event. The company acknowledged that this was inappropriate, and that it needed to make improvements to its current process regarding representative training days to ensure records were retained for each training day held. However, the company strongly refuted any suggestion that the payment made to doctors was in any way made for

the grant of an interview in contravention of Clause 15.3 of the Code.

PANEL RULING

The case now under consideration had arisen from Case AUTH/1216/8/01. In that case Wyeth had supplied copies of standard letters used to set up training exercises but had stated that the representatives' training exercise in question was organised via the practice manager and that the relevant letters were not utilised. The Panel had expressed concern that there appeared to be no written record that the doctors had agreed that a formal training session could take place in their practice. In response to the case now at issue, Case AUTH/1238/10/01, Wyeth submitted that a letter was sent to the practice manager approximately one month before the training exercise. Although the company did not have a copy of the actual letter sent the content would have been as per the letter previously supplied. Wyeth had explained the inconsistency in its accounts of how the training exercise was set up by the fact that in its investigation of the original case, Case AUTH/1216/8/01, it had spoken to the trainer and representative involved and not to the regional business manager who had instigated the training exercise and sent the letter to the practice manager. The Panel was extremely concerned that it was not until this second case, Case AUTH/1238/10/01, that Wyeth had spoken to the person who had set up the training exercise. It appeared that, with respect to the processes involved in setting up the training exercise, Wyeth's response to Case AUTH/1216/8/01 had been inaccurate.

Wyeth had supplied a copy of a letter from the practice manager which stated that written notification of the representatives' training exercise was received in the practice and that the correct procedures were followed. The Panel noted, however, that one paragraph of the practice manager's letter also stated 'On the day in question I was unfortunately unable to be in the practice, although a member of staff was made aware of the event. The visit did not run as smoothly as I would have wished although many factors contributed to this fact. Neither [named individual] nor myself were in surgery (the two people who had organised the event), the proceedings were poorly managed and, on the day, the doctors were uncertain as to their role'.

The Panel noted that no copy of the correspondence between Wyeth and the practice had been provided by either party. The feedback forms and other documentation from the event had been destroyed once the information from them had been collated; a copy of the information collated from the feedback forms had not been submitted to the Panel. Wyeth thus had no documentation regarding the arrangements for the event. The Panel noted that contrary to Wyeth's submission that all parties involved in the event were aware that this was a training exercise and took part on that basis, the practice manager had stated that the proceedings were poorly managed and that on the day the doctors were uncertain as to their role.

The Panel noted that the training event had taken place with actual GPs in the surgery. This was not necessarily unacceptable but the arrangements and programme for the event had to comply with the Code such that it amounted to a *bona fide* training exercise rather than a promotional event. It was beholden upon the company to ensure that each GP was clear about his/her respective role and responsibility. It was not necessarily unacceptable in such circumstances to provide an honorarium but the overall arrangements had to comply with the Code. It was apparent that the GPs were uncertain as to their role. The practice manager stated that the proceedings were poorly managed. This was unacceptable. Overall the Panel considered that the arrangements did not amount to a *bona fide* training exercise and thus the payment amounted to a fee for the grant of an interview contrary to Clause 15.3. A breach of that clause was ruled.

Proceedings commenced 19 October 2001

Case completed 8 January 2002

CASE AUTH/1239/10/01

HEALTH AUTHORITY PRIMARY CARE MEDICAL ADVISER v PFIZER

Invitation to meeting

A health authority primary care medical adviser complained that at a meeting for general practitioners arranged at a hotel by Pfizer, delegates were offered the opportunity of an overnight stay and dinner on the night prior to the meeting on the Saturday. There was no clinical input on the Friday whatsoever. Given that the event was within easy travelling distance, the complainant did not believe GPs would have paid for an overnight stay and a dinner if they were making their own arrangements. The complainant believed that this degree of hospitality was outside the guidance in the Code.

The Panel noted that the invitation gave no indication of any medical or educational content on the Friday evening. Pfizer had submitted that there was to have been a presentation on the Friday evening and that this was mentioned when inviting GPs. The educational content lasted 30 minutes on the Friday evening and the Saturday programme lasted for four hours. On balance the Panel considered that that total educational content as submitted by Pfizer was on the limits of acceptability. The provision of accommodation on the Friday evening was not unreasonable given the submission that there was an educational session, although this was limited to a 30 minute presentation. Many of the delegates had to travel some distance to attend and the Saturday programme started at 9am. In the Panel's view the costs of the meeting at £210 (for only those staying the night) or £186 (for those staying the night plus the four delegates who did not) per delegate did not exceed that level which the recipients would normally adopt when paying for themselves and were thus consistent with the requirements of the Code.

In the Panel's view, however, the impression from the invitation was that the educational content was not sufficient to justify the associated hospitality. It was not sufficient to verbally inform GPs of the presentation on the Friday evening. The Panel therefore ruled a breach of the Code.

A health authority primary care adviser complained about a meeting arranged by Pfizer Limited for general practitioners at a hotel in Wales on 12 and 13 October.

The invitation, dated 19 September, included the agenda. The meeting was to start on Friday, 12 October, with registration and dinner at 8.30pm. The next day the programme started at 9am with 'NICE Guidelines and Coxibs, their implications to prescribing'. Two speakers were listed: a GP specialist in sports medicine and a consultant rheumatologist. The meeting ended at 1pm with lunch.

COMPLAINT

The complainant stated that the invitation had been sent to a number of practitioners in the area. GPs were offered the opportunity of an overnight stay and a dinner on the night prior to the meeting. There was no clinical input on the Friday whatsoever.

Given that the event was held within easy daytime travelling distance, the complainant did not believe that the GPs, if they were providing their own arrangements, would have sought to pay for an overnight stay and a dinner. The complainant believed that this degree of hospitality was well outside the guidance in the Code.

RESPONSE

Pfizer requested that the case be considered under the 1998 edition of the Code rather than the 2001 edition by virtue of the transitional provision in the 2001 Code. The meeting and arrangements were first discussed in a regional sales managers' meeting on 1 August and the invitations were delivered to doctors between early August and mid-September, at a time when Clause 19.1 regarding certification of meetings was still subject to the transitional provision in the 2001 Code.

With regard to the allegation that there was no clinical input on the Friday whatsoever, Pfizer submitted that although the invitations which were delivered to proposed attendees did not mention any educational content for Friday, 12 October, there was in fact an educational content. The omission of any mention of the educational content on the Friday was due to a clerical oversight. An educational presentation was always intended and was indeed made on Friday, 12 October. A consultant was approached to give a talk on the 'Arthritic Complications of Gun Shot Wounds'. Unfortunately, he could not attend and it was decided to ask the GP specialist to speak instead. It was this last minute change of plan which might have led to the invitation not being correctly finalised. Pfizer accepted that an adverse impression could be created by the fact that there appeared to be no educational content on the Friday night. Invitees were informed that there would be some educational content on the Friday when the invitations were delivered to them.

On the Friday evening, the GP specialist gave a short presentation on orthopaedic injuries. The presentation and a brief question and answer session afterwards lasted for approximately 30 minutes. As to the educational content in general, a letter from the doctor who chaired the meeting was provided. He was very clear in his view that there was a robust educational content throughout the meeting.

General practitioners were offered the opportunity to stay overnight and attend a dinner. However, this was due partly to the fact that there was to be an educational presentation on the Friday night and also because a large number of delegates were attending the meeting from the Liverpool and Manchester area and the main meeting was to begin on the Saturday

morning at 9am. Given that many of the delegates needed to travel in excess of 200 miles for an early morning start, Pfizer submitted that it was not inappropriate to provide an overnight stay. Whilst there were several delegates attending from the local area, the average distance travelled by all delegates was approximately 150 miles.

On the Saturday morning there were talks on the subject of the National Institute of Clinical Excellence (NICE) Guidance on the use of Cox II inhibitors and the implications of that guidance for prescribing. The GP specialist's lecture lasted for one hour and 15 minutes and concerned the role of the GP specialist and musculoskeletal problems in general practice and the long term consequences. The slides shown were supplied. This was followed by the consultant rheumatologist's lecture and a general question and answer session lasting approximately one hour and 10 minutes. Pfizer had been unable to obtain a copy of the slides in time for its response but had requested them.

Pfizer believed that the subject of the NICE guidance on the use of Cox II inhibitors and the implications of that guidance for prescribing was an important area of current concern for GPs and, as such, the educational content of the meeting was a key factor in attracting these delegates.

Approximately 40 – 50 doctors were invited from Wales and 30 from the north west. There were 19 doctors and one practice nurse from Wales and 15 doctors and one practice nurse from the north west at the meeting. The rate per delegate for the meeting was £170 plus VAT. The cost per delegate included room hire, overnight accommodation (where relevant), dinner, lunch, some refreshments and facilities charges. Pfizer calculated the overall cost of the meeting based on (a) 30 doctors and 2 practice nurses who attended the meeting and stayed overnight at £209.71 including VAT, and (b) 34 doctors and 2 practice nurses who attended the meeting (ie including the 4 day delegates who did not stay overnight) at £186.42 including VAT. Pfizer had not included the cost of the five Pfizer staff at the meeting in the calculation. It could not apportion the cost per delegate any further as the hotel rate included the above with no breakdown and any attempt to produce such figures would be purely arbitrary. The hotel was considered to be a suitable venue as there were doctors attending from the South Wales and the Liverpool areas and the hotel rates were comparable with similar hotels with conference facilities of a similar size in the north west.

Pfizer submitted that there had been no breach of Clause 9.1 of the Code. Although the invitations omitted to mention the educational meeting on the Friday night, invitees were informed of it when the invitations were handed out. The company submitted that, in assessing the meeting in accordance with Clause 9.1 of the Code, both the invitation and the verbal information conveyed to the doctors should be considered. If this assessment was made, there was no breach of Clause 9.1 of the Code.

With regard to Clause 19.1, Pfizer submitted that there was substantial educational content throughout the Friday and Saturday sessions which was the primary purpose of the meeting. The hospitality was secondary: it would have been impractical for doctors to attend a seminar commencing at 9am on a Saturday morning, especially as many of them had to travel a considerable distance. Since the hotel's rate was comparable with other available hotels in the north west area, the hospitality was appropriate and not out of proportion to the meeting.

Pfizer submitted that no breach of Clause 2 had been committed. Pfizer accepted that it was important not to give a wrong impression, the invitees were informed of the educational content and the clerical error relating to the omission of this from the invitation was an oversight. The likelihood of this occurring in the future had been substantially reduced with the introduction of its meetings, hospitality and related expenditure policy in line with the guidance to Clause 19.1 of the 2001 Code.

PANEL RULING

The Panel noted that the meeting and arrangements had to comply with the 2001 Code. The transitional arrangements were operative from 1 July 2001 to 30 September 2001. Clause 14.2 of the 2001 Code newly introduced the requirement that meetings involving travel outside the UK had to be certified in advance. The meeting in question had been held within the UK and therefore the requirement did not apply.

The Panel noted Clause 19 and its supplementary information which stated that meetings must have a clear educational content. Companies were permitted to provide appropriate hospitality to health professionals in association with such meetings. Hospitality had to be secondary to the purpose of the meeting, the level must be appropriate and not out of proportion to the occasion and the costs must not exceed that level which the recipients would normally adopt when paying for themselves. The Panel examined the invitation. There was no indication of any medical or educational content to the Friday evening.

The Panel noted from the company's submission that there was to have been a presentation on the Friday evening and this was mentioned when inviting GPs. The educational content lasted 30 minutes on the Friday evening and the Saturday programme lasted for four hours. On balance the Panel considered that the total educational content as submitted by Pfizer was on the limits of acceptability. The Panel noted that 15 of the 19 doctors attending from Wales stayed the night as did the practice nurse from Wales. The provision of accommodation on the Friday evening was not unreasonable given the submission that there was an educational session, although this was limited to a 30 minute presentation.

Many of the delegates had to travel some distance to attend and the Saturday programme started at 9am. In the Panel's view the costs of the meeting at £210 (for only those staying the night) or £186 (for those staying the night plus the four delegates who did not) per delegate did not exceed that level which the recipients would normally adopt when paying for themselves.

In the Panel's view the impression from the invitation was that the educational content was not sufficient to justify the associated hospitality. It was not sufficient to verbally inform GPs of the presentation on the Friday evening. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel did not consider that the arrangements were in breach of Clause 9.1 and ruled accordingly.

The circumstances did not warrant a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **22 October 2001**

Case completed **11 December 2001**

CASE AUTH/1240/10/01

GENERAL PRACTITIONER v NOVARTIS

Conduct of representative

A general practitioner complained that during a presentation on its product Diovan (valsartan) a Novartis representative had claimed that Micardis (telmisartan) should not be used in patients who were currently on digoxin, whereas this did not seem to be a problem for patients using valsartan. The complainant was surprised at this information as he was not aware that concomitant use of telmisartan and digoxin was contraindicated; he had not previously heard of this recommendation.

Further information led the complainant to believe that digoxin and telmisartan were not absolute contraindications in concomitant use; studies had indicated that digoxin levels might rise with high dose telmisartan and it was therefore suggested that routine digoxin levels were performed on such patients.

The Panel noted that Novartis had not dissented from the complainant's account of what had taken place.

The Micardis summary of product characteristics (SPC) stated that compounds which had been studied in pharmacokinetic trials included, *inter alia*, digoxin for which a 20% increase in median plasma digoxin trough concentration had been observed (39% in a single case). Monitoring of plasma digoxin levels should be considered. A representatives briefing document on Micardis featured a table which listed 'Causes plasma concentration of digoxin to increase by up to 39%' as a key weakness. A bullet point beneath a heading 'Handling Telmisartan' stated 'Has a drug interaction with digoxin, causing increases in plasma levels by up to 39% (median 20% increase) (digoxin can be very toxic outside of 'normal' ranges and is commonly used in patients with heart failure)'. The Panel noted that the information from the Micardis SPC had been misquoted. The SPC referred to increases in median plasma digoxin trough (emphasis added) levels not to plasma levels generally as inferred in the briefing material. In addition the briefing material referred to increases of plasma levels of up to 39% and then stated that the median increase was 20%. In the Panel's view this added emphasis to the single case of a 39% increase. There was no mention of digoxin toxicity in the SPC. The briefing material stated that digoxin could be very toxic outside of normal ranges implying that concomitant use with Micardis might result in digoxin toxicity. The increased digoxin plasma levels seen with concomitant use of Micardis, however, were increased trough levels. A separate representatives briefing document listed 'digoxin, lithium' as drug interactions of Micardis. No further explanation was provided. The Panel considered that the information given in the representatives briefing material was misleading and likely to lead to a breach of the Code. The information in the Micardis SPC had been misquoted. There was no evidence before the Panel that the concomitant use of Micardis and digoxin would lead to digoxin toxicity. A breach of the Code was ruled.

The Panel considered that the representative's statement that Micardis was contraindicated in concomitant use with digoxin was misleading. It was not a fair reflection of the digoxin interaction mentioned in the Micardis SPC and nor was the representative's statement in line with the briefing material. The representative had failed to comply with all the relevant requirements of the Code and a breach of the Code was ruled.

A general practitioner complained about statements made by a representative from Novartis Pharmaceuticals UK Ltd during a presentation on Diovan (valsartan).

COMPLAINT

The complainant stated that the representative presented her product, needless to say, in a more favourable light than her competitors. Unfortunately, at the end of her talk she claimed that Micardis (telmisartan) was contraindicated in concomitant use with digoxin and therefore should not be used in any patients who were currently on digoxin, whereas this did not seem to be a problem for patients using valsartan.

The complainant stated that he was surprised at this information as he was not aware that concomitant use of telmisartan and digoxin was contraindicated. He was also a little puzzled. As telmisartan was the practice's Ace II antagonist of choice it had fair experience with regard to this medicine and the

complainant had not previously heard of this recommendation.

Further information acquired from the British National Formulary, issue 42, and the information service of Boehringer Ingelheim led the complainant to believe that in fact digoxin and telmisartan were not absolute contraindications in concomitant use and he believed that the only suggestion was that studies concerning the two had indicated that digoxin levels might rise with high dose telmisartan and it was therefore suggested that routine digoxin levels were performed on such patients.

Whilst the complainant understood that particular companies should obviously promote their own products within a particular area of pharmacology, he always thought that it was possibly against the Code in that attempting to belittle competitor products with false information was regarded as poor promotional practice. Whilst the complainant was far from condemning excessive enthusiasm for a particular product promotion by a company, he thought it was rather counter productive that it should do so in such a manner as described above, as this particular incident would make him even less likely to prescribe Diovan as one would feel information from this particular company might be unreliable.

When writing to Novartis the Authority drew attention to Clauses 7.2, 8.1, 15.2 and 15.9 of the Code.

RESPONSE

Novartis stated that a full and detailed investigation had been put in place and the representative involved closely questioned. At the time of the interview with the complainant, the representative in question had been contracted to the Novartis field team on a three month review basis. During this three month review period such representatives were subjected to close scrutiny by senior field staff. This scrutiny had identified some concerns with product knowledge in this individual, which had necessitated some urgent remedial action by a regional training manager.

Unfortunately, this remedial action was not considered to have been sufficient to bring the individual up to the level of excellence expected of the Novartis field teams and the necessary processes were put into place to remove the representative from the team. Although some product knowledge issues had been identified, they were not initially considered sufficient to dismiss the representative. In the light of the failure of the additional training, however, and this subsequent complaint, the representative had now been permanently suspended from the Novartis fieldforce.

The representative in question had been contracted to Novartis since mid 2001 and was scheduled to sit the ABPI examination in May 2002. Prior to promoting Novartis products, the representative had received thorough, appropriate product training and had been supplied with briefing materials, copies of which were provided. Novartis submitted that the briefing materials did not at any point suggest that the use of telmisartan in association with digoxin was contraindicated but instead included a summary of the warning information included in the Micardis summary of product characteristics (SPC).

Novartis was very concerned that the complainant should have been disappointed in this way by the service provided by the company. Novartis would have valued the opportunity to address this issue directly with the complainant and could only apologise that, on this occasion, it had failed to provide the level of support which the practice could reasonably expect to receive from the company.

Novartis hoped that this information would help to demonstrate the company's ongoing commitment to the maintenance of high standards in all promotional activity.

PANEL RULING

The Panel noted that, according to Novartis, the representative at issue was a contract representative. The supplementary information to Clause 15 of the Code, Contract Representatives, stated that companies employing or using contract representatives were responsible for their conduct and must ensure that they complied with all the relevant clauses in the Code.

The Panel noted that the representative was alleged to have claimed that Micardis was contraindicated in concomitant use with digoxin and therefore should not be used in any patients who were currently on digoxin. Novartis had not dissented from the complainant's account of what had taken place.

The Panel noted that Section 4.5 of the Micardis SPC (Ref Electronic Medicines Compendium (emc.vhn.net) last updated on the eMC on 15 August 2001) headed 'Interaction with other medicinal products and other forms of interaction' stated that compounds which had been studied in pharmacokinetic trials included, *inter alia*, digoxin for which a 20% increase in median plasma digoxin trough concentration had been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

The Panel noted that a representatives briefing document headed 'Chapter 6 Micardis (Telmisartan)' featured a table which listed 'Causes plasma concentration of digoxin to increase by up to 39%' as a key weakness. A bullet point beneath a heading 'Handling Telmisartan' stated 'Has a drug interaction with digoxin, causing increases in plasma levels by up to 39% (median 20% increase) (digoxin can be very toxic outside of 'normal' ranges and is commonly used in patients with heart failure)'. The Panel noted that the information from the Micardis SPC had been misquoted. The SPC referred to increases in median plasma digoxin trough (emphasis added) levels not to plasma levels generally as inferred in the briefing material. In addition the briefing material referred to increases of plasma levels of up to 39% and then, in brackets, stated that the median increase was 20%. In the Panel's view this added emphasis to the single case of a 39% increase. There was no mention of digoxin toxicity in the SPC. The briefing material stated that digoxin could be very toxic outside of normal ranges implying that concomitant use with Micardis might result in digoxin toxicity. The

increased digoxin plasma levels seen with concomitant use of Micardis, however, were increased trough levels. The Panel did not know if these increased trough levels would exceed peak plasma levels of digoxin and so lead to digoxin toxicity. A separate representatives briefing document, presented in tabular format, listed 'digoxin, lithium' as drug interactions of Micardis. No further explanation was provided. The Panel considered that the information given in the representatives briefing material was misleading and likely to lead to a breach of the Code. The information in the Micardis SPC had been misquoted and the material had referred to digoxin toxicity. There was no evidence before the Panel that the concomitant use of Micardis and digoxin would lead to digoxin toxicity. A breach of Clause 15.9 was ruled.

The Panel considered that the representative's statement that Micardis was contraindicated in concomitant use with digoxin was misleading. It was not a fair reflection of the digoxin interaction mentioned in the Micardis SPC and nor was the representative's statement in line with the briefing material. By stating that Micardis was contraindicated in concomitant use with digoxin, the representative had failed to comply with all the relevant requirements of the Code and a breach of Clause 15.2 was ruled. The Panel did not consider that the representative had disparaged Micardis as alleged; no breach of Clause 8.1 was ruled on this point.

Complaint received **22 October 2001**

Case completed **2 January 2002**

CASE AUTH/1242/10/01

PROFESSOR OF RESPIRATORY MEDICINE v GLAXOSMITHKLINE

Seretide 'Dear Doctor' letter

A professor of respiratory medicine complained about a 'Dear Doctor' letter about the pricing of Seretide (fluticasone and salmeterol) sent by GlaxoSmithKline. Page 1 of the letter featured a cost comparison chart headed 'The cost and available presentations for initiation of therapy in the patient groups described above of Seretide and Symbicort' which compared Symbicort Turbohaler (budesonide and formoterol) with Seretide MDI (metered dose inhaler). Various doses presented in ascending order of cost were given as was the total daily dose of inhaled steroid (fluticasone or budesonide). The fluticasone column also gave the CFC BDP (beclometasone) equivalent which was twice the fluticasone daily dose. The cost per month was given. The maximum dose of budesonide available was 800mcg. The maximum dose of fluticasone was 1000mcg which was listed as equivalent to 2000mcg of beclometasone. Page 2 stated that 'No studies comparing regular dosing schedules of Seretide and Symbicort have been carried out'.

The complainant stated that the letter made implicit comparisons with the AstraZeneca combination inhaler Symbicort. Two generally agreed facts which were endorsed by the British Thoracic Society in the British Guidelines on Asthma Management (the BTS guidelines) were firstly, that fluticasone was twice as potent as budesonide and secondly, that the Turbohaler delivered a greater proportion of the inhaled dose to the lungs and required a two to one dosage adjustment when compared with an MDI. The letter highlighted the first point but did not deal with the second, leading the reader to an erroneous conclusion, which was reinforced by the way the table was set out. There was no study in the literature directly comparing the two preparations. At best, therefore, this table would only add to confusion since from what was already known the comparison made was likely to be grossly inaccurate.

The Panel noted that in a paragraph about fluticasone the BTS guidelines stated that 'Fluticasone should be included in the guidelines as an alternative inhaled steroid at half the doses recommended for beclomethasone and budesonide when given by metered dose inhaler (MDI)'. A paragraph about delivery devices stated that 'The Turbohaler delivers approximately twice as much inhaled steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be titrated against control of asthma and treatment reduced when control is achieved' referenced to Thorrson *et al* (1994) which compared a budesonide Turbohaler with budesonide MDI. In this study participants were trained to inhale at a flow rate of 60 litres per minute for the Turbohaler and 30 litres per minute for the pMDI. The Panel queried GlaxoSmithKline's view that the comparative efficacy between the budesonide Turbohaler and budesonide MDI could not be extrapolated to any other medicine or device given what the BTS guidelines stated. The BTS guidelines were more general. The Panel noted the data supplied by GlaxoSmithKline, including a meta-analysis which GlaxoSmithKline stated concluded that fluticasone, whether delivered via Diskhaler, MDI or Accuhaler, demonstrated a 2:1

microgram for microgram efficacy when compared to budesonide via a Turbohaler.

The letter advised that it was important that patients received the appropriate dose of inhaled corticosteroid to manage their asthma and that the dose was titrated to the lowest effective dose. The letter did not mention the statement in the BTS guidelines about the delivery of steroid via the Turbohaler. Nor were the constituent components of Symbicort mentioned. In the Panel's view, GlaxoSmithKline had introduced a comparative element by including the beclometasone equivalent of the fluticasone dose and this was re-inforced by the budesonide dose appearing in the next column and the statement above the table that it was usually recommended that fluticasone be used at half the microgram dose of budesonide or belcometasone. There was no data directly comparing Symbicort with Seretide. The position was not as straightforward as implied by the letter. Overall the Panel considered that the letter was misleading and a breach of the Code was ruled.

A professor of respiratory medicine complained about a 'Dear Doctor' letter (ref HM5950-FP/September 2001) about the pricing of Seretide (fluticasone and salmeterol) sent by GlaxoSmithKline.

Page 1 of the letter featured a cost comparison chart headed 'The cost and available presentations for initiation of therapy in the patient groups described above of Seretide and Symbicort'. The chart compared Symbicort Turbohaler (budesonide and formoterol) with Seretide MDI (metered dose inhaler). Various doses were given as was the total daily dose of inhaled steroid (fluticasone or budesonide). The fluticasone column also gave the CFC BDP (beclometasone) equivalent which was twice the fluticasone daily dose. The cost per month was given in the final column. The doses were presented in ascending order of cost. The maximum dose of budesonide available was 800mcg. The maximum dose of fluticasone was 1000mcg which was listed as equivalent to 2000mcg of beclometasone. Page 2 stated that 'No studies comparing regular dosing schedules of Seretide and Symbicort have been carried out'.

COMPLAINT

The complainant stated that he had received an unsolicited letter from GlaxoSmithKline which dealt with the dosing and relative costs of Seretide and made implicit comparisons with the AstraZeneca combination inhaler Symbicort. A knowledge of the cost effectiveness of inhaled medication was aided by the understanding of two generally agreed facts which were endorsed by the British Thoracic Society in the British Guidelines on Asthma Management (the BTS guidelines). Firstly, that fluticasone was twice as potent as budesonide. Secondly, that the Turbohaler delivered a greater proportion of the inhaled dose to the lungs and required a two to one dosage adjustment when compared with an MDI. The letter highlighted the first point but did not deal in any fashion with the second. The unwary reader was therefore led to an erroneous conclusion, which was reinforced by the way the table was set out.

As the letter pointed out, there was no study in the literature directly comparing the two preparations. At best, therefore, this table would only add to confusion since from what was already known the comparison made was likely to be grossly inaccurate. The complainant suggested however that this was designed to show a competitor product in a poor light.

The complainant contacted the sender personally on receipt of the letter to express concern. He promised that the complainant would receive a reply in the near future. Having waited a week the complainant stated that there was no alternative but to officially complain. The complaint was based on the complainant's knowledge of the clinical evidence combined with a desire for prescribers not to be misled by unsupported and highly dubious comparisons.

Finally, the complainant would like to make commentary as to what should be done about this letter. It presumably had a very wide circulation and the complainant would suggest that a simple ticking off would be inappropriate since virtually none of the recipients would be aware of such a judgement. Were this to be a complaint against a national newspaper a prominent correction would almost certainly be required. The complainant suggested that the author of the letter, should he still be with the company, be made to write round a letter truly clarifying the situation, which had previously been agreed to the satisfaction of all parties concerned.

When writing to GlaxoSmithKline, the Authority drew attention to Clauses 7.2 and 8.1 of the Code.

RESPONSE

GlaxoSmithKline stated that it would like to apologise sincerely to the complainant for the delay in responding and it regretted very much the distress caused. However GlaxoSmithKline had attempted to contact the complainant who was first unavailable at the time of the calls and subsequently on leave. It had been planned to make further attempts to contact the complainant.

The BTS guidelines did refer to the increased deposition from a Turbohaler, but GlaxoSmithKline noted that this reference was only in comparing budesonide when delivered via a Turbohaler with budesonide delivered by an MDI. No statement of suggested equivalence was made between the budesonide Turbohaler and the delivery by an MDI of another inhaled corticosteroid, such as fluticasone. The reason for this caveat within the guidelines was that the only research supporting such a 2:1 ratio was carried out using a budesonide Turbohaler against a budesonide MDI. It was also important to note that in this research patients were not admitted to the Turbohaler arm of the study unless they were able to achieve the optimum inspiratory flow of 60litres/minute via the Turbohaler. Accordingly this comparative efficacy between the budesonide Turbohaler and budesonide MDI could not be extrapolated to any other medicine or device, or in patients who were not able to achieve a peak inspiratory flow of ≥60litres/minute.

There were no studies that showed that the ratio in efficacy, microgram for microgram, between

budesonide and beclometasone was other than 1:1. However, it was accepted that there were differences in efficacy at a microgram for microgram level between fluticasone and budesonide or beclometasone. This was supported by the summary of product characteristics (SPC) for fluticasone which stated that: 'The dose required for disease control with fluticasone propionate may be lower than that required with some other inhaled steroids'. There was no such statement within the SPC for budesonide Turbohaler. This microgram for microgram efficacy difference was also recognised within the BTS guidelines which recommended lower doses of fluticasone compared with budesonide or beclometasone. These microgram for microgram efficacy differences were derived from a number of trials, including what was considered by the Cochrane group to be a robust form of evidence, a meta-analysis.

Ringdal *et al* evaluated fluticasone 400mcg bd via the Diskhaler with budesonide 800mcg bd via the Turbohaler in a twelve-week, randomized, double blind, double dummy, parallel group study of 518 patients. With the doses/devices studied it was shown that fluticasone was more effective than budesonide in terms of improvement in all of the parameters of mean morning PEF, percent predicted PEF, FEV, FVC and clinic PEF in patients with moderate-to-severe asthma. Therefore in this study, fluticasone was more effective than budesonide, at half the microgram dose.

Berend *et al* carried out a 6 month, randomized parallel group study in 133 adult asthmatics. The patients required at least 170mcg daily of beclometasone or budesonide and were randomized to either remain on their current therapy or change to fluticasone (via MDI + spacer) at half the microgram dose. Budesonide was administered via the Turbohaler and beclometasone via MDI + spacer. The authors concluded that fluticasone at half the microgram dose was at least as effective as budesonide via a Turbohaler.

Nielson *et al* carried out a double-blind, dose-ranging study in 66 adult stable asthmatics who were responsive to methacholine. The patients were randomized to three consecutive 2-week treatment periods with either fluticasone Diskhaler 250mcg bd, 500mcg bd and 1000mcg bd or budesonide 400mcg bd, 800mcg bd and 1600mcg bd. The outcome measures were bronchial hyper-reactivity and 24 hour urinary cortisol measures. The study demonstrated the dose response relationship of fluticasone and budesonide in adults with asthma over a wide dose range. The comparison revealed an approximate 4:1 ratio in favour of fluticasone, but with a wide confidence interval.

The meta-analysis by Barnes and Hallett further demonstrated that fluticasone was at least twice as effective on a microgram for microgram basis as budesonide across a range of different inhaler devices. The authors carried out a meta-analysis of seven trials comparing fluticasone with budesonide, for the treatment of asthma of all severities in adult and paediatric patients. In all cases the medicines were compared at clinically equivalent doses ie fluticasone was given at half (or less) the microgram dose. A table provided by GlaxoSmithKline showed the range of inhaler devices tested by the different studies within the meta-analysis. The results of the meta-analysis showed that fluticasone significantly improved mean morning peak expiratory flow rate compared with at least twice the microgram dose of budesonide. The authors concluded that fluticasone at half the dose (or less) of budesonide was more effective than budesonide. As shown in the table, fluticasone whether delivered via Diskhaler, MDI, or Accuhaler demonstrated a 2:1 microgram for microgram efficacy when compared to budesonide via Turbohaler.

To summarise, GlaxoSmithKline was unaware of any evidence that supported the ratio between budesonide delivered via the Turbohaler and any other inhaled corticosteroid was greater than 1:1. Indeed, the available evidence, the BTS guidelines and the SPC for fluticasone inhalers supported a microgram for microgram efficacy ratio of at least 2:1 in favour of fluticasone.

GlaxoSmithKline considered that the 'Dear Doctor' letter at issue was simply a statement of the available ways in which a prescriber might prescribe a combination of a long-acting $ß_2$-agonist and an inhaled corticosteroid. No claims were made regarding the value of these treatments or their efficacy. Two of the prescribing options for Symbicort cost less than the least expensive option for Seretide, and GlaxoSmithKline had pointed this out in the letter.

GlaxoSmithKline referred to a previous ruling where the issue of a 2:1 ratio of efficacy between fluticasone and budesonide was discussed in an appeal hearing, Case AUTH/1205/8/01. In this case GlaxoSmithKline successfully appealed a Panel ruling of no breach about a cost comparison chart used promotionally by AstraZeneca. In its arguments GlaxoSmithKline presented the evidence for a 2:1 efficacy ratio between fluticasone and budesonide. Whilst GlaxoSmithKline was still awaiting the summary of the case and the reasons for the decision of the Appeal Board, it appeared that the Appeal Board was accepting of the 2:1 potency arguments for fluticasone that were presented. As an aside, it was as a result of the cost leavepiece produced by AstraZeneca that confusion with health professionals in respect of the comparative pricing of Seretide and Symbicort first arose. The letter to health professionals was an attempt to address this confusion and not, as the complainant alleged, to cause confusion.

GlaxoSmithKline did not accept the complaint as being justified, it considered that had the complainant been in possession of all the available evidence such an allegation might not have been made. GlaxoSmithKline regretted that it was unable to contact the complainant in a time-span considered reasonable by the complainant.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/1205/8/01, referred to by GlaxoSmithKline,

the Appeal Board had made no comment about the evidence presented by GlaxoSmithKline in relation to the 2:1 efficacy ratio between fluticasone and budesonide.

Turning to the present case, the Panel noted that in a paragraph about fluticasone the BTS guidelines stated that 'Fluticasone should be included in the guidelines as an alternative inhaled steroid at half the doses recommended for beclomethasone and budesonide when given by metered dose inhaler (MDI)'. A paragraph about delivery devices stated that 'The Turbohaler delivers approximately twice as much inhaled steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be titrated against control of asthma and treatment reduced when control is achieved'. This statement was referenced to a study by Thorrson *et al* (1994) which compared a budesonide Turbohaler with budesonide MDI. In this study participants were trained to inhale at a flow rate of 60 litres per minute for the Turbohaler and 30 litres per minute for the pMDI.

The Panel queried GlaxoSmithKline's view that the comparative efficacy between the budesonide Turbohaler and budesonide MDI could not be extrapolated to any other medicine or device given what the BTS guidelines stated. The BTS guidelines were more general.

The Panel noted the data supplied by GlaxoSmithKline, including the meta-analysis which GlaxoSmithKline stated concluded that fluticasone, whether delivered via Diskhaler, MDI or Accuhaler, demonstrated a 2:1 microgram for microgram efficacy when compared to budesonide via a Turbohaler. There was no study comparing Symbicort with Seretide.

The letter advised that it was important that patients received the appropriate dose of inhaled corticosteroid to manage their asthma and that the dose was titrated to the lowest effective dose.

The letter did not mention the statement in the BTS guidelines about the delivery of steroid via the Turbohaler. Nor were the constituent components of Symbicort mentioned. In the Panel's view, GlaxoSmithKline had introduced a comparative element by including the beclometasone equivalent of the fluticasone dose and this was re-inforced by the budesonide dose appearing in the next column and the statement above the table that it was usually recommended that fluticasone be used at half the microgram dose of budesonide or belcometasone. There was no data directly comparing Symbicort with Seretide. The position was not as straightforward as implied by the letter.

Overall the Panel considered that the letter was misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that Symbicort had been disparaged. No breach of Clause 8.1 of the Code was ruled.

Complaint received **31 October 2001**

Case completed **9 January 2002**

HEALTH AUTHORITY JOINT PRESCRIBING COMMITTEE v NOVARTIS

Expanded Access Programme for Glivec

The chairman of a joint prescribing committee to a health authority complained on its behalf that an 'Expanded Access Programme' for Glivec (imatinib) run by Novartis undermined the ability of health authorities to perform their statutory duties. They had a duty to make prioritization decisions on what treatments to approve for their populations subject to a financial ceiling. In this instance it would mean that they could only take over the funding of Glivec at the volume imposed through the expanded access programme at the expense of other service provision. The complainant also noted that there was no evidence of improved survival, clinical benefit or comparative trials. The complainant believed, given these circumstances, that the behaviour of Novartis in instigating its expanded access programme was unreasonable, and prejudicial to the performance of NHS statutory duties.

The Panel noted that companies often provided medication to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available.

The purpose of the expanded access programme was to ensure the ongoing availability of Glivec to eligible patients who fell outside the scope of the registration trials and who had no alternative effective treatment. The programme had been established in response to requests for Glivec from clinicians and patients and had been set up at ten centres. It had received both multi-centre and local ethics committee approval.

The letter of agreement for the expanded access programme clearly stated that if at any time during the course of therapy Glivec became commercially available then it would no longer be provided by Novartis and the per patient payments would cease. The patient information form stated that the study would stop as soon as the medicine became commercially available and therapy might be continued via prescription from the treating physician. It was stated that health authorities, hospital trusts, The National Institute for Clinical Excellence or other bodies might implement prescribing restraints which would mean that the medicine would not be available to the patient.

The Panel considered that the arrangements for the expanded access programme were subject to the Code. It could be argued that the programme met the definition of promotion given in Clause 1.2 of the Code in that it promoted the administration of Glivec. It was a question of whether the arrangements were reasonable. Novartis was meeting all the costs of the medicine and of monitoring its effects until such a time as it was licensed. The Panel noted Novartis' submission that it had made stringent efforts to ensure that relevant clinicians and purchasers were aware of the cost implications of commencing patients on Glivec treatment.

With regard to the allegation that the expanded access programme undermined the ability of health authorities to perform their statutory duties, the Panel noted that Novartis had made the arrangements clear. Further, Department of Health guidance stated that there was scope for the £255 million provided for cancer services to pick up new items.

In the circumstances, the Panel did not consider that the expanded access programme was unreasonable and prejudicial to the performance of NHS statutory duties as alleged nor that the arrangements as described amounted to either promotion of an unlicensed medicine or disguised promotion. No breach of the Code was ruled.

The chairman of the joint prescribing committee of a health authority wrote on its behalf to complain about the actions of Novartis Pharmaceuticals UK Ltd in introducing its expanded access programme for Glivec (imatinib), a product used in chronic myeloid leukaemia. A copy of a memorandum from a regional medicines information service describing the background to the situation was provided.

COMPLAINT

The complainant stated that the committee's concerns were that the expanded access programme undermined the ability of health authorities to perform their statutory duties. They had a duty to make prioritization decisions on what treatments to approve for their resident populations subject to a financial ceiling. In this case this would mean that they could only take over the funding of Glivec at the volume Novartis had imposed through its expanded access at the expense of disinvesting from other service provision.

The committee noted on the available information that there was no evidence of improved survival, clinical benefit or comparative trials. Also the National Institute for Clinical Excellence (NICE) did not anticipate publishing guidance on this product until August 2002.

The committee believed, given these circumstances, that the behaviour of Novartis in instigating its expanded access programme was unreasonable, and prejudicial to the performance of NHS statutory duties.

The memorandum from the regional medicines information service provided by the complainant was dated 18 September 2001 and was headed 'URGENT NOTICE Imminent launch of imatinib (Glivec) for CML'. It stated in its introductory paragraphs:

'The imminent launch of imatinib for chronic myeloid leukaemia (CML) has immediate funding implications for trusts and health authorities in [named] Region. This is because imatinib has been available on an expanded access programme within this region.

An expanded access programme for this drug has been operating from [a named city] and some other UK centres. This followed patient pressure to make it available prior to licensing. Patients have been referred to these centres for receipt of free imatinib until it is launched in the UK.

Once the drug is licensed (expected date October 2001), patients will be transferred back to their referring centre which has to decide whether to fund further treatment or not. Before entering the programme, patients signed forms indicating they understood there may be funding issues when the product was launched. There is already discussion about the cost and continued funding on the patient website …'.

When writing to Novartis, the Authority drew attention to Clauses 2, 3.1, 9.1 and 10.1 of the Code.

RESPONSE

Novartis summarized some key facts regarding Glivec and its efficacy in the treatment of chronic myeloid leukaemia (CML). Glivec had received its marketing authorization on 7 November 2001 and a copy of its summary of product characteristics (SPC) was provided.

1 Glivec – the product and the disease area

CML was a disorder accounting for 15-20% of all cases of leukaemia in adults; its incidence was 1-1.5 per 100,000 and around 500-800 new cases were presented each year in the UK. The estimated prevalence was 3,000-4,000 patients.

Chronic leukaemias had a clinical course of months or years, as opposed to acute leukaemias, where survival of untreated patients was a matter of weeks or months. CML had three phases: chronic, accelerated and blast crisis. Disease progression occurred over 3-5 years and the final phase was rapidly fatal.

Prior to the advent of Glivec, effective treatment options for CML were few; long-term survival could only be achieved by allogeneic bone marrow transplantation. Of the 20% of patients who could be offered potentially curative bone marrow transplants, around half would achieve long-term disease free survival. The mortality of the procedure was up to 50%.

For patients unsuitable or unwilling to undergo allogeneic bone marrow transplantation various medicines were available. The main medicines used to treat CML in chronic phase included interferon-alfa, busulfan and hydroxyurea. Interferon-alfa had demonstrated that it prolonged survival and cytogenetic response was increased in comparison to both busulfan and hydroxyurea. However, prolonged cytogenetic response (a critical predictor of disease outcome) was rarely attained. Studies looking at the combination of cytarabine and interferon-alfa to interferon-alfa alone had suggested that the combination had a higher incidence of cytogenetic response and longer survival. Therapy should be continued until relatively low levels of residual disease were reached. Toxicity was common, but usually mild. However most published studies on interferon-alfa suggested that the medicine had minimal cost-effective benefit.

Despite these treatments improved treatment options for CML were still needed and this had led to the development of molecularly-targeted agents such as Glivec.

Of patients with CML, 95% had a genetic abnormality known as the Philadelphia chromosome. This abnormality led to the production of the BCR-ABL protein kinase, which led to the unregulated 'turn-off' of the cell signal pathway. This in turn led to a clone of proliferating cells, which was the known cause of CML.

Glivec was a molecularly-targeted therapy, which worked to suppress the growth of CML by inhibiting the action of the BCR-ABL protein kinase. In order to treat CML effectively, the BCR-ABL tyrosine kinase must be continually suppressed. The half-life and bioavailability of Glivec allowed a once-daily oral dose to fulfil this requirement in an easily administered fashion.

In the treatment of chronic phase CML, Glivec produced substantially improved haematological and cytogenetic responses compared to those that had historically been achieved with interferon-alfa. In a study of Glivec in patients with CML in chronic phase refractory or intolerant to interferon-alfa, 91% showed complete haematological response and 55% achieved a major cytogenetic response.

In a study of Glivec in accelerated phase patients, 68% of patients showed a sustained haematological response and 23% achieved a major cytogenetic response.

In a study of patients in myeloid blast crisis, 29% had a sustained haematological response to Glivec and 15% a major cytogenetic response.

Glivec was well tolerated and during phase I dose-finding studies a maximum tolerated dose was not reached. Side effects were manageable both in severity and nature.

In conclusion, Glivec was a new treatment for CML and was the first molecularly-targeted therapy for this disease. It had shown excellent response rates in trials that were substantially better than those seen with historical treatments, especially in the chronic phase of the disease, and it had a manageable side effect profile. Its oral formulation enabled convenient out-patient usage.

Glivec had received marketing authorization in a large number of countries worldwide, including the USA. Glivec's registration had been fast-tracked by both the FDA and the EMEA. European approval was received in November 2001. These registration authorities fast-tracked the product's approval having recognized its major benefits to patients with CML in comparison with current treatments.

2 The Glivec expanded access programme

At the closure of registration trials for Glivec in July 2000 it was clear that impressive clinical results were being obtained with Glivec in a disease with hitherto

few effective treatment options. In addition, it was clear that the marked efficacy of Glivec was matched by side effects that were manageable in both severity and frequency. Following very high demand from both patients and clinicians for access to Glivec, the expanded access programme was set up to ensure the ongoing availability to Glivec to eligible CML patients who fell outside the scope of the registration trials, and who had no alternative effective treatment. The expanded access programme was set up at ten specialist haematology centres across the UK. It was approved by the Multicentre Research Ethics Committee (MREC) as well as by the Local Research Ethics Committee (LREC) and was passed via the principal investigator at each site to the hospital's drug and therapeutics committee. This programme had the same indications as the original registration studies for Glivec.

To date there were some 500 UK patients in the expanded access programme being treated at the ten specialist centres. The majority of these were patients with chronic phase CML failing interferon treatment, although there were significant numbers with accelerated phase disease and blast crisis. Unlike the registration studies where Glivec was provided free of charge indefinitely, the understanding for all patients in the expanded access programme was that Glivec would be provided free of charge until the product licence was granted, at which point patients would convert to purchased commercial stock.

Prior to initiating patients into the expanded access programme, each investigator at the specialist centres was required to sign a letter of agreement confirming their understanding of the above. Similarly, patient consent forms also made reference to this point. Copies of these letters/consent forms were provided.

Following the initiation of the expanded access programme, Novartis made stringent efforts to ensure that relevant clinicians and purchasers were aware of the cost implications of commencing patients on Glivec treatment as part of the expanded access programme. A high level of communication was maintained on this subject with the expanded access programme specialist centres, the referring centres, cancer network leads and professional societies covering haematology and oncology pharmacy. An extensive programme was also instigated by Novartis to ensure that relevant persons at health authority and primary care trust level were aware and had made appropriate provision. Following contacts made by Novartis a letter was issued by the Department of Health requesting that health authorities continue the funding of the expanded access programme patients upon commercialization (a copy was provided).

3 Specific responses to the issues raised by the complainant

Novartis stated that with regard to the view that the expanded access programme undermined the ability of health authorities to perform their statutory duties, there was no contractual obligation for the health authority to fund Glivec for patients in the expanded access programme once this programme discontinued at licence for Glivec. Ethics committees, investigators and patients were informed about the commercialization of the expanded access programme prior to study start. The commercialization procedure was part of the ethics submission and approval as well as the contracts between the investigator, the hospital trust and Novartis.

Patient consent forms contained the following paragraph:

'The study will stop as soon as the drug, STI571, becomes commercially available at which time drug administration as part of this trial will stop and you will continue therapy via prescription from your treating physician. STI571, like other chronic treatments, is likely to require a positive funding decision by the Health Authority responsible for your care. Your local Health Authority may implement prescribing restrictions, which could mean that STI571 would not be available to you.'

Novartis drew attention to the wording of the guidance issued by the Department of Health on 24 October 2001 which stated:

'Since June over 500 patients in the country have had the drug [Glivec] provided free of charge at the expense of the pharmaceutical company on an Extended Access Programme (EAP). When patients were accepted onto the EAP we understand it was agreed that Novartis would fund the drug until it achieved a commercial licence. The 100 patients who were on the original registration trial and a further 100 on a current trial will continue to have their treatment funded by Novartis.

Ministers are clear that there is no question of treatment being withdrawn from patients on funding grounds once the drug is licensed and the free Extended Access Programme supplies end. Treatment should only cease on clinical grounds. They will be replying to PQs [parliamentary questions] and letters on that basis.

NICE are appraising Glivec and their guidance is expected to be issued next August. The appraisal was originally timed to coincide with the expected licensing process but the latter has gone more quickly than expected. Health Authorities should bear in mind that delaying a decision until NICE has issued its advice is a refusal to fund the treatment and would be regarded as a negative judgement.

We should also remind you that health authorities received £255 million for cancer services this year, a large proportion of which was in anticipation of NICE appraisals and use of high cost treatments. There has been some slippage in this programme, leaving scope to pick up new items.'

Novartis did not therefore accept that the expanded access programme had undermined the statutory duties of health authorities or had forced them to disinvest from other service provision.

Novartis stated that with regard to the view that there was no evidence of improved survival, clinical benefit or comparative clinical trials, Glivec had been developed in indications where there was no comparative therapy, eg where there was the greatest medical need and there were few effective alternative

treatments. The level of medical need had led to the accelerated approval, the registration process being completed in record time (10 weeks FDA, 4.5 months EMEA).

Novartis provided two comprehensive literature surveys outlining the clinical benefit data for Glivec when compared to non-approved other therapies for the relevant stages of CML. The clinical benefit of Glivec in CML was well-established. Specifically:

In chronic phase CML, Glivec given as second line therapy (study 0110) induced a higher rate of haematologic, major and complete cytogenetic response in comparison to: first line chemotherapy with hydroxyurea or busulfan; second line investigational homoharringtonine therapy; first line interferon-alfa therapy; there was no available therapy which yielded higher rates of cytogenetic response.

Prospectively-collected data on the response to second line treatments was not available in historical large randomized studies, therefore a formal comparison was not feasible.

Glivec was orally available and in accelerated phase CML had a good safety profile and was mostly given as outpatient treatment. Using a rigorously-developed definition of AP (study 0109) Glivec was consistently associated with: high rates of haematologic response; high rates of cytogenetic response (including complete responses), which correlated with improved survival; and encouraging initial survival and time-to-progression data, confirmed with additional follow-up. A formal comparison with matched historical controls was not feasible given the lack of standardized criteria for AP definition and the great variability in therapy.

In blast crisis Glivec was an active, well-tolerated, orally available therapy as an alternative to multi-agent chemotherapy. In comparison with complex, acute-leukaemia chemotherapy regimens, Glivec was associated with favourable risk-benefit ratio on the basis of: similar rates of haematologic response; higher rates of cytogenetic response, including complete responses; median survival of 7.1 months compared to 3-6 months with chemotherapy; and better safety profile, orally available, mostly outpatient treatment.

A formal comparison with well-matched historical controls was unlikely to yield significant additional information.

The complete data set was accepted by the regulatory authorities as a basis for fast-track approval. Novartis did not accept therefore that the clinical benefit of Glivec in CML had not been demonstrated. Surrogate markers of improved survival predicted that Glivec would have a beneficial effect upon survival. Novartis awaited the outcome of the long-term studies to support this point.

With regard to the fact that NICE did not anticipate publishing guidance until August 2002, Novartis stated that Glivec had been fast-tracked by the EMEA as a result of its marked clinical benefits in CML. As a result, marketing authorization was received in November 2001, well ahead of the anticipated date of appraisal by NICE (August 2002).

Novartis referred to the Department of Health communication of 24 October 2001, as previously cited above. This commented upon the comparatively late appraisal of Glivec by NICE, and stated:

'NICE are appraising Glivec and their guidance is expected to be issued next August. The appraisal was originally timed to coincide with the expected licensing process but the latter has gone more quickly than expected. Health Authorities should bear in mind that delaying a decision until NICE has issued its advice is a refusal to fund the treatment and would be regarded as a negative judgement.'

Further guidance on NICE for NHS personnel could be found in the Health Service Circular HSC 1999/176 which was provided. Lord Hunt (Parliamentary Under-Secretary of State, Department of Health) commented in Parliament on HSC 1999/176 and stated the following (Hansard, April 2001, extract provided):

'Policy guidance issued to health authorities was set out in National Health Service Circular HSC/1999/176. In the light of that overriding guidance, we made clear that health authorities and primary care groups and trusts should not wait for guidance from NICE ...'

A recent Lancet editorial (copy provided) had also commented on the situation described above, and stated: 'NICE's process is so slow and its appraisal of imatinib now seems completely superfluous'.

The comparative lateness of the NICE judgement might be regrettable, but was unavoidable under the circumstances and was obviously beyond the control of Novartis.

4 Specific responses to the complaints under the clauses raised by the Authority

With regard to Clause 2, Novartis stated that the expanded access programme as outlined above had helped more than 500 patients in the UK. Many of these patients had received Glivec free of charge for up to 18 months. On a worldwide basis, Novartis had treated more than 10,000 patients with CML as part of the expanded access programme. The expanded access programme had been well received internationally.

As stated above, at the closure of registration trials for Glivec in July 2000 it was clear that impressive clinical results were being obtained with Glivec in a disease with hitherto poor survival and with few effective treatment options. Following very high demand from both patients and clinicians for access to Glivec, the expanded access programme was set up to ensure the ongoing availability of Glivec to eligible CML patients who fell outside the scope of the registration trials, and had no alternative effective treatment. Novartis had made stringent efforts to ensure that all relevant clinicians and purchasers were aware of the implications of entering patients into the expanded access programme, and of the need to make relevant cost provision.

The 500 patients in the UK who were still alive were unequivocal witnesses of the unprecedented success

of the drug. Novartis did not accept that the expanded access programme brought the pharmaceutical industry into disrepute. In fact, it could be argued that the advance in CML treatment which Glivec represented, and the opportunity which the expanded access programme had provided, could enhance the reputation of the industry.

With regard to Clause 3.1, Novartis stated that Glivec was developed from first use in man to filing with the regulatory authorities in two years and eight months, and had been fast-tracked by the EMEA. Marketing authorization had been received in November 2001, some six months earlier than anticipated. As stated above, the rapid regulatory approval resulted from Glivec's marked clinical benefits in CML.

As outlined above, the issue of funding was brought to the attention of relevant health service providers from the start of the expanded access programme in June 2000. Novartis had gone through a lengthy consultation programme with senior purchasers in the NHS who had been consulted and provided advice on the issue in question. Following the initiation of the expanded access programme, Novartis made stringent efforts to ensure that relevant clinicians and purchasers were aware of the cost implications of commencing patients on Glivec treatment as a part of the expanded access programme. A high level of communication was maintained on this subject with the expanded access programme specialist centres, the referring centres, cancer network leads and professional societies covering haematology and oncology pharmacy. An extensive programme was also instigated by Novartis to ensure that relevant persons at health authority and primary care trust level were aware and had made appropriate provision. Specific materials were issued as soon as Novartis had filed for regulatory approval with a full and relevant data set. Senior purchasers in the NHS had commented on these materials as being of an exceptional quality.

Novartis believed that in relation to drug development milestones it had succeeded in making relevant information available to purchasers as soon as this was available to Novartis.

Novartis did not believe that there had been a breach of Clause 3.1.

With regard to Clauses 9.1 and 10.1, Novartis did not accept that the expanded access programme was a disguised promotional programme. As already outlined, it was an ethical programme to supply medicines for patients who had no other effective treatment alternative, and which was instigated in response to massive demand from clinicians and patients. Novartis did not accept therefore that there had been a breach of Clause 10.1.

As stated above, senior purchasers in the NHS had commented upon the materials provided to NHS personnel in relation to the expanded access programme as being of an exceptional quality.

Novartis noted that the document provided by the complainant was not produced by Novartis. Novartis did not accept that there had been a breach of Clause 9.1.

Novartis trusted that the information provided was sufficient to allay any concerns regarding Glivec, the expanded access programme and its management.

PANEL RULING

The Panel noted that companies often provided medication to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available.

The purpose of the expanded access programme was to ensure the ongoing availability of Glivec to eligible CML patients who fell outside the scope of the registration trials and who had no alternative effective treatment. The programme had been established in response to requests for the product from clinicians and patients and had been set up at ten haematology centres. It had received both multi-centre and local ethics committee approval.

Prior to initiating patients into the expanded access programme each investigator at the specialist centre had to sign a letter of agreement. The letter stated that evaluable clinical experience with the product would be obtained for internal decision making by Novartis. An integrated clinical statistical study report would be prepared and submitted to the main investigator for approval. There were various protocols covering the different phases of CML. The protocols consisted of the original study protocols with certain of the objectives deleted. They were variously dated. The patient information form was dated 26 April 2001.

The patient information form provided to the Panel included a similar section to that quoted by Novartis in its submission but it was not identical.

The Panel examined the arrangements for the expanded access programme. The letter of agreement clearly stated that if at any time during the course of therapy the medicine became commercially available the study medicine would not be provided by Novartis and the per patient payments would cease. The patient information form stated that the study would stop as soon as the medicine became commercially available and therapy might be continued via prescription from the treating physician. It was stated that health authorities, hospital trusts, NICE or other bodies might implement prescribing restraints which would mean that the medicine would not be available to the patient.

The Panel considered that the arrangements for the expanded access programme were subject to the Code. It could be argued that the expanded access programme met the definition of promotion given in Clause 1.2 of the Code in that the programme promoted the administration of Novartis' medicine Glivec. It was a question of whether the arrangements were reasonable. Novartis was meeting all the costs of the medicine and of monitoring its effects until such a time as it was licensed. The Panel noted Novartis' submission that it had made stringent efforts to ensure that relevant clinicians and purchasers were aware of the cost implications of commencing patients on Glivec treatment.

With regard to the allegation that the expanded access programme undermined the ability of health authorities to perform their statutory duties, the Panel noted that Novartis had made the arrangements clear. Further the Department of Health guidance stated that there was scope for the £255 million provided for cancer services to pick up new items.

In the circumstances, the Panel did not consider that the expanded access programme was unreasonable and prejudicial to the performance of NHS statutory duties as alleged. Novartis had made the position clear. The Panel did not consider that the arrangements for the expanded access programme as described amounted to either promotion of an unlicensed medicine or disguised promotion. No breach of Clauses 3.1 and 10.1 was ruled. The Panel did not consider that there had been a breach of Clauses 2 or 9.1 and no breach of those clauses was ruled.

Complaint received **1 November 2001**

Case completed **16 January 2002**

CASES AUTH/1244/11/01 and AUTH/1245/11/01

CONSULTANT PHYSICIAN v SANOFI-SYNTHELABO and BRISTOL-MYERS SQUIBB

Meeting about Plavix

A consultant physician complained about being invited by Sanofi-Synthelabo and Bristol-Myers Squibb to attend a 2¼ hour meeting as an 'advisor' to discuss new data for Plavix (clopidogrel) for which an honorarium of £400 was offered.

The complainant considered the meeting to be promotional and that its purpose was to ensure exposure to information about Plavix which the companies believed would influence prescribing. It was disingenuous and unethical to suggest that presence at the meeting represented a service to the pharmaceutical companies which deserved payment of a fee. The complainant would not be acting as a 'consultant' or 'advisor' and therefore interpreted the offer of an honorarium as a bribe to encourage attendance which constituted a breach of the Code. These meetings were promotional and the complainant considered it to be an insult to be offered bribes to attend promotional meetings.

The Panel noted that a communications agency had written, on behalf of Sanofi-Synthelabo and Bristol-Myers Squibb, to local specialists in primary and secondary care inviting them to act in an 'advisory role for us at one of a very small number of roundtable meetings …'. New data on Plavix in patients who were at particularly high risk of further vascular events would be presented and the recipient's views on the relevance of the data to clinical practice sought. An honorarium of £400 would be provided for the consultancy role, along with reasonable travelling expenses. Once invitees had accepted the invitation they received a confirmation letter, agenda and five clinical papers for review prior to the meeting. Delegates were also asked to consider three questions regarding identification of high risk patients and the use of anti-platelet treatment and to be prepared to contribute to the expert opinion feedback. Reference was made to the honorarium which reflected 'attendance at a two and a half hour meeting, preparation time for the meeting which we envisage will take one and a half hours and travel time'. Reasonable travel expenses were also reimbursed. The Panel noted that the programme lasted from 6 - 8.20pm and was followed by dinner at 8.30pm.

The meeting was one of a series of three planned for the UK. Seventeen experts had been invited to the meeting in question and a maximum of 6-8 delegates were permitted per meeting.

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. The selection of consultants had to stand up to independent scrutiny and the arrangements had to comply with the Code. The Panel noted the companies' submission that the purpose of the meeting was to increase their understanding of how prescribers identified appropriate patients, to define high risk patient groups and to discuss how Plavix data could best be communicated to clinicians. 1½ hours of the 2½ hour meeting were dedicated to expert feedback. The Panel also noted that participants were asked to undertake some pre-reading and consider three pre-specified questions.

The Panel considered that given the extra information supplied by the companies, the nature of the meeting was not unacceptable. The companies were in effect intending to employ the health professional to act as a consultant to them. The Panel considered that it would have been helpful if the initial letter had provided further detail about the amount of work to be undertaken by the consultants. There was no mention of any pre-reading and nor was an agenda supplied so that potential consultants could see how much time was given to feedback/discussion. The letter did state that recipients were being invited to act in an advisory role at one of a very small number of roundtable meetings. New data on Plavix and its relevance to clinical practice was to be discussed. The Panel had some sympathy for the concerns of

the complainant but on balance ruled no breach of the Code in that regard.

The Panel considered, however, that the failure to make the purpose of the meeting clear to the recipient of the initial letter meant that the impression was given that a payment was to be made for what appeared to be a promotional meeting. The Panel considered that this meant that the companies had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled.

A consultant physician complained about being invited by Sanofi-Synthelabo Limited and Bristol-Myers Squibb Pharmaceuticals Limited to attend one of a series of meetings on Plavix (clopidogrel).

COMPLAINT

The complainant had previously complained to the Authority about a meeting for which an attendance fee of £250 was offered, Case AUTH/1142/2/01. The Panel ruled that the company organizing the meeting had breached Clause 18.1 of the Code and that ruling was upheld on appeal.

The complainant had recently received an invitation on behalf of Sanofi-Synthelabo and Bristol-Myers Squibb to attend a $2^1/_4$ hour meeting as an 'advisor' to discuss new data for clopidogrel. The honorarium offered for this 'consultancy' was £400.

The complainant considered this meeting to be promotional and that its purpose was to ensure exposure to information about Plavix which the pharmaceutical companies believed would influence prescribing. While this in itself was standard and ethical practice, it was disingenuous and unethical to suggest that presence at the meeting represented a service to the pharmaceutical companies which deserved payment of a fee. The complainant would not be acting as a 'consultant' or 'advisor'. The complainant therefore interpreted the offer of an honorarium as a bribe to encourage attendance, and believed that this constituted a breach of Clause 18.1 of the Code.

Irrespective of how well they were disguised as 'advisory panels' or 'roundtable discussions', these meetings were promotional and the complainant considered it to be an insult to personal and professional integrity to be offered bribes to attend promotional meetings.

The complainant was disappointed that this type of breach of the Code was occurring so often (as evidenced by the large numbers of examples in the Code of Practice Review) and would continue to bring to the Authority's attention any examples of this malpractice. The complainant hoped that by doing so the Authority could effect significant change in the attitude and behaviour of the offending companies.

RESPONSE

Sanofi-Synthelabo and Bristol-Myers Squibb submitted a joint response.

The companies stated that the complaint pertained to one of three roundtable advisory meetings for clinicians with expertise in diabetes care, from primary and secondary care, and was to take place on 11 December in Northern Ireland. The companies considered that the arrangements did not constitute a breach of Clause 18.1 or any other aspect of the Code.

Background to the meeting

Plavix was licensed for the secondary prevention of atherosclerotic events in patients with a history of recent myocardial infarction, recent ischaemic stroke or established peripheral vascular disease.

Consultative roundtable advisory meeting

The meeting in question was one in a series of three. The purpose of these meetings was for the companies to increase their understanding of how prescribers identified appropriate patients, to define high risk patient groups and to discuss how the data in relation to Plavix could best be communicated to clinicians.

A member of the medical department from either Sanofi-Synthelabo or Bristol-Myers Squibb would chair the meeting. In addition, a representative from the marketing department would be present to receive feedback from the advisory board members.

Meeting logistics

The local area business manager nominated local specialists from primary and secondary care with an interest in diabetes as potential invitees. The manager forwarded nominations to the marketing department but there was no involvement of the salesforce in the invitation process. The invitations were sent directly by the communications agency involved with organizing the meeting on behalf of Sanofi-Synthelabo and Bristol-Myers Squibb. A total of seventeen local experts from across Northern Ireland were invited to the meeting with the expectation that six to eight would accept the invitation.

Once invitees had accepted the invitation, they were sent a formal letter of confirmation (a copy was provided) and a number of clinical papers. The letter of confirmation set out questions which, along with the clinical papers, should be considered prior to the meeting. The discussion time on each topic was timetabled in the agenda and exceeded the time allotted to the presentations that prefaced each subsequent discussion. In order to ensure the meeting was as interactive as possible, a maximum of six to eight attendees was permitted per meeting. These were selected from across primary and secondary care and had been selected for their specialist interest and knowledge in the area of diabetes.

The expert feedback received at the meeting would be collated by the communications agency organizing the meeting and used to shape future marketing campaigns (a template was provided).

The time required for participation at the meeting included approximately 2.5 hours for the meeting itself, of which 1.5 hours were dedicated to seeking expert feedback on specific questions. An anticipated 1.5 hours of reading and preparation time were required in addition to travel time to and from the venue. Informal discussions were also expected to continue over dinner. In total, attendees therefore committed to dedicating more than four hours to the

meeting. The honorarium of £400 appropriately reflected the time, expertise and seniority of the clinicians invited, as well as the complexity of the area under discussion.

A summary of the breakdown of costs for the meeting, excepting honoraria, was provided.

This consultative roundtable advisory meeting had been examined closely for content and adherence to the Code and had been judged to be compliant by the companies.

Sanofi-Synthelabo and Bristol-Myers Squibb considered that the consultative roundtable advisory meetings provided an essential forum to ensure that its medical and marketing activities were tailored to, and appropriate for, the audience for whom they were intended, and that such advisory meetings were not prohibited by the Code. This meeting was advisory and not promotional in nature or content and arrangements for the meeting were entirely appropriate. The companies therefore submitted that the meeting would not be in breach of Clause 18.1, or any other aspect, of the Code.

PANEL RULING

The Panel noted that the complainant had referred to a previous case, Case AUTH/1142/2/01, which concerned, *inter alia*, the acceptability in relation to Clause 18.1 of an advisory board meeting. The meeting was one in a series of eight such meetings.

In Case AUTH/1142/2/01 the Panel had considered that it was difficult in such cases to decide precisely where the boundary lay. In that case the Panel was concerned that the delegates were not asked to do a sufficient amount of work to justify the fee. The meeting only lasted three hours, less than half of which, according to the Chairman's brief, was allocated to feedback and discussion. The meeting included a presentation from the marketing director and an update on the development of the product. The Panel considered that the cost of the buffet at £20 per head was not unreasonable. Nevertheless, on balance the Panel considered that the arrangements for the meeting meant that it constituted one in a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Panel ruled a breach of Clause 18.1 of the Code. Upon appeal, the Appeal Board decided that on balance the arrangements for the meeting, particularly the invitation and the agenda, created the impression that it was one in a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1 of the Code.

Turning to the present cases, Cases AUTH/1244/11/01 and AUTH/1245/11/01, the Panel noted that a communications agency had written, on behalf of Sanofi-Synthelabo and Bristol-Myers Squibb, to local specialists in primary and secondary care inviting them to attend the meeting at issue. The letter stated that the recipient was being invited to act in an 'advisory role for us at one of a very small number of roundtable meetings …'. New data on Plavix in patients who were at particularly high risk of further vascular events would be presented and the recipient's views on the relevance of the data to clinical practice sought. An honorarium of £400 would be provided for the consultancy role, along with reasonable travelling expenses. Once invitees had accepted the invitation they received a confirmation letter, agenda and five clinical papers. Recipients were asked to review the agenda and papers prior to the meeting and to consider the following questions; how can one get to grips with defining patients at high risk of further vascular events?; what makes one patient at higher risk than another?; anti-platelet treatment-how are patients currently treated? Delegates were asked to be prepared to contribute to the expert opinion feedback. Reference was made to the honorarium which reflected 'attendance at a two and a half hour meeting, preparation time for the meeting which we envisage will take one and a half hours and travel time'. Reasonable travel expenses were also reimbursed. The letter was signed by a medical advisor for both companies and a communications agency executive. The Panel noted that the programme lasted from 6 - 8.20pm and was followed by dinner at 8.30pm. After a 10 minute introduction delegates were to receive a 10 minute presentation on Atherothrombosis and Anti-platelet Trialists' Collaboration data, a five minute presentation on the CAPRIE study followed by a 20 minute expert opinion feedback session. A 10 minute presentation on recently published data was followed by a further 20 minute feedback session. The final presentation entitled 'Future trials update' and a 50 minute expert feedback session followed by dinner concluded the event.

The meeting was one of a series of three planned for the UK. Seventeen experts in Northern Ireland had been invited and a maximum of 6-8 delegates were permitted per meeting. The Panel also noted the form used by the communications agency to collate data from the meeting.

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. The selection of consultants had to stand up to independent scrutiny and the arrangements had to comply with the Code. The Panel noted the companies' submission that the purpose of the meeting was to increase their understanding of how prescribers identified appropriate patients, to define high risk patient groups and to discuss how Plavix data could best be communicated to clinicians. 1.5 hours of the 2.5 hour meeting were dedicated to expert feedback. The Panel also noted that participants were asked to undertake some pre-reading and consider three pre-specified questions.

The Panel considered that given the extra information supplied by the companies, the nature of the meeting was not unacceptable; the companies were in effect intending to employ the health professional to act as a consultant to them. The Panel considered that it would have been helpful if the initial letter had provided further detail about the amount of work to be undertaken by the consultants. There was no

mention of any pre-reading and nor was an agenda supplied so that potential consultants could see how much time was given to feedback/discussion. The letter did, however, state that recipients were being invited to act in an advisory role at one of a very small number of roundtable meetings. New data on Plavix and its relevance to clinical practice was to be discussed. The Panel had some sympathy for the concerns of the complainant but on balance ruled no breach of Clause 18.1 of the Code.

The Panel considered, however, that the failure to make the purpose of the meeting clear to the recipient of the initial letter meant that the impression was given that a payment was to be made for what appeared to be a promotional meeting. The Panel considered that this meant that the companies had failed to maintain a high standard of ethical conduct and a breach of Clause 9.1 of the Code was ruled.

Complaint received **1 November 2001**

Case completed **16 January 2002**

CASE AUTH/1246/11/01

HOSPITAL CHIEF PHARMACIST v MERCK SHARP & DOHME

Vioxx leavepiece

The chief pharmacist at a hospital complained about a leavepiece for Vioxx (rofecoxib) issued by Merck Sharp & Dohme. The front cover of the leavepiece gave a summary of the recently issued National Institute for Clinical Excellence (NICE) guidance for the use of cyclo-oxygenase (COX) 2 selective inhibitors. The complainant was concerned that the leavepiece misquoted the NICE guidance in a way that might result in some patients being put at risk. There were two specific points.

Firstly it was stated that COX-2 selective inhibitors should be 'used in preference to standard NSAIDs … in patients who may be 'at high-risk' of developing serious gastro-intestinal adverse events'. The word missed out of the actual NICE guidance was 'only' which gave excessive emphasis to the statement not intended by NICE.

Secondly, below the statement referred to above was a list of categories of patients considered to be at risk of developing serious gastro-intestinal (GI) adverse events. The last category was patients with 'a previous history of perforations, ulcerations or bleeds (PUBs)'. The NICE guidance explicitly stated that 'The use of even a COX-2 selective agent should therefore be considered especially carefully in this situation'. This was clearly intended to mean that there might be some risk attached to the use of COX-2 medicines in patients with a history of PUBs and the omission of this message from the leavepiece might, in the complainant's view, result in patients being put at risk.

The Panel considered that the omission of the word 'only' from the quote in the leavepiece meant that readers would be unaware that, although the four COX-2 selective inhibitors under review were licensed for use in all adult patients with osteoarthritis or rheumatoid arthritis, the view of NICE was that they should only be used in those patients who might be at a high risk of developing serious GI side-effects. NICE was thus recommending that the use of the medicines should be more restricted then their licences allowed. The Panel considered that the NICE guidance had not been accurately quoted and that the statement in the leavepiece was thus misleading. Breaches of the Code were ruled.

Five bullet points in the leavepiece set out which patients might be identified as being at 'high risk' of developing serious GI adverse events. The last bullet point stated 'previous history of perforations, ulcers or bleeds (PUBs)'. The Panel noted that the information about high risk patients appeared as a direct quote from the NICE guidance and this was not so. The document had not been accurately quoted and a breach of the Code was ruled.

Although the last bullet point in the box of text correctly described one group of potentially high risk patients as those with 'previous history of perforations, ulcers or bleeds (PUBs)' it did not state, as did the NICE guidance, that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. It appeared that NICE considered patients in this particularly high risk group to be no more vulnerable than other high risk patients such as those aged 65 years or above which was not so. The Panel considered that the box of text was misleading in this regard; it was immaterial that the issue of patients with a history of PUBs was addressed elsewhere in the leavepiece. A breach of the Code was ruled.

The chief pharmacist at a hospital complained about a 4 page leavepiece (reference 08-02 VOX.01.GB.65131.42m.CW.0801) for Vioxx (rofecoxib) issued by Merck Sharp & Dohme Limited. The front cover of the leavepiece gave a summary of the recently issued National Institute for Clinical Excellence (NICE) guidance for the use of cyclo-

oxygenase (COX) 2 selective inhibitors. The inside pages presented a profile of Vioxx; prescribing information was printed on the back page.

The leavepiece had been used by Merck Sharp & Dohme representatives with GPs, hospital doctors, pharmacists, PCO prescribing leads and pharmaceutical advisers.

COMPLAINT

The complainant was concerned that the leavepiece misquoted the NICE guidance in a way that might result in some patients being put at risk.

There were two specific points. Firstly it was stated that COX-2 selective inhibitors should be 'used in preference to standard NSAIDs … in patients who may be 'at high-risk' of developing serious gastro-intestinal adverse events'. The word missed out of the actual NICE guidance was 'only'. The omission of 'only' gave excessive emphasis to the statement not intended by NICE.

The second point was perhaps more serious. Below the statement referred to above was a list of categories of patients considered to be at risk of developing serious gastro-intestinal (GI) adverse events. The last category was patients with 'a previous history of perforations, ulcerations or bleeds (PUBs)'.

In fact the NICE guidance explicitly stated that 'The use of **even** (emphasis added) a COX-2 selective agent should therefore be considered especially carefully in this situation'. This was clearly intended to mean that there might be some risk attached to the use of COX-2 medicines in patients with a history of PUBs and that great concern was needed. This very important message was completely absent from Merck Sharp & Dohme's material and might, in the complainant's view, result in patients being put at risk. The practice at the complainant's hospital was to suggest that, in such patients who did require non-steroidal anti-inflammatory drug (NSAID) therapy, a proven gastro-protective drug regimen (normally a proton pump inhibitor plus a standard NSAID) was the treatment of choice.

When writing to Merck Sharp & Dohme the Authority asked it to consider the requirements of Clauses 7.2 and 11.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it believed that the leavepiece was an accurate reflection of the guidance issued by NICE on the use of COX-2 selective inhibitors, and that it adequately reflected the meaning intended by the authors of the guidance. As such, Merck Sharp & Dohme did not believe it was in breach of Clauses 7.2 or 11.2 of the Code.

Omission of the word 'only'

The first page of the leavepiece was an attempt to provide a succinct summary of the recommendations issued by NICE with regard to the use of COX-2 selective inhibitors in its technology appraisal guidance no 27. As was customary, the inclusion of an ellipsis in the quotation clearly showed that the quotation had not been reproduced verbatim, and one or more words had been omitted. The omitted words were '… when clearly indicated as part of the management of RA and OA only …'.

On reflection one might view the whole sentence as somewhat ambiguous. Did the 'only' refer to limiting the application of COX-2 selective inhibitors to those with a particular disease (ie rheumatoid arthritis and osteoarthritis) *only*, or did the restriction apply to patients who satisfied NICE's definition of high risk? In Merck Sharp & Dohme's opinion the former would seem to be the more natural construction of that sentence since from the title of the guidance '… on the use of COX-2 selective inhibitors … for osteoarthritis and rheumatoid arthritis' NICE had clearly restricted its review to those two specific conditions rather than the whole spectrum of licensed indications of the four products reviewed.

If, which was not admitted, the latter interpretation was the correct one, presumably the complainant was suggesting that the omission of the word 'only' was misleading because it removed the more restrictive definition of those patients who NICE would categorise as 'high risk'. However, NICE's own definition of 'high risk' covered at least 58% of all patients with osteoarthritis (Paragraph 5.2 of the guidance). Merck Sharp & Dohme would contend that the absence of 'only' in this context was not misleading and therefore not a breach of Clause 7.2.

Merck Sharp & Dohme believed the quote provided a fair reflection of the guidance, and did not give excessive emphasis to the statement. The leavepiece did not suggest or recommend use of COX-2 inhibitors in any patient group outside that recommended by NICE.

Patients with a previous history of perforations, ulcers and bleeds

NICE restated that the propensity for NSAIDs to cause perforations, ulcers and bleeds was well recognised and the risk factors for these side effects were equally well known. Hence, the starting point for guidelines on the use of NSAIDs was usually: was an NSAID really necessary? If it was not, then an alternative such as paracetamol should be used. In high risk patients, such as those with a past history of PUB where treatment with an NSAID was necessary, NICE had concluded that use of a COX-2 selective inhibitor might be an appropriate choice.

The prescribing information for Vioxx included the precaution/warning (in both the precautions and side-effects sections) that 'In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers and bleeds (PUBs). Patients with a prior history of PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB'. The graph reproduced on page 3 of the leavepiece clearly showed that PUBs did occur in patients taking Vioxx, and at a lower rate than the non-selective NSAIDs studied. Contrary to the complainant alleging that Merck Sharp & Dohme had omitted to mention this fact, it had referred to it three times.

In the press release issued by NICE upon release of the guidance it summarised it thus 'They should only

be used instead of standard NSAIDs in people with rheumatoid arthritis or osteoarthritis who may be at 'high risk' of developing serious gastrointestinal problems. High risk patients include those age 65 or over, those already taking other medicines which can cause gastrointestinal problems (such as ulcers) and those who have existing gastrointestinal problems'. No additional precaution was stated for patients with a past history of PUB in this press release. It would seem reasonable to conclude that NICE believed its press release to be a reasonable summary of its guidance that reflected the meaning intended by the authors. If, as the complainant asserted, this was a matter to which NICE attached 'great concern' one would have thought this emphasis would be reflected in its press release. Merck Sharp & Dohme believed the leavepiece to be a fair reflection of the guidance from NICE and the intended meaning of the authors, and it did not breach Clause 11.2.

It was not at all clear what the complainant was specifically alleging although it was suggested that the leavepiece 'might result in some patients being put at risk'. Merck Sharp & Dohme would entirely refute that suggestion. It might be that the basis for the complainant's suggestion was the omission of the sentence 'The use of even a COX-II selective agent should be considered especially carefully in this situation'. A possible construction of this sentence was that the practitioner should further consider the risk/benefit ratio for a patient with a previous history of PUBs. Even with this further consideration in mind, the stark choice could only be to treat or not to treat. If it was the former then Merck Sharp & Dohme's belief was that NICE considered the use of a COX-2 selective inhibitor to be an appropriate choice.

Merck Sharp & Dohme contended that the relative risk data as illustrated in the graph on page 3 would suggest that Vioxx was an entirely appropriate choice. However Merck Sharp & Dohme clearly stated that the use of Vioxx did not entirely remove the risk of PUBs: it reduced the relative risk by 49% compared to a conventional NSAID. In that respect Merck Sharp & Dohme did not believe the piece to be misleading and/or to put patients at risk as the complainant suggested.

With regard to the complainant's suggested solution viz PPI plus standard NSAID, the NICE guidance queried their effectiveness in the prophylaxis and treatment of NSAID related GI events (Paragraph 2.9 of the guidance). Whilst there was some evidence based on endoscopy studies to suggest that PPIs might reduce gastric and duodenal ulcer rates, Merck Sharp & Dohme was unaware of any evidence to support the notion that this regimen reduced the risk of serious GI complications ie perforations and bleeds.

In contrast, data for refecoxib in this particular at risk group (ie previous PUB) were available. In the VIGOR trial, subgroup analysis of patients with previous GI events showed a relative risk for clinical GI events of 0.4 compared with naproxen. More recently Hawkey *et al* (2001) analysed data from two 12 week endoscopy studies which showed that, even in patients with a previous history of GI disease, the cumulative incidence of gastroduodenal ulcers was significantly less for rofecoxib than ibuprofen. In the light of these data Merck Sharp & Dohme felt that the complainant's accusation that it was allowing patients to be put at risk was wholly unjustified.

PANEL RULING

The front page of the leavepiece was headed 'NICE guidance for the use of COX-2 selective inhibitors' below which was a box of text which contained, *inter alia*, the two statements at issue. The first statement was contained within the introductory statement in the box of text which read 'The NICE guidance assessed the use of COX-2 selective inhibitors in the treatment of osteoarthritis and rheumatoid arthritis. The guidance recommends that COX-2 selective inhibitors should be *'used in preference to standard NSAIDs … in patients who may be at 'high-risk' of developing serious gastro-intestinal adverse events"*. The italicized quote was printed in royal blue.

The NICE guidance referred to in the leavepiece was entitled 'Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis'. Paragraph 1.3 of the guidance, from which the introductory statement above was taken, stated 'Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects'.

Within the context of the NICE guidance, which concerned the use of COX-2 medicines in RA and OA, and given that the first sentence of Paragraph 1.3 of the guidance stated the indications, it was clear to the Panel that the word 'only' in the second sentence of Paragraph 1.3 referred to high risk patients and not to RA and OA as submitted by Merck Sharp & Dohme. The Panel considered that the omission of the word 'only' from the quote in the leavepiece meant that readers would be unaware that, although the four COX-2 selective inhibitors under review were licensed for use in all adult patients with osteoarthritis or rheumatoid arthritis, the view of NICE was that they should only be used in those patients who might be at a high risk of developing serious GI side-effects. NICE was thus recommending that the use of the medicines should be more restricted then their licences allowed. The Panel considered that the NICE guidance had not been accurately quoted and that the statement in the leavepiece was thus misleading. Breaches of the Clauses 7.2 and 11.2 were ruled.

Beneath the introductory statement were five bullet points setting out which patients might be identified as being at 'high risk' of developing serious GI adverse events. The last bullet point stated 'previous history of perforations, ulcers or bleeds (PUBs)'. The information about high risk patients appeared in quotes as if taken directly from the NICE guidance.

Paragraph 1.4 of the NICE guidance described high risk patients. The first half of the paragraph identified such patients as, *inter alia*, those age 65 years or above or those taking concomitant medicines known to

increase the likelihood of upper GI adverse events. The second half of the paragraph read 'The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation'.

The Panel noted that the information in the leavepiece appeared as a direct quote from the NICE guidance and this was not so. The description of patients at risk appeared to be based on Paragraph 1.4 in the section headed 'Guidance' but was set out more like Paragraph 2.10 in the section headed 'Clinical Need and Practice'. The document had not been accurately quoted and a breach of Clause 11.2 was ruled.

Although the last bullet point in the box of text correctly described one group of potentially high risk patients as those with 'previous history of perforations, ulcers or bleeds (PUBs)' it did not state, as it did in the NICE guidance (Section 1), that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. It appeared that NICE considered patients in this particularly high risk group to be no more vulnerable than other high risk patients such as those aged 65 years or above which was not so. The Panel considered that the box of text was misleading in this regard; it was immaterial that the issue of patients with a history of PUBs was addressed elsewhere in the leavepiece. A breach of Clause 7.2 was ruled.

Complaint received **2 November 2001**

Case completed **14 December 2001**

CASE AUTH/1252/11/01 *NO BREACH OF THE CODE*

ANONYMOUS v ASTRAZENECA

Meeting at cinema complex

An anonymous complaint was received about meetings held at a local cinema complex, in particular a meeting held by AstraZeneca in November. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

The complainant stated that as a general practitioner he was very concerned about the number of meetings which were being held at the complex. The complainant provided the invitation to the latest meeting, which was being held by AstraZeneca. After the lecture a film was shown which was totally against the Code, and also non-health professionals were attending.

The Panel noted that the venue for the meeting was to be one auditorium of a multi-screen cinema complex. There was no implication in the invitation to the meeting that the viewing of a film was included as part of the evening's agenda. Only health professionals had been invited to the meeting and arrangements with staff at the venue were such that entry to the auditorium would be monitored. Before the meeting started a modest hot buffet was to be provided. The educational content of the meeting was to last one hour. While it was probably to be expected that some delegates might stay on at the cinema complex when the meeting had ended to watch a film, AstraZeneca had submitted that it would have no involvement in the showing of any films after the close of the meeting and that it had made this clear to delegates prior to the meeting.

The Panel appreciated that the proposed venue for the meeting might attract comment but considered that the arrangements for it had been acceptable. No breach of the Code was ruled.

An anonymous complaint was received about meetings held at a local cinema complex, in particular a meeting held by AstraZeneca UK Limited on 21 November. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

COMPLAINT

The complainant stated that as a general practitioner he was very concerned about the number of meetings which were being held at the complex. Obviously this was against the Code. The complainant attached the invitation to the latest meeting, which was being held by AstraZeneca. After the lecture a film was shown which was totally against the Code, and also non-health professionals were attending.

The complainant hoped that the Authority would clamp down on this.

When writing to AstraZeneca the Authority drew attention to Clauses 2, 15.2 and 19.1 of the Code.

RESPONSE

AstraZeneca stated that although no previous meetings had been arranged by AstraZeneca at the complex, it appeared to be a popular venue and was suitable for holding conference type meetings. AstraZeneca's understanding was that this venue had been used by several pharmaceutical companies for educational meetings. Although the venue was a cinema complex, the auditorium was closed to the

general public and separate events management staff were available to monitor entry into the auditorium. AstraZeneca believed the venue was suitable for such meetings since it offered dedicated facilities. The venue was easy to drive to and there were extensive car parking facilities. Clinical experts could present effectively using a wide range of audio-visual equipment and were happy to do so at such a venue. In AstraZeneca's opinion a venue with adjacent facilities such as a cinema or restaurant was similar to a conference room in a hotel, where there might be a restaurant and/or leisure facilities available in the hotel itself or vicinity. AstraZeneca provided details of the costs for auditorium hire and the hospitality.

The invitations were sent to fifty health professionals, all of whom were general practitioners, with the exception of two pharmacists. As indicated on the invitation, a hot buffet was offered on registration at a cost of £7 per head. The clinical presentation on the management of reflux oesophagitis lasted for 45 minutes and was followed by 15 minutes for questions and discussion after which the meeting closed.

Representatives of the venue verbally offered AstraZeneca the opportunity for a popular film to be shown after the close of the meeting. However, AstraZeneca declined on the basis of inappropriate hospitality. AstraZeneca made clear to the delegates prior to the meeting that it would have no involvement with the showing of any films after the close of the meeting as this would be inappropriate hospitality.

All sales representatives involved in the organisation of this meeting had passed the ABPI Representatives Examination and were fully aware of the proper code of conduct when offering hospitality at a promotional meeting.

In conclusion, AstraZeneca believed that the meeting was of a high educational content with PGEA approval and was of interest to local general practitioners. AstraZeneca did not believe the venue or the content of the meeting was inappropriate for the health professionals invited. In AstraZeneca's view, the hospitality offered was secondary to the purpose of the meeting and the associated costs were not excessive. The auditorium was closed to the public and no film was to be shown in the auditorium used after the close of the meeting. AstraZeneca was firmly of the belief that the arrangements for the meeting were entirely consistent with the Code.

AstraZeneca received this complaint before the meeting was scheduled to be held. As this was the first time the company had arranged a meeting at the complex, the area sales manager decided to change the venue and transferred it to a local postgraduate centre. This action was taken to allow the meeting to progress without any potential issues arising because the venue was the subject of a complaint under the Code. The area sales manager also felt a responsibility towards the clinical speaker under these circumstances. This action was taken without prejudice as AstraZeneca believed that the original arrangements were compliant with the Code.

PANEL RULING

The proposed venue for the meeting in question was one auditorium of a multi-screen cinema complex. There was no implication in the invitation to the meeting that the viewing of a film was included as part of the evening's agenda. The Panel noted AstraZeneca's submission that only health professionals had been invited to the meeting and that arrangements with staff at the venue were such that entry to the auditorium would be monitored. Before the meeting started a modest hot buffet was to be provided. The educational content of the meeting was to last one hour. While it was probably to be expected that some delegates might stay on at the cinema complex when the meeting had ended to watch a film, AstraZeneca had submitted that it would have no involvement in the showing of any films after the close of the meeting and that it had made this clear to delegates prior to the meeting.

The Panel appreciated that the proposed venue for the meeting might attract comment but considered that the arrangements for it had been acceptable. No breach of Clauses 19.1, 15.2 and 2 was ruled.

Complaint received **13 November 2001**

Case completed **4 December 2001**

CODE OF PRACTICE REVIEW – FEBRUARY 2002

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1183/5/01 & 1184/5/01	**Biogen v Teva and Aventis Pharma**	**'Dear Health Professional' letter about Copaxone**	**Three breaches Clause 7.2 Two breaches Clause 7.3 (1998 Code)**	**Appeal by respondents**	**Page 3**
1186/5/01	**Anonymous v Pfizer**	**Promotion of unlicensed medicines/ indications**	**Breaches Clauses 2, 3.1, 3.2 and 9.1** **Audit of relevant Pfizer procedures required by ABPI Board** **Public reprimand by ABPI Board**	**Appeal by respondent** **Report from Appeal Board to ABPI Board**	**Page 10**
1204/7/01	**Roche v Ortho Biotech**	**Promotion of Eprex**	**Breach Clause 3.2**	**Appeal by complainant**	**Page 30**
1205/7/01	**GlaxoSmithKline v AstraZeneca**	**Promotion of Symbicort**	**Breach Clause 4.1 Five breaches Clause 7.2 Breaches Clauses 7.4 and 7.10**	**Appeals by complainant and respondent**	**Page 37**
1207/7/01	**AstraZeneca v GlaxoSmithKline**	**Promotion of Seretide**	**Five breaches Clause 7.2 Breaches Clauses 7.4 and 7.10**	**Appeal by complainant**	**Page 58**
1210/7/01	**Schwarz Pharma/Director v Schering-Plough**	**Breach of undertaking**	**Breaches Clauses 2 and 22** **Audit of Schering-Plough's procedures required by Appeal Board**	**No appeal** **Report from Panel to Appeal Board**	**Page 78**
1215/8/01	Hospital Consultant v Aventis Pharma	Conduct of representative	No breach	No appeal	Page 81
1216/8/01	**General Practitioner v Wyeth**	**Representative training exercise**	**Breach Clause 15.8**	**No appeal**	**Page 82**
1217/8/01	**Yamanouchi Pharma v Pfizer**	**Promotion of Cardura XL**	**Three breaches Clause 7.2 Breaches Clauses 7.3, 7.4 and 7.6 (all 1998 Code) Breach Clause 20.2**	**No appeal**	**Page 84**
1218/8/01	**AstraZeneca/Director v GlaxoSmithKline**	**Promotion of Seretide and breach of undertaking**	**Breach Clause 22**	**Appeal by complainant**	**Page 94**
1224/8/01	**Aventis Pharma v Pharmacia**	**Fragmin leavepiece**	**Five breaches Clause 7.2**	**No appeal**	**Page 109**
1228/9/01	**General Practitioner v GlaxoSmithKline**	**Medical information letter**	**Two breaches Clause 7.2**	**No appeal**	**Page 116**
1229/9/01	**Merck Sharp & Dohme v Pfizer**	**Lipitor abbreviated journal advertisement**	**Breaches Clauses 4.1 and 7.2**	**No appeal**	**Page 118**
1230/9/01	**Procter & Gamble and Aventis Pharma/Director v Merck Sharp & Dohme**	**Fosamax journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 121**

1232/9/01	**Alcon Laboratories v Allergan**	**Promotion of Lumigan**	**Breach Clause 3.1**	**No appeal**	**Page 126**
1233/9/01	Merck Sharp & Dohme v Novartis	Promotion of Lescol	No breach	No appeal	Page 128
1235/10/01	Wyeth v Novo Nordisk	Kliovance leavepiece	No breach	No appeal	Page 131
1236/10/01	**Lilly v Janssen-Cilag**	**Misleading claims about Zyprexa**	**Breaches Clauses 7.2, 7.9, 8.1 and 15.2**	**No appeal**	**Page 134**
1237/10/01	**Wyeth v AstraZeneca**	**Nexium journal advertisements**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 140**
1238/10/01	**Paragraph 17 v Wyeth**	**Representative training exercise**	**Breach Clause 15.3**	**No appeal**	**Page 144**
1239/10/01	**Health Authority Primary Care Medical Adviser v Pfizer**	**Invitation to meeting**	**Breach Clause 19.1**	**No appeal**	**Page 147**
1240/10/01	**General Practitioner v Novartis**	**Conduct of representative**	**Breaches Clauses 15.2 and 15.9**	**No appeal**	**Page 149**
1242/10/01	**Professor of Respiratory Medicine v GlaxoSmithKline**	**Seretide 'Dear Doctor' letter**	**Breach Clause 7.2**	**No appeal**	**Page 151**
1243/11/01	Health Authority Joint Prescribing Committee v Novartis	Expanded Access Programme for Glivec	No breach	No appeal	Page 155
1244/11/01 & 1245/11/01	**Consultant Physician v Sanofi-Synthelabo and Bristol-Myers Squibb**	**Meeting about Plavix**	**Breach Clause 9.1**	**No appeal**	**Page 160**
1246/11/01	**Hospital Chief Pharmacist v Merck Sharp & Dohme**	**Vioxx leavepiece**	**Two breaches Clause 7.2 Two breaches Clause 11.2**	**No appeal**	**Page 163**
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PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).