PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 29 AUGUST 2000

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.

1999 Annual Report

The Annual Report for 1999 of the Prescription Medicines Code of Practice Authority has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 127 complaints in 1999 as compared with 144 in 1998 and 145 in 1997. The number of cases dealt with usually differs from the number of complaints because some complaints involve more than one company and some complaints are not proceeded with because, for example, no *prima facie* breach is established. There were 126 cases in 1999 as compared with 138 in 1998 and 165 in 1997. The number of allegations which had to be considered in 1999 was, however, high, 350 being ruled upon by the Code of Practice Panel as compared with 306 in 1998 and 298 in 1997.

Unusually, in 1999 the greatest number of complaints, 61, came from pharmaceutical companies with 48 coming from health professionals. This was also the case in 1996 but in every other year there have been more complaints from health professionals than from pharmaceutical companies.

Of the 350 rulings made by the Code of Practice Panel in 1999, 290 (82.9%) were accepted by the complainants and respondents involved, 34 (9.7%) were unsuccessfully appealed to the Code of Practice Appeal Board and 26 (7.4%) were successfully appealed.

The Code of Practice Panel met 86 times in 1999 (74 in 1998) and the Code of Practice Appeal Board met 8 times (10 in 1998).

Correction

It is regretted that there was an error in the report for Case AUTH/947/10/99 published in the May 2000 edition of the Code of Practice Review.

In the first paragraph of the summary on page 49, the words '… Lipostat (atorvastatin)' should have read '… Lipostat (pravastatin)'.

New Code and Constitution and Procedure in 2001?

Proposals for amendment of the Code of Practice for the Pharmaceutical Industry and the Constitution and Procedure for the Prescription Medicines Code of Practice Authority have been circulated for comment to the chief executives of ABPI member companies and those non-member companies which have agreed to comply with the Code of Practice and accept the jurisdiction of the Code of Practice Authority. The British Medical Association, the Medicines Control Agency and the Royal Pharmaceutical Society of Great Britain are also being consulted.

The ABPI Board of Management agreed that the proposals could be sent out for consultation but has not itself as yet considered them in detail. It will do that at its September meeting in the light of comments upon the proposals.

The proposed changes to the Code itself arise from problems of interpretation which have occurred, from recommendations of the Code of Practice Appeal Board, from recommendations of working parties and from external factors. The proposed changes to the Constitution and Procedure arise partly from problems which have emerged in its operation and partly from external factors.

If all goes according to plan, the proposals will go before member companies at the ABPI Half-Yearly General Meeting in October with a view to a new Code taking effect at the beginning of 2001.

Chairman of Appeal Board appointed High Court Judge

The Chairman of the Code of Practice Appeal Board, Mr James Hunt QC, has been appointed a High Court Judge, assigned to the Queen's Bench Division.

The Authority congratulates Mr Hunt on this prestigious appointment but will be sorry to lose him as Chairman of the Appeal Board.

Doctors seeking payment for seeing representatives

From time to time a company informs the Authority that particular doctors are seeking payment for seeing representatives. Where there is supporting evidence, the Authority writes to the doctors concerned to draw their attention to the Code of Practice (which applies to pharmaceutical companies) and to the UK Advertising Regulations (which apply to both companies and doctors).

In a recent case, the doctors concerned did not indicate that charging would end and the matter was referred by the Authority to the General Medical Council (GMC). The GMC took the matter up with the doctors and later advised the Authority that the practice of requesting payments from representatives had now ceased.

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:

Thursday, 26 October

Friday, 10 November

Friday, 8 December

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/966/1/00

LUNDBECK v SMITHKLINE BEECHAM

'Dear Doctor' letter about Seroxat and citalopram

Lundbeck complained about a letter sent to a doctor by SmithKline Beecham which compared that company's product Seroxat (paroxetine) with Lundbeck's product Cipramil (citalopram). The letter was sent by SmithKline Beecham's medical information department.

Lundbeck said that the letter said that the recommended daily dose of paroxetine was 20mg and that in practice the majority of prescriptions had been for 20mg/day. When discussing citalopram, the letter correctly stated that the recommended daily dose was 20mg and then discussed clinical data mainly referring to severe or recurrent depression in support of higher doses. It failed to say that 86% of all UK prescriptions were for 20mg. It was alleged that the letter, by stating SmithKline Beecham's opinion of what the dose should be, disparaged Cipramil. The Panel noted that with regard to citalopram it was stated that the recommended dose was 20mg daily. However, the letter went on to state that there was some debate as to whether this should be increased to an optimum dose of 40mg daily. The Panel noted that 86% of all UK prescriptions for Cipramil were for 20mg. The Panel considered that the failure to include such data for citalopram, having included the comparable information for Seroxat, was misleading. A breach of the Code was ruled. This ruling was not appealed. The Panel noted that one of the references cited in support of the optimum dose of Cipramil being 40mg/daily was the US data sheet for Celexa (citalopram). The Panel noted that the UK summary of product characteristics (SPC) for Cipramil represented the agreed details about the product. The SPC for Cipramil stated that in the treatment of depression the initial dose was 20mg daily and that dependent upon patient response this could be increased to a maximum of 60mg daily. There was no mention of an optimum dose. The reference to 40mg daily being an optimum dose was thus not consistent with the dosage information given in the Cipramil SPC. The Panel considered that the letter would raise doubts in the prescriber's mind about the efficacy of the 20mg dose. This was misleading and disparaged Cipramil. Breaches of the Code were ruled. Upon appeal by SmithKline Beecham the Appeal Board considered that the letter implied that there was a single recommended dose of Cipramil which was generally regarded as inadequate. The Panel's rulings in this regard was upheld.

With regard to adverse events Lundbeck alleged that SmithKline Beecham persisted in a biased, unbalanced and misleading interpretation of a possible negative cardiac impact of citalopram using a highly selective choice of information. The Panel noted that although the two paragraphs of the letter discussing adverse events began by stating that they seemed to be of a similar type and incidence for both Seroxat and citalopram, they dealt in the main with the adverse cardiovascular effects of citalopram. In the Panel's view the information regarding the cardiovascular effects of citalopram was unbalanced and misleading. Breaches of the Code were ruled. Upon appeal by SmithKline Beecham, the Appeal Board considered that the letter did not give a balanced view. The information had not been put in clinical context and the letter presented an unfair account of the safety profile of Cipramil which would deter prescribers from using the product. The Panel's rulings were upheld.

Lundbeck noted that the letter cited a review paper as evidence of a lack of citalopram's efficacy in the elderly. This review considered data from a single study only and Lundbeck alleged that it was not now a fair and balanced review of all the available data. The Panel noted that the statement in the letter that, in the elderly, citalopram was not always superior to placebo, had been taken from a review paper and not the original study. The original six week study had shown that while there had been no statistical difference in some efficacy scores between placebo and citalopram after four weeks' treatment, at six weeks there was a difference in favour of citalopram. The authors postulated that elderly people might require a longer treatment period than younger patients before responding. The Panel noted that Cipramil was indicated for the treatment of depression in adults, including the elderly. In the Panel's view the statement in the letter would raise doubts as to the efficacy of the product in this patient group. The statement gave a misleading impression as to the efficacy and suitability of Cipramil in the elderly and was thus disparaging. Breaches of the Code were ruled. Upon appeal by SmithKline Beecham, the Appeal Board accepted that with regard to treatment of the elderly there might be a difference in the amount of available clinical data for Cipramil compared with Seroxat. Nevertheless Cipramil was licensed for treatment of the elderly. The Panel's rulings were upheld.

Lundbeck noted that the summary of the letter stated that citalopram offered no advantage over the other medicines in its class for the treatment of depression. Lundbeck contended that this was misleading and intentionally 'knocking' Cipramil. A more balanced and representative view of the class, selective serotonin reuptake inhibitors (SSRIs), came from Edwards *et al* which suggested that no single SSRI was more effective than another. The Panel noted that the summary of the letter was positive for Seroxat but with regard to citalopram it only stated that 'The Drug and Therapeutics Bulletin concludes that citalopram appears to have few if any advantages over other available SSRIs' and The Medical Letter concludes 'citalopram offers no advantage over other SSRIs for treatment of depression'.' The Panel noted that both publications had been correctly quoted but considered that given the general tone of the letter both statements would be interpreted to mean that other SSRIs had shown advantages over citalopram which was not so. The Panel considered that the summary of the letter was disparaging of Cipramil and ruled a breach of the Code. Upon appeal by SmithKline Beecham, the Appeal Board upheld the Panel's ruling.

Lundbeck stated that SmithKline Beecham's selective use of data was intended to confuse and alarm prescribers and was to be deprecated. The company was obviously 'knocking' citalopram. Such persistent behaviour was contrary to the spirit of the Code. Furthermore, it brought the whole industry into disrepute in contravention of Clause 2 of the Code. It was also inappropriate for such knocking copy to be part of a medical information letter, which was, in fact, disguised promotion. The Panel noted that the letter had been sent in response to a request from a doctor for further information on Seroxat and citalopram. The Panel considered that the content and the tone of the letter did not provide a balanced discussion of Cipramil; the letter disparaged Cipramil and was thus disguised promotion of Seroxat. A breach of the Code was ruled. The Panel considered that the letter was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2. Upon appeal by SmithKline Beecham, it was the Appeal Board's opinion that prescribers and others viewed medical information departments as the independent face of the industry and held them in high regard. If prescribers could not rely on the quality and accuracy of the information issued by such departments then the pharmaceutical industry would have no credibility. Overall the Appeal Board considered that the letter in question amounted to disguised promotion. The Panel's ruling of a breach of the Code was upheld. The Appeal Board considered that the letter brought discredit upon and reduced confidence in the industry. The Panel's ruling of a breach of Clause 2 was also upheld.

Lundbeck Ltd complained about a letter which had been sent to a doctor by SmithKline Beecham Pharmaceuticals. The letter was headed with the company name in logo type beneath which was a Medical Information Department logo; the letter was signed by a member of the Medical Information Department. The letter compared SmithKline Beecham's product Seroxat (paroxetine) with Lundbeck's product Cipramil (citalopram). Lundbeck stated that the letter had been sent to practices that had switched to Cipramil as first choice SSRI (selective serotonin reuptake inhibitor) for depression. Lundbeck stated that it was of great concern to the company that SmithKline Beecham appeared to be employing Medical Information in an attempt to undermine confidence in Cipramil and, to this end, the data supplied to new customers of the product was biased and attempted to bring Cipramil into discredit. Such activities were reprehensible and contrary to Clauses 7.2, 7.7 and 8 of the Code.

SmithKline Beecham stated that the letter was sent by Medical Information only in response to a request from a health professional for information on how Seroxat compared with citalopram. Between June and December 1999 similar letters had been sent out on 530 occasions – this compared with 2395 requests for written information on Seroxat in the same period. In the case in question the request for information had come via a representative.

1 Dosage

COMPLAINT

Lundbeck noted that the letter stated that the recommended daily dose for paroxetine was 20mg daily in depression, and supported that statement with 'in clinical practice … the majority of prescriptions (78%) have been for 20mg/day'.

When discussing the dose of citalopram, the letter correctly stated that the recommended daily dose was 20mg. The letter then discussed clinical study data – mainly referring to severe or recurrent depression in support of higher doses.

In the letter SmithKline Beecham failed to state that 86% of all UK prescriptions for citalopram were for 20mg. As the company considered it appropriate to reinforce recommendations from the Seroxat summary of product characteristics (SPC) with current market data, Lundbeck requested that its own statement regarding marketed use of Cipramil was used in all future medical information letters where citalopram was mentioned.

Lundbeck objected to the use of the Celexa (US) data sheet as a reference. The benchmark for UK prescribing was the SPC for Cipramil which had been approved by the Medicines Control Agency, not the opinion of another regulatory body. Lundbeck stated that it would not seek to influence UK prescribers of SmithKline Beecham products such as co-amoxiclav by reference to the many different formulations and posologies recommended elsewhere in the world.

Lundbeck stated that, in its opinion the letter, by stating SmithKline Beecham's opinion of what the dose of Cipramil should be, disparaged Cipramil and a breach of Clause 8 was alleged.

RESPONSE

SmithKline Beecham stated that its published data indicated that 78% of prescriptions for Seroxat were for a 20mg dose (Donoghue 1996). The company considered that this figure would be higher if it did not reflect its leading position in hospital psychiatry, where higher doses were often used.

SmithKline Beecham stated however that that was not the point it was trying to make as this data only reflected prescribing habits which could be in error. For instance the average dose of a tricyclic antidepressant was nearly 60mg despite the fact that it was widely accepted that this was a sub-therapeutic dose. Seroxat had been shown to have an optimal dose of 20mg/day for depression and this had been reflected in SPCs world-wide. This was not the case with citalopram and that was the point the company was endeavouring to make. SmithKline Beecham noted that Bech (1993), in a meta analysis of clinical trials, specifically found citalopram 40mg to be the most 'appropriate dose'. Another study by Montgomery *et al* (1992) found 'the 20mg dose is associated with a slightly better response than placebo but at no stage in the study was the difference statistically significant on any of the measures used'. The author went on to state that 'This suggests that patients with major depression should be treated with

40mg'. Feighner *et al* (1998) reported 'Citalopram 40mg and 60mg/day reduced HAMD total score to a significantly ($p<0.01$) greater degree than placebo.' The study found that 10mg or 20mg doses did not produce a statistically significant difference on all measures of the study. The authors concluded that 'citalopram 40mg/day showed greater efficacy than citalopram 10mg and 20mg/day'. SmithKline Beecham noted that two of the recent references supplied by Lundbeck supported this view. Labbate *et al* (1999) examined efficacy citing Montgomery and Feighner and also referred to a flexible dosing study by Mendels *et al* (1997) which found that citalopram 20mg-80mg was effective in the treatment of depression with an average dose of 52mg at endpoint. Similarly, the second reference supplied by Lundbeck, Tan *et al* (1999), cited Montgomery, Fieghner and Mendels again. The author concluded that dosing should start at 20mg/day and generally increase to 40mg after one week, echoing almost word for word the US data sheet. This advice was also issued in the Spanish data sheet which stated that citalopram 20mg was the minimum effective dose and 40mg was the optimal dose, and very similar wording was found in the French data sheet.

SmithKline Beecham stated that in the studies cited above, depression scores of patients involved were not unduly biased to the more severe and resistant end of the depressive spectrum, rather mean scores reflected standard entrance depressive scores.

SmithKline Beecham stated that it thus continued to consider that its contention that 20mg of citalopram might not be the optimum dose was fair and balanced. The company did not consider that referencing the US data sheet in a medical information letter was in breach of the Code.

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 Seroxat and citalopram, discussed comparative clinical trials, dosage, adverse events and their 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.

The Panel noted that in the discussion of dosage it was stated that in depression the recommended dose of Seroxat was 20mg daily and that this had been found to be the optimal dose for most patients. In support of this it was stated that 78% of prescriptions in clinical practice were for 20mg/day. With regard to citalopram it was stated that the recommended dose was also 20mg daily. However, the letter went on to state that there was some debate as to whether this should be increased to an optimum dose of 40mg daily. The Panel noted Lundbeck's submission that 86% of all UK prescriptions for Cipramil were for the 20mg dose. The Panel considered that the failure to include such data for citalopram, having included the comparable information for Seroxat, was misleading. The letter was therefore subject to the Code and a breach of Clause 7.2 was ruled.

The Panel noted that one of the references cited in support of the optimum dose of Cipramil being 40mg/daily was the US data sheet for Celexa (citalopram); in its response SmithKline Beecham had also referred to data sheets from a number of other countries. The Panel noted that the UK SPC for Cipramil represented the agreed details about the product. Information from other countries might be of interest but the UK SPC took priority. The Panel noted that the SPC for Cipramil stated that in the treatment of depression the initial dose was 20mg daily and that dependent upon patient response this could be increased to a maximum of 60mg daily. There was no mention of an optimum dose in the SPC. The reference to 40mg daily being an optimum dose was thus not consistent with the dosage information given in the Cipramil SPC. The Panel considered that the letter would raise doubts in the prescriber's mind about the efficacy of the 20mg dose. The Panel considered that in this regard the letter was misleading and disparaged Cipramil as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham agreed to the inclusion of the fact that 86% of all UK prescriptions for citalopram were for 20mg. This would have provided a balance to the statement on Seroxat prescriptions. It therefore accepted a breach of Clause 7.2.

The written appeal stated that SmithKline Beecham wished to appeal the breach of Clause 8.1 with regard to the optimum dose of Cipramil being 40mg daily. The company's representatives indicated to the Appeal Board that the ruling of Clause 7.2 was also appealed.

SmithKline Beecham said that with regard to the 40mg dose of citalopram, the letter stated 'For citalopram, the recommended dose is 20mg daily but, although clinical trials have been conducted where a daily dose of 20mg has been used, there is some debate as to whether this should be increased to an optimum dose of 40mg in the majority of depressed patients'. The statement was based on several published papers (which were disappointingly not referred to by the Panel).

The published literature stated:

1 Bech in a meta analysis of clinical trials specifically found citalopram 40mg to be the 'most appropriate dose'.

2 Montgomery *et al* found 'the 20mg dose is associated with a slightly better response than placebo but at no stage in the study was the difference statistically significant on any of the measures used'. The paper went on to state 'This suggests that patients with major depression should be treated with 40mg'.

3 Feighner *et al* revealed statistically insignificant HAMD total improvement scores for placebo, 10mg and 20mg of Cipramil. Only the 40mg and 60mg doses had statistically significant improvement scores.

The statement in the letter was also substantiated by the currently approved US data sheet and many other approved data sheets across Europe. The statement thus reflected a wide variety of well regarded sources which concluded a 40mg daily dose of citalopram might elicit a better clinical response than 20mg a day.

The statement in the letter was also in accordance with the UK SPC for citalopram which stated that according to individual patient response the 20mg dose might be increased to a maximum of 60mg a day (maximum of 40mg a day in the elderly). Furthermore SmithKline Beecham agreed that although the UK SPC should always take priority over other SPCs, reference to other SPCs could be pertinent and provided useful clarity to UK prescribing information without being inconsistent with the UK SPC. Given that the statement in question described the 20mg daily dose as the recommended licensed daily dose but that its clinical usefulness had been questioned by a number of regarded and competent authorities (a point of fact), the statement remained an accurate and balanced summary of medical information available on citalopram. SmithKline Beecham therefore strenuously denied a breach of Clause 8.1.

APPEAL BOARD RULING

The Appeal Board noted that the Cipramil SPC stated that, for the treatment of depression, 'Citalopram should be administered as a single oral dose of 20mg daily. Dependent on individual patient response this may be increased to a maximum of 60mg daily'. For elderly patients the SPC gave a recommended dose of 20mg. The letter, however, stated 'For citalopram, the recommended dose is 20mg daily but … there is some debate as to whether this should be increased to an optimum of 40mg in the majority of depressed patients.' The letter had thus not reflected the information given in the Cipramil SPC. In the Appeal Board's view the letter was misleading and disparaging as it implied that there was a single recommended dose of Cipramil which was generally regarded as inadequate. The Panel's rulings of breaches of Clauses 7.2 and 8.1 were upheld. The appeal on this point was unsuccessful.

2 Adverse events

COMPLAINT

Lundbeck stated that SmithKline Beecham persisted in a biased, unbalanced and misleading interpretation of a possible negative cardiac impact of citalopram. SmithKline Beecham used the Öström paper in support of its contentions. Lundbeck stated that in continuing this negative perspective of Cipramil SmithKline Beecham was not providing a balanced and up-to-date view of all the available literature in breach of Clause 7.2 and, more importantly, Clause 7.7 of the Code.

In contradiction to the highly selective choice of information presented by SmithKline Beecham, Lundbeck cited the following papers that had reviewed Cipramil and safety issues: Labbate *et al* (1999) where the animal data were refuted and 'didesmethylcitalopram forms in minuscule concentrations [in man] and is clinically irrelevant.' Tan *et al* (1999) 'no serious cardiovascular adverse events in humans have been reported in association with [Cipramil]'. Feighner (1999) 'Although more than 12 million patients have been exposed to citalopram, only 2 fatalities have been reported in patients who ingested citalopram alone.'

The data from Edwards *et al* (1999) showed a rate of fatal adverse events from paroxetine of 5.78 per 100,000 prescriptions in the first 2 years post launch in the UK compared to a rate of 2.1 per 100,000 for citalopram in an equivalent period. This hardly supported the tone of SmithKline Beecham's letter and was more relevant to UK clinical practice.

RESPONSE

SmithKline Beecham noted that the letter stated, '… citalopram has not been shown to be cardiotoxic.' The letter then cited the SPC for citalopram, which stated, 'consideration should be given to factors that effect the disposition of a minor metabolite of citalopram didesmethylcitalopram that could theoretically prolong the QTc interval in susceptible individuals.' SmithKline Beecham accepted that the SPC went on to mention that in 2500 patients, including 277 with pre-existing cardiac conditions, no clinically significant changes were noted and this was now included in the letter.

SmithKline Beecham stated that the papers cited by Lundbeck, Labbate *et al* and Tan *et al*, clearly demonstrated a theoretical potential for citalopram to exert cardiotoxicity in the pre-clinical studies. These reviews noted that intravenous administration of citalopram produced QTc prolongation and Torsades de Pointes in beagle dogs. Citalopram was metabolised in the liver by CYP 2C19 and CYP 3A4 to desmethylcitalopram and then further broken down by CYP 2D6 to didesmethylcitalopram. It was this latter metabolite that had been implicated in cardiotoxicity. SmithKline Beecham accepted that in man it reached a tenth to fifteenth the concentration of its parent drug and under normal circumstances this was not clinically significant.

However, there might well be circumstances that departed from the normal state of affairs and SmithKline Beecham considered that they could not be necessarily dismissed out of hand. By urging doctors to give consideration to this the authors of citalopram's UK SPC were equally not being dismissive. Pharmacokinetic factors to consider in the disposition of medicines included overdose and renal and hepatic impairment.

SmithKline Beecham stated that in cases of overdose with citalopram ECG abnormalities and convulsions had been reported (Personne *et al* (1997); Grundemar *et al* (1997)). Equally, Öström *et al* reported on 6 fatalities attributed to overdose with citalopram. These authors proposed that prolongation of QTc interval was a possible mechanism leading to fatal ventricular arrhythmia.

SmithKline Beecham noted that Lundbeck chose to quote Edwards *et al* who derived a rate of adverse events, using CSM data and IMS data. Edwards *et al* acknowledged that this data did not allow causal association and did not refer to a fatality rate in their text. The CSM data that Edwards *et al* presented were from two separate time periods (1991-93 and 1995-97) and during this time suicides (as recorded in a verdict by a coroner) fell (13, ONS data). The ONS data did not include death where the coroner had recorded an open verdict. Even so, SmithKline Beecham considered that the rate that Lundbeck derived from the data sources was spurious. Indeed, Edwards *et al* stated that, '… in suicidal patients and also in people with personality disorders and others prone to incidents of self poisoning, citalopram may not be the first line treatment in view of the reports of death resulting from this compound'.

SmithKline Beecham considered that it had been balanced when it stated, 'Such views have been challenged by others'. Since the citalopram SPC urged consideration of the factors that affected the disposition of didesmethylcitalopram, the company considered that it would not be in patient or prescriber interests not to do this.

In highlighting all of these factors SmithKline Beecham did not consider that it was in breach of the Code.

PANEL RULING

The Panel noted that although the two paragraphs of the letter discussing adverse events began by stating that they seemed to be of a similar type and incidence for both Seroxat and citalopram the paragraphs dealt, in the main, with the adverse cardiovascular effects of citalopram. The first paragraph stated that although citalopram had not been shown to be cardiotoxic the SPC did warn that increased levels of one of its metabolites, didesmethylcitalopram, could theoretically prolong the QTc interval in susceptible patients. The second paragraph drew attention to ECG abnormalities and convulsions which had been reported following citalopram overdose. The paper by Öström *et al* which reported on six forensically investigated suicides where overdose with citalopram was found was discussed. It was stated that the authors had proposed that one possible mechanism of death was prolongation of the QTc interval by citalopram and/or its active metabolites leading to ventricular arrhythmias and that they had recommended the same precautions in prescription of citalopram as with tricyclic antidepressants. The paragraph ended with the sentence 'Such views have been challenged by others' for which Hale (1998) was cited in support although no further details were given. No information about the possible toxicity of Seroxat in overdose was given.

The Panel noted that the theory that didesmethylcitalopram could prolong the QTc interval, and thus precipitate ventricular arrhythmias, was based on work in dogs. The relevance of this finding to humans had been disputed (Labbate *et al* 1999) and there was data to show that, in the clinic, citalopram did not cause any clinically significant changes in ECG readings, even in patients with ischaemic heart disease or in those taking other medicines that might prolong the QTc interval (Labbate *et al*; Cipramil SPC). This information had not been given in the letter and so the theoretical cardiovascular effects of citalopram had not been put into a clinical context. The Panel did not consider that the last sentence 'Such views have been challenged by others' was sufficient to counterbalance the previous two paragraphs of information. The Panel noted SmithKline Beecham had now included the positive SPC statement in the letter.

In the Panel's view the information regarding the cardiovascular effects of citalopram was unbalanced and misleading. Breaches of Clauses 7.2 and 7.7 were ruled.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham stated that it denied breaches of Clause 7.2 and 7.7 and wished to appeal these.

SmithKline Beecham quite clearly highlighted in the first paragraph that adverse events were of a similar type and incidence for both Seroxat and citalopram.

It was clear that citalopram in situations of overdose could cause QTc prolongation with resultant arrhythmia risk. This was not simply a theoretical risk from preclinical animal studies and SmithKline Beecham referred to a paper by Grundemar *et al* (1997) entitled 'Symptoms and signs of severe citalopram overdose'. Five patients who all survived an overdose of citalopram all showed QTc prolongation. The paper further stated that these electrocardiographic changes had been associated with an increased risk of developing dysrrythmia or arrhythmia. These were the effects that Öström *et al* postulated were the cause of fatality in six cases of citalopram overdose.

SmithKline Beecham noted that Lundbeck quoted Feighner, suggesting just two deaths in citalopram overdose. There were numerous further reports of fatalities from citalopram overdose when used alone. Worm *et al* noted four deaths from 92 autopsy deaths attributable to citalopram overdose on its own. There were a further 21 deaths of the 92 in which citalopram was taken together with other compounds.

The Cipramil SPC itself stated six fatalities had been reported in overdose.

SmithKline Beecham noted that Lundbeck also quoted from Tan *et al* that 'no serious cardiovascular adverse events have been reported from citalopram'. This was in reference to routine dosing of citalopram. In overdose Tan *et al* stated 'In a review of overdose cases over 1 year, ECG changes were noted in 6 out of 18 patients who ingested more than 60mg …. All patients who invested more than 1900mg had widened QRS intervals, convulsions or both'. They

recommended cardiac monitoring for citalopram overdose.

SmithKline Beecham noted that Lundbeck also made a direct comparison from Edwards *et al* between 2 year post-marketing data for Seroxat and citalopram. This data was clearly not compatible for a number of reasons not least because of the number of years between the two sets of data accumulation and the completely different life cycle stages of the SSRI market. It was therefore not comparing like with like. This paper even highlighted concerns of Cipramil's safety in overdose by stating 'Research has shown that SSRIs are relatively safe in overdose … citalopram may be a possible exception to the safety profile of SSRIs in overdose.'

SmithKline Beecham therefore believed that the letter was based on the available literature, and it was therefore reasonable to highlight concerns of cardiotoxicity with citalopram overdose.

APPEAL BOARD RULING

The Appeal Board noted that the letter referred to a theoretical prolongation of the QTc interval in susceptible patients as did the SPC. The letter omitted the statement in the SPC that 'in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted'.

The Appeal Board noted the Cipramil SPC stated that in eight cases of overdose considered to be due to citalopram alone the clinical picture was inconsistent and that no case was fatal. The SPC continued by stating that six fatalities had been reported; in one overdose was suspected although the post-mortem results had been difficult to interpret with confidence. In the remaining five cases a combination of other medicines had been taken. While the letter stated that in overdose ECG abnormalities and convulsions had been reported the letter did not state that none of the cases of overdose from the papers cited in support of the statement had been fatal. The letter went on to discuss the Öström paper from the Lancet which reported six fatalities associated with Cipramil; it was not stated in the letter, however, that in five of the six cases other medicines had also been taken. The Appeal Board did not know if any of the six fatalities reported by Öström *et al* were the same as any of the six referred to in the Cipramil SPC.

The Appeal Board considered that the adverse event section of the letter did not give a balanced view of Cipramil. The information given had not been put into clinical context. In the Appeal Board's view the letter presented an unfair account of the safety profile of Cipramil which would deter prescribers from using the product. The Panel's rulings of breaches of Clauses 7.2 and 7.7 were upheld. The appeal on this point was unsuccessful.

3 The elderly

COMPLAINT

Lundbeck noted that the letter cited a paper by Noble and Benfield (1997) as evidence of a lack of citalopram's efficacy in the elderly. This review considered data from a single clinical study only and was now not a fair and balanced review of all the available data.

Lundbeck noted that Labbate *et al* had stated 'At week six, mean HAMD scores were significantly lower in the citalopram group …'. Tan *et al* had cited the same paper and had also presented data from a further (albeit) open study of 123 elderly depressed patients where anxiety, depressed mood, fear, panic and restlessness were all significantly improved. Fieghner had cited the same data as supportive of a positive impact of citalopram in elderly depressed patients. Gottfries *et al* (1999) had stated '… the use of citalopram appears to be beneficial in the treatment not only of depressed mood but also of other emotional disturbances (in the elderly)'.

RESPONSE

SmithKline Beecham noted that its letter cited a review by Noble and Benfield that included an analysis of the efficacy of citalopram in the elderly. The authors concluded that in the only clinical trial available in the elderly, citalopram was not always superior to placebo (Nyth *et al* 1992).

With regard to the four reviews cited by Lundbeck, SmithKline Beecham noted that Labbate *et al* referred to the Nyth study, which had not been shown to be conclusive and so added nothing new. Tan *et al* also cited Nyth and an additional study by Ragneskog *et al* (1996). This latter study was an open study of elderly patients suffering from 'emotional disturbance', of whom 76% were suffering from dementia. Ratings were conducted with the GBS, which was a rating scale for dementia and not specific for depression. SmithKline Beecham therefore did not consider that this study lent itself for consideration as a proof of efficacy study in the treatment of depression in the elderly. The review by Gottfries *et al* also cited the Nyth and Ragneskog studies and the Feighner review sourced its reference from Nyth.

SmithKline Beecham stated that no new robust clinical trial data had thus been presented by Lundbeck and the company considered that the case for clear clinical efficacy in the elderly had still not been conclusively demonstrated. This was in contrast to Seroxat, where efficacy in the elderly had been clearly shown in several controlled clinical studies. SmithKline did not consider that the text of the letter was misleading.

PANEL RULING

The Panel noted that the statement in the letter that, in the elderly, citalopram was not always superior to placebo, had been taken from a review paper and not the original study. The original six week study by Nyth *et al* (1992) had shown that while there had been no statistical difference in some efficacy scores between placebo and citalopram after four weeks' treatment, at six weeks there was a difference in favour of citalopram. The authors postulated that elderly people might require a longer treatment period than younger patients before responding.

The Panel noted that Cipramil was indicated for the treatment of depression in adults, including the elderly. In the Panel's view the statement in the letter would raise doubts as to the efficacy of the product in this patient group. The statement gave a misleading impression as to the efficacy and suitability of Cipramil in the elderly and was thus disparaging. Breaches of Clauses 7.2 and 8.1 were ruled.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that it accepted a breach of Clause 7.2. It wished to appeal the breach of Clause 8.1.

The statements given in the medical information letter under this heading were factually correct. They were primarily made to emphasise the wealth of clinical efficacy of Seroxat in elderly patients in comparison to the much smaller and weaker data for citalopram. SmithKline Beecham therefore did not disparage citalopram and it did not accept a breach of Clause 8.1.

SmithKline Beecham accepted a breach of Clause 7.2 in that the statement 'citalopram was not always superior to placebo in the only clinical trial available in the elderly' was too selective as it only described the negative results of the trial.

APPEAL BOARD RULING

The Appeal Board noted the statements in the SPC regarding the use of Cipramil in the elderly. It noted that SmithKline Beecham had accepted the Panel's ruling of a breach of Clause 7.2 as the letter referred to a comment in a review article and the source data was not entirely consistent with the letter.

The Appeal Board accepted that with regard to treatment of the elderly there might be a difference in the amount of available clinical data for Cipramil compared with Seroxat. Nevertheless Cipramil was licensed for treatment of the elderly. In the Appeal Board's view the letter gave a misleading impression as to the efficacy and suitability of Cipramil in the elderly and was thus disparaging. The appeal on this point was unsuccessful.

4 Summary

COMPLAINT

Lundbeck noted that in the summary of the letter, SmithKline Beecham cited both The Drug and Therapeutics Bulletin and The Medical Letter as stating that citalopram 'offers no advantage over the other SSRIs for the treatment of depression'. Lundbeck contended that this was misleading and intentionally 'knocking' Cipramil contrary to Clause 7.7 of the Code.

Lundbeck stated that a more balanced and representative view of the SSRI class came from Edwards *et al*, which suggested that no single SSRI was more effective than another. Lundbeck contended that SmithKline Beecham's reluctance to cite this reference might be based upon the fact that the authors reported that drowsiness, tremor, impotence and ejaculation failure and withdrawal phenomena were more common with paroxetine than other SSRIs.

RESPONSE

SmithKline Beecham stated that it considered that both the Drug and Therapeutics Bulletin and Medical Letter were independent respected publications. The company considered that it had reflected their various authors' views and that the inclusion of these quotes in the summary of the letter was neither inappropriate, nor misleading.

In conclusion, SmithKline Beecham considered that neither the content of the medical information letter nor the way in which it had been used constituted disguised promotion, nor that it breached any clauses of the Code.

PANEL RULING

The Panel noted that Lundbeck had mentioned Clause 7.7 of the Code which did not appear to be relevant to the matter raised. The allegation, however, appeared to relate to Clause 8.1 of the Code.

The Panel noted that the summary of the letter was positive for Seroxat but with regard to citalopram it only stated that 'The Drug and Therapeutics Bulletin concludes that 'citalopram appears to have few if any advantages over other available SSRIs' and The Medical Letter concludes 'citalopram offers no advantage over other SSRIs for treatment of depression'.' The Panel noted that both publications had been correctly quoted but considered that, given the general tone of the letter, both statements would be interpreted to mean that other SSRIs had shown advantages over citalopram which was not so. The Panel considered that the summary of the letter was disparaging of Cipramil and ruled a breach of Clause 8.1 of the Code.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that it wished to appeal the alleged breach of Clause 8.1 regarding the statements made in its summary, which were factually correct and did not unfairly or carelessly denigrate citalopram.

APPEAL BOARD RULING

The Appeal Board considered that in the context of the rest of the letter the summary was disparaging of Cipramil and upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal on this point was unsuccessful.

5 Alleged breaches of Clauses 2 and 10

COMPLAINT

Lundbeck stated that SmithKline Beecham's selective use of data was intended to confuse and alarm prescribers and was to be deprecated. The company was obviously 'knocking' citalopram contrary to Clause 8 of the Code. Such persistent behaviour,

despite requests from Lundbeck for SmithKline Beecham to make changes, was contrary to the spirit of the Code. Furthermore, it brought the whole industry into disrepute in contravention of Clause 2 of the Code as SmithKline Beecham's intention was to undermine the prescriber's confidence in citalopram. It was also inappropriate for such knocking copy to be part of a medical information letter, which was, in fact, disguised promotion contrary to Clause 10 of the Code.

RESPONSE

SmithKline Beecham strongly refuted the alleged breaches of Clauses 2 and 10. The company stated that it operated to the highest standards and rejected wholeheartedly the implications from Lundbeck that it was not observing the letter or spirit of the Code.

PANEL RULING

The Panel noted that the letter had been sent from the Medical Information Department in response to a request from a doctor for further information on Seroxat and citalopram. Health professionals and others must be able to rely on medical information departments as a source of objective information about products, be they those marketed by the company or its competitors. The Panel considered that the content and the tone of the letter did not provide a balanced discussion of Cipramil; the letter disparaged Cipramil and was thus disguised promotion of Seroxat. A breach of Clause 10.1 was ruled.

The Panel considered that the letter, coming as it did from a source that should be relied upon to provide unbiased and non-promotional information, was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that it believed that despite accepting breaches this letter was not disguised promotion and it therefore wished to appeal the ruling of a breach of Clause 10.1.

This led on to the breach of Clause 2. SmithKline Beecham denied that this material was bringing the industry into disrepute. Whilst it accepted breaches of the Code in some regards it strongly denied a breach of Clause 2. A breach of Clause 2 was a sign of particular censure and SmithKline Beecham did not believe it had brought discredit upon, and reduced confidence in, the pharmaceutical industry.

SmithKline Beecham had reviewed the materials at the centre of these alleged breaches and modified them in the light of the findings. At all times it believed it upheld consistent standards and acted both within the spirit and the letter of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the medical information letter at issue (or similar) had been sent out 530 times. In the Appeal Board's opinion prescribers and others viewed medical information departments as the independent face of the industry and held them in high regard. The Appeal Board considered that if prescribers could not rely on the quality and accuracy of the information issued by such departments then the pharmaceutical industry would have no credibility. The Appeal Board noted that there were UK guidelines on standards for medical information departments issued by the Association of Information Officers in the Pharmaceutical Industry (AIOPI).

Overall the Appeal Board considered that the letter in question amounted to disguised promotion. The Panel's ruling of a breach of Clause 10.1 was upheld. The Appeal Board noted that Clause 2 was used as a sign of particular censure. It considered that the letter brought discredit upon and reduced confidence in the industry. The Panel's ruling of a breach of Clause 2 was also upheld. The appeal was unsuccessful.

Complaint received **4 January 2000**

Case completed **16 June 2000**

PARKE DAVIS, PFIZER and MERCK SHARP & DOHME v BAYER

Lipobay journal advertisement

Parke Davis, Pfizer and Merck Sharp & Dohme complained about a journal advertisement for Lipobay (cerivastatin) issued by Bayer. All three companies complained about the claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%', which was referenced to the footnote 'Ose L *et al*. Curr Med Res Opin 1999 … 44% reduction in LDL-C achieved in females, 37% in males: mean change 38%.'

In a joint complaint, Parke Davis and Pfizer alleged that this was likely to mislead in a number of ways. Physicians could believe that all patients, male and female, could reasonably expect a reduction of 44% because of the prominence of that figure relative to the disclosure relating to males and females. The former was in the centre of the advertisement in logo type and the latter was concealed in a footnote. The prominence given to the reduction achieved in females represented cherry picking of the referenced data. The study population was mostly comprised of male patients and the emphasis on efficacy in female patients was inappropriate and misleading. In addition, response by gender was not a primary end-point of the study and did not appear to be a pre-specified analysis. The figure of 44% was not representative of the wider body of evidence which showed that a physician could not reasonably achieve such a reduction in clinical practice. Further two large multicentre studies reported a mean reduction of 34%. The use of the phrase 'up to' was also misleading as it provided no reasonable guide to the physician. In a separate complaint, Merck Sharp & Dohme made similar allegations and also referred to a document sent to health authorities by Bayer prior to the licensing of cerivastatin 400mcg. It was of note that the studies referred to therein showed a mean reduction between 33.4% and 38.4%. No claim was made for a 44% reduction.

The Panel noted that gender response was neither a primary nor secondary efficacy parameter in the Ose *et al* study. The statistically significant difference in effect between men and women treated with 400mcg cerivastatin had been shown in an exploratory sub-group analysis to assess the possible effects of gender and age on LDL-cholesterol changes. The Panel considered that the claim at issue gave the impression that a reduction of 44% in LDL-C could be achieved in the entire patient population. This was not so. It was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. Further, the Panel did not accept that the phrase 'by up to' provided sufficient qualification, nor did it negate the overall impression given. The Panel considered the claim at issue was misleading and ruled a breach of the Code. Upon appeal by Bayer, the Appeal Board considered that the claim was misleading, it gave the impression that the decrease would be reflected in the entire patient population and that was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Merck Sharp & Dohme also complained about the claim 'Bound to drop' which was beneath a picture of an elephant stepping onto a rope spanning a gorge, alleging that it appeared to guarantee that all patients prescribed cerivastatin would inevitably experience a clinically significant fall in LDL-cholesterol. This was alleged to be an exaggerated and all-embracing claim which was incapable of substantiation. The Panel did not accept that the audience would interpret the claim as guaranteeing that all patients prescribed Lipobay would experience a clinically significant fall in LDL-cholesterol. 'Bound to drop' was immediately followed, and qualified, by the claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%'. The Panel noted Bayer's submission that in the Ose study 97% of patients responded and that data on file showed that all patients that complied with the protocol showed a decrease in LDL-cholesterol. The intention-to-treat analysis showed a decrease in LDL-cholesterol in greater than 99% of patients. The Panel considered that given the data and in the context of the advertisement it was not unreasonable to use the claim 'Bound to drop'. There was no implication that patients would respond clinically to such therapy. The Panel ruled no breach of the Code.

CASE AUTH/970/1/00

Parke Davis & Co Limited and Pfizer Limited submitted a joint complaint about an advertisement for Lipobay 400mcg (cerivastatin) issued by Bayer plc, Pharmaceutical Division. The advertisement featured an elephant stepping onto a rope which spanned a gorge above the claim 'Bound to drop'. Another claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%' was referenced to a footnote which stated 'Ose L *et al*. Curr Med Res Opin 1999 … 44% reduction in LDL-C achieved in females, 37% in males: mean change 38%'. The advertisement had appeared during January and February 2000 in medical journals such as Pulse and Doctor.

COMPLAINT

Parke Davis and Pfizer alleged that the claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%' and footnote were likely to mislead in a number of ways:

Physicians could believe that all patients, male and female, who took Lipobay 400mcg could reasonably expect to achieve a 44% reduction in LDL-C because of the prominence of the LDL-C reduction figure of '44%' relative to the disclosure regarding LDL-C reduction in males and females. The promise of achieving 44% reductions in LDL-C was prominently placed in the centre of the advertisement in large type text that was wider than the elephant that hovered above it. The disclosure that the 44% reduction in

cholesterol only applied to the female patients in the study was concealed in a footnote after the reference and could easily be missed by the reader.

The prominence given to the percentage reduction in LDL-C achieved in females represented cherry picking of the referenced data used in the advertisement. The referenced data indicated that the per-protocol study population in the cerivastatin 400mcg group was comprised of mostly male patients (66%). This illustrated that the emphasis on the efficacy of cerivastatin 400mcg in female patients (the minority of the study sample) was inappropriate and misleading.

In addition, the referenced data indicated that the study was designed primarily to compare the percent change in LDL-C of cerivastatin 200mcg and 400mcg in the per-protocol population. The analysis of LDL-C response to cerivastatin 400mcg by gender was not a primary endpoint of the study and did not appear to be a pre-specified analysis. The presentation of the 44% reduction achieved by females in the study was not balanced, fair or objective and was therefore in breach of Clause 7.2 of the Code.

The figure of 44% was not representative of the wider body of evidence for the LDL-C lowering efficacy of cerivastatin 400mcg. The Panel had previously ruled in Case AUTH/735/7/98 that a claim should be 'a balanced reflection of all the available evidence.' The wider body of data for cerivastatin 400mcg showed that a physician could not reasonably achieve a reduction of up to 44% in LDL-C in patients in clinical practice as promised by the advertisement. For example, an analysis involving pooled data from six double-blind, randomised, placebo-controlled studies reported a reduction in LDL-cholesterol of 36.2% in 788 patients on cerivastatin 400mcg/day, (Stein *et al* 1999).

Further, the balance of the available evidence for the LDL-C efficacy of cerivastatin 400mcg was more accurately reflected in the results from two large (n=571), multicentre, placebo-controlled, dose response studies in patients with primary hypercholesterolaemia. Bayer had relied upon these studies in seeking approval of the 400mcg dose (eg by the US Food and Drug Administration). These studies reported that patients on cerivastatin 400mcg daily, in conjunction with dietary therapy, achieved mean reduction in LDL-C of 34%. These data, therefore, illustrated that the implication that cerivastatin 400mcg lowered LDL-C by up to 44% was not accurate nor reflective of the efficacy of cerivastatin 400mcg demonstrated in the wider body of published studies. The claim was therefore in breach of Clause 7.2 of the Code.

Parke Davis and Pfizer stated that the 44% reduction in LDL-C figure was not representative of what the clinician could reasonably expect from cerivastatin 400mcg, therefore, the use of the phrase 'up to' was also highly misleading as it provided no reasonable guidance to the clinician. This, in the context of the reported mean change in LDL-C level in this particular study of 38%, could only serve to mislead (notwithstanding the points made above). Accordingly, the claim was highly misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Bayer did not consider that use of the mean figures of up to 44% decrease in LDL-C, even though relating to a female sub-population in a single study, was misleading.

The decrease in LDL-C was very obviously dose dependent for Lipobay as was seen with all statins. There was one identifier which caused a consistently greater reduction in LDL-C for all doses of Lipobay which was female gender compared with male gender. This appeared to be specific to Lipobay and not other statins, the clinical effect of which had been well documented in previous studies, Roberts (1997), and was dose dependent.

The difference in LDL-C levels between males and females in Ose (1999) was greater than 7% and was statistically significant ($p<0.046$) relating to a population pool of over 300 patients, all of whom complied with the protocol. Also the difference in LDL-C decrease was equivalent to the mean decrease seen by doubling the dose of Lipobay or any other statin showing a linear dose response (Roberts 1997).

The 44% decrease quoted was a mean value for females and not an absolute. It was clearly qualified under the appropriate reference. To quote a mean value for LDL-C values for both genders would not be totally accurate when a statistically significant difference in clinical effect between males and females had been shown. The figure of 44% was in line with the study in general. The original clinical trial report (Study 0161 Bayer, data on file) showed that 37% of all patients taking 400mcg of Lipobay showed a 40-50% decrease in LDL-C and was the responder category containing the largest number of patients. Therefore it did not believe that it was misleading to state that a reduction of up to 44% might be seen in patients on 400mcg Lipobay.

Bayer therefore did not believe it was in breach of Clause 7.2 of the Code. It did not believe that the footnote after the reference was either concealed or would be missed by a reader interested in prescribing Lipobay.

Bayer did not understand the relevance of the complainants' remark regarding the width of the claim in relation to the width of the elephant visual. Surely pharmaceutical promotion was to relay relevant, scientific, product information to doctors, the visual only serving to bring this information to their attention.

Bayer reiterated that there was a definite difference in LDL-C decrease between males and females which was statistically significant at doses of 400mcg Lipobay. The population pool which complied with the Ose study protocol was predominantly male (approximately 60%) as this reflected the natural population which had elevated cholesterol between the ages of 18-75 years as seen in the Lipobay pooled analysis of studies (Stein 1999). Bayer considered that the use of the per-protocol rather than the intention-to-treat (ITT) population was more representative of the true pharmacological efficacy of the drug.

To have quoted either a range of LDL-C decreases of 37-44.4% or to have given a mean cumulative value for males and females would not reflect the Ose data

as accurately as 'up to 44%' with a clear qualifying statement. Bayer therefore did not consider that the prominence given to the reduction in LDL-C in females was either inappropriate or misleading.

Furthermore, although the Ose study was not primarily designed to show a gender difference, Bayer considered that this was irrelevant given the large difference between males and females found on 400mcg of Lipobay. This difference had also been described in other studies (Stein 1999). As there was a large gender difference it was only reasonable and responsible to make this apparent to prescribers in order that they might titrate doses of Lipobay accordingly.

The Ose study represented 75% of all patients in the European Lipobay 400mcg audited fully completed clinical trials in the Bayer data pool (n=302/434). Bayer therefore did not believe that the figure quoted in the reference could be deemed cherry picking.

Bayer therefore considered that the data shown was balanced, fair, objective, not misleading and not in breach of Clause 7.2 of the Code.

A study of a single population group from Scandinavia using the same inclusion/exclusion criteria should give a more accurate mean figure for decreasing LDL-C than a pooled analysis of six studies from different parts of the world, Stein (1999).

Per protocol efficacy analyses from clinical trials with Lipobay 400mcg from the Bayer data pool had shown consistently that there was a difference in effect on LDL-C between European and North American studies. The advertisement to which the complainant referred had been distributed only within the UK, and Bayer therefore considered that it was more relevant to British prescribers to quote data from European rather than US studies.

The Ose study was representative of European data, contributing 302 out of 434 patients on Lipobay 400mcg/day, and approximately one third of the 1009 patients in the total world-wide 400mcg data pool.

A mean figure quoted to represent a balanced reflection of all the available evidence would have to account for all variables between studies and populations. Unless this was done an inaccurate and misleading figure or decrease in LDL-C might well be quoted.

The journal advertisement clearly related to one controlled study conducted in Europe with a highly defined population screened and assessed for other variables to give an accurate value of the pharmacological effect of Lipobay 400mcg.

Bayer therefore submitted that the data quoted in the advertisement accurately reflected the pharmacological effect of the medicine in a controlled setting and was not in breach of Clause 7.2 of the Code.

Data from Ose showed that the mean reduction of LDL-C in all females on Lipobay 400mcg was 44%. The clinical trial report (Study 0161) stated that the responder category for LDL-C reduction containing the largest number of patients treated with Lipobay 400mcg was 40-50% (37% of all patients – male and female). Figure 3 in Study 0161 showed the scatter of LDL-C values for the study population as a whole, with decreases of over 60% in some patients. As a mean value for one dosage form of Lipobay was quoted, Bayer submitted that it was justified in using the phrase 'up to' in the advertisement. Should it have been the intention to mislead, a figure of 'up to 60% plus' could have been used and Bayer agreed that this would not be an accurate reflection of the data as a whole.

The case quoted by the complainants, Case AUTH/735/7/98, was clearly misleading, as all doses of atorvastatin were pooled to promote an effect seen only with the highest doses. The implication being that this effect would be seen at the most commonly and lowest prescribed dose.

All data for the Lipobay 400mcg advertisement related only to the 400mcg dose and no other. Bayer saw no parallel between the case quoted and the current complaint.

Bayer again considered that the use of the phrase 'up to' was not highly misleading and therefore was not in breach of Clause 7.2 of the Code in this instance.

PANEL RULING

The Panel noted that the complainants had referred to a ruling made in Case AUTH/735/7/98 which concerned the promotion of Lipitor by Parke Davis and Pfizer. In relation to an allegation that the claim 'Lowers triglycerides by up to 45%' was exaggerated and misleading, the Panel had noted that the claim was based on a small study the results for which were inconsistent with the information given in the summary of product characteristics and other data. The Panel had considered that the claim was not a balanced reflection of all the available evidence and ruled a breach of Clause 7.2 of the Code. The ruling was upheld on appeal to the Appeal Board.

Turning to the case now before it the Panel noted that Ose *et al* (1999) was a multi-centre randomised double-blind parallel-group study comparing the efficacy and safety of cerivastatin 400mcg/day and 200mcg/day in 494 patients with primary hypercholesterolaemia over a 24 week period. The primary efficacy parameter was the percentage change in LDL-C from baseline to endpoint in the per-protocol population. The study concluded that overall (in the per-protocol population) mean LDL-C reduced by 38.4% from baseline in patients receiving cerivastatin 400mcg (n=302) compared with 31.5% (n=141) in those receiving a 200mcg daily dose. This difference was confirmed in the ITT population. In addition to a responder analysis, exploratory sub-group analyses were performed to assess the possible effects of gender and age on LDL-cholesterol changes. A significant gender difference was evident in patients taking the 400mcg dose. In the per-protocol population LDL-C decreased by 44.4 ± 8.9% (n=102) in woman taking cerivastatin 400mcg compared with a decrease of 37 ± 10.2% (n=200) in men taking the same dose ($p<0.046$). The study authors also noted that a pooled analysis, Stein (1999) had revealed that the greatest efficacy was in elderly women taking cerivastatin 400mcg/day who had a mean LDL-C decrease of 40.4% from baseline.

The Panel had been provided with an extract from the original clinical trial report; Study 0161 which discussed the dose dependent increase in efficacy and stated that the responder category for LDL-C reduction containing the largest number of patients treated with cerivastatin 400mcg was 40-50% (37% of patients). A graph was provided which showed the percentage change LDL-cholesterol v baseline in patients valid for analysis in the per-protocol population for both the 200mcg and 400mcg doses. Bayer had submitted that the graph displayed the scatter of LDL-C values for the study population as a whole. Although limited information had been provided the data appeared to relate to the per-protocol population as stated in the heading rather than the intention to treat population. The scatter values in the figure showed that the greatest individual LDL-C reduction was approximately 66%, followed by two at approximately 63%.

The Panel noted that Stein (1999) was a pooled efficacy analysis of cerivastatin in the treatment of primary hyperlipidaemia of six double-blind randomised placebo controlled or comparative clinical trials where patients had received 100 to 400mcg/day. The study showed that, based on an efficacy population, a statistically significant mean percentage decrease in LDL-C of 36.2% (versus baseline) was achieved in patients receiving 400mg of cerivastatin; a reduction of 38.2% in female patients and 34.9% in male patients. The greatest reduction of 40.4% was seen in elderly females receiving 400mcg/day. The statistical significance of these gender differences was not stated.

The Panel noted that Parke Davis and Pfizer had also referred to the results of two studies (n=571) which reported a mean reduction in LDL-C of 34% achieved in patients with 400mcg. The Panel had not been provided with these studies.

The Panel noted that gender response was neither a primary nor secondary efficacy parameter in the Ose *et al* study. The statistically significant difference in effect between men and women treated with 400mcg cerivastatin had been shown in an exploratory sub-group analysis to assess the possible effects of gender and age on LDL-cholesterol changes. In the study discussion the authors stated that cerivastatin 400mcg appeared to be particularly effective for improving the lipid profile of women. The Panel noted Bayer's submission that it was reasonable and responsible to make the gender difference apparent to prescribers so that they might titrate doses accordingly. The Panel considered that whilst it might be reasonable to provide such information, its provision nonetheless had to comply with the Code.

The Panel considered that the claim at issue gave the impression that a reduction of 44% in LDL-C could be achieved in the entire patient population. This was not so. It was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. Further, the Panel did not accept that the phrase 'by up to' provided sufficient qualification nor did it negate the overall impression given.

The Panel considered the claim at issue was misleading and ruled a breach of Clause 7.2 of the Code.

APPEAL BY BAYER

Bayer did not consider that use of the mean figures of up to 44% decrease in LDL-C, even though relating to a female sub-population in a single study was misleading. Further analysis of the data relating to the study by Ose *et al* for patients with a treatment duration of at least eight weeks showed that in the intention-to-treat population (n=371), the majority of patients – 164 (51.6%) – achieved a decrease in LDL-C of >40% regardless of gender. Similarly, in the per-protocol group (n=283) the majority of patients – 145 (51.1%) - achieved a decrease in LDL-C of >40% regardless of gender.

Bayer did not consider that use of this study, which was representative of the European data on cerivastatin 400mcg, misled the prescriber. The meta-analysis of Stein (1999) included both US and European data; the US data showed lower percentages of patients achieving LDL-C reductions >20%, >30% and >40% compared with European studies. As the UK population was more accurately represented by the European data the company considered that using the meta-analysis would be misleading to UK clinicians.

Bayer supplied a table of data which showed that after at least eight weeks' treatment, LDL-C reductions of >40% were seen in 48.7% in the intention-to-treat population and 48.2% in the per-protocol population irrespective of gender. The gender distribution in this data set consisted of 63% male and 37% female patients in the intention-to-treat population and 62% male and 38% female in the per-protocol population. This would imply that a claim of 44% reduction in LDL-C did not misrepresent the mean level of reduction seen in a European population receiving cerivastatin 400mcg.

Bayer repeated its earlier comments on the use of the words 'by up to'. The scatter plot of LDL-C values for the study population as a whole showed that one patient achieved a level of LDL-C reduction of 66%. It would have been highly misleading to have used this figure in qualifying the words 'by up to', but in the context of the data available in European studies the company considered the use of the mean figure 44% to be representative and not misleading despite the fact that it referred to a sub-population. Bayer did not consider that the claim implied that this level of reduction could be achieved by the entire population. By using the phrase 'by up to' it clearly implied that not all patients would achieve this. Further, the company was unaware that it was implicit in the Code that a claim could not be qualified by reference to a footnote. In Bayer's opinion this reference further informed the prescriber of the efficacy data in the study quoted.

Bayer stated that in its opinion, the advertisement did not mislead either directly or by implication and it therefore appealed against the Panel's ruling of a breach of Clause 7.2 of the Code of Practice.

CASE AUTH/972/1/00

Merck Sharp & Dohme complained about the same claim.

COMPLAINT

Merck Sharp & Dohme stated that in choosing which statin to prescribe one factor which doctors must consider was the percentage reduction in cholesterol it was reasonable to expect from a given dose of a given statin.

Given this and the fact that doubling the dose of any statin (with significant cost implication in some cases) generally produced only about a 6% further reduction in LDL-cholesterol it was essential that the percentage reductions quoted in advertising reflected the general body of evidence.

In quoting a 44% LDL-cholesterol reduction for cerivastatin 400mcg Merck Sharp & Dohme did not believe Bayer was reflecting the body of evidence. Neither did Merck Sharp & Dohme believe that using the term 'up to' obviated this or was helpful to the clinician. The figure 44% came from reduction in LDL-cholesterol seen in female protocol compliant patients following an 'exploratory' sub-group analysis. Within the main study population there was a 38.4% reduction in LDL-cholesterol but again this was a per-protocol analysis which for the reasons given above could be misleading. The more useful intention-to-treat analysis showed a 37.9% reduction in LDL-cholesterol.

Merck Sharp & Dohme provided a copy of a document circulated to health authorities by Bayer prior to licensing of cerivastatin 400mcg. It was of note that the studies quoted showed a mean LDL-cholesterol reduction between 33.4% (per-protocol in the largest study) and 38.4%. No claim was made for a 44% reduction.

Merck Sharp & Dohme believed that by quoting 44% the advertisement was misleading as to the typical LDL-cholesterol reduction one could expect from cerivastatin 400mcg. It was not clear within the body of the advertisement that this result was from a per-protocol sub-group analysis and this general impression was not corrected by the details given in tiny print within the reference itself.

Similarly the use of the term 'up to' did not correct the overall misleading impression created. For any statin, sub-groups could be found with higher than average percentage reductions in LDL-cholesterol, in the same way that lower than average sub-group reductions could be found. If companies could use high percentages with no qualification other than 'up to' then clinicians would have little indication as to the relative efficacy of each statin at any given dose.

Merck Sharp & Dohme alleged that the use of the percentage was misleading in breach of Clause 7.2 and exaggerated in breach of Clause 7.8.

RESPONSE

Bayer agreed with the first two paragraphs of the complaint. Figures for reductions in LDL-C, especially for a new dosage, should reflect the body of evidence of data accurately, and also as a rule, a 6% extra reduction in LDL-C was expected by doubling the dose of any statin. It was therefore unfortunate that there were no rules relating to the most accurate figure to quote, ie a mean figure, an absolute or a range of decrease in LDL-C that could be expected to be seen with any statin, in order for health professionals to make a valid comparison for their own use.

The figure 44% reduction in LDL-C was a mean figure for females in a controlled, clinical trial setting and was not misleading. The difference in mean values in LDL-C reduction between male and female patients in the referenced study by Ose was 7.4% and this was statistically significant ($p<0.045$). This difference was greater than that which would be expected by doubling a dose of any statin (6%) as stated by Merck Sharp & Dohme. Bayer submitted that it was important to make this large difference known in order for doctors to dose titrate accordingly.

The mean value of LDL-C was nearer to the male figure of 37.5% due to the predominance of men in the study and was not therefore representative of the population as a whole. The Ose study was reflective of the European data pool as it included 302 out of 434 patients in European registration clinical trials. In the Ose study, 37% of all patients showed a decrease of between 40-50% and was the group with the largest number of patients.

The female sub-group in Ose was over 100 patients and was 25% of the European clinical trial data pool. Bayer considered that it was not inappropriate to use this group of patients in order to bring attention to the large difference in gender response seen with Lipobay 400mcg and as far as Bayer knew this was not seen with other statins. The data had implications for prescribing.

Bayer did not accept that to quote a mean figure of 44% was exaggerated or misleading. It reflected the decrease found in the largest group of patients. Had it been the intention of Bayer to mislead, a decrease of up to 60+% in LDL-C could have been used from the absolute values shown in the clinical trials report.

The complainant referred to a document circulated by Bayer with reductions in LDL-C quoted. The document was produced prior to the Ose data being fully analysed and the document was withdrawn prior to the launch of Lipobay 400mcg, it was therefore neither up-to-date nor relevant.

Bayer submitted that 44% was a reasonable mean figure to quote for LDL-C reduction taking into account the large gender difference in response seen with Lipobay and no other statin. The fact that the 44% mean reduction was in females was stated on the advertisement, and was therefore not misleading.

The use of the phrase 'up to' was appropriate when using a mean value and not an absolute value and referred to one dosage of Lipobay only. The advertisement and the quotation referred only to data for the 400mcg dose.

Bayer therefore did not believe that it was in breach of Clauses 7.2 and 7.8 of the Code.

PANEL RULING

The Panel considered that its ruling in Case AUTH/970/1/00 of a breach of Clause 7.2 also applied in Case AUTH/972/1/00.

APPEAL BY BAYER

The appeal in Case AUTH/970/1/00 was taken as the appeal in this case. Bayer submitted no additional comments.

CASES AUTH/970/1/00 and AUTH/972/1/00

APPEAL BOARD RULING

The Appeal Board noted that the 44% decrease in LDL-C cited in the advertisement related to women taking the 400mcg dose in the Ose *et al* (1999) study. Gender response was neither a primary nor a secondary efficacy parameter. Approximately two thirds of the patients were male. The Appeal Board considered that the claim was misleading, it gave the impression that the decrease would be reflected in the entire patient population and that was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

CASE AUTH/972/1/00

In Case AUTH/972/1/00, Merck Sharp & Dohme also complained about the claim 'Bound to drop' which appeared beneath a picture of an elephant stepping onto a rope spanning a gorge.

COMPLAINT

Merck Sharp & Dohme alleged that the claim appeared to guarantee that all patients prescribed cerivastatin would inevitably experience a clinically significant fall in LDL-cholesterol. This was an exaggerated and all-embracing claim which was incapable of substantiation.

In response to this criticism Bayer had sent Merck Sharp & Dohme further information from the referenced study indicating that all patients responded to cerivastatin 400mcg. Merck Sharp & Dohme alleged, however, that there were two significant fallacies within this argument. Firstly, a responder was defined as someone showing >15% decrease in LDL-cholesterol. Three percent of patients did not show this response and although their LDL-cholesterol levels fell they were non-responders according to the definition given within the study. Secondly and more importantly it was of note that Bayer stated that '100% of patients in the Ose study *who complied with the protocol* and who received 400mcg of Lipobay/day showed a decrease in LDL-C.' Merck Sharp & Dohme stated that in clinical practice patients did not always comply with medication as prescribed, particularly if they did not tolerate the medication. In patients experiencing side-effects from Lipobay and as a result discontinuing treatment, LDL-cholesterol was not 'bound to drop'. Indeed within the study 28 patients in the 400mcg group were not included in the per-protocol analysis and 2.6% of all patients treated with cerivastatin were withdrawn.

Merck Sharp & Dohme alleged that the claim was in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Bayer submitted that the claim was appropriate and capable of substantiation. It stated that 100% of patients in the Ose *et al* (1999) study showed a decrease in LDL-cholesterol. This was consistent with the European data pool of clinical trials for registration for patients who took 400mcg Lipobay (n=434), of whom greater than 99% showed a decrease in LDL-C (Bayer Data on file). Merck Sharp & Dohme alleged that this was a misleading figure as Ose stated that a responder was defined as someone showing a decrease in LDL-C of 15% of more. However, the advertisement did not state 'bound to respond' nor did it mention responder rates. Bayer submitted that over 99% of patients showing a decrease in LDL-C overall and 100% in the Ose study was very substantial evidence of the pharmacological effect of the medicine.

The fall in LDL-C with Lipobay 400mcg was an efficacy parameter and not a safety or compliance issue, and Bayer therefore submitted that the use of a per protocol analysis was a more relevant analysis for the data than the intention to treat analysis.

Bayer agreed with Merck Sharp & Dohme that many patients in real life situations did not comply with prescribed medication, especially for asymptomatic conditions, such as hypercholesterolaemia. However, it was unreasonable to look at efficacy data in non-compliant patients when an objective measurement such as LDL-C was being measured as the response would tell the prescriber nothing about the effect of the medicine. This might be different for a subjective parameter as one might expect a placebo response, which would have to be taken into account. In patients who did not tolerate Lipobay 400mcg, there was still a decrease in LDL-C prior to withdrawal of treatment and therefore Lipobay 400mcg did actually have the desired pharmacological effect. Only 2.4% of patients on Lipobay 400mcg withdrew and not 2.6% as stated by Merck Sharp & Dohme. The intention-to-treat (ITT) analysis referred to as a more 'appropriate' analysis by Merck Sharp & Dohme still showed some decrease in LDL-C in greater than 99% of patients. Bayer therefore was justified in the use of the claim.

The definition of 'bound' according to Webster's Dictionary (online) was 'very likely' and Bayer believed that when Lipobay 400mcg gave a decrease in LDL-C of over 99% in all patients in the European data pool, the use of the phrase 'bound to drop' was justifiable.

PANEL RULING

The Panel noted the definition of 'bound to' provided by Bayer. The claim was reinforced by the illustration of the elephant about to walk a tightrope. The elephant would fall and the implication from the claim and the illustration was that Lipobay would always lower LDL-cholesterol.

The Panel did not accept, however, that the audience would interpret the claim as guaranteeing that all patients prescribed Lipobay would experience a clinically significant fall in LDL-cholesterol. 'Bound to drop' was immediately followed, and qualified, by the claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%'.

The Panel noted the submission that in the Ose study 97% of patients responded and that data on file

showed that all patients that complied with the protocol showed a decrease in LDL-cholesterol. The intention-to-treat analysis showed a decrease in LDL-cholesterol in greater than 99% of patients.

The Panel considered that given the data and in the context of the advertisement it was not unreasonable to use the claim 'Bound to drop'. There was no implication that patients would respond clinically to such therapy. The Panel ruled no breach of Clauses 7.2 and 7.8 of the Code.

Complaints received	
Case AUTH/970/1/00	**25 January 2000**
Case AUTH/972/1/00	**27 January 2000**
Cases completed	**16 June 2000**

CASE AUTH/971/1/00

SMITHKLINE BEECHAM v FERRING

Promotion of Pentasa

SmithKline Beecham complained about a promotional campaign for Pentasa (mesalazine) by Ferring which announced a 20% reduction in the price of the product. SmithKline Beecham alleged that the campaign inferred that Pentasa was interchangeable with its own formulation of mesalazine (Asacol) which was not so. SmithKline Beecham noted that the claim that £6 million could be saved if doctors prescribed Pentasa instead of Asacol took no account of the cost or the clinical appropriateness of such a switch; the projected saving was based entirely on sales data. In addition the implication that the resultant saving in the medicines budget could be easily realised in other parts of the Health Service was misleading.

The Panel noted that Pentasa and Asacol were different formulations of mesalazine and, although they were not directly interchangeable, for a newly diagnosed ulcerative colitis patient a doctor could simply choose to prescribe one or the other. Once therapy with one form of mesalazine had been established it was important to ensure that it was continued but it would be possible for a doctor to choose to switch to another form, provided patients were monitored and restabilized. The Panel noted that in a leavepiece and an advertisement the resultant £6 million possible saving was based on an analysis of comparative prescription costs and took no account of the costs incurred in switching patients from Pentasa to Asacol. The basis of the calculation had not been adequately explained and breaches of the Code were ruled.

A letter written by the product manager announced the price reduction for Pentasa and noted that as there was a 29% difference in the prescription cost of Pentasa and Asacol, then the use of Pentasa 'could result in considerable savings'. Letters sent to hospital staff and PCG board members gave more detail and quantified the possible savings which could be made. Although neither letter took account of the cost of switching patients the basis for the calculation of the savings was given. The Panel did not consider that the letters were misleading and no breach of the Code was ruled. Upon appeal by SmithKline Beecham, the Appeal Board noted that although the projected savings only related to the comparative purchase costs of the two medicines, doctors would appreciate that in switching patients from Asacol to Pentasa some extra time might be needed to explain the change in therapy. There was, however, no need for clinical monitoring with ECG or blood tests etc. The Appeal Board did not consider that the letters were misleading and the Panel's ruling of no breach of the Code was upheld.

The Panel noted that claims which referred to a cost saving in the medicines budget being easily realisable elsewhere in the NHS had been considered in Case AUTH/952/11/99 and ruled in breach of the Code. The Panel considered that its ruling in the previous case covered the allegation in this case.

SmithKline Beecham Pharmaceuticals complained about a promotional campaign for Pentasa (mesalazine 500mg tablets) by Ferring Pharmaceuticals Ltd. The main message of the campaign was that, following a 20% reduction in the cost of Pentasa, prescribers could save significant amounts of money if they would 'simply prescribe Pentasa' instead of the current most commonly prescribed mesalazine brand. A figure of £6 million was stated as the overall saving to the NHS. The campaign also included claims about what the £6 million saving could be otherwise used to fund in the NHS. The current most commonly prescribed mesalazine brand was SmithKline Beecham's product Asacol (mesalazine 400mg tablets).

SmithKline Beecham provided copies of a journal advertisement (ref G/44/10/99) and a 'Dear Doctor' letter (G07/RMS2944/2608). Ferring provided copies of a journal advertisement (ref G/51/01/99), a leavepiece (ref G/47/10/99) and three 'Dear Doctor' letters. Ferring stated that the campaign was directed principally at hospital-based gastroenterologists of consultant status, and associated medical staff, such as endoscopy nurses, IBD nurses and clinical assistants. The journal advertisements had appeared in Hospital Doctor, BMJ, MIMS and Gastroenterology Today.

COMPLAINT

SmithKline Beecham considered that the campaign inferred that other products in use in this therapeutic

area (eg its own product Asacol) and Pentasa were interchangeable. This was not the case and there was a significant body of evidence demonstrating the differences in pharmacokinetics and in colonic concentrations of these two mesalazine preparations. Indeed, in a letter to The Lancet, Dr Alastair Forbes, a gastroenterologist at St Mark's Hospital, Harrow, stated about mesalazine preparations that '… the delivery characteristics of the pharmaceutical preparations make it clear that they are not identical, and that they should not be regarded as interchangeable' and went on to state 'mesalazine is a rare example of a drug for which prescription should be by proprietary name rather than generic drug name'.

SmithKline Beecham noted that the claim that £6 million could be saved was based entirely on sales data and took no account of the clinical appropriateness of such a switch. Because the products were not interchangeable the company considered that the claimed potential savings could never be realised. In any event, no account was taken of the cost of switching patients from one agent to the other and therefore the simplistic use of a cost minimisation argument was of itself misleading.

SmithKline Beecham noted that in addition, the campaign implied that a cost saving in the medicines budget could be easily realised in other parts of the Health Service. This was not the case and once again Ferring's claims were misleading.

SmithKline Beecham considered that advertising such as this damaged the image of the pharmaceutical industry and that the industry should attempt to distance itself from simplistic arguments that treated medicines like commodities. The company considered that the campaign was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Ferring stated that the heart of SmithKline Beecham's complaint lay in the fact that it did not consider that Pentasa and Asacol were interchangeable in clinical practice, and referred to the personal views of a gastroenterologist, published in a letter to The Lancet. This letter was intended to address the suitability of direct generic substitution of Asacol with Coltec, a then recently introduced pH dependent form of mesalazine. Coltec was a direct generic competitor to Asacol and had taken a substantial share of SmithKline Beecham's business in a relatively short space of time. This was supported by audited data available from IMS. The letter also highlighted the fact that Coltec had no clinical data to support its product licence and therefore its use in patients with ulcerative colitis, which was not the case with Pentasa.

Ferring noted that, in his letter, the gastroenterologist stated that all the mesalazine products had been shown to be clinically effective, although they should not be regarded as interchangeable (from the standpoint of generic substitution). Ferring stated that it would agree with this point of view. It was important to note that the company was advocating switching patients from treatment with Asacol to treatment with Pentasa at the recommended dose, rather than tablet for tablet generic substitution. Indeed it would be patently ridiculous to suggest generic substitution of Asacol 400mg with Pentasa tablets which contained 500mg of prolonged release mesalazine.

Ferring stated that it did not claim that Pentasa was a generic substitute for Asacol and the company would not wish Pentasa to be regarded as such. The unique prolonged release formulation of Pentasa tablets conferred distinct advantages over positioned release products including reliability and predictability of the release of mesalazine in the gut, together with low plasma levels of free mesalazine. It was also noteworthy that Pentasa tablets had a wider licensed dose range (1.5 – 4g daily) than Asacol tablets (1.2 – 2.4g daily).

Ferring noted that both Pentasa and Asacol were indicated for the treatment of mild to moderate ulcerative colitis, and that there would be few occasions when Pentasa tablets would not be a perfectly acceptable and proper treatment for patients suffering from this condition.

In response to an earlier challenge from SmithKline Beecham, Ferring had asked five independent consultant gastroenterologists if they would express their views on the following questions:

1 What is your clinical view on the interchangeability of Asacol and Pentasa for patients suffering from ulcerative colitis?

2 On what basis do you believe that most gastroenterologists make their choice of mesalazine for patients with ulcerative colitis?

3 What is your reaction to the suggestion that the advertising campaign 'threatens your ability to make an informed choice and see this decision through into the patient's ongoing management' or that patients could be put at risk?

Confidential copies of responses were provided, the summary of which showed that gastroenterologists: considered treatment with Asacol and Pentasa to be interchangeable in clinical practice; historically had continued to prescribe Asacol on the basis of habit, as it was the first to the UK marketplace, rather than through a conscious clinical decision; considered the advertising campaign in no way threatened their ability to make an informed choice in treating patients with ulcerative colitis.

Ferring stated that in terms of clinical efficacy and safety, there was a wealth of published information to support the use of Pentasa in the treatment of acute and long-term management of patients with ulcerative colitis. 80% of patients with mild to moderate ulcerative colitis could be expected to benefit from Pentasa therapy and 30-50% should have complete relief of symptoms and mucosal healing after 8 weeks of treatment (Hanauer (1993)). Pentasa was also an effective single agent for maintaining remission of ulcerative colitis, with 64% of patients maintaining remission for 12 months (Miner (1995)). For both acute and maintenance therapy, Pentasa was as effective and better tolerated than sulphasalazine (Munakata (1995) and Mulder (1998)). In addition, Pentasa significantly improved quality of life for

patients with mild to moderate ulcerative colitis (Robinson (1994)).

With patient acceptability and compliance in mind, Pentasa could be taken 2 or 3 times daily and for those patients who might have difficulty swallowing, tablets could be broken in two or dispersed in a small amount of water.

Ferring noted that a recent publication by Wilding reported that '…the disintegration of the Asacol preparation was varied with the complete break up of the tablet occurring in many different parts of the gut ranging from the small intestine to the splenic flexure. The results of the study are therefore consistent with previous research, which has suggested that the Eudragit S coating should not be used to reliably deliver drugs specifically to the colon. Pentasa on the other hand performed much more consistently. Disintegration of the capsule occurred in the stomach. The microspheres then dispersed throughout the entire gastrointestinal tract from the small intestine through to the distal colon in both the fed and fasted subjects'.

Relating to the delivery issue, Ferring noted that an article published by Mills stated that '… it is possible that low colonic pH may render drugs based on acrylic resin and azo-bonds less available. Rapid transit may also impair release of azo bonded and acrylic-coated mesalazine. Pentasa, which is released continuously throughout the GI tract, seems to be the form of mesalazine that is least influenced by change in pH and transit time'.

Ferring noted that on the issue of tolerability, an article by Harris referred to 'The potential adverse event of the most concern in sulphasalazine or mesalazine therapy is nephrotoxicity …'. He then went on to state that 'On the basis that acetylation is a common route of amine detoxification, it has been suggested that nephrotoxicity could therefore be minimised by decreasing the plasma concentrations of [5-amino salicylic acid] 5ASA. Different formulations of mesalazine are associated with different plasma levels of acetylated and unacetylated concentrations of 5ASA. Pentasa therapy has been associated with significantly lower plasma levels than those seen with Asacol and Salofalk, where plasma peaks of drug and metabolite suggest a more abrupt release of 5ASA. By contrast, Pentasa therapy may not saturate the acetylation capacity of gut mucosa, because of its gradual controlled release of 5ASA. The lower plasma levels of 5ASA that are associated with Pentasa therapy may be associated with a lower risk of nephrotoxicity'.

Ferring stated that one could only conclude from the nature of SmithKline Beecham's complaint that it was concerned at losing market share to a therapeutically equivalent yet lower priced competitor. By challenging the Pentasa advertising campaign, Ferring considered that SmithKline Beecham was attempting to restrict the awareness of the benefits that Pentasa had to allow prescribers the opportunity to save the NHS valuable financial resources. Ferring viewed this as protectionist in nature which in itself was in danger of bringing the pharmaceutical industry into disrepute.

Ferring noted that in a letter to SmithKline Beecham, dated 5 January 2000, it stated that it would be happy to debate the merits of the controlled release of mesalazine from Pentasa in comparison with Asacol. Indeed when invited to do so by the consultant gastroenterologist team in Edinburgh, Pentasa was chosen as the medicine for the first-line use due to its clinical and cost effectiveness.

Ferring stated that it was encouraging a re-evaluation of prescribing habits for mesalazine and it considered that this could only be in the best interest of patients and the NHS.

In conclusion, Ferring strongly defended its advertising campaign as being accurate, balanced, fair and objective and in no way misleading. All claims were capable of substantiation and therefore it considered that no breach of the Code had taken place. The company considered that there was sufficient evidence to support its position that patients with ulcerative colitis undergoing treatment with Asacol could be switched to treatment with Pentasa without a reduction in the quality of their management in terms of either safety or efficacy.

PANEL RULING

The Panel noted that Pentasa slow release tablets 500mg were indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis and also for the maintenance of remission of ulcerative colitis. The total daily dose in acute treatment was up to 4g and for maintenance therapy it was to be started at 1.5g. Asacol enteric coated tablets 400mg were indicated for the same patient group; the total daily dose in acute treatment was six tablets (2.4g) and for maintenance therapy it was three to six tablets (1.2 – 2.4g). Asacol was also indicated for the maintenance of remission in Crohn's ileo-colitis (Ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000).

The Panel noted that, in addition to the differences in dosage, Pentasa was a slow release formulation while Asacol was enteric coated; the delivery characteristics of mesalazine from the two types of tablets would thus be different. Although the two medicines were not directly interchangeable they were indicated in the same patient group and so, in the Panel's view, for a newly diagnosed patient a doctor could simply choose to prescribe one or the other. Once the doctor had decided to use Pentasa or Asacol it would be important to prescribe by brand name to ensure that patients were not indiscriminately switched from one to the other during the course of therapy. Once therapy with one form of mesalazine had been established it would be possible for a doctor to choose to switch to another form, provided that patients were monitored and restabilized.

The Panel considered that the impression given was that if doctors would 'simply prescribe Pentasa' instead of Asacol, then each year they could help the NHS save £6 million. The projected saving was based on an analysis of prescription costs in 1998 which showed that an average Pentasa prescription cost 29% less than Asacol. In the Panel's view 'simply prescribe' inferred that, at all times, doctors had a simple choice between writing Pentasa or Asacol on a prescription and that the two medicines were freely

interchangeable which was not so. The Panel noted that the £6 million possible saving was based solely on the comparative prescription costs and took no account of the cost incurred in switching patients from Asacol to Pentasa. The basis of the calculation had not been adequately explained. The Panel considered that the leavepiece and the advertisement were misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

None of the 'Dear Doctor' letters contained the phrase 'simply prescribe' nor did they take into account the cost incurred in switching patients from Asacol to Pentasa. A letter signed by the product manager announced the 20% price reduction on Pentasa 500mg tablets but made no claim with regard to projected savings if the medicine was used instead of Asacol – only that there was a 29% difference in cost per prescription between the two. It was stated that 'The use of Pentasa 500mg tablets could result in considerable savings …'. This letter was supplied by Ferring in its response. Letters directed at hospital staff and PCG board members, on the other hand, referred to switching patients from Asacol to Pentasa and stated projected annual savings of £61,776/300 patients and £20,592/100 patients respectively. Although neither letter took account of the cost involved in switching patients the basis for the calculations in these two letters were given in the letters. Both referred to the 29% difference in prescription price and both referred to the fact that around 80% of ulcerative colitis patients could be expected to benefit from Pentasa therapy. The letters gave examples of the savings that might be made. The Panel did not consider that the letters were misleading as alleged and no breach of the Code was ruled.

The Panel noted that claims which referred to a cost saving in the medicines budget being easily realisable elsewhere in the NHS had been considered in Case AUTH/952/11/99. A breach of Clause 7.2 of the Code had been ruled. The Panel considered that its ruling in the previous case covered the allegation in the case now before it.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that it wished to appeal the ruling that the 'Dear Doctor' letters were not in breach of the Code.

Firstly the letter signed by the product manager announcing a 20% price reduction on Pentasa 500mg tablets noted that the use of Pentasa 500mg tablets could result in 'considerable savings'. This statement was misleading given that the Panel's own view was that the two medicines were not freely interchangeable and that there were costs to be taken into account with regard to the switching of patients from Asacol to Pentasa and their stabilisation on a new therapy. The reference to 'considerable savings' was therefore an over-statement of the likely magnitude of savings which would be involved.

Secondly the letters addressed to hospital staff and PCG board members referred to cost savings of £61,776 per 300 patients and £20,592 per 100 patients, respectively. These two figures in fact represented a direct down-scaling of the £6 million wrongly claimed by Ferring as the realisable savings in treating approximately 29,000 patients with Pentasa 500mg in its initial response to the complaint. Since the letters to hospital staff and PCG board members would have been interpreted in the context of the press advertisements ruled in breach by the Panel, they implied that the realisable savings at hospital or PCG level might be of this magnitude, ie £20,592 per 100 patients. SmithKline Beecham believed these letters to be misleading because they again assumed that large numbers of patients could be switched quickly and easily within a hospital or a PCG from Asacol to Pentasa. This assumption was false given the considerable amount of consultation time that would be required to effect these changes.

In conclusion, SmithKline Beecham wished to appeal against the ruling of no breach regarding Ferring's 'Dear Doctor' letters and those directed at hospital staff and PCG board members on the grounds that the representation of potential savings remained spurious and non-realisable given that in the Panel's own view the two medicines were not freely interchangeable.

RESPONSE FROM FERRING

Ferring said that it noted that the appeal was based on SmithKline Beecham's assertion that the Panel's view was that Pentasa and Asacol were not freely interchangeable and that costs might be incurred in switching a patient from one product to the other. However, the relevant part of the ruling actually stated that '… it would be possible for a doctor to choose to switch to another form, provided that patients were monitored and restabilized.'

In reviewing this appeal, it was important for the Appeal Board to understand the mode of action of mesalazine and the differences between Asacol and Pentasa.

- mesalazine acted locally in the gut to exert its efficacy in ulcerative colitis.
- unprotected mesalazine was rapidly absorbed from the stomach and was absorbed less rapidly from the small intestine. Mesalazine therefore required chemical or physical protection to reach its site of action in the colon.
- blood levels were not relevant for therapeutic efficacy, although they might have some bearing on systemic toxicity.
- Asacol and Pentasa both delivered mesalazine to the colon to treat ulcerative colitis.
- there was no recommendation for dose stabilisation for mesalazine. Standard doses were used in maintenance treatment at the discretion of the physician.
- Asacol and Pentasa were both designed to protect mesalazine from absorption in the upper gastrointestinal tract to maximise availability in the gut, while reducing the potential for unnecessary systemic absorption.
- the method of release of mesalazine from the two products was different; Asacol had a pH dependent bolus release mechanism, whereas Pentasa employed a granular slow release formulation.

- Pentasa tablets had been shown in the vast majority of publications to result in lower plasma levels of free mesalazine than Asacol. Although these data could not yet be used to support a claim that Pentasa had a superior safety profile compared with Asacol, they would certainly support a position that the safety of Pentasa was not worse than that of Asacol.

Ferring had discussed the clinical and financial implications of switching patients from Asacol to Pentasa with a number of independent gastroenterologists. Their views on the implementation of such switching were outlined below:

Ulcerative colitis was a biphasic disease with periods of remission interrupted by acute episodes of active disease and there were two main times when patients could switch treatment. When an acute flare up occurred, the patient's treatment would obviously be reviewed and changes would be made to either the medicines used or the dose of existing treatments. There would therefore be no incremental cost in switching a patient from one product to another at this point.

Switching of treatments could also be undertaken during the maintenance phase. Patients were often maintained on long-term treatment with mesalazine to reduce the likelihood or severity of an acute flare up. The aim of treatment was to deliver clinically relevant levels of mesalazine to the gut, while minimising systemic absorption. Patients generally required little or no follow-up in terms of stabilisation because mesalazine was normally well tolerated at standard doses and there was no need for fine adjustment of dose on an individual basis. The most notable side effect of treatment with mesalazine was nephrotoxicity and it would be wise to periodically check the kidney function of any patient treatment with mesalazine.

Patients could easily be switched from Asacol to a comparable standard dose of Pentasa. It would be difficult to envisage what additional monitoring and stabilisation could be recommended, given that the two products had both demonstrated efficacy in the treatment of ulcerative colitis in comparative studies against sulphasalazine and that in moving from Asacol to Pentasa, safety was not an issue. Patients would normally be told to contact the clinic if they experienced any problems. As there were no data that suggested that a patient would be at a greater risk of relapse when treated with Pentasa or Asacol, the general consensus was that there would no great cost involved in switching patients' treatments between the two products.

Dealing then with the points raised by SmithKline Beecham.

Firstly a saving of 29% per prescription would genuinely result in a considerable cost saving, both in terms of the medicines' bill and when any switch costs were taken into account. The letter from the product manager that mentioned the 'considerable savings' contained sufficient information to make it entirely transparent on what basis the cost saving had been calculated. Following discussions with gastroenterologists, Ferring did not anticipate that there would be substantial costs involved in switching patients from Asacol to Pentasa.

Secondly the Panel's ruling of breach regarding the magnitude of the cost saving described in the leavepiece and advertisement centred on the absence of clarity regarding the basis of the calculations. Its view was not that medicines' cost savings of £6 million were not possible, but that there might be costs associated with switching patients from Asacol to Pentasa and it was not clear in these items that this potential cost had not been included.

However, the Panel was quite clear in its ruling of no breach in respect of the 'Dear Doctor' letters that the transparency of the calculations left the recipient in no doubt of the fact that the claimed savings represented reduced medicines' costs. Ferring believed that these letters were in no way misleading because they described the nature of the saving to the medicines' bill and gave the basis on which the calculations were made. The fact that no additional costs for switching patients were included was not relevant, since this was apparent from the calculations, which were fully described in the letters. Again, as stated above, Ferring did not anticipate that there would be substantial costs involved in switching patients from Asacol to Pentasa. Whatever costs there were would be highly specific to each unit depending on its policy with regard to the frequency of patient visits.

FURTHER COMMENTS FROM SMITHKLINE BEECHAM

SmithKline Beecham stated that its appeal was based upon the fact that the Panel found Ferring to be in breach of Clauses 7.2 and 7.3 of the Code with regard to its leavepiece and advertisement for Pentasa. The basis of this ruling was that the Panel considered the words 'simply prescribe' to infer the free interchangeability of Pentasa and Asacol, which in its view was not possible. In addition the Panel noted that the projected £6 million total NHS saving was based solely on the comparative prescription costs and took no account of the cost incurred of switching patients from Asacol to Pentasa. In SmithKline Beecham's view, the Panel correctly identified that switching from one form of mesalazine to another would require patients to be monitored and stabilised. Of course, this would not be cost neutral under most circumstances.

SmithKline Beecham also noted that in Case AUTH/952/11/99 the Panel ruled a breach of the Code against a complaint by a pharmaceutical advisor regarding a Pentasa mailing by Ferring which oversimplified funding issues within the NHS.

SmithKline Beecham's appeal was based upon the fact that the £6 million figure for possible savings, calculated by Ferring without taking into account the costs incurred in switching from Asacol to Pentasa, was ruled to be in breach in the leavepiece and advertisement and yet were effectively reproduced in the 'Dear Doctor' letter signed by the product manager and the letters directed at hospital staff and PCG board members. In the case of the letter from the product manager, the words 'considerable savings' were misleading and, rather more blatantly

in the letters directed at the hospital staff and PCG board members, the projected annual savings were pro rata expressions of the same £6 million figure which the Panel regarded as misleading in the leavepiece and the advertisement.

In its response, Ferring sought to provide a bulleted summary of the differences between Asacol and Pentasa. However, it had failed to acknowledge that the different formulations of mesalazine in oral presentations of Asacol and Pentasa led to very considerable differences in release profile. Moreover, Ferring made two statements about systemic toxicity and safety with regard to the two products. By its own admission, Ferring stated that 'These data cannot yet be used to support a claim that Pentasa has a superior safety profile to Asacol…'. Therefore, SmithKline Beecham regarded these comments to be at least speculative and certainly completely irrelevant to its ongoing appeal.

SmithKline Beecham noted that Ferring had provided a synthesis of the views and opinions of a small number of independent gastroenterologists in support of its claim that Asacol and Pentasa were readily interchangeable. SmithKline Beecham itself had gathered conflicting information from published data and other independent gastroenterologists.

In summary, SmithKline Beecham maintained its assertion that the misleading figure of £6 million potential savings was without due consideration of the costs of monitoring and stabilisation which would be inherent upon switching medications. The Panel ruled against this misleading figure in terms of the leavepiece and advertisement and SmithKline Beecham argued that the same error was perpetuated in the 'Dear Doctor' letters and therefore these should also be withdrawn.

SmithKline Beecham therefore strongly contended that this material was in breach of the Code as outlined in its original complaint. It believed that in this regard the Panel ruling was incorrect and when heard afresh should be overturned.

APPEAL BOARD RULING

The Appeal Board considered that it was clear from the 'Dear Doctor' letters in question that the projected savings only related to the comparative purchase costs of the two medicines. In reading the letters doctors would appreciate that in switching patients from Asacol to Pentasa some extra time might be needed to explain the change in therapy; there was, however, no need for clinical monitoring with ECG or blood tests etc. The letters gave examples of the savings that might be made. The Appeal Board did not consider that the letters were misleading and the Panel's ruling of no breach of the Code was upheld.

The appeal was thus unsuccessful.

Complaint received **21 January 2000**

Case completed **25 May 2000**

CASE AUTH/977/2/00

SOLVAY HEALTHCARE v NOVO NORDISK

Kliovance leaflet

Solvay Healthcare complained about a claim made for Kliovance (estradiol 1mg and norethisterone acetate 0.5mg) in a leaflet issued by Novo Nordisk. The claim 'Additional protective effect of NETA [norethisterone acetate] – the only progestogen shown to have an independent anabolic effect on bone' was alleged to be misleading, exaggerated and not capable of substantiation.

The Panel noted that the summary of product characteristics (SPC) discussed the effect of oestrogen on bone mineral density and stated that the effect was dose dependent and therefore the effects of Kliovance might be less than observed with higher doses of estradiol. The reference for the claim stated that 'The type of progestogen added … does not affect the skeletal response to oestrogen with the exception of some compounds with androgenic effects such as norethisterone acetate which has an anabolic effect on bone tissue'. The Panel noted that data provided by Novo Nordisk did not give sufficient detail to determine whether the additional effect of NETA at any dose tested in comparison to 1mg estradiol was statistically significant. The studies to support the submission that NETA was the only progestogen proven to exert an anabolic effect on bone showed a positive effect for NETA but did not use NETA at the same dose as in Kliovance ie 0.5mg continuously. The Panel ruled that the claim was misleading and unsubstantiated in breach of the Code.

Solvay Healthcare Limited complained about a six page leaflet (ref KV/99/56) for Kliovance (estradiol 1mg and norethisterone acetate (NETA) 0.5mg) issued by Novo Nordisk Pharmaceuticals Ltd. The product was for hormone replacement therapy (HRT) for oestrogen deficiency symptoms in women more than one year past the menopause and for the prevention of osteoporosis in postmenopausal women.

The allegations concerned the second page of the item which was headed 'Low dose HRT with the benefits of NETA' and related to the statement 'Additional protective effect of NETA – the only progestogen shown to have an independent anabolic effect on bone' which was referenced to the Clinical Synthesis Panel on HRT, Lancet (1999).

COMPLAINT

Solvay alleged that the statement 'Additional protective effect of NETA – the only progestogen shown to have an independent anabolic effect on bone' included three misleading claims for the product which were not supported by the evidence:

a) Additional protective effect of NETA

Solvay stated that the efficacy of HRT in preventing osteoporosis was known to be due primarily to the oestrogenic component of HRT products. The claim made for Kliovance was that 0.5mg NETA provided protection over and above that achieved by 1mg estradiol alone. No reference was provided to substantiate this claim and no information had been provided to Solvay by Novo Nordisk in support of the claim. In fact, reference 4 in the promotional item, McClung *et al* (1998), was an abstract of a study comparing different doses of oestrogen and NETA with placebo. Although the authors claimed that NETA had an additive effect on estradiol, the data in fact showed no statistically significant additional effects of NETA at any dose tested in comparison with 1mg estradiol alone. It was pertinent to record that the summary of product characteristics (SPC) for Kliovance made no reference to additional effects of NETA on bone in the pharmacodynamic section. Solvay alleged that the claim contravened Clauses 7.2 and 7.3 of the Code.

b) The only progestogen shown to have an independent anabolic effect on bone'

Solvay alleged that the claim that NETA was the only progestogen to have this effect was neither supported by the reference given in the leaflet (reference 6) nor by the literature in general. Reference 6, The Clinical Synthesis Panel on HRT (1999) which was a general review of HRT, stated that 'The type of progestogen added to the regimen does not affect the skeletal response to oestrogen, with the exception of some compounds with androgenic effects, such as norethisterone acetate which has an anabolic effect on bone tissue' (emphasis added). The claim therefore did not reflect the evidence and was in breach of Clause 7.2. The claim also breached Clause 7.8 since it falsely suggested that NETA had unique properties.

c) The only progestogen shown to have an independent anabolic effect on bone'

Solvay alleged that the claim that NETA had an independent anabolic effect on bone was misleading since this implied that this effect occurred with 0.5mg NETA, the dose in Kliovance. However, an anabolic effect on bone had only been demonstrated at doses 5 to 20 times higher than the dose in Kliovance according to the references quoted by Novo Nordisk in another promotional item (KL/99/42b). The claim therefore breached Clauses 7.2 and 7.3 of the Code.

RESPONSE

Novo Nordisk stated that it was the first to produce a low dose period-free hormone replacement therapy, soon to be followed by Solvay. There was extensive clinical data demonstrating the bone sparing effects of norethisterone acetate alone and in addition to estradiol. The Kliovance clinical expert report approved by the Medicines Control Agency stated clearly the independent bone-sparing effect observed with the addition of low dose NETA to 1mg 17ß estradiol alone. Similar efficacy was observed in the control of hot flushes when adding low dose NETA to 1mg 17ß estradiol alone. NETA was the only progestogen where bone mineral density (BMD) data was published confirming an independent effect on bone. Data on other progestogens, including dydrogesterone used in the Solvay product, had a neutral or negative effect on bone.

The claim at issue was supported by the view of the Clinical Synthesis Panel on HRT, consisting of international experts in HRT and related fields, on the basis of data reviewed at the Clinical Synthesis Conference on HRT (Milan, 1999). The conference objective was to review the current clinical and epidemiological evidence relating to HRT. A summary document (Lancet, 1999) reported the key findings and recommendations of the conference. Making reference to the skeletal effects of HRT, the document stated that 'The type of progestogen added to the regimen does not affect the skeletal response to oestrogen with the exception of some compounds with androgenic effects, such as norethisterone acetate which has an anabolic effect on bone tissue.'

Further, although the statement alluded to the fact that other progestogens might have an anabolic effect on bone, NETA was the only progestogen proven to exert this effect, as documented in the results of the following three studies:

Prevention of bone mineral loss in postmenopausal women by norethisterone, Abdalla *et al* (1985). This was a prospective controlled 2 year study. Women experiencing menopausal symptoms were allocated to treatment with norethisterone (5mg twice daily). Metacarpal bone mineral content (BMC) was measured using single photon absorptiometry. Results showed BMC increased in the norethisterone group at a rate of 1.65% per year compared with a decrease of 5% BMC over 2 years in the untreated group ($p<0.002$). Norethisterone was seen to confer significant protection against bone loss, with an effect thought to be independent of any estrogenic activity.

The effects of low dose norethisterone on biochemical variables in postmenopausal women, Scopacasa *et al* (1999). In this study norethisterone 2.5mg/day was administered to 26 postmenopausal women with low bone density. Results indicated a 2.5mg dose of norethisterone to be as effective as 5mg in reducing bone resorption, as judged by the observed decreases in urinary hydroxyproline and calcium and serum alkaline phosphatase. The authors concluded that 'the observed beneficial effects of norethisterone on calcium excretion, which are comparable to those of oestrogen, should not be extrapolated to other progestogens, particularly C21 derivatives'.

Uncoupling of bone formation and resorption by combined oestrogen and progestogen therapy in postmenopausal osteoporosis, Christiansen *et al* (1985). In this study ten healthy, early postmenopausal women were treated with oestrogen and progestogen for 2 cycles of 28 days, and changes

in markers of bone turnover were monitored over the treatment period. Results showed that serum alkaline phosphatase and bone Gla protein increased during progestogen administration, whereas urinary excretion of calcium and hydroxyproline fell significantly, and independently of progestogen intake. This indicated that bone formation increased when norethisterone acetate was added to oestrogen treatment, whereas bone resorption might be kept constantly low during oestrogen plus progestogen treatment, leading to a positive calcium balance.

Novo Nordisk stated that the efficacy of Kliovance in the prevention of osteoporosis had been demonstrated in two randomised, placebo controlled trials of two years' duration:

Efficacy of [Kliovance] to increase bone mineral density in postmenopausal women, McClung *et al* (1998). The aim of this trial was to investigate the effects of 17ß estradiol, unopposed or in combination with NETA, on bone mineral density at the spine and proximal femur. Treatment regimens were 0.25, 0.5 and 1mg estradiol unopposed, and continuous combinations of 1mg estradiol/0.5mg NETA (Kliovance) or 2mg estradiol/1mg NETA. At 2 years, mean BMD at the lumbar spine in women randomised to Kliovance increased by 7% over women randomised to placebo. Additionally, the Kliovance combination was seen to be associated with a greater mean % increase in BMD over 1mg estradiol unopposed, which gave a mean 4.76% increase over placebo at the lumbar spine. Thus, the addition of NETA at low doses (0.5mg) to 1mg estradiol increased the lumbar spine BMD response associated with 1mg estradiol.

Combinations of 1mg 17 estradiol and low doses of norethisterone acetate prevent bone loss in postmenopausal women, Delmas *et al* (1999). In this study the effects of 17ß estradiol in combination with low doses of NETA were investigated in 135 postmenopausal women, mean age of 58 years. Women were treated daily with either placebo, or continuous combined formulations of estradiol 1mg/NETA 0.25mg or estradiol 1mg/NETA 0.5mg (Kliovance). After 2 years, the mean BMD at the lumbar spine had increased significantly ($p<0.001$) by 5.4% in the Kliovance group, whereas the placebo group showed a decrease in BMD of 0.9% at the lumbar spine, an overall increase of 6.3%, Kliovance vs. placebo.

PANEL RULING

The Panel noted that Kliovance was indicated for hormone replacement therapy for oestrogen deficiency symptoms in women who were more than one year past the menopause and prevention of osteoporosis in postmenopausal women. Each tablet of Kliovance contained 1mg estradiol and 0.5mg NETA. The SPC stated that the progestogen component of Kliovance, ie NETA, provided protection for the oestrogen-induced increased risk of endometrial hyperplasia and carcinoma and against the oestrogen-induced proliferative changes in the endometrium. The SPC did not refer to the effect of NETA on bone turnover. The section of the SPC headed 'Pharmacodynamic properties' discussed, *inter alia*, the effect of oestrogen on bone mineral density and stated that the effect was dose dependent and therefore the effects of Kliovance might be less than observed with higher doses of estradiol.

The claim at issue was referenced to the Clinical Synthesis Panel in HRT (1999) which sought to synthesise the clinical data in this field. With regard to osteoporosis the authors stated that 'The type of progestogen added to the regimen does not affect the skeletal response to oestrogen with the exception of some compounds with androgenic effects such as norethisterone acetate which has an anabolic effect on bone tissue'. There was no further discussion of this point.

The Panel noted that McClung *et al* (1998) was an abstract which examined the safety, efficacy and additive effect of NETA on estradiol to prevent osteoporosis by increasing bone mineral density. Treatment regimens were 0.25, 0.5 and 1mg estradiol unopposed, and continuous combinations of 1mg estradiol/0.25mg NETA, 1mg estradiol/0.5mg NETA [Kliovance] or 2mg estradiol/1mg NETA. The study concluded that NETA had an additive effect on estradiol in increasing bone mineral density as shown by increases in the percentage change from baseline increases caused by 1mg estradiol alone and that NETA provided the required protective effect on the endometrium. The Panel noted that no p values were stated; it was thus not possible to determine whether the additional effect of NETA at any dose tested in comparison with 1mg estradiol was statistically significant. The Panel examined the studies referred to by Novo Nordisk in support of its submission that NETA was the only progestogen proven to exert an anabolic effect on bone. While the studies showed a positive effect for NETA the Panel noted that Abdalla *et al* used NETA at 5mg twice daily, Scopacasa *et al* used NETA at 2.5mg per day and Christiansen *et al* treated only 10 patients with 1mg NETA for only ten days each cycle on a background of continuous oestrogens. None of the studies therefore used NETA at the same dose as in Kliovance ie 0.5mg continuously.

The Panel noted that whilst the Clinical Synthesis Panel in HRT appeared to support an independent effect of NETA, no evidence had been produced to support such an effect at 0.5mg, the dosage level in Kliovance. The Panel considered that the claim was misleading and unsubstantiated as alleged and ruled a breach of Clauses 7.2 and 7.3 of the Code.

The Panel considered that the alleged breach of Clause 7.8 was covered by this ruling.

Complaint received **11 February 2000**

Case completed **4 May 2000**

WYETH v EISAI and JANSSEN-CILAG

Pariet journal advertisements

Wyeth complained about the claim 'Unbeaten on price' which appeared in journal advertisements for Pariet (rabeprazole) issued by Eisai and Janssen-Cilag. The claim was the only claim in an abbreviated advertisement. A double-page advertisement also featured the claim 'Pariet 10mg prevents GORD [gastro-oesophageal reflux disease] recurrence as effectively as omeprazole 20mg,' and the strapline 'George decided it was time to give his PPI costs a bit of a trim'.

Wyeth alleged that the claim regarding price was misleading as the first impression was that both strengths of Pariet were less expensive than all other proton pump inhibitors (PPIs). The lowest doses of both Zoton and Protium were less expensive than the highest dose of Pariet. The claim was insufficiently qualified in the double-page advertisement in that it was not immediately obvious that the comparison was between Pariet 10mg and omeprazole 20mg whilst in the abbreviated advertisement it was totally unqualified.

The Panel noted that the claim 'Pariet 10mg prevents GORD recurrence as effectively as omeprazole 20mg' was referenced to a study which had compared the efficacy and safety of both licensed doses of Pariet with only the highest licensed dose of omeprazole in the maintenance treatment of healed erosive or ulcerative GORD. While the study demonstrated equivalent efficacy and safety of the medicines studied, the lowest maintenance dose of omeprazole had not been included and so its comparative efficacy and safety was not known. No other clinical data was submitted which compared Pariet to any other PPI in any indication.

The Panel noted that the abbreviated advertisement listed all of the licensed indications for Pariet. In this instance the Panel considered that the impression given by the claim 'Unbeaten on price' was that whenever a patient required a PPI for any of the indications listed then, assuming equivalent efficacy, no other PPI would be cheaper than Pariet. The double-page advertisement related only to the treatment and maintenance of GORD. The Panel considered that given the strapline the advertisement encompassed treatment with all PPIs and that the impression of the claim regarding price was that in the treatment and maintenance of GORD, again assuming equal efficacy, no other PPI would be cheaper than Pariet. In the Panel's view there was insufficient evidence to support either impression. The Panel considered that on the basis of the data available the claim was misleading and a breach of the Code was ruled.

On appeal the Appeal Board noted the submission that the companies were comparing the cost of low dose Pariet with the cost of the low dose of other PPIs and the cost of high dose Pariet with the cost of the high dose of the other PPIs. In each instance Pariet was less expensive. In the circumstances the Appeal Board did not consider that the full advertisement was misleading. The claim 'Unbeaten on price' was linked to the costs of PPIs. No breach of the Code was ruled.

The Appeal Board considered that the abbreviated advertisement was misleading as it was not clear that the claim 'Unbeaten on price' was restricted to the costs of PPIs. The Appeal Board upheld the ruling of a breach of the Code.

Wyeth alleged that the word 'unbeatable' which appeared in the claim 'Pariet's unbeatable low price was an endless source of pleasure to George' was a superlative. The Panel considered that a product could be regarded as unbeatable even if it was in fact equalled though not improved upon by others. No breach of the Code was ruled.

Wyeth complained about journal advertisements for Pariet (rabeprazole) issued by Eisai Ltd and Janssen-Cilag Ltd. Wyeth produced Zoton (lansoprazole).

1 Claim 'Unbeaten on price'

This claim appeared in a prominent oval panel on a double page spread advertisement (ref 00663) and on an abbreviated advertisement (ref 00686). The double page spread also carried the claim 'Pariet 10mg prevents GORD recurrence as effectively as omeprazole 20mg' which was referenced to Humphries *et al* (1998).

COMPLAINT

Wyeth considered that the depiction of the claim that Pariet was 'Unbeaten on price' was misleading and alleged that it was in breach of Clause 7.2 of the Code.

Wyeth alleged that the claim was misleading as the first impression was that both strengths of Pariet were less expensive than all other proton pump inhibitors, as the claims were inadequately qualified and both Zoton 15mg (£14.21) and Protium 20mg (£14.21) (Knoll's product pantoprazole) were less expensive than Pariet 20mg (£23.75). The claim was insufficiently qualified in the two page advertisement, in that it was not immediately obvious that the comparison was between Pariet 10mg and omeprazole 20mg, whilst in the abbreviated advertisement it was totally unqualified.

RESPONSE

Responding on behalf of both itself and Janssen-Cilag, Eisai stated that it did not accept that the claim was in breach of Clause 7.2.

Pariet was licensed in the UK for the treatment of duodenal ulcer (DU), gastric ulcer (GU), gastro oesophageal reflux disease (GORD) plus the maintenance of GORD. The other proton pump inhibitors (PPIs) were also licensed for these indications.

Eisai set out in detail the dosages and durations of treatment, taken from the summaries of product characteristics (SPCs) of pantoprazole, lansoprazole, omeprazole and Pariet in the treatment of DU, GU and GORD plus the maintenance doses in GORD. The prices for 28 day packs were as follows: pantoprazole 40mg (£26.50), 20mg (£14.21); lansoprazole 30mg (£28.15), 15mg (£14.21);

omeprazole 20mg (£28.56), 10mg (£18.91); Pariet 20mg (£23.75), 10mg (£12.98).

Eisai stated that the Code emphasised the importance of comparing equivalent dosages of products in comparative advertising. Eisai interpreted this clause as the comparison of equivalent doses as stated in the SPC, rather than strict pharmacodynamic equivalence. If the latter definition were applied then most cost comparisons would be in breach of Clause 7.2.

The comparison of equivalent doses showed that Pariet was less expensive than the competitor products based upon prices published in MIMS. Eisai believed it was disingenuous to claim that Pariet was not the lowest cost PPI by comparing its high dose against a low dose of lansoprazole.

PANEL RULING

The Panel noted that Eisai had stated that the Code emphasised the importance of comparing equivalent dosages of products in comparative advertising. The Panel noted, however, that the supplementary information to Clause 7.2, price comparisons, stated that such comparisons should be made on the basis of the equivalent dosage requirement for the same indication. In other words there must be a clinical basis for price comparisons.

The Panel noted that the claim 'Pariet 10mg prevents GORD recurrence as effectively as omeprazole 20mg' was referenced to a study by Humphries *et al*. The study had compared the efficacy and safety of Pariet 10mg or 20mg with omeprazole 20mg in the maintenance treatment of healed erosive or ulcerative GORD. The study had thus compared both of the doses licensed for GORD maintenance of Pariet with the highest licensed dose of omeprazole (Ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). While the study demonstrated equivalent efficacy and safety of the medicines studied the lowest maintenance dose of omeprazole (10mg) had not been included and so its comparative efficacy and safety was not known.

There were no other clinical papers submitted which compared Pariet to any other PPI in any indication.

The Panel noted that the abbreviated advertisement listed all of the licensed indications for Pariet. In this instance the Panel considered that the impression given by the claim 'Unbeaten on price' was that whenever a patient required a PPI for any of the indications listed then, assuming equivalent efficacy, no other PPI would be cheaper than Pariet. The two page advertisement related only to the treatment and maintenance of GORD. Although one claim compared the efficacy of Pariet 10mg with omeprazole 20mg in maintenance therapy the strapline beneath the cartoon featured in the advertisement read 'George decided it was time to give his PPI costs a bit of a trim'. The Panel considered that the advertisement thus encompassed treatment with all PPIs and that the impression of the claim regarding price was that in the treatment and maintenance of GORD, again assuming equal efficacy, no other PPI would be cheaper than Pariet. In the Panel's view there was insufficient evidence to support either impression. The Panel noted for instance that if in the maintenance of GORD, lansoprazole 15mg was shown to be as clinically effective as Pariet 20mg but more effective than Pariet 10mg then treatment with lansoprazole would be less expensive.

The Panel considered that on the basis of the data available the claim was misleading and a breach of Clause 7.2 was ruled.

APPEAL BY EISAI AND JANSSEN-CILAG

On behalf of both companies, Eisai appealed the ruling of a breach of Clause 7.2.

The companies agreed with the Panel that comparisons should be made on the basis of the equivalent dosage requirement for the same indications. They had summarised this information in a table which was provided and, for each licensed indication (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000), the price comparisons clearly showed that Pariet was 'Unbeaten on price', based on equivalent doses for the same indication, across the whole range of PPIs.

The companies understood the meaning of equivalent to be that one should compare doses of similar value ie low dose with low dose and high dose with high dose. The companies' comparison of prices was clearly on that basis and not necessarily cost-effectiveness.

The clinical basis for the comparisons was clearly derived from their published summaries of product characteristics, thus the companies compared the equivalent licensed dose of each PPI across the whole range, concluding that Pariet was 'Unbeaten on price'.

The companies therefore believed that the above comparison was fair and correct, their supporting argument having been built directly from the supplementary information detailed in Clause 7.2.

The companies referred to the Panel's comments regarding the claim that 'Pariet 10mg prevents GORD recurrence as effectively as omeprazole 20mg' referenced to a study by Humphries *et al*. The Panel had stated that 'the study had thus compared both of the doses licensed for GORD maintenance of Pariet with the highest licensed dose of omeprazole. While the study demonstrated equivalent efficacy and safety of the medicines studied the lowest dose of omeprazole (10mg) had not been included and so its comparative efficacy and safety was not known'. In the Humphries *et al* study, the companies had shown that both Pariet 10mg and 20mg were as effective as omeprazole 20mg, a high dose strength, in the maintenance of GORD patients over 52 weeks. This trial was designed to compare both high and low dose Pariet, against high dose omeprazole only, based on the logical assumption that high dose omeprazole was more effective than low dose omeprazole. The companies believed that the onus was not on them to prove this in their clinical trial. The trial compared both doses of Pariet against the higher (20mg) dose of omeprazole and proved equivalence. This equivalence was stated clearly and separately from the claim 'Unbeaten on price' but still remained true at both doses.

The indication GORD maintenance included four PPIs at both high and low dose. A table was provided

which showed that the response rates of the PPIs (measured by the relapse rates) published in the literature were high and the higher doses gave better or equal response. On the basis of these points the companies believed that a cost comparison of high to high dose, low to low dose was fair and reflected what a reasonable doctor or health authority would do.

The Panel had noted that the abbreviated advertisement listed all of the licensed indications for Pariet. In this instance the Panel had considered that the impression given by the claim 'Unbeaten on price' was that whenever a patient required a PPI for any indication listed then, assuming equivalent efficacy, no other PPI would be cheaper than Pariet.

The companies agreed and had illustrated in their first table that for any licensed indication that a patient required a PPI, for the indications listed, assuming equal efficacy of equivalent doses, Pariet was the cheapest PPI. This supported the claim 'Unbeaten on price'.

The companies had based their cost comparisons on the comparable licensed indications and dosages for each product, as specified in Clause 7.2 of the Code. These were direct price comparisons, assuming equivalent doses of each PPI. The Panel ruling implied a cost effectiveness argument that was not being made. Again the companies referred to their second table which illustrated the response rates from published studies in GORD maintenance and these data supported the comparison of high dose with high dose and low dose with low dose.

Eisai and Janssen-Cilag believed that they had remained within Clause 7.2 on all the points made by the Panel.

APPEAL BOARD RULING

The Appeal Board noted the submission that the companies were comparing the cost of low dose Pariet with the cost of the low dose of the other PPIs and the cost of high dose Pariet with the cost of the high dose of the other PPIs. In each instance Pariet was less expensive.

In the circumstances the Appeal Board did not consider that the full advertisement (00663) was misleading. The claim 'Unbeaten on price' was linked to the costs of PPIs. No breach of Clause 7.2 of the Code was ruled. The appeal was successful.

The Appeal Board considered that the abbreviated advertisement (00686) was misleading as it was not clear that the claim 'Unbeaten on price' was restricted to the costs of PPIs. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

2 Claim 'Pariet's unbeatable on price was an endless source of pleasure to George'

This claim appeared on a double page spread advertisement (00718).

COMPLAINT

Wyeth alleged that to state that Pariet's low price was 'unbeatable' was the use of a superlative as it suggested that the price of Pariet could never be beaten. A breach of Clause 7.8 was alleged.

RESPONSE

Eisai said that it accepted that the word unbeatable might be regarded as a superlative and regretted that this was not spotted during the approval of the advertisement. It had now been withdrawn.

PANEL RULING

The Panel did not consider that the use of the word 'unbeatable' in the claim amounted to the use of a superlative. A superlative as referred to in the Code was a grammatical expression such as best, strongest, widest, etc. A product could be regarded as unbeatable even if it was in fact equalled, though not improved upon, by others. No breach of Clause 7.8 of the Code was ruled in relation to the allegation.

Complaint received **21 February 2000**

Cases completed **15 June 2000**

CASE AUTH/981/2/00

DRUG INFORMATION PHARMACIST v SCHERING HEALTH CARE

Samples provided by a representative

A drug information pharmacist complained about the provision of samples to a hospital ward by a representative of Schering Health Care. It was alleged that there had been a breach of hospital policy.

The Panel noted that it appeared that two of the products, Microgynon and Logynon, had been supplied as free goods and not as samples. The supply of free contraceptives had been agreed with a number of the hospital staff some years ago. The provision of free goods was not covered by the Code. The Panel queried the arrangements but no breach was ruled.

Four packs of Femodette had been supplied as an identification sample. The Panel queried whether this quantity was necessary for identification purposes. Sampling of medicines was against hospital policy and a breach of the Code was ruled. A further breach of the Code was ruled as the sample request form had not been dated as required by the Code. The representative had failed to comply with all the relevant requirements of the Code in the discharge of his duties and a further breach of the Code was ruled.

COMPLAINT

A drug information pharmacist complained about the provision of samples of a number of different oral contraceptives to one of the hospital wards by a representative of Schering Health Care Limited, in breach of hospital policy. The samples included Femodette, Microgynon and Logynon.

The complainant stated that one of the oral contraceptives, Femodette, which was not on the regional joint formulary, was given to a patient by a member of the hospital staff. This led to a letter of complaint from a general practitioner who saw it as undermining his efforts to stick to the joint formulary.

RESPONSE

Schering Health Care stated that it assumed that the complaint related to the provisions of Clause 17.8 of the Code but noted that the Authority, in its letter informing the company of the complaint, suggested that the representative might also have breached Clauses 9.1 and 15.2, but without giving any grounds for such a suggestion. Clause 9.1 dealt with the maintenance of high standards and stated, in particular, that all activities must (i) recognise the special nature and professional standing of the audience to which they were directed; and (ii) must not be likely to cause offence. Schering Health Care noted that although the complainant was clearly annoyed that samples had been provided in breach of hospital policy, there was nothing in his letter which substantiated a claim that the behaviour of the representative was inappropriate in the context of a professional relationship with the medical staff with whom he dealt. As indicated below, the activities of the representative were not considered in any way to be inappropriate by these medical professionals. If a breach of Clause 9.1 was to be pursued then Schering Health Care considered that more specificity of such a claim was necessary before it could properly respond.

Schering Health Care noted that Clause 15.2 required representatives to maintain a high standard of ethical conduct in the discharge of their duties and comply with all relevant parts of the Code. Again, the company could find nothing in the letter from the complainant to suggest that its representative acted in any way unethically and, as far as compliance with the relevant requirements of the Code was concerned, the company considered that the explanation given below should satisfy the Panel that the representative endeavoured at all times to ensure such compliance.

Schering Health Care submitted that the only breaches of the Code which were apparent from the complainant's letter related to Clauses 17.3 and 17.8. These provided that samples might only be supplied in response to a written request and that distribution of samples in hospitals must comply with individual hospital requirements. The first thing to consider was whether the product supplied in this case was a sample as defined in the Code. According to the supplementary information to Clause 17 samples were small supplies of a medicine provided to members of the health professions in order that they might familiarise themselves with it. That was not the purpose of the supplies provided in this case, with the exception of Femodette. The purpose of the other supplies was to ensure that women had supplies of oral contraceptives following termination of pregnancy. Schering Health Care stated that in its opinion, therefore, as no samples were supplied, Clause 17.8 was irrelevant to the supplies, with the exception of Femodette.

Schering Health Care stated that its representative was currently on holiday and, despite attempts to contact him, it had been unsuccessful. His manager had, however, confirmed that the only supplies which were left were at the termination of pregnancy unit, where patients, following their termination, were given one pack of an oral contraceptive before they left the unit. The arrangement was agreed four years ago following discussions with one of the termination counsellors at the time, Head of Family Planning, Professor of Obstetrics and Gynaecology and a pharmacist. The arrangement was that stock from Schering Health Care and two other companies would be kept in the unit and that one month's supply would be issued to patients. A decision would then be taken by the patient and her GP on whether to continue with the pill.

Schering Health Care stated that following receipt of the complaint, the manager of the representative concerned spoke with three of the four healthcare professionals regarding any change in policy by the hospital and all three advised him that they had no knowledge of any such change. The company considered that its representative should be able to assume that an arrangement agreed with a number of senior members of the hospital's staff represented hospital policy, and it did not believe that a breach of the Code should be established on the basis of an unannounced change in policy, which was unknown even to the hospital's own senior staff with whom the representative dealt.

Schering Health Care stated that with regard to Femodette, the representative's manager had confirmed that these were samples (as defined by the Code) as they were provided for identification purposes. Unfortunately, no written requests were in the company's possession and, as the representative was on holiday, it could not confirm that such written requests were, in fact, received. Schering Health Care had also not been able to establish whether the samples of Femodette actually breached hospital policy, due to the representative's absence and the confusion about the policy mentioned above in regard to the other oral contraceptive samples supplied.

Schering Health Care considered that the fact that hospital staff supplied a product in breach of trust guidelines was not something for which it could be held responsible. Indeed, it seemed that such a supply by the member of staff supported the company's suspicion that the trust's guidelines and policies had not been properly communicated, either internally or externally.

Following the representative's return to work Schering Health Care supplied a copy of a signed form requesting samples of Microgynon 30 and Femodette. The company stated that Microgynon 30 were not samples as defined in the Code and so it did not consider that the sample request forms were strictly required for them.

Schering Health Care stated that all other points made in its response had been confirmed by the representative.

PANEL RULING

The Panel noted Schering Health Care's comments about the Authority's reference to Clauses 9.1 and 15.2 in its letter advising of the complaint. It was the practice of the Authority when dealing with complaints from health professionals to suggest those clauses of the Code which the company should consider when responding. It did not imply that any judgement had been made as to whether they had been breached but was intended to reduce the need for further correspondence.

The Panel noted that supplies of a number of different oral contraceptives had been left on the termination unit but Schering Health Care submitted that the basis on which they had been provided differed. It was important that companies and their representatives were clear as to the basis on which goods were supplied so that they could ensure compliance with the Code.

The supplementary information to Clause 17 stated that a sample was a small supply of a medicine provided to members of the health professions in order that they might familiarise themselves with it and acquire experience in dealing with it. This included samples for identification purposes. Titration packs, free goods and bonus stock provided to pharmacists and others were not samples. Neither were starter packs. This was because they were not for the purpose described above. Starter packs were defined as small packs designed to provide sufficient medicine to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable but unavoidable delay in filing a prescription.

The Panel noted that it appeared that Microgynon and Logynon but not Femodette had been supplied as free goods and not as samples. This arrangement, whereby stocks of oral contraceptives were routinely supplied free of charge to the termination unit, had been agreed with a number of members of the hospital staff some years ago. A recent enquiry from Schering Health Care, following receipt of this complaint, showed that the hospital staff knew of no change to that policy. Given the supplementary information referred to above it followed that the provision of such goods was not subject to the requirements of Clause 17 of the Code. Although the Panel queried the arrangements, no breach of Clause 17 was ruled.

The Panel noted that Femodette had been supplied as an identification sample. The sample request form showed that four packs had been provided and the Panel queried whether this quantity was necessary for identification purposes. The supplementary information to Clause 17 stated that the provisions of that clause equally applied to identification samples. Clause 17.8 stated that the distribution of samples in hospitals must comply with individual hospital requirements. In this case the Panel noted that the sampling of medicines was against hospital policy and a breach of Clause 17.8 was ruled. The question of the inclusion or not of Femodette on the regional joint formulary was not relevant.

Clause 17.1 of the Code stated that samples might only be provided to health professionals. Clause 17.3 stated that samples could only be supplied in response to written requests which had been signed and dated. The Panel noted that the sample request form for Femodette, although signed by a staff nurse, had not been dated; there was in fact no indication on the form that it needed to be dated. A breach of Clause 17.3 was ruled.

The Panel considered that as breaches of Clauses 17.3 and 17.8 had occurred the representative had not complied with all relevant requirements of the Code in the discharge of his duties as required by Clause 15.2. A breach of that clause was ruled. The Panel did not consider that there had been a breach of Clause 9.1.

Complaint received **22 February 2000**

Case completed **18 April 2000**

CASE AUTH/982/2/00

PARKE DAVIS and PFIZER v MERCK SHARP & DOHME

Promotion of Zocor

Parke Davis and Pfizer complained jointly about the promotion of Zocor (simvastatin) by Merck Sharp & Dohme, the materials at issue being a journal advertisement, a leavepiece and a brochure. Parke Davis and Pfizer co-marketed Lipitor (atorvastatin). As part of the complaint involved a possible breach of undertaking, the matter was also taken up by the Director as the Authority itself was responsible for ensuring compliance with undertakings.

The claim 'Zocor – Proven efficacy 9 out of 10 CHD patients reach the LDL-C goal of <3mmol/l using 40mg Zocor plus diet' was alleged to be misleading. A similar claim previously ruled in breach had been changed but Parke Davis and Pfizer did not consider that it had been brought into compliance with the Code. The data cited by Merck Sharp & Dohme did not support the claim and the wider body of data suggested that it was false as more robust data that was available contradicted it. The Panel considered that the claim was misleading, exaggerated and not capable of substantiation. The Pedersen *et al* abstract cited by Merck Sharp & Dohme appeared to support the claim but the data were not sufficiently robust to support a major headline claim. The Panel noted that other studies, none of which were directly comparable with the Pedersen study, reported success rates of less than 90%. Given the variance in inclusion criteria, baseline lipid levels and target LDL-C the Panel queried whether the claim, based only on the Pedersen study, was a fair reflection of the overall evidence. The Panel therefore ruled breaches of the Code. The Panel did not consider that the claim represented a breach of the undertaking given in the previous case. No breach of the Code was ruled in that regard.

Upon appeal by Merck Sharp & Dohme, the Appeal Board examined the Pedersen abstract which gave limited information about the study. Patients received 40mg simvastatin once daily. The patients were divided into two groups, one group received immediate treatment with simvastatin, the other group received deferred treatment with simvastatin. At six months 82% of the deferred patients had reached target and 90% of the immediate treatment patients had reached target. The Pedersen abstract concluded that almost all patients (90%) reached target with 40mg simvastatin daily combined with dietary advice. The Appeal Board noted that the Zocor summary of product characteristics (SPC) stated that for hyperlipidaemia the recommended dose was 10mg once daily taken in the evening. The dose range was 10 to 40mg a day in single doses taken at night. For coronary heart disease patients the starting dose was 20mg/day. Not all patients on Zocor would therefore receive the 40mg dose administered in the Pedersen study and referred to in the materials. The Appeal Board did not consider that the data supported the claim. It was not a fair reflection of the evidence. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Parke Davis and Pfizer noted that the claim at issue above emphasised the 40mg dosage thereby potentially confusing physicians and misleading them into believing that 40mg was the recommended starting dose of Zocor for lowering cholesterol in CHD patients. The Zocor SPC stated that 20mg was the recommended starting dose for post-MI patients and otherwise that 10mg and 20mg were the recommended starting doses of simvastatin. A breach of the Code was alleged. The Panel considered that the claim 'CHD patients reach the LDL-C goal of <3mmol/l using 40mg Zocor plus diet' in the context of the claim that immediately followed, 'Many patients will reach <3mmol/l at starting doses' was not misleading as alleged. No breach of the Code was ruled.

The claim 'Major differences between Zocor and atorvastatin [Zocor proven natural statin – atorvastatin unproven synthetic statin]' appeared in the brochure. Parke Davis and Pfizer alleged that the claim was ambiguous, misleading and disparaging with regard to the unqualified use of the term 'unproven'. The Panel noted that there were differences between the licensed indications of Zocor and atorvastatin. The description of atorvastatin as an 'unproven synthetic statin' was too general for it to be read as referring to the differences in the licensed indications. The Panel considered that the description was disparaging and a breach of the Code was ruled. The Panel noted that Zocor was derived from a fermentation process of naturally-occurring fungi. It also noted Merck Sharp & Dohme's submission that it was not known whether the derivation and therefore structure of each product was important to its effect on mortality over and above the lipid lowering effect. This was an ongoing debate The Panel considered that the way in which the issue of synthetic vs natural statin had been highlighted was misleading given that its importance was unknown and a breach of the Code was ruled.

Upon appeal by Merck Sharp & Dohme, the Appeal Board noted there were differences between the licensed indications of Zocor and atorvastatin. It was acceptable to refer to the differences in promotional material provided the requirements of the Code were met. The Appeal Board did not accept that the reference to 'unproven synthetic statin' would only be read as meaning that atorvastatin, unlike Zocor, had not demonstrated an effect on clinical endpoints. In the Appeal Board's view, the term unproven implied that atorvastatin did not work. The term was not sufficiently qualified and as such was disparaging of atorvastatin. The Appeal Board upheld the Panel's ruling of a breach of the Code. The Appeal Board noted that there were differences in the way that the statins were produced. Zocor was fermentation-derived and was a semi-synthetic analogue of lovastatin whereas atorvastatin was a synthetically produced statin. A published paper had described the two sub-groups of statins; the fermentation-derived or natural statins and the synthetic statins. The Appeal Board noted the submission that the

word 'natural' was used as a short-hand term to mean fermentation-derived. In the detail aid Zocor was referred to as 'natural' and atorvastatin as 'synthetic'. The Appeal Board considered that although the two sub-groups of statins had recently been described, many readers, still unfamiliar with the use of the terms, would assume that in some way natural was better than synthetic. On balance the Appeal Board considered that it was misleading to use the term 'natural' to describe Zocor and upheld the Panel's ruling of a breach of the Code.

Parke Davis & Co Limited and Pfizer Limited complained about the promotion of Zocor (simvastatin) by Merck Sharp & Dohme Limited. Parke Davis and Pfizer co-marketed Lipitor (atorvastatin). The materials at issue were a journal advertisement (ref 12-OO ZCR.99.GB.70259.J.a.), a leavepiece (ref 12-OO ZCR.99.GB.70299.0.20m.HO.1299) and a brochure (ref 12-OO ZCR.99.GB.70168.DA.2m.HO.1299).

In view of the fact that part of the complaint involved a possible breach of undertaking, the matter was also taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

1 Claim 'Zocor – Proven efficacy 9 out of 10 CHD patients reach the LDL-C goal of <3mmol/l using 40 mg Zocor plus diet'

This claim appeared in the journal advertisement, the leavepiece and the brochure.

COMPLAINT

Parke Davis and Pfizer noted that the Panel had previously ruled that a similar promotional claim used by Merck Sharp & Dohme was in breach of the Code in several respects (Cases AUTH/937/10/99, AUTH/941/10/99 and AUTH/951/11/99). In Case AUTH/951/11/99, the Panel ruled that the claim 'Up to 9 out of 10 CHD patients can reach the LDL-C goal of <3mmol/l' was misleading, exaggerated and not capable of substantiation. Parke Davis and Pfizer noted that the claim no longer included the words 'Up to' and it had had the words '40mg ZOCOR plus diet' added. The companies did not consider that these minor revisions were sufficient to bring the claim into compliance with the Code.

Parke Davis and Pfizer considered that the revised claim contravened the Code and was misleading because: the data on file cited by Merck Sharp & Dohme did not support the claim (Breach of Clauses 7.2 and 7.3 of the Code); the wider body of data suggested that the claim was false as there was more robust data available that contradicted the claim and showed that a physician could not reasonably expect that 9 out of 10 patients in the case of Zocor 40mg, and many patients in the case of other dosages, in clinical practice would achieve the results promised by the claim (Breach of Clauses 7.2 and 7.8 of the Code).

Parke Davis and Pfizer alleged that the reference cited by Merck Sharp & Dohme – an abstract by Pedersen *et al* presented at the European Atherosclerosis Society meeting, 26 May 1999, Athens – was misleading as it did not support the claim that simvastatin got '9 out of 10' CHD patients to the goal of <3mmol/l for a number of reasons.

Parke Davis and Pfizer noted that the Pedersen study was conducted with 151 patients. While the publication failed to disclose the number of patients randomised to each treatment group it was reasonable to assume that patients were equally distributed; 75 randomised to immediate treatment with simvastatin 40mg/day and 76 randomised to deferred treatment with simvastatin 40mg/day. Of the 76 patients randomised to deferred simvastatin treatment, only 68 actually received simvastatin 40mg/day after 3 months of diet. Parke Davis and Pfizer stated that under an intent-to-treat analysis (the applicable statistical analysis for determining how many patients reached their target level), the 8 patients who never received simvastatin should be excluded from all further considerations. Therefore, 75 + 68 = 143 patients who were randomised to treatment with simvastatin 40mg/day had the possibility to reach the LDL-C goal under simvastatin treatment. Of these, 61 patients randomised to immediate simvastatin treatment and 56 randomised to deferred simvastatin treatment reached the LDL-C goal (note that out of the 60 patients who had reached the LDL-C goal at six months in the group of deferred simvastatin treatment, 4 patients reached the goal on diet alone without having been treated with simvastatin). Thus, 61 + 56 = 117 patients reached the LDL-C goal out of 143 patients who were randomised to treatment with simvastatin, resulting in a rate of 117/143 = 81.8%. Therefore, the rate of patients who reached the LDL-C goal was significantly less than the 90% or 9 out of 10 claimed by Merck Sharp & Dohme in its advertisement.

Parke Davis and Pfizer stated that in addition, the 90% figure for the immediate simvastatin treatment group was inaccurate. As discussed above, assuming there were 75 patients in the immediate simvastatin 40mg treatment arm, only 61 of these patients reached the stated goal of <3mmol/l. In percentage terms, this result represented approximately 80% of the patients treated with simvastatin 40mg in this treatment arm reaching the stated goal, not the 90% represented in the claim. As discussed above, the Pedersen study improperly failed to include in the denominator all patients who were randomised to simvastatin treatment in this treatment arm.

Parke Davis and Pfizer noted that the Pedersen study reported its results in a selective and improper fashion. For example, according to the publication, 82% of patients reached the stated goal of <3mmol/l after 6 months, following 3 months of deferred treatment with simvastatin 40mg plus diet. Yet the claim only purported to address those patients who were treated with simvastatin 40mg plus diet during the first 3 months of the study – where, as discussed above, the inaccurate result of 90% was reported. The selective presentation of only one treatment arm, rather than the 82% result in the other treatment arm of the Pedersen study, was misleading.

Parke Davis and Pfizer stated that the omission of any statistical analysis or p values in the publication made

it impossible to conclude that any of the results set out were statistically significant.

Parke Davis and Pfizer noted that the claim was broadly aimed at all CHD (coronary heart disease) patients, but the patients in the Pedersen study were not representative of all patients with CHD. The study included only patients who suffered from acute CHD. Patients who had acute CHD were a select sub-population of CHD patients, forming approximately 5% of those patients in the UK who actually suffered from CHD. This particular patient group had a lipid profile that was not consistent with a typical lipid profile in CHD patients. Patients with acute CHD were known to have reduced LDL-cholesterol levels secondary to the acute event, thus the study population of patients had lower baseline LDL-cholesterol levels than typical CHD patients, which made attainment of the stated goal of <3mmol/l easier to achieve than in the broader population of CHD patients. The Pedersen study did not include a broad enough range of CHD patients or patients at risk from CHD to support the claim. Parke Davis and Pfizer stated that accordingly the claim was not accurate, fair or balanced and was incapable of substantiation and therefore was in breach of Clauses 7.2 and 7.3 of the Code.

Parke Davis and Pfizer noted that the Panel had previously ruled that a claim should be a balanced reflection of all the available evidence. Other more robust published data on simvastatin from larger studies in patient populations with baseline LDL-C more representative of the average CHD patient demonstrated that 9 out of 10 CHD patients treated with simvastatin would not reach the target promised in the claim.

The Target Tangible trial, for example, included 959 CHD patients who were treated with simvastatin (10-40mg). The patients represented the broad range of CHD patients encountered by physicians in practice. Proven CHD was found in 1,652 patients (58%) and presented with a history of myocardial infarction, coronary angiography, percutaneous transluminal coronary angiography, and/or bypass operation. CHD was rated as highly probable in the remaining 42% of patients. The patients presented with angina pectoris and electrocardiographic abnormalities (ST-segment depressions, T-wave depressions). Only 72.6% (n=696) of these patients achieved the LDL-C goal of <3mmol/l at any time during the study – the same target set out in the claim.

The AAA study included 337 patients who were treated with simvastatin (10-40mg plus Questran). By week 24, only 69.7% of patients treated with simvastatin 40mg plus Questran achieved the LDL-C goal of <3mmol/l ($p<0.0005$) – the same target set out in the claim.

Parke Davis and Pfizer noted that a very recent Merck Sharp & Dohme-sponsored study, which included 436 patients randomised to treatment with simvastatin 40mg, also demonstrated that 9 out of 10 CHD patients treated with simvastatin would not reach the target promised in the claim. In this study, in patients with CHD and LDL-C ≥3.4mmol/l, only 10 of the 33 patients (30%) completing 24 weeks of treatment with simvastatin 40mg reached the target of ≤2.6mmol/l.

It was unclear from the publication how many patients within the risk category were actually randomised to treatment, but it was almost certainly greater than 33 patients, suggesting that the percentage of patients reaching goal using the customary treat-to-target analysis would be lower than 30% and even further removed from the 9 out of 10 promised in the claim.

Parke Davis and Pfizer noted that for the same reasons as outlined in Case AUTH/951/11/99, the unpublished Heart Protection Study involving treatment of CHD patients with simvastatin 40mg with placebo/antioxidant vitamins also did not support the current claim.

Parke Davis and Pfizer stated that as previously outlined in Case AUTH/951/11/99, other available published data on simvastatin suggested it was unlikely that 9 out of 10 patients taking simvastatin 40mg would achieve the promised results (Smith *et al* 1999; Simons 1998). In the Smith study, the average baseline LDL-C for patients on simvastatin was 4.86mmol/l. This study included 66 patients who were treated with simvastatin. Only 71% of the patients treated with simvastatin (10-40mg) monotherapy reached the target of 2.6mmol/l and even with cholestyramine, the figure was still only 80%. The Simons study showed that only 6% of patients treated with simvastatin 40mg (plus 4g cholestyramine in 84% of the patients by study end) achieved LDL-cholesterol target of <3.5mmol/l and just 26% of these patients achieved a less aggressive goal of <4.5mmol/l.

Parke Davis and Pfizer submitted that these data therefore illustrated that the claim was not reflective of the efficacy of simvastatin 40mg demonstrated in the wider body of published studies and therefore was in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Merck Sharp & Dohme noted that as indicated in the letter of complaint a '9 out of 10' claim featured in a recent case, Case AUTH/937/10/99. The claim now at issue was essentially different from the one subject to the initial ruling and reflected closely the Panel's comments on the original claim.

Merck Sharp & Dohme noted that the Panel ruling in Case AUTH/937/10/99 stated that 'overall the data were not sufficient to support the claim 'Up to 9 out of 10 CHD patients can reach the LDL-C goal of <3mmol/l'. The Pedersen study supported the claim but only for a 40mg dose of Zocor.' The Panel found the original claim to be in breach of the Code on the grounds that the '9 out of 10' claim could be interpreted as applying to all doses of Zocor. Whilst this was not the intention of this promotion, the company had accepted the ruling and modified the advertisement to make it clear that the claim was for the 40mg dose only.

Merck Sharp & Dohme stated that the analysis of the Pedersen abstract presented in the complaint made several invalid assumptions and arrived at inaccurate conclusions not supported by the study's authors. The abstract did not state the numbers randomised to each treatment group. The numbers assumed to be in

each group were wrong but in any case were not essential for determining the effectiveness of Zocor. As was clear from the original presentation of this data by Pedersen the primary endpoint in this study was the number of patients with LDL-C <3mmol/l at 3 months and 6 months. The definition of an intention-to-treat analysis used by Parke Davis and Pfizer was inaccurate.

To state that the 8 patients who never received simvastatin should be excluded from all further considerations was incorrect. For the record 7 patients died during the study, 2 just after randomisation the other 5 during the next 12 months. It was therefore clear from the data and from the abstract that the numbers presented by Parke Davis and Pfizer, and the calculations on these numbers, were inaccurate.

Merck Sharp & Dohme stated that in the group randomised to immediate treatment with Zocor the percentages reaching a target LDL-C of <3mmol/l at 3 and 6 months were 90% and 92% respectively. In the deferred treatment group the percentage of patients at goal at these time points was 7% and 82%. Calculating the percentage of patients reaching goal at 6 months on Zocor could be approached in several ways. If one took the whole study group who were assigned Zocor at any time and had results available then the total number of patients in the analysis would be 136 (66 patients with results available and randomised to immediate treatment and 68 assigned Zocor treatment after 3 months – the 5 patients who were not assigned Zocor after 3 months could not be included). Of these patients 117 reached goal (61 patients reached goal in the immediate treatment group and 56 patients reached goal on Zocor 40mg who were not controlled on diet) ie 87%. However there was no requirement within the licence for Zocor in CHD to be used after dietary measures were taken, and the claim made in the advertisement was for the joint benefits of Zocor and dietary measures, therefore one could reasonably justify this claim by looking only at the immediate treatment arm where, as stated earlier, the percentages reaching goal at 3 and 6 months were 90% and 92% respectively. The percentage quoted by Parke Davis and Pfizer of approximately 80% reaching target was completely without foundation since the denominator they had used was inaccurate.

Merck Sharp & Dohme noted that Parke Davis and Pfizer commented on the lack of statistical analysis in the paper. As stated in the response to the earlier complaint the difference between the deferred treatment group and the immediate treatment group on percentage reaching target was statistically significant and Merck Sharp & Dohme had added this to the data on file. At six months the majority in both groups were on simvastatin and therefore the percentages of patients at target were simply descriptive.

Merck Sharp & Dohme noted that Parke Davis and Pfizer further claimed that the patients in the Pedersen study were not representative of CHD patients as a whole on the basis that they were acute CHD patients. Identifying acute coronary events however was simply a means of easily identifying patients with coronary heart disease within the hospital setting. These patients could be quickly identified and were representative of the coronary disease population as a whole. Most importantly the average cholesterol of the population within this study was in-line with that one would see in a UK population of untreated CHD patients with total cholesterol levels >5mmol/l (roughly equivalent to an LDL >3mmol/l) ie those requiring lipid lowering therapy according to UK guidelines. In an audit conducted by Merck Sharp & Dohme of 24,431 CHD patients in primary care (the Healthwise database) 8,071 patients required lipid lowering therapy according to current UK guidelines, that is they had CHD and total cholesterol levels >5mmol/l (LDL >3mmol/l). In this population the average total cholesterol level was 6.25mmol/l – actually below the baseline level in the Pedersen study and therefore if anything, more CHD patients in the UK requiring therapy might reach goal on 40mg Zocor than did in that study. Thus, directly contrary to the unsubstantiated claim within the complaint, the population within the Pedersen study had cholesterol levels slightly higher than typical of a UK CHD population making the target cholesterol more difficult to reach than would be the case in a UK CHD population. Merck Sharp & Dohme stated that the point made by Parke Davis and Pfizer regarding the lowering of cholesterol in acute coronary syndromes thus became superfluous, although the company would also point out that this effect would have resolved by three months post event when the numbers reaching goal were first assessed.

Merck Sharp & Dohme stated that the claim was therefore a fair and balanced representation of the available evidence fully substantiated by the quoted reference and it denied breaches of Clauses 7.2 and 7.3.

Merck Sharp & Dohme noted that the Parke Davis and Pfizer sponsored Target Tangible trial, quoted as evidence against the 9 out of 10 claim for Zocor 40mg, worked to a lower target LDL-cholesterol of 2.6mmol/l, making this study irrelevant to the claim. The complainants stated that in this study only 72.6% of patients reached an LDL-C of <3mmol/l. As rightly pointed out a claim must be based on 'a balanced reflection of all the available evidence'. However this percentage was not presented in the paper on the trial and was thus not available and therefore difficult to comment upon. Merck Sharp & Dohme noted that since only patients with a baseline LDL-cholesterol >3.4mmol/l were included in the study this percentage excluded a group of patients with an LDL-C between 3 and 3.4mmol/l which would reach target more easily.

Merck Sharp & Dohme stated that, as noted in previous correspondence on this issue, the AAA study was conducted in patients who were markedly more hypercholesterolaemic than typical CHD patients and thus this paper was also not relevant to its claim. Similarly the Merck Sharp & Dohme sponsored trial quoted by the complainants was in a population of patients with higher cholesterol levels than typical of a CHD population and was working to a target lower than that within UK guidelines. Clearly one would expect lower percentages of

patients to reach a lower goal from a higher baseline. Likewise the papers by Simons (severe primary hypercholesterolaemia) and Smith (working to a lower target) provided no information regarding the claim Merck Sharp & Dohme was making in the CHD population.

Merck Sharp & Dohme noted that, as in the previous complaint, Parke Davis and Pfizer quoted from a large variety of data which was irrelevant to the claim and thus they had not demonstrated the presence of a 'wider body of evidence' showing the claim to be false. Merck Sharp & Dohme stated that it rejected the allegation that it was in breach of Clauses 7.2 and 7.8 of the Code.

PANEL RULING

The Panel noted that the claim at issue was an amendment of a claim '… up to 9 out of 10 patients can reach the LDL-C goal of <3mmol' previously ruled in breach of Clauses 7.1, 7.3 and 7.8 of the Code. In the previous case the Panel considered that overall the data were not sufficient to support the claim. The Panel noted that the Pedersen study supported the claim but only for a 40mg dose of Zocor. Data from the Giles study which used Zocor 10mg and the Heart Protection Study which used Zocor 40mg lacked sufficient detail to allow the clinical significance of either to be assessed.

The claim now at issue was also referenced to the Pedersen study. The study, reported as an abstract, was carried out in patients with acute myocardial infarction (n = 112) or unstable angina (n = 39) and LDL-C ≥3mmol/l who were allocated to one of two interventions. Both groups received dietary counselling, one group received simvastatin 40mg daily from the day of randomisation whereas the other started simvastatin after three months if LDL-C was still ≥3mmol/l. At six months 82% of patients in the deferred group had reached target. 90% of patients in the immediate treatment group reached target after three months and remained on target at six months.

The Panel noted that Parke Davis and Pfizer had recalculated the data from the Pedersen study and that Merck Sharp & Dohme submitted that the numbers assumed to be in each group were incorrect. The Panel considered that the calculations used by the complainants were inappropriate.

The Panel noted Merck Sharp & Dohme's comments about the various studies referred to by the complainants and that additional information about the Target Tangible trial had been provided in the complaint.

The Panel noted that none of the studies provided by the complainants were exactly comparable with the Pedersen study in terms of patient population and treatment target. The closest was the reanalysis of the Target Tangible trial which had a mean baseline LDL level of approximately 4.4mmol/l which was similar to the Pedersen study (4.54 and 4.39mmol/l). The Panel noted that Zocor did not achieve close to 90% success in any of the studies referred to by Parke Davis and Pfizer.

The Panel noted Merck Sharp & Dohme's comments about the ruling in the previous case. The Panel noted that in a concluding paragraph of its ruling it was stated that the Pedersen study supported the claim but only for a 40mg dose of Zocor. However the paragraph continued by referring to data from two other studies one of which used 10mg Zocor in post-MI patients and the other which used 40mg Zocor in patients considered to be at elevated risk of CHD. The penultimate sentence of the paragraph stated that 'Overall the Panel considered that the claim was misleading, exaggerated and not capable of substantiation'. The Panel considered that it was implicit that its ruling was based on the data as a whole and was not limited to just the Pedersen abstract.

Turning to the case now before it the Panel considered that the claim was misleading, exaggerated and not capable of substantiation. The Pedersen abstract appeared to support the claim but the data were not sufficiently robust to support a major headline claim. The Panel noted that other studies, none of which were directly comparable with the Pedersen study, reported success rates of less than 90%. Given the variance in inclusion criteria, baseline lipid levels and target LDL-C the Panel queried whether the claim based only on the Pedersen study, was a fair reflection of the overall evidence. The Panel therefore ruled breaches of Clauses 7.2, 7.3 and 7.8 of the Code.

The Panel did not consider that the claim represented a breach of the undertaking given in the previous case. No breach of Clause 21 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme stated that there were several points on which it was basing its appeal. Firstly, Parke Davis and Pfizer had not provided any published evidence to demonstrate the presence of a wider body of evidence showing the claim to be false in the population to which it claim referred. The claim was very specific and referred to CHD patients treated with diet and 40mg of simvastatin who were treated to a goal of 3mmol/l LDL-cholesterol (equivalent to 5mmol/l total cholesterol).

Reference by Parke Davis and Pfizer to studies in which the baseline cholesterol level of the study population was appreciably higher than that in a typical CHD population was inappropriate – one was bound to get lower percentages reaching goal from a higher baseline but this was irrelevant to the claim in question.

Similarly studies which worked to a lower target LDL-cholesterol such as 2.6mmol/l were bound to demonstrate lower percentages reaching goal with 40mg Zocor since this target was lower and more difficult to reach. This was again however irrelevant to the claim which was quite specific and not randomly chosen but based on the National Service Framework for CHD and the Joint British Recommendations on prevention of CHD in clinical practice which set out these particular cholesterol goals.

Merck Sharp & Dohme submitted that too much credence had been given to the data presented by Parke Davis and Pfizer which had no bearing on the validity of the claim.

Secondly, the claim for 9 out of 10 CHD patients reaching the goal of LDL-cholesterol <3mmol/l on 40mg Zocor was based solely on the referenced Pedersen study. The reason for this, as implied above, was that to the company's knowledge this was the only published data looking at this target cholesterol in this population in patients treated with Zocor 40mg. Merck Sharp & Dohme submitted that this data represented all that was known about Zocor in the population which the claim described and it did not understand the implication in the ruling that the claim was misleading as it was not based on 'the data as a whole'. The Panel had already stated that the Pedersen study supported the claim.

Finally, Merck Sharp & Dohme disagreed with the view that the data were not robust enough to support a major headline claim. The study took place at an internationally acknowledged centre for cardiovascular research and was based on the results from 151 patients – Parke Davis and Pfizer, in addition to many other companies, supported claims with smaller studies than this.

APPEAL BOARD RULING

The Appeal Board examined the Pedersen abstract which gave limited information about the study. Patients received 40mg simvastatin once daily. The patients were divided into two groups, one group received immediate treatment with simvastatin the other group received deferred treatment with simvastatin. At six months 82% of the deferred patients had reached target and 90% of the immediate treatment patients had reached target. The Pedersen abstract concluded that almost all patients (90%) reached target with 40mg simvastatin daily combined with dietary advice. The Appeal Board noted the representatives' submission that the figures had been rounded up to the nearest whole person. The Appeal Board noted that the Zocor summary of product characteristics (SPC) stated that for hyperlipidaemia the recommended dose was 10mg once daily taken in the evening. The dose range was 10 to 40mg a day in single doses taken at night. For coronary heart disease patients the starting dose was 20mg/day. The Appeal Board noted that not all patients on Zocor would therefore receive the 40mg dose administered in the Pedersen study and referred to in the materials.

The Appeal Board did not consider that the data supported the claim. It was not a fair reflection of the evidence. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.8 of the Code. The appeal was unsuccessful.

2 Emphasis on the 40mg dosage

COMPLAINT

Parke Davis and Pfizer noted that the claim at issue in point 1 emphasised the 40mg dosage thereby potentially confusing physicians and misleading them into believing that 40mg was the recommended starting dose of Zocor for lowering cholesterol in CHD patients. The Zocor SPC stated that 20mg was the recommended starting dose for post-MI patients and otherwise that 10mg and 20mg were the recommended starting doses of simvastatin. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Merck Sharp & Dohme noted that below the claim it stated clearly that 'Many patients will reach <3mmol/l at starting doses' and so it was at a loss to see how the claim could mislead physicians into thinking that 40mg was the starting dose of Zocor. The clear implication of this statement was that 40mg was not the starting dose for Zocor. The company denied any breach of Clause 7.2.

PANEL RULING

The Panel considered that the claim in point 1 'CHD patients reach the LDL-C goal of <3mmol/l using 40mg Zocor plus diet' in the context of the claim that immediately followed, 'Many patients will reach <3mmol/l at starting doses' was not misleading as alleged. No breach of Clause 7.2 of the Code was ruled.

3 Claim 'Major differences between Zocor and atorvastatin [Zocor proven natural statin – atorvastatin unproven synthetic statin]'

The claim appeared in the brochure on a page headed 'Major differences between Zocor and atorvastatin'. Beneath the heading the chemical structures of 'Proven natural statin Zocor' and 'Unproven synthetic statin atorvastatin' were given. Beneath this was a chart comparing certain features of the two products.

COMPLAINT

Parke Davis and Pfizer stated that this claim was ambiguous and misleading with regard to the unqualified use of the term 'unproven'. The claim suggested to the physician that, with regard to its licensed indications, the efficacy of atorvastatin was unproven and should therefore not be prescribed. Atorvastatin had been approved by the Medicines Control Agency (MCA) for its licensed indications. In light of the approval by the MCA of atorvastatin, it was disparaging and inaccurate for Merck Sharp & Dohme to suggest that atorvastatin was 'unproven'. A breach of Clause 8.1 of the Code was alleged.

Parke Davis and Pfizer added that the reference to method of derivation of atorvastatin was of no proven clinical relevance to the prescriber and thereby likely to mislead and only serve to confuse physicians. Published data indicated that the process of manufacturing simvastatin was not purely 'natural' as implied by the claim but was in fact a semi-synthetic process. Simvastatin was derived as a 'semi-synthetic' analogue of lovastatin. The latter was a fermentation product of *Aspergillus terreus*. Further, the first sentence in the American prescribing information for Zocor read 'Zocor (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*.'

Parke Davis and Pfizer alleged that the claim was also misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it was a matter of debate whether it was simply cholesterol lowering or a combination of cholesterol lowering and the nature

of the statin used which resulted in the mortality benefits observed with statins. The fact remained that only two statins, simvastatin and pravastatin, had shown mortality reductions in CHD patients. There was no evidence available to show that atorvastatin reduced cardiac endpoints or mortality in CHD patients. Thus in this respect it was unproven.

Merck Sharp & Dohme stated that in this way it was clear from the detail aid what the terms 'proven' and 'unproven' related to. This theme ran throughout the detail aid with each page being marked 'ZOCOR: a first-line statin proven to improve survival'. It was not tenable to suggest that this could be seen as referring to the licensed indications for atorvastatin particularly since the table below this strap-line showed that the majority of patients on atorvastatin reached cholesterol target with lowered triglycerides – all in line with the licence. The company therefore rejected the claim that it was in breach of Clause 8.1.

Merck Sharp & Dohme stated that it considered that it was important for physicians to be aware of the debate described above – some would choose to stick to proven molecules, others might assume a class effect and rely on extrapolating evidence from the medicines with a proven benefit on hard endpoints. As part of this debate the company considered that it was entitled to point out the large differences between the simvastatin molecule which had proven effects on cardiac endpoints and mortality and the atorvastatin molecule which had no proven effect. If some of the benefit of using simvastatin or pravastatin (very similar molecules) was due to effects other than lipid lowering then atorvastatin might well not produce benefits on hard endpoints.

Merck Sharp & Dohme stated that the very different nature of atorvastatin and simvastatin at a molecular level was related to their method of production. Simvastatin and pravastatin were derived from a natural fermentation process as the detail aid made clear and atorvastatin was completely synthetic. Put simply the company did not know whether the derivation and therefore structure of each product was important to its effect on mortality over and above the lipid lowering effect but it was an ongoing debate within medicine and was a valid question to raise. Merck Sharp & Dohme rejected therefore that this was misleading or irrelevant and it did not consider that it was in breach of Clause 7.2.

PANEL RULING

The Panel noted that there were differences between the licensed indications of Zocor and atorvastatin. The description of atorvastatin as an 'Unproven synthetic statin' was too general for it to be read as referring to the differences in the licensed indications. The Panel considered that the description was disparaging and a breach of Clause 8.1 of the Code was ruled.

The Panel noted that Zocor was derived from a fermentation process of naturally-occurring fungi. It also noted Merck Sharp & Dohme's submission that it was not known whether the derivation and therefore structure of each product was important to its effect on mortality over and above the lipid lowering effect. This was an ongoing debate. The supplementary information to Clause 7.2 on emerging clinical or scientific opinion stated that where an issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel considered that the way in which the issue of synthetic vs natural statin had been highlighted was misleading given that its importance was unknown. A breach of Clause 7.2 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme stated that the items in question left little doubt that it was the ability of atorvastatin to reduce clinical adverse outcomes which was the issue and not whether the medicine was proven to reduce cholesterol, which no reasonable physician would question. Merck Sharp & Dohme therefore did not believe that it had been disparaging to atorvastatin and it was not in breach of Clause 8.1.

Merck Sharp & Dohme stated that atorvastatin had not been proven to save lives and clinicians who prescribed it to lower cholesterol must assume that a statin class effect existed since there was no intrinsic value in lowering cholesterol. Merck Sharp & Dohme believed very strongly that given the clear differences between the atorvastatin and simvastatin molecules, between their pharmacokinetic profiles and between their effects on such things as HDL-cholesterol, that it was not appropriate to assume a class effect and each statin should prove its clinical benefit.

Merck Sharp & Dohme stated that it was not known how important such distinctions between the molecular structures were but it was the company's prerogative to raise the issue within promotional material just as it was the prerogative of Parke Davis and Pfizer to ignore the issue and assume a class effect within their materials. The structure of each statin was clearly related to its derivation and pravastatin and simvastatin (the statins with proven effect on clinical outcomes) were produced via a natural fermentation process, whereas the statins without any proof of clinical benefit were produced entirely synthetically.

A paper by Furberg (1999) which referred to two sub-groups of statins; the fermentation-derived or natural statins and the synthetic statins was provided. The company thus submitted that natural was a short-hand term referring to fermentation-derived statins.

APPEAL BOARD RULING

The Appeal Board noted that there were differences between the licensed indications of Zocor and atorvastatin. It was acceptable to refer to the differences in promotional material provided the requirements of the Code were met. The Appeal Board did not accept that the reference to 'unproven synthetic statin' would only be read as meaning that atorvastatin, unlike Zocor, had not demonstrated an effect on clinical endpoints.

In the Appeal Board's view the term unproven implied that atorvastatin did not work. The term was not sufficiently qualified and as such was disparaging

of atorvastatin. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal on this point was thus unsuccessful.

The Appeal Board noted that there were differences in the way that statins were produced. Zocor was fermentation-derived and was a semi-synthetic analogue of lovastatin whereas atorvastatin was a synthetically produced statin. The Appeal Board noted the submission from the representatives that the word 'natural' was used as a short-hand term to mean fermentation-derived. The Appeal Board noted that in the Furberg paper, a table comparing the chemical structures of the two sub-groups of statins used the heading 'Fermentation-Derived Statins' to describe that group to which Zocor belonged. In the detail aid, however, a similar table referred to Zocor as 'natural' and atorvastatin as 'synthetic'. The Appeal Board considered that although the two sub-groups of statins had recently been described, many readers, still unfamiliar with the use of the terms, would assume that in some way natural was better than synthetic. On balance the Appeal Board considered that it was misleading to use the term 'natural' to describe Zocor. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received **24 February 2000**

Case completed **22 June 2000**

CASE AUTH/983/2/00

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Conduct of representative

A general practitioner complained that during a sales call a contract representative promoting Merck Sharp & Dohme's product Zocor (simvastatin) had told him that he should switch his patients from atorvastatin to Zocor on the grounds that atorvastatin reduced HDL-cholesterol and was therefore not as effective as Zocor. No substantiation was offered to support this claim. Conversely the complainant noted that atorvastatin's licensed indications included raising HDL-cholesterol.

The Panel considered that the representative had misled the complainant and had been incorrect in what she had said with regard to the effect of atorvastatin on HDL-cholesterol. The representative's statement was not capable of substantiation. Breaches of the Code were ruled as acknowledged by Merck Sharp & Dohme. A further breach was ruled as the representative had failed to comply with all relevant requirements of the Code.

A general practitioner complained about the conduct of a contract representative from Innovex/Asceplion Healthcare. The representative was promoting Merck Sharp & Dohme Limited's product Zocor (simvastatin). In accordance with the supplementary information to Clause 15 on contract representatives, Merck Sharp & Dohme was responsible for the representative's conduct under the Code.

COMPLAINT

The complainant stated that during a sales call from the representative, she told him that he should switch patients from Parke Davis and Pfizer's product atorvastatin (Lipitor) to simvastatin on the grounds that atorvastatin reduced HDL-cholesterol and therefore was not as effective as simvastatin. The representative offered no clinical papers or other documentation to support this claim.

The complainant stated that he objected to this claim, because, according to MIMS (January 2000), atorvastatin's licensed indications included raising HDL-cholesterol. A breach of the Code was alleged.

RESPONSE

Merck Sharp & Dohme stated that it was clear from several large studies that HDL-cholesterol (the 'good' cholesterol) was raised significantly more by Zocor than by atorvastatin both at milligram equivalent doses and at doses equipotent for lowering LDL-cholesterol (the 'bad' cholesterol). This effect at higher doses was an important distinction between Zocor and atorvastatin, since Zocor was proven to reduce cardiovascular endpoints and mortality and atorvastatin was not. The company considered that it was important that doctors were aware of the significant differences between these two statins so that they were in the optimum position to judge whether the proven benefits of Zocor necessarily extended to atorvastatin.

Merck Sharp & Dohme stated that whilst atorvastatin did not raise HDL-cholesterol as effectively as Zocor at all doses it did still raise HDL-cholesterol and had recently acquired the licence for this indication. It would therefore be untrue to state that atorvastatin lowered HDL-cholesterol.

Unfortunately in this instance it appeared that the representative concerned gave the doctor concerned the impression that atorvastatin lowered HDL-cholesterol and therefore the company conceded that breaches of Clauses 7.2 and 7.3 had occurred.

Merck Sharp & Dohme stated that the impression given by the representative was not one it wished to be conveyed and the representative would receive detailed follow-up training on these issues. The

company was confident that this was a one-off incident but had also taken steps to re-affirm the position as regards the HDL-cholesterol issue with all of its Zocor sales force.

Merck Sharp & Dohme stated that whilst it agreed that breaches of Clauses 7.2 and 7.3 had occurred, in this instance it denied that a breach of Clause 15.2 had occurred. The wording of Clause 15.2 in its view implied that a breach of this clause occurred if a representative behaved unethically or with intent to mislead or breach the Code.

The company strongly believed that the representative concerned made a genuine error and was not in any way intending to misrepresent the data.

Merck Sharp & Dohme stated that whilst it believed that Zocor therapy offered advantages over atorvastatin therapy with regard to the effect on HDL-cholesterol it was not its intention to give the impression that atorvastatin lowered HDL-cholesterol. In this isolated incident the company accepted that Clauses 7.2 and 7.3 of the Code had been breached and the matter had been addressed with the representative involved. In as much as this was a genuine error and not a conscious effort to mislead in an unethical manner the company considered that a breach of Clause 15.2 had not occurred.

PANEL RULING

The Panel considered that the representative had misled the complainant with regard to the effect of atorvastatin on HDL-cholesterol. The representative had incorrectly told the complainant that atorvastatin lowered HDL-cholesterol. The representative's statement was not capable of substantiation. The Panel noted that Merck Sharp & Dohme accepted that the representative had breached Clauses 7.2 and 7.3 of the Code. The Panel ruled breaches of those clauses. The Panel also ruled a breach of Clause 15.2 of the Code as the representative, albeit unintentionally, had failed to comply with all relevant requirements of the Code as required by that clause.

Complaint received **25 February 2000**

Case completed **10 April 2000**

CASE AUTH/984/2/00

ASTRAZENECA v PFIZER

Istin detail aid

AstraZeneca made a number of allegations about a detail aid for Istin (amlodipine) produced by Pfizer. The detail aid was entitled 'The evidence is stacked in its favour Istin' and compared Istin with felodipine ER (extended release), AstraZeneca's product Plendil.

Page 2 was headed 'For reducing cardiovascular (CV) mortality and morbidity' beneath which the claim 'Protection has been demonstrated for stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension and all-cause mortality' appeared. The strapline at the foot of the page stated 'Istin Achieving targets can help reduce deaths.' A highlighted column at the outside edge summarised key messages and was headed 'The evidence favours aggressive blood pressure control.' The page featured a table of data from four studies which showed the benefit of aggressive blood pressure control in terms of the reduction in stroke risk and CV events. The Panel considered that the title of the detail aid 'The evidence is stacked in its favour Istin' set the tone for the entire document. The Panel considered that the layout and content of the page was misleading as it gave the impression that the claims and material related to Istin and this was not so. A breach of the Code was ruled. The Panel accepted that the control of blood pressure would lead to other benefits but the context and layout of the page gave the impression that Istin was licensed for reducing cardiovascular events and morbidity which was not so. Breaches of the Code were ruled.

On page 3 of the detail aid the claim 'Evidence favouring Istin over felodipine ER' headed a highlighted column along the inside edge of the page which featured the claims 'Studies showing superior efficacy' and 'Better BP reduction'. The claim 'With Istin more patients could achieve better BP control than with felodipine ER' appeared as a subheading which was followed by a graph, beneath which the claim 'With Istin, patients got closer to their goals than with felodipine ER' appeared. The Panel considered that the claim 'Studies showing superior efficacy' was a broad and unambiguous claim; a reader would assume that each study cited would demonstrate the superior efficacy of Istin over felodipine ER and that was not so. The studies cited had varying primary endpoints and patient populations. The Panel noted that whilst there were statistically significant outcomes in favour of amlodipine in some parameters of some studies, a number of the studies stated there was no difference in efficacy. Overall the claim was not a fair reflection of the totality of the evidence and was not capable of substantiation. Breaches of the Code were ruled. The claims 'Better BP reduction', 'Evidence favouring Istin over felodipine ER', 'With Istin more patients could achieve better BP control than with felodipine ER', 'Istin higher response rate than felodipine ER', 'With Istin, patients got closer

to their goals than with felodipine ER' were all considered to be misleading and not capable of substantiation and breaches of the Code were ruled.

On page 4 of the detail aid the heading to the highlighted column 'Evidence favouring Istin over felodipine ER' appeared above the claim 'Better trough:peak ratios'. The claim 'Istin exceeds the 50% trough:peak ratio recommended by the FDA – felodipine ER does not' was referenced to two published studies. On balance the Panel considered that given all the data the claim 'Better trough:peak ratios' was not misleading or disparaging and no breach of the Code was ruled. The Panel considered that the claim 'Evidence favouring Istin over felodipine ER' was not misleading with reference to the claim 'Better trough:peak ratios' and no breach of the Code was ruled in that regard. The Panel noted that the claim 'Istin exceeds the 50% trough:peak ratios recommended by the FDA – felodipine does not' appeared above a table which read 'Trough:peak ratios Istin 67% felodipine ER 36%'. The Panel noted the wording in the Plendil summary of product characteristics (SPC) that the trough:peak ratio was usually above 50%. The Panel noted that whilst there was evidence to show that Istin, overall, had better trough:peak ratios than felodipine ER there was evidence that the trough:peak ratio for felodipine ER was usually above 50%. The claim and the table gave the impression that felodipine ER never exceeded the 50% trough:peak ratio and that was not so. The Panel considered that the claim was misleading and disparaging and ruled breaches of the Code.

The claim 'felodipine trials cannot offer proven assurance' appeared on page 9 beneath the statement 'Prospective Randomised Amlodipine Survival Evaluation (PRAISE) a major study in coexisting heart failure (CHF) offered extensive and conclusive safety data'. The Panel noted that the Plendil SPC stated that it was indicated for the management of hypertension and prophylaxis of chronic stable angina pectoris. A section headed 'Preclinical safety' stated that felodipine was well tolerated in patients with congestive heart failure. The Panel considered that the phrase '… felodipine trials cannot offer proven assurance' was a strong claim and given the statement in the Plendil SPC considered that it was misleading, disparaging and not capable of substantiation. It might be read as implying that adverse safety data had been obtained in felodipine trials in patients with co-existing heart failure. That was not so. No such major trials had been conducted. Breaches of the Code were ruled.

The Panel noted that on page 3 of the detail aid a study by Schaefer *et al* (1998) had been cited in support of the following claims 'Studies showing superior efficacy', 'Better BP reduction' and 'With Istin, patients got closer to their goals than with felodipine ER'. Page 7 of the detail aid was headed 'Has it been well interpreted?' and unfavourably compared the results obtained in Schaefer with other studies with regard to the comparative tolerability and vasodilatory side effects of Istin and felodipine ER. The greater blood pressure reduction obtained with Istin was noted in conjunction with its higher average dose of 7.3mg compared with felodipine ER 5.5mg. This information was not given on page 3. The Panel considered the inconsistent use of such data misleading. A breach of the Code was ruled.

The claims 'Switching from Istin to felodipine increases costs – US based study' and 'Switching to felodipine ER may increase your costs' appeared on page 10 headed 'What switching from Istin really entails'. The Panel noted that the data was from an American study in 142 patients which sought to determine whether an amlodipine to felodipine switch program would result in anticipated cost savings of over $18,000 annually on a facility wide basis. The analysis showed that whilst the monthly medicine acquisition cost decreased the concomitant monthly drug cost increased resulting in a net increase in annual costs to treat 142 patients of $4,867 and a facility wide increase of more than $14,000. Pre-switch patients had received a daily dose of 2.5mg to 20mg amlodipine. The post conversion felodipine dose was not stated. The Panel noted AstraZeneca's submission that there was no evidence of formal clinical trial structure, etc. The nature and cost of the concomitant medication was not stated. The patient population was not identified and the pre-switch amlodipine dosage was inconsistent with the UK SPC. The acquisition cost of the medicines would differ in the US. The Panel considered that the calculation could not be directly applied to the UK setting. The Panel considered the claim 'Switching from Istin to felodipine ER increases costs' and table misleading and a breach of the Code was ruled. The Panel considered that although the strapline claim 'Switching to felodipine ER may increase your costs' acknowledged that a switch to felodipine might not always result in increased costs it would be read in light of the information on the page which had been ruled to be misleading. A further breach of the Code was ruled.

Finally, the Panel considered that the claim 'The evidence is stacked in its favour Istin', which appeared on the front page of the detail aid, gave the impression that with regard to the claims made in the detail aid the evidence clearly favoured Istin over felodipine. Given the Panel's rulings above this was not so. The claim was a strong claim and the Panel considered that it did not represent a balanced overview of all the evidence and a breach of the Code was ruled.

AstraZeneca UK Limited submitted a complaint about a 12 page detail aid (ref 62311) for Istin (amlodipine) produced by Pfizer Limited. The detail aid was entitled 'The evidence is stacked in its favour Istin', and compared Istin with felodipine ER (extended release), AstraZeneca's product, Plendil.

1 Page 2 was headed 'For reducing cardiovascular (CV) mortality and morbidity' beneath which the claim 'Protection has been demonstrated for stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension and all-cause mortality' appeared. The strapline at

the foot of the page stated 'Istin Achieving targets can help reduce deaths'. A highlighted column at the outside edge of the page summarised key messages and was headed 'The evidence favours aggressive blood pressure control.'

The page featured a table of data from four studies which showed the benefit of aggressive blood pressure control in terms of the reduction in stroke risk and CV events.

COMPLAINT

AstraZeneca noted from Istin's summary of product characteristics (SPC) that Istin did not have a licensed indication for reducing cardiovascular (CV) mortality and morbidity. Indeed, data from the PRAISE study as mentioned in the pharmacodynamics section of the SPC stated that '… Istin did not lead to an increase in the risk of mortality or combined mortality and morbidity with heart failure', but importantly, no reductions in mortality were seen. Further, a review of the literature used to support the table on this page revealed that Istin was not used in any of the studies quoted, but the trial which did demonstrate a reduction in cardiovascular mortality and morbidity used felodipine ER and not Istin (Hansson *et al* 1998). Therefore AstraZeneca believed that there was no evidence to support the assertion that Istin reduced mortality or morbidity from cardiovascular events even if target blood pressure was reached.

AstraZeneca alleged that the context and juxtaposition of the above statements was misleading by implication and inconsistent with the SPC due to the prominence of the brand name combined with the flow, font and colouring format of the text. This belief was reinforced by Pfizer in a letter (a copy of which was provided), where it acknowledged that the format of the positioning of Istin-supported claims was consistent throughout the detail aid. Therefore, AstraZeneca believed that these claims were in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Pfizer stated that page 2 of the detail aid set the context for the piece by demonstrating the importance of blood pressure lowering for reducing cardiovascular mortality and morbidity. It highlighted the evidence from major studies (specifically Syst-Eur Staessen (1998), UK Prospective Diabetes Study Group (1998) [UKPDS] and the Hypertension Optional Treatment trial [HOT] Hansson *et al* (1998)) and cited various authoritative hypertension guidelines, namely The Sixth Annual Report of the Joint National Committee in Prevention, Detection, Evaluation and Treatment of High Blood Pressure (1997) [JNC V1], 1999 World Health Organisation – International Society of Hypertension Guidelines for the Management of Hypertension, [WHO/ISH], Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and the European Society of Hypertension (ESH) Pyoralak *et al* (1994) and Joint British Guidelines on prevention of coronary heart disease in clinical practice, (JBG) Wood *et al* (1998).

From the key trials referred to, and others, the JNC-VI had concluded that protection had been demonstrated for stroke, coronary events, heart failure, progression of renal disease, severe hypertension and all cause mortality. The National Service Framework for Coronary Heart Disease in the UK had recently endorsed the importance of aggressive blood pressure lowering.

The table which took up the bulk of this page was clearly headed 'Beneficial effects of aggressive BP control'. The clear intent of the page was to set out the background to the need to reduce blood pressure, since the detail aid went on to demonstrate Istin's well documented ability to do so. On this page, however, no specific claim was made for Istin and indeed the product was not mentioned until the bottom left-hand corner of the page, where the logo appeared as a 'footer' or reminder. This featured on each page and was a common technique in pharmaceutical promotion; contrary to the claim in the complaint Pfizer had not acknowledged any other purpose or meaning for this positioning.

At the centre of the bottom of the page was a separate statement which read 'Achieving targets can help reduce deaths'. This was in line with the introduction explained above on the importance of blood pressure lowering. From all major epidemiological and clinical studies, it was well accepted that aggressive lowering of blood pressure to achieve targets by anti-hypertensive agents – as set out in treatment guidelines – could help to reduce deaths. Indeed, the JNC VI Guidelines stated that 'reducing blood pressure by the means of drugs [unspecified] is clearly protective'. Istin, being indicated for the treatment of hypertension, could not be excluded from consideration in this context.

Pfizer did not believe that the context and juxtaposition of statements on this page were misleading; rather they led the reader through a logical sequence of reasoning for reducing cardiovascular mortality and morbidity when treating blood pressure aggressively; therefore, there was no breach of Clauses 3.2 or 7.2 of the Code.

PANEL RULING

The Panel noted that the Istin SPC stated that it was indicated for hypertension, prophylaxis of chronic stable angina pectoris and Prinzmetals' (variant) angina when diagnosed by a cardiologist. Istin was well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease. The section headed 'Pharmacodynamic Properties' stated that a placebo controlled study (PRAISE) designed to evaluate patients in NYHA (New York Heart Association) Class III – IV heart failure receiving digoxin, diuretics and ACE inhibitors had shown that Istin did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

The Panel noted that the table entitled 'Beneficial effects of aggressive BP control' provided the percentage reduction in stroke risk and cardiovascular events in prominent typeface and BP reduction obtained in four separate studies but mentioned no

product name. The Panel also noted that the statement 'Rx 5mg o.d.' appeared at the bottom of the highlighted column at the outside edge of the page.

The Panel noted that Istin was available in a 5mg or 10mg tablet; the usual initial dose for both hypertension and angina was 5mg once a day.

The Panel did not accept the submission that the clear intent of the page was to set out the background to the need to reduce blood pressure. The title of the detail aid 'The evidence is stacked in its favour Istin' set the tone for the entire document. A reader would assume that page 2 of the detail aid reviewed the evidence for Istin and that was not so. In this regard the Panel noted the prominence of the brand name in logo format, the reference to dosage of 5mg o.d. and that the style and format of the page was similar throughout the detail aid.

In the opinion of the Panel a reader would assume that the data presented in the table regarding reduction in stroke risk and CV events related to Istin and supported the claims at issue. The Panel noted however that Istin was not examined in any of the studies referenced in the table; Collins *et al* (1990) Staessen *et al* (1998), UKPDS (1998) and Hansson *et al* (1998).

The Panel also noted that none of the references cited in support of the claims beneath the heading 'The evidence favours aggressive blood pressure control' related to Istin.

The Panel considered that the layout and content of the page was misleading as it gave the impression that the claims and material related to Istin and this was not so. A breach of Clause 7.2 of the Code was ruled. The Panel accepted that the control of blood pressure would lead to other benefits but the context and layout of the page gave the impression that Istin was licensed for reducing cardiovascular events and morbidity which was not so. Breaches of Clauses 3.2 and 7.2 were ruled.

2 On page 3 of the detail aid the claim 'Evidence favouring Istin over felodipine ER' headed a highlighted column along the inside edge of the page which featured the claims 'Studies showing superior efficacy' and 'Better BP reduction.' The claim 'With Istin more patients could achieve better BP control than with felodipine ER' appeared as a subheading to the main page which was followed by a graph, beneath which the claim 'With Istin, patients got closer to their goals than with felodipine ER' appeared.

COMPLAINT

AstraZeneca stated that these claims formed the message regarding supposed efficacy advantages of Istin over felodipine ER and alleged that the references used in support of such claims did not provide data that could substantiate these claims. For example, the claims '… better BP control …', 'With Istin, patients got closer to their goals than with felodipine ER' or an all-embracing claim such as 'superior efficacy' was not supported by the cited reference Van der Krogt *et al* (1996) since the primary efficacy endpoint of this study was not reached. The primary endpoint was to determine whether the study was 'successful' or 'unsuccessful'.

AstraZeneca stated that 'success' as a goal of the study was pre-defined as a composite endpoint of several parameters, namely response to treatment, lack of serious adverse events, no withdrawal from the study due to a serious adverse event and no increase in heart rate. AstraZeneca noted that the primary endpoint, ie the difference in 'success' rates, was not statistically significant between the amlodipine and felodipine ER groups. Therefore it was clear that Istin patients did not get closer to their goals than felodipine ER in this study.

This study also did not support the claim of 'Better BP reduction' as no statistically significant differences were seen between the amlodipine and felodipine groups in terms of diastolic or systolic blood pressure, or in terms of withdrawals from the study due to adverse events. This point was noted by the authors with their statement 'There was no significant difference in efficacy between the two drugs'.

In addition, the literature used to support this claim did not reflect the balance of evidence. There were numerous studies not quoted in the materials showing equivalent efficacy for amlodipine and felodipine ER (eg Lefebvre 1998, Koenig 1993). AstraZeneca noted that it had already described the problems of using the Van der Krogt trial in support of superior efficacy of Istin over felodipine ER. Similar statistical issues regarding non-statistically significant primary endpoints were equally applicable to the Hoegholm, Schaefer, and Östergren studies with respect to this all-embracing claim of 'superior efficacy'. AstraZeneca believed that the supplementary information associated with Clause 7.2 succinctly highlighted that trends toward significance (ie non-statistical significance) should not be used in a manner that might mislead.

AstraZeneca alleged that these claims were ambiguous, misled by implication were not capable of substantiation and all-embracing and thus were in breach of Clauses 7.2, 7.3 and 7.8 of the Code.

RESPONSE

Pfizer stated that the references cited in the detail aid clearly substantiated all the statements referred to in the complaint (although it was not entirely clear whether the complaint referred to each of them or only those specifically criticised). The evidence came from five comparative clinical studies of Istin versus felodipine, which had been published in peer reviewed journals and which were summarised below in order to address the complaint that they provided insufficient data to support the claims.

- **Van der Krogt *et al***

This was a multicentre, double-blind, parallel group study involving 201 patients. Treatment was defined as 'successful' by the composite primary endpoint of number of responders, serious adverse events, withdrawals due to adverse events and no increase in heart rate. (Responders were defined as those at the

end of treatment to have a DBP of ≥90mmHg, or a reduction of ≥10mmHg if baseline was at DBP>100mmHg). Although both medicines effectively reduced blood pressure, the number of responders were higher in the Istin group compared to the felodipine group (p=0.046). Similarly, there were statistically significantly more serious adverse events suffered in the felodipine group compared to Istin (p=0.048). However, the withdrawal rates were not significantly different between the two groups. Treatment was considered successful in 50.5% of the Istin patients compared to 37.5% in the felodipine group. Although there was no statistical difference between the two groups, the results were in favour of Istin The authors concluded that 'at equipotent antihypertensive doses, amlodipine has a more favourable clinical profile than felodipine'.

- **Hoegholm *et al***

This was a 24-hour ambulatory blood pressure monitoring (ABPM) study with 118 patients in general practice. The findings showed that amlodipine induced a larger fall in systolic ambulatory blood pressure than felodipine during both day and night-time periods. Both medicines had a similar effect on office BP. Systolic hypertension was indicated from the Framingham data to be a major cardiovascular risk factor for coronary heart disease and stroke. The average effective dose of felodipine was higher than that for amlodipine (11.2mg vs 7.4mg), which showed that amlodipine was more potent on a mg per mg basis.

- **Schaefer *et al***

The primary aim of this double-blind, parallel group trial was to compare the incidence of newly occurring vasodilatory adverse events in elderly patients. However, it was also set out to measure blood pressure prospectively. There was a difference in the overall incidence of vasodilatory adverse events between the two groups, with more peripheral oedema in the amlodipine group. According to the author, 'Amlodipine produced a somewhat greater blood pressure reduction' – this was statistically significant compared to felodipine. Both the differences in efficacy and adverse events might be due to the higher doses of amlodipine used compared to felodipine.

- **Östergren *et al***

As the elimination half-life of amlodipine was longer than that of felodipine, this study was set up to investigate whether this difference would be reflected in different duration of BP control as measured by ABPM. From the total of 216 patients who participated, significantly more patients responded to treatment after 4 weeks with amlodipine (50%) compared with felodipine (33%), p=0.03. Night-time systolic and diastolic BP were more effectively reduced by amlodipine than felodipine. After eight weeks, 82% of patients achieved target pressure with amlodipine and 69% with felodipine (p=0.036).

The authors added that 'for individual patients for whom it is believed to be especially important to control night-time and morning BP, amlodipine seems to be a more reliable alternative than felodipine ER'.

In conclusion, 'the findings are compatible with the longer duration of action of amlodipine than of felodipine ER, and may have therapeutic implications for the prevention of BP increases in the morning hours in patients at high risk of cardiovascular events'.

- **Smilde**

The antihypertensive effects of amlodipine and felodipine were assessed at steady state and after one and two consecutively missed doses. This study was particularly relevant as hypertension was a chronic condition in which patients might not always be compliant. After missing the first dose, blood pressure increased significantly in the felodipine ER group but did not change significantly in the amlodipine group. The difference in blood pressure change between the two treatment groups was statistically significant for diastolic BP in favour of amlodipine. The statistically significant increase in blood pressure in the felodipine ER group was more pronounced after two missed doses, which was not found in the amlodipine group. In summary, one or two missed doses of amlodipine did not adversely affect the mean ambulatory blood pressure. However, felodipine was associated with a greater variation in the 24-hour blood pressure profile after one or two missed doses. The author concluded that 'amlodipine appears to be preferable to felodipine ER for the long-term management of hypertension, particularly because occasional failure of daily compliance is not uncommon'.

Claim 'Evidence favouring Istin over felodipine ER'

Pfizer stated that this claim was clearly substantiated by all of the studies referred to above. Taking into consideration the other two studies referred to in the complaint, Lefebvre and Koenig, there were a total of five studies favouring the evidence towards Istin compared to the two which only demonstrated equivalent efficacy. Overall, it was reasonable to conclude that the evidence was in favour of Istin over felodipine. This was based on an up-to-date and balanced evaluation of available data on the comparison of the two products. The statement was clear, did not mislead by implication and was not all embracing. Hence Pfizer did not believe that there was a breach of Clause 7.2, 7.3 or 7.8 of the Code.

Claim 'Studies showing superior efficacy'

The references provided for the above claim (from the studies as summarised above) had demonstrated superiority to felodipine in terms of amlodipine's clinical profile, 24-hour ambulatory blood pressure reduction, office blood pressure reduction, night-time and early morning reduction of blood pressure and less blood pressure variation after missed doses.

Pfizer believed that the claim was clear, had been substantiated fully by the references provided and, therefore, did not breach Clauses 7.2, 7.3 or 7.8 of the Code.

Claim 'Better BP reduction'

Pfizer stated that this claim was substantiated fully by Hoegholm *et al*, Van der Krogt *et al* and Schaefer *et al*

as explained above and was not ambiguous, misleading nor all embracing. It therefore did not breach Clause 7.2, 7.3 or 7.8 of the Code.

Claim 'With Istin, patients got closer to their goals than with felodipine ER'

Pfizer stated that both the Van der Krogt and Schaefer studies substantiated this claim. There were more responders in the Van der Krogt study, which meant that more amlodipine patients achieved their blood pressure lowering targets than the felodipine group. Similarly, in the Schaefer study, amlodipine reduced blood pressure to a significantly greater degree than felodipine. In doing so, amlodipine patients got closer to their blood pressure targets or goals than those on felodipine.

The relevance of reducing blood pressure had been explained above, and a large body of literature defined the 'goals' of blood pressure treatment, which were well accepted in clinical practice. Getting patients 'closer to their goals' meant reducing their blood pressure adequately in line with relevant targets and the Schaefer study gave clear evidence of the statistical significance of Istin over felodipine in doing this.

Claim 'With Istin more patients could achieve better BP control than felodipine ER'

On the same basis as above, the claim that 'With Istin more patients could achieve better BP control than felodipine' was substantiated. The study by Van der Krogt clearly showed a significant difference in the number of responders between Istin and felodipine ER. The legitimacy of this claim was further supported by the fact that all the other parameters measured, including the primary parameter, showed a trend towards Istin. When comparing two different products, it was always a question of judgement as to which data might be quoted in support of claims. It was worth noting, however, that in all the direct comparisons of the efficacy of Istin and felodipine ER, there was never a significant difference in favour of the latter. Where there were significant differences in efficacy between the two, these were in favour of Istin.

For these reasons Pfizer did not believe that the claims referred to above breached Clause 7.2, 7.3 or 7.8 of the Code.

PANEL RULING

The Panel noted Pfizer's submission that it was not entirely clear whether the complaint concerned each of the five claims listed, or only those specifically criticised. The Panel considered that the complaint clearly referred to each of the claims listed by AstraZeneca and mentioned in the preamble to point 2 of the complaint above.

A Claim 'Studies showing superior efficacy'

The Panel noted that the claim 'Studies showing superior efficacy' appeared beneath a depiction of five studies and was referenced to Van der Krogt *et al* (1996), Hoegholm *et al* (1995), Schaefer *et al* (1998), Östergren *et al* (1998) and Smilde (1997).

The Panel noted that the aim of Van der Krogt *et al* (1996) was to compare the effectiveness of amlodipine and felodipine ER monotherapy in providing blood pressure control without concomitant severe or serious adverse events, increased heart rate or premature drug withdrawal due to any adverse event. Initially, patients received 5mg once daily of either medicine. This dose was doubled to 10mg daily if, after four weeks or eight weeks of treatment, sitting DBP was ≥95mmHg. If DBP remained ≥95mmHg after four weeks at 10mg of either medicine the dosage was halved and lisinopril added to the regimen at a dosage of 5mg once daily. The primary endpoint of the study was to determine whether treatment was successful or unsuccessful. The difference in success rates between the two patient groups was not statistically significant. The authors stated that there was no significant difference in efficacy between the two medicines; although more patients in the felodipine ER group required combination therapy with lisinopril this difference was not statistically significant. The difference in numbers of responders, amlodipine 68%, felodipine ER 53%, was statistically significant (p=0.046). A patient was considered as a responder if after 12 weeks of monotherapy with either of the study medications a sufficient blood pressure response (defined in the study) was achieved. A patient was considered a non responder if after 12 weeks of monotherapy with either product an insufficient blood pressure response was achieved or if there was a need for the addition of lisinopril during the study. The study authors noted that amlodipine presented a more favourable tolerability profile than felodipine ER.

Hoegholm *et al* (1995) compared amlodipine (5 or 10mg) and felodipine ER (5, 10 or 20mg) on office and ambulatory blood pressure in patients with mild to moderate hypertension. The study concluded that both medicines had a similar effect on office BP although there was, on average, a significantly larger 24-hour reduction in systolic ambulatory BP in the amlodipine group (p=0.0014). The difference was significant for day and night time readings and could, according to the study authors, be attributed in part to the slightly higher baseline in the amlodipine group. The diastolic ambulatory BP showed no significant difference in response between the groups.

The Panel noted that the primary objective of Schaefer *et al* (1998) was to compare the tolerability of felodipine ER and amlodipine in elderly hypertensives. The secondary objective was to compare how blood pressure and quality of life were affected. The study authors stated that there was a small but statistically significant difference in diastolic blood pressure (p=0.008) and systolic blood pressure (p<0.001) between the two groups. This might be attributable to higher mean daily doses in the amlodipine group. The study authors further noted that previous trials in younger patients had shown equal efficacy and tolerability with the two medicines.

The primary objective of Östergren *et al* (1998) was to investigate whether starting doses of 5mg of amlodipine versus 5mg felodipine were equipotent in the treatment of primary mild to moderate

hypertension with focus on the antihypertensive effect at the end of the dosing interval. After four weeks night-time systolic and diastolic blood pressure was significantly more reduced (p=0.026 and p=0.019 respectively) by amlodipine than by felodipine. A significantly greater number of patients in the amlodipine group thus reached their target BP. The Panel noted that Pfizer had referred to the analyses after eight weeks and in this regard noted the study authors had cautioned that 'analyses after eight weeks must be regarded as explorative rather than confirmative'.

The fifth study, Smilde (1997), compared amlodipine and felodipine ER in the treatment of hypertension at steady state and after one and two consecutively missed doses. The study concluded that equipotent doses of amlodipine and felodipine ER in patients with mild to moderate hypertension were equally effective in reducing 24-hour ambulatory blood pressure. The differences between the two patient groups were not statistically significant with regard to ambulatory blood pressure after 10 weeks of treatment nor with regard to the blood pressure change after two consecutively missed doses at 12 weeks. However there was a statistically significant difference in blood pressure change between the two groups after the first missed dose. The data showed a greater variation in blood pressure with felodipine ER than with amlodipine after one and two missed doses. The Panel noted the submission of Pfizer about the relevance of this study. However the Panel noted the study author's conclusion that the patients' awareness of the missed doses was a weakness in the study design and these results should thus be verified in a placebo-missed dose design study.

The Panel also examined the studies referred to by AstraZeneca; Koenig *et al* (1993) and Lefebvre *et al*. Koenig *et al*, a comparative study of felodipine and amlodipine 5-10mg od in the treatment of mild to moderate hypertension, concluded that they were equally effective and there were no statistically significant differences between the products. The possibility of a clinically significant difference in favour of felodipine ER was mentioned. Lefebvre *et al* concluded that there was no evidence of a difference between felodipine ER and amlodipine in lowering ambulatory or clinic BP.

The Panel considered that the claim 'Studies showing superior efficacy' was a broad and unambiguous claim; a reader would assume that each study cited would demonstrate the superior efficacy of Istin over felodipine ER and that was not so. The studies cited had varying primary endpoints and patient populations. The Panel noted that whilst there were statistically significant outcomes in favour of amlodipine in some parameters of some studies, a number of the studies stated there was no difference in efficacy. Overall the claim was not a fair reflection of the totality of the evidence and was not capable of substantiation. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that the allegation of a breach of Clause 7.8 was covered by this ruling.

B Claim 'Better BP reduction'.

The Panel noted that this claim was referenced to Van der Krogt *et al* (1996) and Schaefer *et al* (1998). Pfizer had also referred to Hoegholm *et al* (1995) in its response.

The Panel considered that its previous comment on these studies was relevant here. Van der Krogt did not demonstrate a between group significant difference in BP reduction, although the between group differences in response were statistically significant. The Panel noted that the primary endpoint in Schaefer related to tolerability, not efficacy, and although a significant reduction in BP was achieved the mean dose used was not 5mg. The Panel considered that a reader would assume that Istin gave better BP reduction than felodipine ER and that this was substantiated by the studies cited. This was not so. The Panel considered that the claim was misleading and unsubstantiated as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that the alleged breach of Clause 7.8 was covered by this ruling.

C Claim 'Evidence favouring Istin over felodipine ER'.

The Panel noted that the claims at issue in points 2A and 2B above appeared in the highlighted column along the inside edge of the page and together with the claim 'Better continuous ambulatory control' purported to summarise the 'Evidence favouring Istin over felodipine ER'. The Panel noted its rulings at points 2A and B above and considered that the claim at issue in point 2C was unsubstantiated and misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that the alleged breach of Clause 7.8 was covered by this ruling.

D Claim 'With Istin more patients could achieve better BP control than with felodipine ER'.

The Panel noted that this claim was referenced to the Van der Krogt *et al* study. The claim appeared above a bar chart headed 'Istin higher response rate than felodipine ER' which depicted the response rates achieved in Van der Krogt *et al* by Istin and felodipine ER in successful monotherapy (50% and 37% respectively, p=NS) and in those responders >10mmHg or target BP with or without added lisinopril (68% and 53% respectively, p>0.05).

The Panel noted that whilst it had no complaint about the bar chart as such, the claim at issue would be read in light of the data depicted in the chart as well as the rest of the page.

The Panel considered that its comments regarding Van der Krogt at point 2A and regarding 'Better BP reduction' at point 2B applied here. The Panel further noted that whilst there was a between group difference in the number of responders in Van der Krogt *et al* the difference with regard to success rates were not statistically significant. The Panel was unsure of the origin of the monotherapy data given in the detail aid given that the figures in the study were 37.5% and 50.5%. The Panel considered the claim misleading and unsubstantiated as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that the allegation of a breach of Clause 7.8 was covered by this ruling.

E Claim 'With Istin, patients got closer to their goals than with felodipine ER'.

The Panel noted that this claim was referenced to Van der Krogt and Schaefer *et al* and considered that its comments upon these studies at point 2A, B and D were relevant.

The Panel considered that given its rulings at points 2A, B, C and D above the claim was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that the allegation of a breach of Clause 7.8 was covered by this ruling.

3 On page four of the detail aid the heading to the highlighted column 'Evidence favouring Istin over felodipine ER' appeared above the claim 'Better trough:peak ratios'. The claim 'Istin exceeds the 50% trough:peak ratio recommended by the FDA – felodipine ER does not' appeared on the main page and was referenced to Meredith PA *et al* (1994) and Videbaek *et al* (1997).

COMPLAINT

AstraZeneca stated that the trough:peak ratio (TPR) was a parameter proposed by the FDA as a means of establishing the efficacy and dosing interval of an anti-hypertensive medicine. Unfortunately, there were no definitive guidelines provided by the FDA or other regulatory bodies on the methodology required to define the trough:peak ratio and a range of methods existed. Therefore values quoted for TPR should state a range, to reflect the clinical data and to provide a balanced and objective view. AstraZeneca noted that the studies Pfizer had quoted did indeed show results where the TPR for felodipine ER was <50%. However, Pfizer had failed to mention the many studies where felodipine ER TPR was >50%, ie Bonaduce, Zhu, Morgan, Pannarale, Lederle, Weber and Shapiro. Further, this was substantiated by the SPC for Plendil which stated that 'a reduction in blood pressure usually occurs within 2 hours after the first oral dose and lasts at least 24 hours with a trough/peak ratio usually above 50%.'

In view of these facts, AstraZeneca was of the opinion that the claim was disparaging to an AstraZeneca product, inaccurate, misleading, unfair, did not reflect the evidence appropriately and was thus in breach of Clauses 7.2 and 8.1 of the Code.

RESPONSE

Pfizer stated that TPRs were an important measurement of the efficacy and consistency of effects of any antihypertensive agent to be used as a once daily drug. Values quoted for TPR did not have to be from a range.

Pfizer noted that the SPC for felodipine included the word 'usually' to qualify the trough:peak ratio being above 50% and this reflected the real inconsistency found in the literature. The studies quoted by AstraZeneca were all, with the exception of Weber and Shapiro, small studies. Moreover the Bonaduce, Zhu and Pannarale studies were all performed on the 10mg dose. Whilst the small Morgan and Lederle studies claimed trough:peak ratios above 50%, the considerably larger study by Weber *et al* showed a ratio of considerably less than 50% (in fact 25% when adjusted for the placebo effect) for the 5mg dose. The Shapiro abstract quoted appeared to be the same data set although the Weber study was only published four years later. It was worth noting that Rose and McMahon particularly criticised an earlier abstract by Shapiro for failing to subtract the placebo effect first properly and hence miscalculating the TPR for felodipine ER.

It therefore appeared that, in relation to the 5mg dose at least, for the majority of patients reported in the literature the TPR for felodipine ER was indeed less than 50%. The balance of evidence was clearly in favour of the superior TPR of Istin. The claim was therefore accurate and not misleading, unfair or disparaging, and reflected the evidence appropriately. It did not breach Clauses 7.2 or 8.1 of the Code.

PANEL RULING

The Panel noted that the claim 'Better trough:peak ratios' was referenced to three separate studies; Videbaek *et al* (1997), Meredith *et al* (1994) and Zannad *et al* (1996). Videbaek *et al* (1997) concluded that the peak-to-trough plasma concentration ratios were more favourable for amlodipine (1.58) compared to felodipine (4.43). Meredith *et al* (1994) stated that although the peak effect was greater there was less variability with amlodipine and the trough effect was consistently superior with amlodipine. The figures were 67 ± 8% for amlodipine and 36 ± 13% for felodipine. Zannad *et al* (1996) was a retrospective literature analysis of 24 ACE inhibitor and 34 calcium antagonist studies with comparable methodologies. The study authors whilst noting that the analysis might have some theoretical limitations, stated that the mean trough:peak ratio of amlodipine was in the average range of 50-100% and felodipine ER 30-45%. On balance the Panel considered that given all the data the claim 'Better trough:peak ratio' was not misleading or disparaging. No breach of Clauses 7.2 and 8.1 was ruled.

The Panel considered that the claim 'Evidence favouring Istin over felodipine ER' was not misleading with reference to the first claim listed 'Better trough:peak ratios'. No breach of Clauses 7.2 and 8.1 was ruled in that regard. There was no complaint about the other two claims listed in the highlighted column.

The Panel noted that the claim 'ISTIN exceeds the 50% trough:peak ratio recommended by the FDA – felodipine does not' appeared above a table which read 'Trough:peak ratios ISTIN 67% felodipine ER 36%.' The Panel noted the wording in the Plendil SPC that the trough:peak ratio was usually above 50%. The Panel noted that whilst there was evidence to show that Istin, overall, had better trough:peak ratios than felodipine ER there was evidence that the trough:peak ratio for felodipine ER was usually above 50%. The claim and the table gave the impression that felodipine ER never exceeded the 50% trough:peak ratio and that was not so. The Panel

considered that the claim was misleading and disparaging and ruled breaches of Clauses 7.2 and 8.1 of the Code.

4 Claim: 'felodipine trials cannot offer proven assurance.'

This claim appeared on page 9 of the detail aid beneath the statement 'Prospective Randomised Amlodipine Survival Evaluation (PRAISE) a major study in coexisting heart failure (CHF) offered extensive and conclusive safety data.'

COMPLAINT

AstraZeneca pointed out that the claim appeared on a page which attempted to highlight the ongoing clinical trials with Istin and mentioned several studies looking at patient groups with several independent cardiac risk factors such as hypercholesterolaemia, the elderly and congestive heart failure.

AstraZeneca alleged that this claim was an all-embracing claim and was an attempt at disparaging felodipine ER's safety data when used in patients with coexisting heart failure. AstraZeneca referred to the SPC for Plendil which stated in Section 5.1 that 'Felodipine is well tolerated in patients with concomitant diseases such as congestive heart failure well-controlled on appropriate therapy,…' as an indicator and as evidence of the accepted safety data for felodipine ER in this patient group.

With respect to the use of PRAISE data, in intercompany correspondence Pfizer mentioned 'improved survival with Istin compared to placebo in patients with (heart failure and) non-ischaemic heart disease' as evidence to support this claim even though this was an efficacy claim and was inconsistent with the Istin SPC. AstraZeneca's view was that PRAISE was of no relevance in supporting this tolerability claim versus felodipine ER.

AstraZeneca stated that an unrepresentative selection of the available literature had been used to imply favourable safety or tolerability claims of Istin over felodipine ER. For example, studies such as Koenig, Schaefer, Corradi and Achilli showed tolerability results that favoured felodipine ER over Istin or showed comparable tolerability but were not mentioned. AstraZeneca believed that the tolerability of felodipine ER in a wide range of co-morbidity conditions, including angina, was relevant to this claim and to the context of a page that discussed different co-morbid states.

AstraZeneca alleged that the claim was disparaging to an AstraZeneca product, misleading and not capable of substantiation and was in breach of Clauses 7.2, 7.3, 7.7, 7.8 and 8.1 of the Code.

RESPONSE

Pfizer submitted that this claim was a fair reflection of the data available on congestive heart failure with Istin and felodipine. In particular, it should be read in the context of the statement made regarding the heart failure study with amlodipine – PRAISE. This major study in heart failure showed that Istin was well tolerated in patients with severe heart failure as defined by the New York Heart Association classification of III and IV. It also demonstrated improved survival with Istin compared to placebo in patients with non-ischaemic heart disease, and in addition a non-statistically significant improvement with Istin in patients with ischaemic heart disease. These findings were reflected in Istin's SPC with the specific indication 'Istin is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease'. A similar trial using felodipine, known as V-HeFT III, did not show such improvements in patients with CHF grade III and IV, and felodipine did not have the same indication.

Therefore the published data on the performance of felodipine in heart failure was less consistent than those on Istin and, moreover, no data was published on the use of felodipine in Class IV heart failure. This was the basis for the claim that, in this context, felodipine could not offer the same proven assurance.

Pfizer did not therefore accept that the claim was disparaging to AstraZeneca's product nor was it misleading or incapable of substantiation and for this reason it was not in breach of Clauses 7.2, 7.7 or 8.1 of the Code.

PANEL RULING

The Panel noted that PRAISE (Packer *et al*) examined the effect of amlodipine on morbidity and mortality in severe chronic heart failure. The study authors concluded that the trial established the safety of amlodipine for the treatment of angina or hypertension in patients with advanced left ventricular dysfunction. In response to the question should amlodipine be used for the treatment of heart failure in patients without these associated cardiovascular conditions, the authors stated that although amlodipine might reduce the risk of death in patients with nonischaemic dilated cardiomyopathy such an effect required confirmation in a second trial.

The Panel noted its comments regarding the licensed indication for Istin and the conclusions of the PRAISE study at point 1 above. The Panel noted that the Plendil SPC (ref: ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000) stated that it was indicated for the management of hypertension and prophylaxis of chronic stable angina pectoris. A section headed 'Preclinical safety' stated that felodipine was well tolerated in patients with congestive heart failure.

The Panel noted Pfizer's submission that the basis of the claim at issue was that the published data on the performance of felodipine ER in heart failure was less consistent than those on Istin and no data was published on the use of felodipine in Class IV heart failure. The Panel considered that a reader would assume that felodipine trials did not offer proven assurance when compared to the 'extensive and conclusive safety data' obtained with amlodipine in the PRAISE study in patients with co-existing heart failure.

The Panel noted the trials referred to by AstraZeneca but noted that they related to a wider range of co-morbidity conditions.

The Panel considered that the phrase '…felodipine trials cannot offer proven assurance' was a strong claim and given the statement in the Plendil SPC considered that it was misleading, disparaging and not capable of substantiation. It might be read as implying that adverse safety data had been obtained in felodipine trials in patients with co-existing heart failure. That was not so. No such major trials had been conducted. Breaches of Clauses 7.2, 7.3, 7.7 and 8.1 were ruled. The Panel considered that the alleged breach of Clause 7.8 was covered by this ruling.

5 Use of Schaefer study

COMPLAINT

AstraZeneca stated that certain inconsistencies had been applied to the use of the available data. For example the Schaefer study was presented in a negative light on page 7 since this favoured felodipine ER over Istin. However, on page 3, the materials highlighted the apparent efficacy benefits from this same study in favour of Istin. Also, the V-HeFT reference used by Pfizer in intercompany correspondence of 12 January to support this argument actually delivered the following quote from the investigators' clinical trial experience with felodipine ER:

'Nonetheless, the data suggests that felodipine ER can be used safely in patients with heart failure if used for another indication. Furthermore, this study provided no evidence for an excess of cardiovascular events in response to dihydropyridine therapy, as suggested by other recent analyses.'

RESPONSE

Pfizer's view was that the Schaefer data were presented consistently throughout the detail aid and were not selected in an unrepresentative manner in order unfairly to imply favourably claims for Istin. On page 7, the detail aid clearly highlighted the higher incidence of adverse events observed with Istin over felodipine. At no point was the Schaefer study presented in a negative light as alleged. On page 3 (as discussed above), the evidence of Istin's efficacy was presented. Comparative data with felodipine, such as the Schaefer study, clearly demonstrated the greater efficacy of amlodipine compared to felodipine. It was relevant to substantiate the statement made on page 3 with the appropriate data. Therefore, the Schaefer study was presented in a fair and balanced manner.

PANEL RULING

The Panel noted that on page 3 of the detail aid Schaefer had been cited in support of the following claims 'Studies showing superior efficacy,' 'Better BP reduction' and 'With Istin, patients got closer to their goals than with felodipine ER'. The Panel noted its rulings at point 2 above on page 3 of the detail aid.

Page 7 of the detail aid was headed 'Has it been well interpreted?' and unfavourably compared the results obtained in Schaefer *et al* (1998) with other studies with regard to the comparative tolerability and vasodilatory side effects of Istin and felodipine ER.

The greater blood pressure reduction obtained with Istin was noted in conjunction with its higher average dose of 7.3mg compared with felodipine ER 5.5mg. This information was not given on page 3. The Panel considered the inconsistent use of such data misleading. A breach of Clause 7.2 was ruled.

6 Claims: 'Switching from ISTIN to felodipine ER increases costs – US based study' and 'Switching to felodipine ER may increase your costs'.

These claims appeared on page 10 of the detail aid headed 'What switching from ISTIN really entails' which discussed relevant differences between the two products with regard to a switch. A table headed 'Switching from ISTIN to felodipine ER increases costs – US based study' showed a 13% overall increase in drug costs after switch. The number of angina patients withdrawing increased from 15.6% to 50% after switch. The 50% figure was referenced to a footnote which stated 'Felodipine discontinued because physicians deemed its use inappropriate (non FDA approved indication)'. The second claim 'Switching to felodipine ER may increase your costs' appeared as a strapline at the bottom of the page.

COMPLAINT

AstraZeneca noted that these statements were referenced to a US based analysis in Formulary, 1998. This analysis highlighted the apparent increased costs associated with switching from amlodipine to felodipine ER.

AstraZeneca considered the data presented in the detail aid to be misleading and not relevant to UK based practice. Firstly this study as presented was an observational exercise with no evidence of formal clinical trial structure such as a suitable cross-over group as a control or a formal statistical plan to analyse the data prospectively. Therefore there was no evidence to suggest that there were any statistical differences in the cost analysis between amlodipine and felodipine, despite the apparent absolute increases. AstraZeneca noted the supplementary statistical information for Clause 7.2 of the Code, which stated the need for a sound statistical basis for all information, claims or comparisons.

Secondly, the post-conversion withdrawal rate displayed in the angina patients as displayed was misleading since this was due to physicians complying with the FDA approved indications for the two drugs. With reference to the UK SPC for Plendil, the indications included 'prophylaxis of chronic stable angina'. Therefore for those US physicians who felt that their patients with angina were now inadequately treated but were adequately controlled by felodipine for hypertension, it was obvious that costs would increase due to the addition of therapy for prophylaxis and treatment of angina. This would not be relevant in the UK due to the difference in licensed indications.

AstraZeneca alleged that the claim and table were misleading in breach of Clause 7.2 of the Code.

RESPONSE

Pfizer stated that hypertension was a chronic condition which required careful management. If a calcium channel blocker was switched from even within the same anti-hypertensive class, it might have important consequences. These might include an increase in the costs of treatment due to differences in antihypertensive efficacy and adverse events, resulting in higher use of concomitant medication. This had been shown in the case in patients being switched from amlodipine to felodipine ER and other calcium channel blockers.

The US based study was a good example of such a switch programme, and therefore it was relevant to point out the costs consequences. This study was conducted in a real-life kind of study which was a cost-analysis study and not a clinical trial. Whilst this was a US study, no equivalent study had been carried out in the UK and Pfizer believed that the US findings might indeed be relevant to UK clinical practice in some important respects, if not all.

The detail aid clearly noted at the end of the table that angina was not an approved indication for felodipine in the US. It was necessary to provide all the relevant data which resulted in the overall increase in drug costs, since to omit this information on angina patients withdrawing would be misleading. However, felodipine was only discontinued in 17 patients (50% of the angina group) and therefore the patients who continued on treatment were numerous enough for meaningful assessments of additional medications to be made.

Pfizer believed these data were presented in an accurate format which did not mislead. Therefore, Pfizer did not believe that this page was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the data was from an American study in 142 patients which sought to determine whether an amlodipine to felodipine switch program would result in anticipated cost savings of over $18,000 annually on a facility wide basis. The analysis showed that whilst the monthly medicine acquisition cost decreased (22 patients receiving felodipine were lost to follow up post conversion) the concomitant monthly drug cost increased by $1,305 resulting in a net increase in annual costs to treat 142 patients of $4,867 and a facility wide increase of more than $14,000. The increased number of concomitant medications was required to achieve clinical efficacy in the post conversion period. Pre switch patients had received a daily dose of 2.5mg to 20mg amlodipine. The post conversion felodipine dose was not stated. The Panel noted AstraZeneca's submission that there was no evidence of formal clinical trial structure etc. The nature and cost of the concomitant medication was not stated. The patient population was not identified and the preswitch amlodipine dosage was inconsistent with the UK SPC. The acquisition cost of the medicines would differ in the US. The Panel considered that the calculation could not be directly applied to the UK setting.

The Panel noted that the increase in the number of angina patients withdrawing from 15.6% before the switch to 50% post switch was because physicians deemed the use of felodipine ER inappropriate for a non FDA approved indication. The UK licensed indication for felodipine included 'prophylaxis of chronic stable angina'. The costs of treating such patients in the US would increase due to the cost of concomitant medication for prophylaxis and treatment of angina.

The Panel considered the claim 'Switching from Istin to felodipine ER increases costs' and table misleading; a breach of Clause 7.2 was ruled.

The Panel considered that although the strapline claim 'Switching to felodipine ER may increase your costs' acknowledged that a switch to felodipine might not always result in increased costs it would be read in light of the information on the page which had been ruled to be misleading. Another breach of Clause 7.2 was ruled.

7 Claim 'The evidence is stacked in its favour Istin'.

This claim appeared on the front page of the detail aid above a pyramidal stack of studies.

COMPLAINT

AstraZeneca alleged a breach of Clause 7.2 of the Code.

RESPONSE

Pfizer stated that this statement appeared on the front cover, on the basis that the detail aid outlined the evidence for Istin from various clinical trials, its summary of product characteristics and outcomes research, all clearly demonstrating the use of amlodipine as an effective blood pressure lowering agent.

PANEL RULING

The Panel considered that the claim gave the impression that with regard to the claims made in the detail aid the evidence clearly favoured Istin over felodipine ER. Given the Panel's rulings at points 1-6 above this was not so. The claim was a strong claim and the Panel considered that it did not represent a balanced overview of all the evidence and a breach of Clause 7.2 was ruled.

Complaint received **25 February 2000**

Case completed **30 May 2000**

CASE AUTH/989/3/00

GENERAL PRACTITIONER v ASTRAZENECA

Promotion of Losec

A general practitioner complained about a journal advertisement for Losec (omeprazole) issued by AstraZeneca which featured a lifeboat man comforting a young boy who was wrapped in a blanket. Superimposed on the photograph were 'Lifeboat man. Relied on by millions' and 'Losec. ditto'.

The complainant had reservations about the ethical nature of the advertisement. The implication was that children's lives would be saved but this was seriously misleading as Losec was not licensed for use by general practioners in children, such use being restricted to consultant recommendation. It had therefore certainly not been used millions of times. The claim was misleading in its implications for children's treatment and could in this aspect be considered dangerous. The Panel considered that the claim 'Relied on by millions' was a general claim for Losec implying that the product could be trusted or depended upon with confidence and did not accept that, in conjunction with the picture, the claim would generally be interpreted as 'Saving the lives of millions' of children or adults. The Panel noted that Losec was licensed for use in children over two years of age with severe ulcerating reflux oesophagitis, although the summaries of product characteristics (SPCs) for Losec Capsules and Losec MUPS stated that experience in this patient group was limited and that a hospital based paediatrician should initiate treatment. Such treatment could be continued by a general practitioner. The Panel accepted that the advertisement was open to interpretation. Although the photograph was of a child who had just been rescued by a lifeboat man the Panel considered that the work of the RNLI was so well known that most readers would see the visual in its widest context. In the Panel's view the advertisement would not be read as Losec would save the lives of millions of children. It was more likely to be read that Losec could be depended upon to help millions of patients. The Panel decided that, on balance, the advertisement was not misleading as alleged and no breach of the Code was ruled.

The complainant also stated that whilst in conversation with AstraZeneca he had raised the question of 'flare up of disease' when changing from Losec capsules to Losec MUPS tablets. This would seem to indicate a variable bio-availability or was there another explanation for the need to produce this statement in the literature? The company quoted experience of the change in Canada. The regulatory authorities then required it to include this phrase in its literature but representatives in this country were not explaining this point when seeing general practitioners to promote the product.

The Panel noted that a section of the Losec MUPS tablets SPC headed 'Special Warnings and Precautions for Use' stated that 'When treatment with Losec MUPS tablets is instituted patients on previous Losec capsule therapy should be monitored for any reports of 'flare up' of disease symptoms'. The Panel examined the representatives' briefing material. The representatives were not directed to mention the possibility of flare up when discussing a switch from Losec capsules to MUPS. Given the statement in the SPC the Panel considered that when promoting a switch from capsules to MUPS the possibility of flare up should be mentioned. The Panel considered that this omission was likely to lead to a breach of the Code contrary to the requirements relating to representatives' briefing material. A breach of the Code was ruled.

A general practitioner complained about the promotion of Losec (omeprazole) by AstraZeneca UK Limited.

1 Use of the photograph of a child

A journal advertisement (ref LOS ADV 5822) featured a photograph of a lifeboat man comforting a young boy who was wrapped in a blanket. The claims superimposed on the photograph were 'Lifeboat man. Relied on by millions' and 'Losec. ditto'.

COMPLAINT

The complainant stated that recently his primary care group had been pressurising his practice's prescribing of proton pump inhibitors and he had become interested in the field. This had lead to his interest in the advertisement and promotion of these medicines. The complainant stated that he had telephoned AstraZeneca to ask about claims in its advertisements. Although he had received a written response he still had some reservations about the ethical nature of its recent advertisements for Losec which showed a lifeboat man and a child.

The complainant noted that this advertisement claimed 'Relied on by millions' and implied to 'save lives'. Unfortunately the lifeboat man was clearly an adult but the implication from the picture was that the lives saved would be those of children as the victim of the disaster shown was a child.

The complainant alleged that this was seriously misleading, perhaps under Clause 7.2 of the Code, as this product was not licensed for use by general practitioners to treat children. Its use being restricted to consultant recommendation only and had therefore certainly not been used millions of times. This advertisement appeared frequently in general practitioner magazines and was not restricted to journals circulated to consultants. The claim was misleading in the implications for children's treatment and could in this aspect be considered dangerous.

RESPONSE

AstraZeneca stated that with regard to the claim 'Relied on by millions', a photograph of a lifeboat man was selected because he was relied on by millions of people. Everyone who went to the beach, went sailing, was a professional mariner, travelled by air etc gained reassurance and trust by knowing that the Royal National Lifeboat Institute (RNLI) would be there, if required.

Like lifeboat men, Losec was relied on by millions of patients with acid related disorders. Up to the end of February 2000, over 449 million patient treatments worldwide had been performed with Losec.

Furthermore, as 'relied on' was meant to infer trust and did not mean 'saving lives', as alleged by the complainant, the company denied any breach of Clauses 3.2 and 7.2.

AstraZeneca stated that it did not consider this depiction of a child to be promotion outside the licence. Oral Losec was licensed for use in children aged over two years with severe ulcerating oesophagitis, as stated in the prescribing information, and the boy was an illustrative example of the type of patient that could be seen by a general practitioner.

Although treatment of paediatric patients had to be initiated by a hospital based paediatrician and as GPs could continue treatment, the company did not consider it either misleading or dangerous to place this advertisement in a GP journal.

AstraZeneca stated that a GP involved in the management of a child with severe ulcerating reflux oesophagitis would be advised on prescribing Losec by a hospital based paediatrician. However, should a GP wish to initiate treatment it would not be unreasonable to expect reference to the prescribing information where it stated that treatment initiation should be made by a hospital paediatrician.

PANEL RULING

The Panel considered that the claim 'Relied on by millions' was a general claim for Losec implying that the product could be trusted or depended upon with confidence. The Panel did not accept that, in conjunction with the picture, the claim would generally be interpreted as 'Saving the lives of millions' of children or adults.

The Panel noted that the young boy in the photograph had just been rescued by the lifeboat man. Losec was licensed for use in children over two years of age with severe ulcerating reflux oesophagitis although the SPCs for Losec Capsules and Losec MUPS stated that experience in this patient group was limited. The SPCs also stated that a hospital based paediatrician should initiate treatment. Such treatment could be continued by a general practitioner.

The Panel accepted that the advertisement was open to interpretation. Although the photograph was of a child who had just been rescued by a lifeboat man the Panel considered that the work of the RNLI was so well known that most readers would see the visual in its widest context. In the Panel's view the advertisement would not be read as Losec would save the lives of millions of children. It was more likely to be read that Losec could be depended upon to help millions of patients. The Panel decided that, on balance, the advertisement was not misleading as alleged and no breach of Clauses 7.2 and 3.2 of the Code was ruled.

2 'Flare up' of disease symptoms

COMPLAINT

The complainant stated that whilst in conversation with AstraZeneca he had also raised the question of 'flare up of disease' when changing from Losec capsules to Losec MUPS tablets. This would seem to indicate a variable bio-availability or was there another explanation for the need to produce this statement in the literature? The company quoted experience of the change in Canada, the regulatory authorities then required it to include this phrase in its literature but the representatives in this country were not explaining this point when seeing general practitioners to promote the product.

RESPONSE

AstraZeneca stated that the SPC did advocate monitoring for 'flare up' of symptoms if patients were switched from Losec capsules to Losec MUPS tablets. However, this did not assign causality, but was precautionary advice in the unlikely event of the occurrence of 'flare up'. AstraZeneca noted that the licence did not state that there was a difference between the two formulations, including adverse events.

AstraZeneca stated that due to lack of experience in EC countries, the 'flare up' warning was put on the SPC at the request of the assessor at the Medicines Control Agency (MCA). This was based on the pattern of Canadian adverse events, following the introduction of an enteric coated form of Losec. It was important to note that the Canadian formulation was a single unit pellet system and not the multiple unit pellet system (MUPS) available in the UK. The MUPS formulation was not yet available in Canada.

With regard to the complainant's query concerning the bio-availability between the two formulations, according to the Losec SPC, 'Bioequivalence between Losec capsules and Losec MUPS tablets based on the omeprazole plasma concentration-time curve (AUC) has been demonstrated.'

AstraZeneca stated that on the basis of the data submitted to the MCA, the bioequivalence of the two formulations supported the interchangeable use of either Losec MUPS tablets or Losec capsules for the licensed indications. Thus, as Losec MUPS and Losec capsules were bioequivalent and interchangeable, any claims relating to omeprazole could be used between the two formulations. The company, therefore, did not consider it necessary to highlight the precautionary statement regarding 'flare up'.

In response to a request for further information AstraZeneca stated that for the launch of Losec MUPS tablets in primary care in September 1999 a representative briefing document was issued to the field force. As the two formulations of Losec were interchangeable, this document did not specifically address the switching of patients from Losec capsules to Losec MUPS tablets. A copy of the pertinent section of the briefing document was provided.

AstraZeneca stated that when the SPC was revised in December 1999 its field force was appropriately advised of the change by memo, a copy of which was provided.

AstraZeneca denied any breach of Clause 7.2.

PANEL RULING

The Panel noted that Section 4.4 of the Losec MUPS tablets SPC headed 'Special Warnings and Precautions for Use' stated that 'When treatment with Losec MUPS tablets is instituted patients on previous Losec capsule therapy should be monitored for any reports of 'flare up' of disease symptoms'. The Panel noted the explanation provided by AstraZeneca regarding the inclusion of the statement in the SPC.

The Panel examined the representatives' briefing material as required by Clause 15.9. The document headed 'Losec MUPS tablets' September 1999 briefed representatives on a detail aid which discussed and compared Losec capsules and Losec MUPS tablets. The Panel noted that further to the revision to the Losec MUPS SPC in December 1999 the representatives were provided with a memorandum dated 3 December which outlined these alterations and, *inter alia*, stated that 'representatives should now feel confident to deal with any questions relating to these changes.' The representatives were not directed to mention the possibility of flare up when discussing a switch from Losec capsules to MUPS. Given the statement in the SPC the Panel considered that when promoting a switch from capsules to MUPS the possibility of flare up should be mentioned.

The Panel considered that this omission was likely to lead to a breach of Clause 7.2 of the Code contrary to the requirements of Clause 15.9 which referred to representatives' briefing material. The Panel ruled a breach of Clause 15.9.

Complaint received **22 March 2000**

Case completed **24 May 2000**

CASE AUTH/992/3/00

WYETH v ASTRAZENECA

Losec leavepieces

Wyeth complained about the depiction of prescription event monitoring (PEM) data in two Losec (omeprazole) leavepieces issued by AstraZeneca. A page in each headed 'Losec is very well tolerated' featured a chart showing the relative risk of six adverse events with lansoprazole and Losec. In each adverse event listed (diarrhoea, myalgia, migraine/headache, malaise, depression, nausea and vomiting), the relative risk was greater with lansoprazole than Losec ($p<0.05$) and ranged from 2.2 (diarrhoea) to 1.4 (nausea and vomiting). Wyeth marketed Zoton (lansoprazole).

Wyeth alleged that the text clearly suggested that lansoprazole was not well tolerated and alleged that this was disparaging. It was further alleged that clear references had not been given to clinical trials referenced as 'Data on file'. Wyeth considered that the chart was misleading as the initial visual impression was that there was a substantiated clinical difference between lansoprazole and Losec. There were however two very important qualifications associated with the PEM data which suggested that such a direct comparison might be questionable. They were the accompanying statements 'bias cannot be excluded from these results and further analyses are being performed', which appeared in the text above the chart, and 'These results may suggest differences between the tolerability of these two agents', which appeared beneath the chart. These statements were not part of the chart and were not cross-referenced in any way. In addition, Wyeth did not consider that AstraZeneca's claims regarding the safety profiles of lansoprazole and omeprazole could be substantiated by actual clinical experience. The PEM data was non-comparative, taken from two different time points, and reflected different experiences and use of proton pump inhibitors. If claims regarding side effects were to be substantiated by clinical experience then the experience should be directly comparative. AstraZeneca clearly acknowledged that on the page in question by use of the statement '… randomised controlled trials have not shown a difference between Losec and lansoprazole in the rate of adverse events reported'.

The Panel noted that six adverse events were listed in the chart and in all cases the relative risk was greater with lansoprazole than with Losec ($p<0.05$). A footnote to the chart stated that for five other adverse events no significant differences in the relative risk was shown. In the Panel's view the impression created by the chart, particularly in association with the page heading, was that Losec was better tolerated than lansoprazole. The first of three paragraphs of text above the chart stated that randomised, controlled clinical trials had not shown a difference between Losec and lansoprazole in the rate of adverse events reported. Immediately above the chart it was explained that with regard to the data therein, bias could not be excluded and that further analyses were being performed. Text below the chart stated that the data shown might suggest differences in the tolerability of Losec and lansoprazole. The Panel noted that the authors of the poster from which the PEM data was taken acknowledged that selection and response bias and the four year difference in the two periods of observation influenced the comparability of the cohorts. The Panel considered that the prominence of the chart and heading were such that, despite qualifying text, the impression that most readers would gain was that Losec was better tolerated than lansoprazole. The Panel considered that the way in

which the PEM data had been presented gave a misleading impression of the comparative tolerability of Losec and lansoprazole. It had not been set in the context of the overall data nor had its limitations been adequately explained. PEM data showing no significant difference between omeprazole and lansoprazole had only been mentioned in the chart by way of a footnote. Breaches of the Code were ruled. The Panel did not consider that the pages disparaged lansoprazole and no breach was ruled in that regard.

The Panel noted that the first paragraph of text referred to results from randomised controlled clinical trials but did not state that the trials had been published. No other details of the trials were given. The Panel considered that in the circumstances there was no need to give a reference to every single trial and ruled no breach of the Code.

Wyeth Laboratories complained about the depiction of prescription event monitoring (PEM) data in two Losec (omeprazole) leavepieces (LOS MUPS 5347 and 5349) issued by AstraZeneca UK Limited. The leavepieces each consisted of eight pages. Both leavepieces included the page at issue which was headed 'Losec is very well tolerated' and featured a chart showing the relative risk of six adverse events with lansoprazole versus Losec. In each adverse event listed (diarrhoea, myalgia, migraine/headache, malaise, depression, nausea and vomiting) the relative risk was greater with lansoprazole than Losec ($p<0.05$) and ranged from 2.2 (diarrhoea) to 1.4 (nausea and vomiting). AstraZeneca stated that neither of the leavepieces were being used any longer. Wyeth marketed Zoton (lansoprazole).

COMPLAINT

Wyeth stated that the text below the headline 'Losec is very well tolerated' focused on lansoprazole and omeprazole, and clearly suggested that lansoprazole was not well tolerated. The company alleged that this was disparaging in breach of Clause 8.1.

Wyeth noted that the statement 'To date, randomised controlled trials have not shown a difference between Losec and lansoprazole in the rate of adverse events reported' which appeared beneath the headline 'Losec is very well tolerated' was referenced to 'Data on file'. A closer examination of the data on file revealed a list of randomised clinical trials comparing lansoprazole and omeprazole. Wyeth noted that the Code clearly stated that where claims referred to published studies, clear references must be given. The company did not consider 'Data on file' to be a clear reference. A breach of Clause 7.5 was alleged.

Wyeth noted that the chart showing the relative risk of adverse events with lansoprazole versus Losec appeared extensively throughout the current Losec campaign and the company considered that the chart was misleading as the initial visual impression was that there was a substantiated clinical difference between lansoprazole and Losec. There were however two very important qualifications associated with the PEM data which suggested that such a direct comparison might be questionable. They were the accompanying statements 'bias cannot be excluded from these results and further analyses are being performed' which appeared in the text above the chart and 'These results may suggest differences between the tolerability of these two agents' which appeared beneath the chart. These statements were not part of the chart and were not cross-referenced in any way. Wyeth considered this to be highly misleading, as the chart was constructed in such a way that a representative could easily 'talk through' the item alone, without referring to the relevant qualifications. A breach of Clause 7.2 was alleged.

In addition Wyeth did not consider that AstraZeneca's claims regarding the safety profiles of lansoprazole and omeprazole could be substantiated by actual clinical experience as required by Clause 7.7. The PEM data was non-comparative, taken from two different time points, and reflected different experiences and use of proton pump inhibitors. In the discussion section of the PEM data the authors clearly stated 'Selection and response bias, and the different periods of observation, influence comparability of the cohorts'.

Wyeth stated that if claims regarding side effects were to be substantiated by clinical experience then the experience should be directly comparative. AstraZeneca clearly acknowledged that on the page in question by use of the statement '… randomised controlled trials have not shown a difference between Losec and lansoprazole in the rate of adverse events reported'.

Wyeth alleged that the overall portrayal of the PEM data was misleading, disparaging and clinically unsubstantiated in breach of Clauses 7.2, 7.5, 7.7 and 8.1.

RESPONSE

AstraZeneca stated that the headline 'Losec is very well tolerated' was in keeping with the rest of the piece which made statements about Losec. The following text then made factual statements regarding the tolerability profiles of Losec and lansoprazole and the company did not consider this to be disparaging. AstraZeneca, therefore, did not consider that there had been any breach of Clause 8.1.

AstraZeneca noted that the statement 'To date, randomised controlled trials have not shown a difference between Losec and lansoprazole in the rate of adverse events reported' was referenced to 'Data on file', which cited the 27 randomised controlled studies that compared Losec with lansoprazole. It was the company's understanding of Clause 7.5 that, provided any claim could be substantiated, references only needed to be cited when reference was made to work by a particular author, for example, Smith *et al* (1998). As the 'Data on file' made clear reference to the 27 cited studies, the company did not consider there to be any breach of Clause 7.5.

AstraZeneca stated that the chart depicting the PEM data was appropriately referenced to a poster presentation by Martin *et al* (1998). As randomised controlled clinical trials were powered to show differences in efficacy and not tolerability, PEM was generally considered useful as it reflected clinical

usage in a large number of patients and was a recognised tool for highlighting potential differences in tolerability between medicines.

As acknowledged by Martin *et al*, due to the inherent bias in the collection of PEM data, such as selection and response bias, the authors performed analyses to address the most obvious causes of bias. However, it was pertinent to note that bias could cause the results to go either way. For example, as lansoprazole was second to market the level of adverse events reported might have been diminished due to previous exposure and experience with Losec and the assumption of class effects.

For this reason, the statements 'bias cannot be excluded from these results and further analyses are being performed' and 'these results may suggest differences in the tolerability of these two agents' were included within the leavepiece. As these statements, although relating to PEM, were not direct quotations from the poster by Martin *et al* (1998) it would be misleading to infer such by placing them within the chart.

AstraZeneca noted that the statements were clearly above and below the chart and, therefore, the representative could not easily 'talk through' it as alleged by Wyeth. Moreover, AstraZeneca's representatives had been trained to present the PEM data in context.

AstraZeneca considered the PEM data to be particularly relevant as it reflected usage in a large cohort in clinical practice. It was not an isolated observation and it was of relevance to note the findings of other groups which had examined the effects of switches from Losec to lansoprazole and observed emergent adverse events. The following was a brief review of the relevant data:

Creed and Moran (1999) reported details of a retrospective study in north Devon, after a policy of switching from omeprazole to lansoprazole was introduced in 1997. Of the 109 GPs sent questionnaires, 75% returned the questionnaires, of whom 70 had experience of changing patients on long-term Losec to lansoprazole. Twelve had not noted any problems in terms of side effects or symptom control; 38 reported a problem frequency of <25%; 18 estimated a problem frequency of 25-50% and one could not estimate the frequency of problems. Of the 57 GPs reporting problems, 38% detected both inadequate symptom control and side effects occurring and 25% reported side effects only.

A recent US study by Condra *et al* (1999) assessed patients' perceived differences in side effects of omeprazole vs lansoprazole following a formulary conversion. More patients reported side effects with lansoprazole ($p<0.001$); the majority (64%) preferred omeprazole ($p<0.005$).

A further analysis of this US formulary switch was undertaken by Krinsky (1999). Overall, 10% of patients had been changed back to omeprazole. Diarrhoea was the most common reason for the switch and had been seen in 56% ((23/41). Other reasons attributed to side effects included: dizziness (5%); rash (7%); abdominal cramps (7%); dyspnoea (5%) and dry mouth (5%).

As PEM data provided valid supplementary adverse event data to that reported in randomised controlled clinical trials, AstraZeneca concluded that it was appropriate to include such data, provided that its interpretation and limitations were understood. On this basis, its exclusion could be considered potentially misleading and unethical.

In summary, AstraZeneca did not consider the use of, or the chart showing, PEM data to be misleading, disparaging and clinically unsubstantiated and, therefore, denied any breach of Clauses 7.2, 7.5, 7.7 and 8.1.

PANEL RULING

The Panel noted that the pages at issue in the two leavepieces were headed 'Losec is very well tolerated'. Beneath the heading, and below three short paragraphs of text, the reader's eye was drawn to a chart showing the relative risk of adverse events with lansoprazole versus Losec. Six adverse events were listed and in all cases the relative risk was greater with lansoprazole than with Losec ($p<0.05$). A footnote to the chart stated that for five other adverse events no significant difference in the relative risk was shown. In the Panel's view the impression created by the chart, particularly in association with the heading, was that Losec was better tolerated than lansoprazole.

The first paragraph of text on the page stated that randomised, controlled clinical trials had not shown a difference between Losec and lansoprazole in the rate of adverse events reported.

The Panel noted that the second and third paragraphs of text above the chart explained that the data shown therein had come from prescription event monitoring in general practice; n>30,000. The rates of eleven commonly reported adverse events had been compared. The relative risk of six adverse events was significantly greater with lansoprazole. It was explained that bias could not be excluded and that further analyses were being performed. Text below the chart stated that the data shown might suggest differences in tolerability profiles of Losec and lansoprazole.

The PEM analysis was referenced to a poster presentation by Martin *et al* (1998). Data was collected for Losec between June 1989 and June 1990 and for lansoprazole between May and November 1994. The Panel noted that the authors acknowledged that selection and response bias and the different periods of observation influenced the comparability of the cohorts.

The Panel considered that the prominence of the chart and heading were such that despite qualifying text, the impression that most readers would gain from the pages in question was that Losec was better tolerated than lansoprazole. This was based only on PEM data which in itself had inherent weaknesses. (The Panel noted that clinical trials also had their own weaknesses with regard to using them to identify adverse events.) The Panel considered that the way in which the PEM data had been presented gave a misleading impression of the comparative tolerability of Losec and lansoprazole. It had not been set in

context of the overall data and nor had its limitations been adequately explained. PEM data showing no significant difference between omeprazole and lansoprazole had only been mentioned in the chart by way of a footnote. Breaches of Clauses 7.2 and 7.7 were ruled. The Panel did not consider that the pages disparaged lansoprazole and no breach of Clause 8.1 was ruled.

The Panel noted that Clause 7.5 of the Code stated that when promotional material referred to published studies clear references must be given. The Panel considered that Clause 7.5 meant that if promotional material used the phrase 'in a published study' or similar in support of a claim etc, then a reference needed to be given. The Panel further considered that if promotional material referred to published studies by author's name, then this amounted to referring to a published study and references should be given. The Panel noted that the first paragraph of text referred to results from randomised controlled clinical trials but did not state that the trials had been published. No other details of the trials were given. The Panel considered that in the circumstances there was no need to give a reference to every single trial and ruled no breach of Clause 7.5.

Complaint received **29 March 2000**

Case completed **25 May 2000**

CASE AUTH/994/3/00

SMITHKLINE BEECHAM v LUNDBECK

Cipramil journal advertisement

SmithKline Beecham complained about the claim 'Cipramil … is associated with fewer adverse events than other SSRIs [selective serotonin reuptake inhibitors], so patients are more likely to keep taking it' which appeared in a journal advertisement for Cipramil (citalopram) issued by Lundbeck. SmithKline Beecham alleged that with regard to adverse events the claim did not reflect the data, was inaccurate and could not be clinically substantiated given its exaggerated nature. With regard to the second part of the claim, about continuity of therapy, it was alleged that the claim was unbalanced as there were other reasons, apart from adverse events, as to why a patient might stay on Cipramil longer than any other SSRI, not least that a longer course of therapy might be required.

The first part of the claim, about adverse events, was referenced to a review of SSRIs. The authors had examined data collected from short term comparative studies as well as from major published reviews, the Committee on Safety of Medicines (CSM) 'yellow card' reports and data from the Prescription Event Monitoring (PEM) system. The strengths and weaknesses of various methods of identifying unwanted events were discussed. Taking all of the data into account it was stated that an advantage for citalopram was that it had a probable lower potential for drug interactions although its disadvantages were that it was comparatively new with therefore less chance of rare adverse reactions having been identified. It was not stated that citalopram was associated with fewer adverse events than the other SSRIs. The Panel considered that the claim overstated the data and breaches of the Code were ruled.

The Panel noted that with regard to continuity of therapy, Lundbeck submitted data which it stated showed that patients on Cipramil took it for a longer mean duration than other SSRIs. The company stated that this was an indication of compliance although other explanations were possible. The Panel noted that Cipramil was to be taken for at least six months whereas no similar statements appeared in the summaries of product characteristics for the other SSRIs. The Panel considered the second part of the claim was misleading and a breach of the Code was ruled.

SmithKline Beecham Pharmaceuticals complained about a journal advertisement for Cipramil (citalopram) issued by Lundbeck Ltd.

The advertisement appeared in Pulse, 19 February 2000. The copy read 'Annoying isn't it? Just like when a patient starts a course of antidepressants but doesn't finish. Cipramil, however, is associated with fewer adverse events than other SSRIs [selective serotonin reuptake inhibitors] so patients are more likely to keep taking it. After all there is nothing funny about a patient not sticking to their treatment.'

COMPLAINT

SmithKline Beecham was concerned about the claim 'Cipramil … is associated with fewer adverse events than other SSRIs, so patients are more likely to keep taking it'. SmithKline Beecham alleged that the first part of the claim that 'Cipramil is associated with fewer adverse events than other SSRIs' was completely without foundation and a wholly unacceptable breach of Clause 7.2 of the Code.

The claim was referenced to the review article of Edwards and Anderson (1999), but the authors themselves concluded that the inherent weaknesses and lack of uniformity in the methodology used in assessing the different SSRIs made comparisons extremely difficult. Moreover the authors actually stated that no single SSRI had a better safety and efficacy profile than another. Nor were there any data in the review article to justify that citalopram had a favourable adverse event profile.

Additionally, SmithKline Beecham alleged that the claim neither reflected all of the available evidence on side effects of SSRIs nor was capable of being clinically substantiated given the exaggerated nature of the claim. A breach of Clause 7.7 of the Code was alleged.

SmithKline Beecham referred to Lundbeck's response to its concerns that the reference to fewer side effects was taken from post marketing data for SmithKline Beecham's product Seroxat (paroxetine) and Cipramil. Lundbeck further quoted from a paper by Labbate, although this seemed irrelevant, given that no comparative data or claims were made in relation to citalopram and other SSRIs. There was no post marketing evidence either in the quoted articles or elsewhere to prove that the adverse event profile was better than any other SSRI.

SmithKline Beecham pointed out that the second part of the claim 'patients are more likely to keep taking it', was referenced to DIN-Link. The claim was based on an assumption from Lundbeck's data on continuity of therapy that more new patients stayed on Cipramil for longer than new patients on any other SSRI. Clearly there could be many other reasons why a patient might stay on Cipramil for longer than any other SSRI, not least that a longer course of therapy might be required with Cipramil. SmithKline Beecham alleged that this second claim was unbalanced in breach of Clause 7.2 of the Code.

SmithKline Beecham stated that Lundbeck's response on this matter did not give any justification to establish the assumption that new patients remained on Cipramil for longer because of fewer side effects. Lundbeck stated in its letter of response that it agreed that 'there can be many reasons why patients stay on treatment'.

RESPONSE

Lundbeck submitted that it had used the findings of the Edwards and Anderson review article to support its contention that Cipramil was indeed associated with fewer adverse events than other SSRIs. The authors compared equivalent time periods, these being the first two years post UK launch, and collated the 'yellow card' reports to the Medicines Control Agency. Though the authors admitted to inherent weaknesses in reporting, it was clear that in equivalent time periods with equivalent reporting requirements – black triangle placed after the product name – that there was a four fold difference in reports between Cipramil and fluoxetine and an almost seven fold difference versus paroxetine.

Lundbeck was interested that SmithKline Beecham sought to down play the value of the review article, since its field force was instructed to use it specifically to undermine clinicians' confidence in Cipramil. On the basis of the Edwards and Anderson review article Lundbeck submitted that it had not breached the Code.

With regard to the second complaint regarding duration of treatment, Lundbeck submitted that it had used the DIN-Link data to confirm compliance with Cipramil to counter the persistent claims made by the SmithKline Beecham field force that Cipramil did not work. Lundbeck pointed out that the Authority was aware that SmithKline Beecham had tried (and failed) to claim that 20mg of Cipramil was an inadequate therapeutic dose. SmithKline Beecham's contention regarding the DIN-Link data was similarly disparaging.

Lundbeck's view was that the letter of complaint repeated the disparaging comments about Cipramil by suggesting 'not least that a longer course of therapy might be required with Cipramil'.

Lundbeck submitted that the DIN-Link data clearly indicated that patients on Cipramil took it for a longer mean duration than other SSRIs, which was an indication of compliance though other explanations were possible. Lundbeck refuted that there had been a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel examined the Edwards and Anderson review article. It included a meta-analysis of twenty short term comparative studies of five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline). The review article stated that there was no difference in efficacy between individual compounds but a slower onset of action of fluoxetine. More patients discontinued fluvoxamine and fewer patients stopped sertraline because of adverse events than their comparator SSRIs. The review stated that although the total discontinuation rate was the most objective measure it only partially reflected tolerability as patients in trials stopped treatment for a number of reason. In the three studies of citalopram there were no consistent differences in the adverse event profile compared with the comparator SSRIs (fluoxetine and fluvoxamine). The quantitative analyses failed to show any differences. The authors advised caution in interpreting the results of the studies analysed because of the relatively small number of trials and potential biases arising from selective reporting. The review article also presented adverse event monitoring data from three sources: major published reviews; data from the Committee on Safety of Medicines (CSM) 'yellow card' reports and data from the Prescription Event Monitoring (PEM) system. The strengths and weaknesses of the various methods of identifying unwanted effects were discussed. These included, for example, small sample sizes and unrepresentative patients in controlled clinical trials and under-reporting of suspected adverse events, lack of data for assessing incidence and inability to establish a cause-and-effect relationship with the medicine with the CSM 'yellow card' system. Taking all of the data from the various sources into account the advantages and disadvantages of the various SSRIs were listed. It was stated that an advantage of citalopram was that it had a probable lower potential for drug interactions although its disadvantages were that it was comparatively new with therefore less chance of rare adverse reactions having been identified and there were case reports of lethality in overdose.

The Panel considered that the claim overstated the data from the review article to which it was

referenced. The situation with regard to adverse events was more complicated than merely the number of reported adverse events. The review article did not state that citalopram was associated with fewer adverse events that the other SSRIs. The Panel ruled breaches of Clauses 7.2 and 7.7 of the Code.

The Panel did not consider that the evidence supplied by Lundbeck had supported the claim that patients were more likely to keep taking Cipramil. There were differences between the SSRIs in that Cipramil was to be taken for at least six months whereas there were no similar statements in the summaries of product characteristics (SPCs) for the other SSRIs. The SPC for Lustral (sertraline) stated that it had to be taken for 2-4 weeks for the full effect. The Panel considered that this part of the claim was misleading and a breach of Clause 7.2 of the Code was ruled.

Complaint received **31 March 2000**

Case completed **2 June 2000**

CASE AUTH/995/4/00 *NO BREACH OF THE CODE*

LUNDBECK v SMITHKLINE BEECHAM

Seroxat mailing

Lundbeck complained about a Seroxat (paroxetine) mailing sent by SmithKline Beecham which consisted of a 'Dear Doctor' letter and leaflet. The leaflet was entitled 'What's your perception of the price difference between Seroxat and citalopram?' and compared the cost per day and per 28 days of treatment with Seroxat and citalopram each at an initial dose of 20mg. It referred to Seroxat having the power to lift mood and treat the underlying anxiety symptoms of depression and said that citalopram was not indicated to treat depression and anxiety. The mailing was dated 20 September 1999. Lundbeck stated that the mailing had been received by a clinician since the Code of Practice Panel's ruling in a previous case, Case AUTH/966/1/00. In Case AUTH/966/1/00, Lundbeck had alleged that statements relating to the dose of its product Cipramil (citalopram) in a letter sent by SmithKline Beecham were in breach of the Code. The Panel had considered that the letter would raise doubts in the prescriber's mind about the efficacy of the 20mg dose. The Panel considered that in this regard the letter was misleading and disparaged Cipramil. Breaches of Clauses 7.2 and 8.1 were ruled. SmithKline Beecham had accepted the ruling of a breach of Clause 7.2 but had appealed the ruling of a breach of Clause 8.1 of the Code. The letter was no longer in use.

Lundbeck alleged that by repeating the insinuation that doctors should be using 20mg of Cipramil only as initiation there had been another breach of the Code. That this should have occurred after SmithKline Beecham had already accepted a ruling against it on this point showed a clear and cynical disregard for the Panel and its ruling. The receipt of the mailing at issue by a doctor the previous week suggested that SmithKline Beecham had not yet actioned the requirements of the recent ruling in Case AUTH/966/1/00. Lundbeck stated that should SmithKline Beecham's actions prove to have occurred despite the Panel's ruling, it would contend that this was a breach of Clause 2 of the Code.

The Panel noted that in Case AUTH/966/1/00 a medical information letter had stated that the recommended dose of citalopram was 20mg per day and although clinical trials had been conducted on 20mg per day there was some debate as to whether this should be increased to an optimum dose of 40mg. The recommended dose of Seroxat was 20mg daily and this had been found to be the optimal dose for most patients, 78% of prescriptions were for 20mg/day. The letter had not mentioned that 86% of UK prescriptions for Cipramil were for 20mg per day. The Panel had noted that the Cipramil summary of product characteristics (SPC) stated that in the treatment of depression the initial dose was 20mg daily and that dependent on patient response this could be increased to a maximum of 60mg daily. There was no mention of an optimal dose. Breaches of Clauses 7.2 and 8.1 had been ruled.

Turning to the case before it the Panel noted that the 'Dear Doctor' letter made no mention of citalopram. The leaflet compared the cost for 28 days at initial dose for Seroxat and for citalopram. It was stated that the initial dose was 20mg for each product. The cost of Seroxat was £16.58 for 28 days at initial dose, 59 pence per day. The cost of citalopram was £16.03 for 28 days at initial dose, 57 pence per day. The Panel noted that the SPC for Seroxat stated that the recommended dose in depression was 20mg and that in some patients it might be necessary to increase the dose. This should be done gradually by 10mg increments to a maximum of 50mg/day according to the patient's response. Seroxat was also licensed for obsessive compulsive disorder (recommended dose 40mg daily, starting at 20mg and increasing weekly in 10mg increments), panic disorder (recommended dose 40mg daily, starting at 10mg and increasing weekly in 10mg increments) and social anxiety disorder/social phobia (recommended dose 20mg daily which could be increased in 10mg increments weekly). The SPC for Cipramil stated that in depression Cipramil should be administered as a single oral dose of 20mg daily. Dependent on individual patient response this might be increased to a maximum of 60mg daily. Cipramil was also indicated for the treatment of panic disorder with or without agoraphobia.

The Panel considered that the leaflet at issue was different to the letter previously at issue in Case

AUTH/966/1/00 which had compared the dosing of Seroxat and citalopram in more detail. The Panel noted that that case had not finished, an appeal was to be heard later in the month. SmithKline Beecham had accepted the ruling of a breach of Clause 7.2 and the letter had been withdrawn.

With regard to the allegation in the present case that the leaflet insinuated that doctors should be using 20mg of citalopram only as initiation, the Panel noted that the leaflet focused on depression and gave the initial dose for each product as 20mg per day. The phrase 'initial dose' had been used to describe both Seroxat and citalopram. There was no implication that this would have to be raised. The SPCs for both products stated in relation to depression that depending on patient response the 20mg dose could be increased, to a maximum of 60mg for Cipramil and 50mg for Seroxat. The Panel considered that as the leaflet did not differentiate between Seroxat and citalopram and that 20mg would be an initial dose for each product in the treatment of depression, the leaflet was not misleading as alleged. No breach of the Code was ruled. The Panel did not accept that the use of the mailing meant that SmithKline Beecham had not complied with the Panel's ruling in the previous case. The material was different. No breach of Clause 2 was ruled.

Lundbeck Ltd complained about a Seroxat (paroxetine) mailing sent by SmithKline Beecham Pharmaceuticals which consisted of a 'Dear Doctor' letter (ref LM: PRE/0/060) and leaflet (ref 0300 LM: MF/0/060). The leaflet was entitled 'What's your perception of the price difference between Seroxat and citalopram?' The leaflet compared the cost per day and for 28 days of treatment with Seroxat and citalopram each at an initial dose of 20mg. It referred to Seroxat having the power to lift mood and treat the underlying anxiety symptoms of depression and said that citalopram was not indicated to treat depression and anxiety. The mailing was dated 20 September 1999. Lundbeck said that the mailing had been received by a clinician since the Panel's ruling in a previous case, Case AUTH/966/1/00.

In Case AUTH/966/1/00 Lundbeck had alleged that statements relating to the dose of its product Cipramil (citalopram) in a letter sent by the medical information department of SmithKline Beecham were in breach of the Code. The Panel had considered that the letter would raise doubts in the prescriber's mind about the efficacy of the 20mg dose. The Panel considered that in this regard the letter was misleading and disparaged Cipramil. Breaches of Clauses 7.2 and 8.1 were ruled. SmithKline Beecham had accepted the ruling of a breach of Clause 7.2 but had appealed the ruling of a breach of Clause 8.1 of the Code. The letter was no longer in use.

COMPLAINT

Lundbeck alleged that by repeating the insinuation that doctors should be using 20mg of Cipramil only as initiation that this was another breach of Clause 7.2 of the Code. That this should have occurred after SmithKline Beecham had already accepted a ruling against it on this point showed a clear and cynical disregard for the Panel and its ruling.

Lundbeck stated that the receipt of the mailing at issue by a doctor the previous week suggested that SmithKline Beecham had not yet actioned the requirements of the recent ruling in Case AUTH/966/1/00. Lundbeck stated that should SmithKline Beecham's actions prove to have occurred despite the Panel's ruling it would contend that this was a further breach of Clause 2 of the Code.

RESPONSE

SmithKline Beecham was somewhat surprised that Lundbeck had tried to link this latest claim with Case AUTH/966/1/00.

SmithKline Beecham pointed out that the leaflet quite clearly stated that the recommended initial dose was 20mg for Seroxat and 20mg for citalopram. Both summaries of product characteristics (SPCs) stated that 20mg was recommended as an initiation dose for the treatment of depression. At no point in the material did it insinuate that 20mg Cipramil was only recommended as initiation. Lundbeck had therefore absolutely no grounds whatsoever to substantiate its complaint. The claims made in this mailing were clearly not the same as those ruled upon by the Panel in Case AUTH/966/1/00 and therefore it had not breached Clause 7.2 or Clause 2 as alleged. It could not ascertain from Lundbeck's letter to the Authority exactly what it was alleging except the link to Case AUTH/966/1/00.

SmithKline Beecham stated that Lundbeck telephoned its Medical Director but when told he was not immediately available (ie that day) said that it would put something in writing. This was not forthcoming. Had this occurred SmithKline Beecham would have been able to resolve the complaint without involving the Authority. As could be seen from correspondence SmithKline Beecham submitted that it responded quickly and appropriately taking into consideration another pharmaceutical company's concerns. Unfortunately this reasonable behaviour had not been reciprocated by Lundbeck.

SmithKline Beecham strongly refuted the alleged breaches of Clauses 7.2 and 2.

PANEL RULING

The Panel noted that Case AUTH/966/1/00 concerned a medical information department letter. This stated that the recommended dose of citalopram was 20mg per day and although clinical trials had been conducted on 20mg per day there was some debate as to whether this should be increased to an optimum dose of 40mg. The letter stated that the recommended dose of Seroxat was 20mg daily and this had been found to be the optimal dose for most patients, 78% of prescriptions were for 20mg/day. The letter had not mentioned that 86% of UK prescriptions for Cipramil were for 20mg per day. The Panel had noted that the Cipramil SPC stated that in the treatment of depression the initial dose was 20mg daily and that dependent on patient response this could be increased to a maximum of 60mg daily.

There was no mention of an optimal dose. Breaches of Clauses 7.2 and 8.1 had been ruled.

Turning to the case before it the Panel noted that the 'Dear Doctor' letter made no mention of citalopram. The leaflet compared the cost for 28 days at initial dose for Seroxat and for citalopram. It was stated that the initial dose was 20mg for each product. The cost of Seroxat was £16.58 for 28 days at initial dose, 59 pence per day. The cost of citalopram was £16.03 for 28 days at initial dose, 57 pence per day.

The Panel noted that the SPC for Seroxat stated that the recommended dose in depression was 20mg and in some patients it might be necessary to increase the dose. This should be done gradually by 10mg increments to a maximum of 50 mg/day according to the patient's response. Seroxat was also licensed for obsessive compulsive disorder (recommended dose 40mg daily, starting at 20mg and increasing weekly in 10mg increments), panic disorder (recommended dose 40mg daily, starting at 10mg and increasing weekly in 10mg increments) and social anxiety disorder/social phobia (recommended dose 20mg daily which could be increased in 10mg increments weekly) (ref ABPI Compendium of Datasheets and Summaries of Product Characteristics 1999-2000). The SPC for Cipramil stated that in depression Cipramil should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response this might be increased to a maximum of 60mg daily. Cipramil was also indicated for the treatment of panic disorder with or without agoraphobia.

The Panel considered that the leaflet at issue was different to the medical information letter previously at issue in Case AUTH/966/1/00 which had compared the dosing of Seroxat and citalopram in more detail. The Panel noted that the previous case had not finished, an appeal was to be held later that month. SmithKline Beecham had accepted the ruling of a breach of Clause 7.2 and the medical information letter had been withdrawn.

With regard to the allegation in Case AUTH/995/4/00 that the leaflet insinuated that doctors should be using 20mg of citalopram only as initiation, the Panel noted that the leaflet focused on depression and gave the initial dose for each product as 20mg per day. The Panel noted the definition of initial was: 'of or pertaining to the beginning; existing at, constituting, or occurring at the beginning; first, primary' (ref The New Shorter Oxford Dictionary). The definition of initiation was 'The action of an act of beginning or originating something; the fact of being begun; commencement.' The Panel noted that the phrase 'initial dose' had been used to describe both Seroxat and citalopram. There was no implication that this would have to be raised. The SPCs for both products in relation to depression stated that depending on patient response the 20mg dose could be increased, to a maximum of 60mg for Cipramil and 50mg for Seroxat. The Panel considered that as the leaflet did not differentiate between Seroxat and citalopram and that 20mg would be an initial dose for each product in the treatment of depression, the leaflet was not misleading as alleged. No breach of Clause 7.2 of the Code was ruled. The Panel did not accept that the use of the mailing meant that SmithKline Beecham had not complied with the Panel's ruling in the previous case. The material was different. No breach of Clause 2 was ruled.

Complaint received **5 April 2000**

Case completed **22 May 2000**

PRESCRIBING ADVISOR and PRIMARY CARE GROUP CHAIRMAN v VARIOUS COMPANIES

Article in the Sunday Mirror

A prescribing advisor and the chairman of a primary care group complained about an article in the Sunday Mirror, 27 February 2000. The article was headed 'The Wonder Drugs' with the subheading 'They can help you lose weight, quit smoking… and save your life'. The article had sections headed 'obesity', 'smoking', 'diabetes', 'blood pressure', 'Crohn's disease', 'arthritis', 'irritable bowel syndrome', 'HRT for men', 'coronaries' and 'heart failure'. Various product names and companies were mentioned; these being sibutramine (BASF), Avandia (SmithKline Beecham), Remicade (Schering-Plough), Zyban and Lotronex (Glaxo Wellcome), Vioxx and Aggrastat (Merck Sharp & Dohme), omapatrilat (Bristol-Myers Squibb), Testoderm (Ferring), carvedilol (Roche), NovoNorm (Novo Nordisk), Actos (Takeda) and Celebrex (Searle and Pfizer). Product or company logos and pack shots were included in some of the sections. The article stated that not all the medicines were available, some were still in development. The article was written by a journalist and each section included a 'Doctor's Verdict' on the medicines mentioned written by a general practitioner.

The complainants stated that a general practitioner in the primary care group had sent the article to them. A patient had asked his doctor to prescribe one of the products mentioned. The complainants stated that although the article could be said to be a feature rather than an advertisement, many of the manufacturers' logos were featured. It was dubious whether some of the statements were presented in a balanced and factual way.

The Panel noted that complaints about articles in the media were judged on the material provided by the company to the journalists and not on the content of the article itself.

BASF Pharma had not been in contact with the journalist. Information about sibutramine had been supplied to the general practitioner in response to a request in relation to another article he had written. The pack shot had not been supplied by the company. No breach of the Code was ruled.

SmithKline Beecham had not been in contact with the journalist or the general practitioner. The logo had not been supplied by the company. No breach of the Code was ruled.

Schering-Plough had not been in contact with the journalist or the general practitioner. The logo had not been supplied by the company. No breach of the Code was ruled.

Glaxo Wellcome had supplied the journalist with information about Zyban and a US pack shot in response to another article she was preparing about smoking cessation. The Panel queried why a US pack shot had been supplied for use in a UK article aimed at the general public. The Panel noted that the pack shot in the article at issue might have been obtained from the company US web site. The general practitioner had contacted Glaxo Wellcome about the article but the company had not provided the general practitioner with any information. No breach of the Code was ruled. Glaxo Wellcome had not been in contact with the journalist about Lotronex. No breach of the Code was ruled.

Merck Sharp and Dohme had not been in contact with the journalist. Information about Vioxx had been supplied to the general practitioner in relation to the launch of the product. The product logos had not been supplied by the company. No breach of the Code was ruled.

Bristol-Myers Squibb had not been in contact with the journalist. The press releases had been issued by the company's corporate office in the US. They referred to the clinical trial programme and results and that the FDA had granted a priority review on the product. The press release was not directed at the UK market. No breach of the Code was ruled.

Ferring had not been in contact with the journalist. Information about Testoderm had been supplied to the general practitioner for a different purpose. The pack shot had not been supplied by the company. No breach of the Code was ruled.

Roche had not been in contact with the journalist or the general practitioner before the article was published. No breach of the Code was ruled.

Novo Nordisk had not been in contact with the journalist or the general practitioner about the content of the article. No breach of the Code was ruled.

Takeda had not been in contact with the journalist or the general practitioner. No breach of the Code was ruled.

Neither Searle nor Pfizer had been in contact with the journalist or the general practitioner. No breach of the Code was ruled.

A prescribing advisor and the chairman of a primary care group complained about an article in the Sunday Mirror, 27 February 2000. The article was headed 'The Wonder Drugs' with the subheading 'They can help you lose weight, quit smoking… and save your life'. The article had sections headed 'obesity', 'smoking', 'diabetes', 'blood pressure', 'Crohn's disease', 'arthritis', 'irritable bowel syndrome', 'HRT for men', 'coronaries' and 'heart failure'. Various product names and companies were mentioned. Product or company logos and pack shots were included in some of the sections. The article stated that not all the medicines were available, some were still in development. The article was written by Sharon Collins and each section included a 'Doctor's Verdict' on the medicines mentioned. The doctor was Dr Mike Mead, a general practitioner.

The doctor stated in a letter to the Authority that he had been an active general practitioner writer for over 15 years. He wrote regularly about new medicines and their implications. He had written an article for Doctor, 17 February 2000, entitled 'Ten drugs to look out for in the year 2 000', which was picked up by the

journalist who wanted a similar piece for the Sunday Mirror. The piece was commissioned by the Sunday Mirror. It was neither his idea nor the idea of the pharmaceutical companies. He had supplied some copy but he was unaware of the final format. He did not supply logos and was unaware that these would appear next to the text. He anticipated that there would be some debate concerning the article and decided to inform the companies about the article as a matter of courtesy. He was not able not to contact everyone. He was concerned that the article had such repercussions and was sorry for any concern caused.

COMPLAINT

The complainants stated that a general practitioner in the primary care group had sent the article to them. A patient had asked his doctor to prescribe one of the products mentioned. The complainants stated that although the article could be said to be a feature rather than an advertisement, many of the manufacturers' logos were featured. It was dubious whether some of the statements were presented in a balanced and factual way.

* * * * *

In writing to the companies attention was drawn to the requirements of Clauses 20.1 and 20.2 of the Code and, in some instances, Clause 3.1.

Clause 20.1 of the Code prohibited advertising of prescription only medicines to the general public. Under Clause 20.2 companies were allowed to provide factual, balanced information to the general public. Such information must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. Clause 3.1 prohibited the promotion of a medicine prior to the grant of the marketing authorization which permitted its sale or supply.

Complaints about articles in the media were judged on the material provided by the company to the journalists and not on the content of the article itself.

Case AUTH/996/4/00: BASF Pharma – Reference to sibutramine

The obesity section featured a pack shot and referred to sibutramine as weight reducing tablets already available in the US and some European countries and expected in the UK during 2000. The medicine acted on the part of the brain controlling food intake. Patients felt satisfied eating less. The doctor's verdict was that diet was still the best way of controlling weight but this medicine might help some people suffering from obesity.

RESPONSE

BASF Pharma stated that there had been no contact between the company and the journalist. The company had not had the opportunity to see or comment on the article. The company had been contacted by the general practitioner two months earlier. He had requested information for an article he was writing for Doctor. The company provided copies of the material it had supplied to the general practitioner. This included a one page sheet on how sibutramine worked. It included a statement as to where the product was authorized for use. Also included was a one page sheet on obesity.

BASF Pharma did not provide the pack shot nor was it asked for permission for its use. The pack shot was of the US product and could have been obtained from a number of Internet sites.

The company understood the frustrations of doctors and patients when unrealistic expectations were raised via sensationalist reports in the lay media. It would continue to provide only fair and balanced information in response to legitimate requests.

PANEL RULING

The Panel noted that there had been no contact between BASF Pharma and the journalist. Information about sibutramine had been supplied to the general practitioner in response to a request in relation to the article in Doctor. The pack shot had not been supplied by the company. The Panel did not consider that there had been a breach of the Code as alleged. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Case AUTH/997/4/00: SmithKline Beecham – Reference to Avandia

The diabetes section featured a visual and product logo and referred to Avandia as one of three new medicines for diabetics not dependent on insulin. Avandia was due in the UK in the summer and acted by improving a patient's sensitivity to their own body's insulin. The doctor's verdict was that Avandia could be vital for diabetics.

RESPONSE

SmithKline Beecham Pharmaceuticals stated that it had had no contact with the newspaper, journalist or the general practitioner. No press articles had been generated or circulated about Avandia. The company did not have any notification about the appearance of the article and therefore had no opportunity to comment on it or amend it. The logo appeared to have been taken from the SmithKline Beecham web site in the US and had been reproduced without permission. The product was not yet licensed in Europe. The company stated that it could not be held responsible for the newspaper or its actions.

PANEL RULING

The Panel noted that SmithKline Beecham had not been in contact with the journalist or the general practitioner. The logo had not been supplied by the company. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Case AUTH/998/4/00: Schering-Plough – Reference to Remicade

The Crohn's disease section featured a product logo

and referred to Remicade as a new medicine given by intravenous drip. The doctor's verdict was that the medicine was a breakthrough but expensive at around £1000 per dose.

RESPONSE

Schering-Plough Ltd stated that it had not circulated any press releases or any other material to the press concerning Remicade. There had been no telephone conversations between Schering-Plough, the journalist and the general practitioner. The company had no prior notification about the appearance of the article and nor was it given any opportunity to amend the article. The use of the brand name in logo format in the article was neither approved nor provided by the company. The logo used was the logo used in the US by Centocor, Schering-Plough's marketing partner. The logo was available at the Centocor US web site.

PANEL RULING

The Panel noted that Schering-Plough had not been in contact with the journalist or the general practitioner. The logo had not been supplied by the company. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1 and 20.2 was ruled.

Case AUTH/999/4/00: Glaxo Wellcome – References to Zyban and Lotronex

The smoking section referred to Zyban as a non-nicotine medicine taken by mouth which had helped millions stop smoking in the US and would be available here soon. The doctor's verdict was that it could be useful as an anti-smoking aid for a lot of people.

The irritable bowel syndrome section gave details of the symptoms and stated that Lotronex which acted on the chemicals which controlled bowel movement and pain would be available next year for treating female patients. The doctor's verdict was that IBS could be difficult to treat and doctors were awaiting this medicine with interest.

RESPONSE

Glaxo Wellcome UK Limited stated that it had not undertaken any proactive press activity about Zyban. It had only responded to direct and specific questions from the media. In the summer of 1999 the company was concerned about some of the articles about Zyban and notified the Medicines Control Agency of its lack of involvement. The company stated that it had had no contact with the journalist or any of her colleagues at the Sunday Mirror in relation to the article in question. It had no prior notification from the Sunday Mirror that it was planning the article and thus had no opportunity to comment on it or amend it. The journalist contacted the company in December 1999 in relation to a separate article she was preparing about smoking cessation and was given background information about Zyban. A copy of the information was provided. She was also provided with a pack shot of the US preparation on the understanding that it was only to be used in the context of the case history and providing it was made clear that the medicine was not yet available in the UK. Other than that which appeared on the pack shot it had not provided her with any other product logos. The logo that appeared in the article looked like the US logo which would not be used in the UK. The logo was accessible on the Glaxo Wellcome Inc (US) web site. Glaxo Wellcome stated that the general practitioner had contacted Glaxo Wellcome to advise that he had been approached by Doctor and had contributed to an article on smoking cessation. Subsequently he informed the company that he was involved in a similar article for the Sunday Mirror as the result of the Doctor article. At no time did Glaxo Wellcome encourage him to write any articles nor have any input to them. The general practitioner could have gained full information from the US web site or from published papers. The company was in the process of applying for a marketing authorization for Zyban.

Glaxo Wellcome stated that it had applied for a marketing authorization for Lotronex and the product was licensed for use in the USA. It had had no contact with the Sunday Mirror with regard to Lotronex and was not aware that the article would appear.

PANEL RULING

In relation to Zyban the Panel noted that Glaxo Wellcome had supplied the journalist with information and a US pack shot in response to another article she was preparing about smoking cessation. The Panel queried why a US pack shot had been supplied for use in a UK article aimed at the general public. The Panel noted that the pack shot in the article at issue might have been obtained from the company US web site. The general practitioner had contacted Glaxo Wellcome about the article but the company had not provided him with any information. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

The Panel noted that Glaxo Wellcome had not been in contact with the journalist about Lotronex. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Case AUTH/1000/4/00: Merck Sharp and Dohme – References to Vioxx and Aggrastat

The arthritis section stated that Vioxx was less likely than other medicines to cause stomach upsets and ulcers. It was already available in the UK. The doctor's verdict was that it had very good potential if the patient had a history of gastric problems.

The coronaries section referred to Aggrastat as a clotbuster medicine for patients with severe chest pain to prevent a heart attack. It was described as one of a new class which reduced stickiness and clumping. The doctor's verdict was that it would be vital in limiting the impact of one of the UK's big killers.

RESPONSE

Merck Sharp and Dohme Limited stated that the article did not present a fair and balanced overview of the product information. It did not support this irresponsible form of media coverage and confirmed

that neither Merck Sharp and Dohme nor its parent company Merck and Company Inc solicited or approved the article and nor did it receive any prior notification of the appearance of the article. There were no press releases circulated to the media or to the general practitioner around the time of the appearance of the article that bore any resemblance to either the content or format of the article.

The journalist was not on the media list of named health correspondents to whom it had proactively released press materials. No communication took place between the company and the journalist. The general practitioner was a speaker at the Vioxx GP launch meeting in Summer 1999. He therefore received media materials at that time together with relevant medical journal publications. He had not received any media materials since then and had not sought approval from Merck Sharp and Dohme or informed the company in advance of the content of the article. The company's first opportunity to review the content of the article was when it appeared in its final printed form. The use of the brand name logos for both products was not approved by the company. The claim for Vioxx 'for everyday victories' which appeared beneath the logo had been used for promotional purposes in the US. Such information could be accessed from the US web site. Merck Sharp and Dohme stated that to the best of its knowledge approval to use the claim had not been given.

PANEL RULING

The Panel noted that Merck Sharp and Dohme had not been in contact with the journalist. Information about Vioxx had been supplied to the general practitioner in relation to the launch of the product. The product logos had not been supplied by the company. The Panel did not consider that there had been a breach of the Code with respect to either Vioxx or Aggrastat. No breach of Clauses 20.1 and 20.2 was ruled.

Case AUTH/1001/4/00: Bristol-Myers Squibb – Reference to omapatrilat

The blood pressure section stated that omapatrilat was the first of a new type of treatment to control high blood pressure and that abnormally high blood pressure was a principal cause of strokes. The product should be available here later in the year. The doctor's verdict was that this product was seen by some as one of the major blockbuster medicines of the year. There was a need to control blood pressure better. This medicine would help improve patients' levels.

RESPONSE

Bristol-Myers Squibb Pharmaceuticals Limited stated that it was not involved in any way in the writing, commissioning or facilitation of the article. The comments about omapatrilat appeared to be entirely factual and consistent with information in a press release issued by the US corporate office in December 1999. As was standard practice the press release gave routine information about the regulatory filings of omapatrilat with the FDA and the EMEA. The press release was in the public domain at the time of publication of the article. No other materials had been provided to the press.

Bristol-Myers Squibb stated that the general practitioner had telephoned the company on the Friday evening prior to publication as a courtesy call to say that he had contributed to the article. No opportunity was given to review the article. The company had no knowledge of telephone conversations between the journalist and the general practitioner. It had had no dealings with the journalist.

PANEL RULING

The Panel noted that Bristol-Myers Squibb had not been in contact with the journalist. The press releases had been issued by the company's corporate office in the US. They referred to the clinical trial programme and results and that the FDA had granted a priority review on the product. The press release was not directed at the UK market. Taking all the circumstances into account, the Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Case AUTH/1002/4/00: Ferring – Reference to Testoderm

The HRT for men section referred to the Testoderm HRT patch for men which delivered testosterone in a steady dose over 24 hours. Deficiency of testosterone was blamed for depression, low sex drive and impotence. The doctor's verdict was that male HRT would soon hit the headlines.

RESPONSE

Ferring Pharmaceuticals Limited stated that it was in no way responsible for providing information or support in relation to the publication of the article. It had had no contact with the journalist. The general practitioner occasionally provided advice to Ferring on medical matters. Ferring had never asked him to become involved in promotional activities on its behalf and he was neither employed nor retained by Ferring.

Ferring only became aware of the article at the end of the week before publication. The general practitioner mentioned that he had written the piece about new products for the 21st century and that he had included Testoderm. There was no opportunity to review or approve the article and the company did not see it before publication.

The Testoderm product logo had not originated from Ferring. The use of the wording 'Testosterone Transdermal System' together with the strength, 4mg/day, which was not marketed in the UK, suggested that the logo originated from material used in the US by the originating company, Alza Corporation, possibly being retrieved from the Alza web site.

Ferring had issued one press release at the time of the launch of Testoderm primarily to medical or pharmaceutical journals. A copy was provided. It had not been sent to the Mirror Group.

PANEL RULING

The Panel noted that Ferring had not been in contact with the journalist. Information about Testoderm had

been supplied to the general practitioner for a different purpose. The pack shot had not been supplied by the company. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1 and 20.2 was ruled.

Case AUTH/1003/4/00: Roche – Reference to carvedilol

The heart failure section stated that carvedilol was a betablocker for patients who had suffered heart failure due to disease. It was hoped that next year GPs would be able to prescribe it as well as hospital doctors. The doctor's verdict was that there was no doubt that these medicines would extend the lives of patients.

RESPONSE

Roche Products Limited stated that it had discussed the matter with the journalist and the general practitioner who acknowledged that he wrote the article from his own clinical experience and general knowledge of the disease area. He had received no briefing from Roche and had no formal or informal relationship with the company. The journalist confirmed that her only source was the general practitioner. Roche had no prior notification about the appearance of the article and no opportunity to amend it.

PANEL RULING

The Panel noted that Roche had not been in contact with the journalist or the general practitioner before the article was published. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1 and 20.2 was ruled.

Case AUTH/1004/4/00: Novo Nordisk – Reference to NovoNorm

The diabetes section referred to NovoNorm as one of three new medicines for diabetes and the doctor's verdict was that these new medicines could be vital for diabetics.

RESPONSE

Novo Nordisk stated that it had no part whatsoever in the construction of the article. It had checked with its communications agency which confirmed that neither Novo Nordisk nor its agency initiated contact with the journalist or with the general practitioner. There had been no press release in the five months preceding 27 February.

Novo Nordisk stated that the general practitioner had contacted Novo Nordisk's communications agency to advise that he was submitting the article. He did not ask for comment and neither the agency nor the company saw the article before publication.

PANEL RULING

The Panel noted that Novo Nordisk had not been in contact with the journalist or the general practitioner about the content of the article. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1 and 20.2 was ruled.

Case AUTH/1005/4/00: Takeda – Reference to Actos

The diabetes section referred to Actos as one of three new medicines for diabetes and said that it would be available in the summer. The medicine worked by improving a patient's sensitivity to their own body's insulin. The doctor's verdict was that the medicine could be vital for diabetics.

RESPONSE

Takeda UK Limited stated that it had no input into the article. It had not circulated any press release or other materials that could have led to the article being written. It had not had any relevant telephone conversations with the journalist or the general practitioner. It had no prior notification of the article nor any opportunity to amend it. The product was currently under review by the EMEA.

PANEL RULING

The Panel noted that Takeda had not been in contact with the journalist or the general practitioner. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Cases AUTH/1006/4/00 and AUTH/1007/4/00: Searle and Pfizer – Reference to Celebrex

The arthritis section referred to Celebrex being a similar medicine to Vioxx which was less likely than other medicines to cause stomach upsets and ulcers. Celebrex was to be launched in the UK within the next three months. The doctor's verdict was that the medicines had very good potential if the patient had a history of gastric problems.

RESPONSE

Searle responded on behalf of both itself and Pfizer Limited.

Searle stated that it was unaware of the mention of Celebrex in the article. It had not issued any press releases or other material on the product that might have been circulated to the press. Neither company had been contacted by the journalist or the general practitioner on this matter. The company had no prior notification about the appearance of the article and no opportunity to amend it. The product was not currently licensed in the UK.

PANEL RULING

The Panel noted that neither Searle nor Pfizer had been in contact with the journalist or the general practitioner. The Panel did not consider that there had been a breach of the Code. No breach of Clauses 20.1, 20.2 and 3.1 was ruled.

Complaint received **5 April 2000**

Cases completed **13 June 2000**

CASE AUTH/1015/4/00

GLAXO WELLCOME v 3M HEALTH CARE

Radio broadcasts about asthma inhalers

Glaxo Wellcome complained about two radio broadcasts about 3M Health Care's CFC-free inhaled beclomethasone (Qvar). The first broadcast involved a general practitioner and 3M Health Care's medical director. The second interview involved the general practitioner.

Glaxo Wellcome alleged that both interviews promoted Qvar to members of the public and encouraged them to ask their doctors to prescribe a specific medicine. Qvar was described as a new inhaler and it had been available for more than 12 months. A reference to the fact that the price of Qvar was fixed whereas the prices of other inhalers had been slowly rising over the past few months was alleged to be misleading and disparaging. The prices of Glaxo Wellcome's inhalers had not risen recently. The inhaler was described as safe. Glaxo Wellcome had grave concerns about the broadcasts and alleged that they brought the industry into disrepute in breach of Clause 2 of the Code.

3M Health Care stated that it launched a press release initiative following findings from a recent study highlighting the cost savings that could be made by following a model of transition to CFC-free inhaled beclomethasone from other inhaled steroids. The media release focussed on cost savings. There was no intention to promote Qvar to the general public.

The general practitioner had been briefed verbally by the company's PR agency. The company did not accept that it had promoted the medicine to the public. At no time was any discussion about patients asking for Qvar from their doctors initiated or encouraged by the general practitioner or the medical director. No exaggerated or inappropriate claims were made for Qvar. The media releases did not use the word new. The company accepted that the use of the word new in the first interview could have been misleading; it was being used in the sense of Qvar being a 'newer' version of beclomethasone. 3M Health Care submitted that the medical director's comments on price were taken out of context. Reference was being made to price increases in generic CFC-beclomethasone inhalers.

The Panel considered that both interviews in effect promoted Qvar, a prescription only medicine, to the general public. The first interview with the general practitioner and the company's medical director was inaccurate with regard to the prices of the inhalers; what was said was true in relation to generic inhalers but not true in relation to Glaxo Wellcome's products. Qvar was described as new which was not so. Both interviews would encourage patients to ask their doctors to prescribe Qvar. Breaches of the Code were ruled.

No breach was ruled in relation to the allegation that the reference to the rising cost of inhalers was disparaging. Nor did the Panel accept that the material warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure and no breach of that clause was ruled.

Glaxo Wellcome UK Limited complained about two radio broadcasts about an asthma inhaler from 3M Health Care Limited. One had been on 12 April on BBC Lincolnshire Action Line and the other on 13 April on IR Mercury News.

COMPLAINT

Glaxo Wellcome said that the first broadcast consisted of an interview with the medical director of 3M Health Care and a general practitioner with a presenter from BBC Lincolnshire.

Glaxo Wellcome did not know whether the participants were in the same studio, or whether the interview took place with the participants in remote locations. It was unaware of how the interview was initiated, whether it originated from an approach by BBC Lincolnshire to 3M Health Care, and what level of briefing took place between 3M Health Care and the general practitioner.

The interview was introduced as focussing on 'a new study [which] says that Health Authorities could save a total of over £56 million if they switch to prescribing an innovative and environmentally friendly agent'. Glaxo Wellcome was not aware of such a study having appeared in a peer-reviewed journal.

1 Promotion to the public

Glaxo Wellcome said that the interview was clearly aimed at the general public, involved the medical director of 3M Health Care, and the whole tone of the interview was promotional for 3M Health Care's CFC-free beclomethasone dipropionate (BDP) inhaler (Qvar).

The medical director made several statements regarding the proposed advantages of this 'new' inhaler.

He stated 'that people will obviously be moving forward with [it]'. This statement implied benefit and might be seen as encouraging members of the public to ask their doctors to prescribe a specific medication.

He stated at a later point in the interview that the inhaler was the leader. At this point the name of the inhaler, Qvar, was stated and the earlier statement regarding the pricing advantages was reinforced.

At the end of the interview the interviewer said 'so people that are listening just mention it to their GP next time they visit for their next prescription'. The general practitioner commented 'or when they go for the next asthma review.' The medical director, although present, made no attempt to rebut or add a note of caution to this suggestion.

Glaxo Wellcome believed that these statements were promotion to the public and might also be seen as encouraging members of the public to ask their doctors to prescribe a specific medication. It was alleged that they were in breach of Clauses 20.1 and 20.2 of the Code.

2 Use of the word 'new'

During the interview the medical director talked about 'The new inhaler'.

Glaxo Wellcome pointed out that Qvar had been on the UK market since September 1998, so the appellation 'new' was not appropriate. This would appear to be part of the materials associated with this campaign as the word 'new' again appeared in the IR Mercury News broadcast (see below). It was alleged that the statement was in breach of Clause 7.9 of the Code.

3 Price

The medical director stated that the price (of Qvar) was 'fixed whereas prices of other inhalers had been slowly rising over the past few months'.

Glaxo Wellcome stated that the prices of its inhalers had not risen recently, in contrast its last price changes were in the form of reductions. The medical director might have been referring to the fluctuating price of generic CFC-BDP inhalers, but he did not make that clear, claiming that there was now a significant difference between 'our inhaler and the alternatives'.

Glaxo Wellcome stated that the comments regarding cost, the rising prices of other inhalers and a further comment regarding the position of Qvar as the leader were misleading and inaccurate and were disparaging of the activities of other companies. Breaches of Clauses 7.2 and 8.1 of the Code were alleged.

Glaxo Wellcome had general concerns regarding the tone of the interview. There were comments concerning the relative dose of Qvar inhaler, and the inhaler was also described as 'safe'. Glaxo Wellcome was concerned at these comments and asked that any briefing materials provided by 3M Health Care be reviewed.

In relation to the second broadcast, which consisted of a brief interview with the general practitioner, Glaxo Wellcome drew attention to the statement by the presenter that '[two] health authorities could save over a million pounds if they prescribe an environmentally friendly asthma inhaler – that's according to 3M Health Care which claims they could use the cash to employ 45 new nurses …'.

Conclusion

Glaxo Wellcome stated that it would seem that there might be a centrally generated campaign, possibly in the form of a press release from 3M Health Care, which was driving these interviews. It requested that the Authority review all briefing materials that had been distributed by 3M Health Care in this regard at the earliest time to forestall what might possibly be a prolonged campaign.

Glaxo Wellcome had grave concerns regarding these activities which involved promotion of medicines to the public. It considered that such activities by the head of the medical department of 3M Health Care could be regarded as bringing the industry into disrepute in breach of Clause 2 of the Code.

RESPONSE

3M Health Care explained that it launched a press release initiative to both the medical and non-medical press following the findings from a recent study (PCG Qvar Cost Projection – Analysis Report) that highlighted the cost savings that could be made by following a model of transition to CFC-free inhaled beclomethasone from other inhaled steroids. This proposition was based on the conclusions of previous studies which had shown that patients with stable asthma taking inhaled CFC beclomethasone could be switched over to half the dose of Qvar without any loss of asthma control or increase in adverse events. The summary of product characteristics (SPC) for Qvar provided guidance on switching from other inhaled steroids to Qvar.

A media information pack was provided and media representatives could request interviews, via 3M Health Care's public relations agency, with either company representatives or independent experts.

3M Health Care believed that the issues of potential cost savings in a resource-constrained health service were of major importance to NHS decision-makers, health care providers, the media and to patients. It also believed that the government driven transition to CFC-free medical products was also an issue of public interest. The media release therefore focussed on the potential for cost saving to the NHS and on the transition to CFC-free products in the treatment of asthma. There was no intention to promote Qvar to the general public.

3M Health Care stated that the BBC Radio Lincolnshire programme requested an interview with a company representative and an independent expert. The general practitioner was well-known and recognised to have a specific interest in asthma in primary care and was acting in this capacity on 3M Health Care's behalf. He was involved in a nationally recognised group promoting the management of asthma in primary care. He continued to speak at national meetings on asthma and had chaired many meetings sponsored by major pharmaceutical companies, including 3M Health Care and Glaxo Wellcome. He was briefed verbally by the public relations agency on the cost research as well as the nature and content of the press releases. He was also made aware of the constraints of the Code and was specifically informed on the non-promotional nature of the interview. Furthermore, he was requested not to mention the product by name.

The medical director of 3M Health Care had been trained in the Code. He was present in his capacity as an experienced pharmaceutical physician with knowledge of the research quoted and of UK CFC-free transition policy. He was also present to ensure that the interview respected the Code within the constraints of a live interview. The general practitioner and the medical director were in a remote location, in the same studio, being interviewed by the presenter from the studio at BBC Lincolnshire.

3M Health Care stated that in reviewing the various papers submitted to the Authority it had noticed that there was an error in the press pack. In this, the switch ratio from fluticasone was suggested as 2:1 compared with Qvar inhaler. This should, of course have been a ratio of 1:1 in accordance with the SPC. 3M Health Care acknowledged this inadvertent error and had ensured it would not be repeated. It had not

put out a correction of this error to the media as, due to the complaint, it felt it was inappropriate to resurrect the matter.

3M Health Care responded to Glaxo Wellcome's specific allegations.

1 Promotion to the public

3M Health Care strongly refuted this allegation. The tone of the interview was directed at highlighting the potential cost savings and the environmental issue. It highlighted the potential cost savings that could be made based on the study findings. The interview discussed the potential cost savings for the specific local health authority and PCG in the area covered by Lincolnshire Radio. The interview also covered the CFC-free transition issue, in the context of clinical efficacy and safety.

The cost of prescription medicines to the NHS was of significant public interest and 3M Health Care strongly believed that the findings of the study should be made available to all. It therefore acted responsibly in providing appropriate information on the results from the study.

The information from the study was provided to relevant health professionals by mail on 27 March supported by appropriate releases to the medical media on 3 April. Press releases with relevant information to non-healthcare professionals were held back until 10 April to ensure that medical professionals had time to digest the information prior to any contact from the non-medical press. All the press and media releases were reviewed according to 3M Health Care standard procedures to ensure that all information on Qvar was entirely consistent with the product licence and to avoid 'raising unfounded hopes of successful treatment …' as per Clause 20.2 of the Code.

The transition to CFC-free inhaled medication was government policy and the UK strategy on CFC-free transition advised all participants involved in the transition process to promote the transition to CFC-free products (UK Transition Strategy for CFC-based MDI, 1999).

3M Health Care anticipated correctly that the study would generate media interest. It was concerned that, left to the media, the results could have been treated in a less objective manner and the medical director, a senior representative of the company, was therefore made available for the interview requested by BBC Lincolnshire.

3M Health Care believed that the press and media information release complied with the guidance in Clause 20.2 in that it was factual and balanced.

The statement by the medical director that '… people will be moving forward with …' was clearly in the context of the CFC-free transition process and reflected the government policy that people would be expected to move to non-CFC inhalation products as these became available. It in no way made any inappropriate claims in respect of the benefits and certainly did not encourage members of the public to ask their doctors to prescribe a specific medication. The product name was not mentioned during this reply.

An examination of the transcript of the interview revealed that the medical director mentioned the brand only once in the course of the seven-minute interview and that the issues of cost and transition to non-CFC containing inhalers were the main subjects of discussion.

In response to a direct question by the presenter on public awareness of the new technology and whether patients should ask their general practitioners for further information at their next visit for a prescription, the general practitioner stated that this should perhaps be done at the time of their next asthma review. 3M Health Care interpreted this as the general practitioner, quite correctly, wanting patients to consult their general practitioners in an appropriate time and manner for further information. There was no mention of the product by name (either branded or generic) during this exchange. This was completely distinct from asking for the product to be prescribed to the patient and 3M Health Care believed that the general practitioner acted in an entirely reasonably and responsible way in answering this direct question.

At no time in the interview did either the medical director or the general practitioner initiate or encourage any discussion about patients asking for Qvar from their doctors. As 3M Health Care had demonstrated, at no time were exaggerated or inappropriate claims made for Qvar, either in the media packs or the interview, and neither had 3M Health Care promoted this product to the public.

With reference to the IR Mercury News Report, this interview arose from the same press briefing regarding the potential cost savings for the NHS and the environmental issues discussed above.

3M Health Care therefore submitted that nothing in the coverage of the study amounted to an advertisement to the general public.

2 Use of the word 'new'

With reference to the word 'new', 3M Health Care acknowledged that this word was used by the interviewer, '… tell us about this **new** inhaler …' at the outset of the interview and was inadvertently responded to by the medical director. It was not used nor implied by either of the interviewees thereafter.

In the context of a non-promotional public broadcast, the word was being utilised in the sense of being a 'newer' version of beclomethasone in being free of CFC propellant. The answer made this clear as it highlighted that the 'older' CFC propellants were being phased out over the next few years. 3M Health Care accepted, however, that the use of the word 'new' could have been misleading in this context. This was not the intention, as was clear from the context in the transcript and from the deliberate avoidance of the word 'new' in the media releases.

3M Health Care denied any breach of Clause 7.9 of the Code and pointed out that there was purposefully no use of the word 'new' in any of the press and media release packs. It was therefore not part of the materials associated with this campaign as suggested by Glaxo Wellcome.

3 Price

Once again 3M Health Care submitted that the medical director's comments on price during the interview had been taken out of context. The comment on the increase in the prices of other inhalers followed on from the reply on how the non-CFC inhaler differed from the CFC propellant containing inhalers. They therefore referred to the price increases in the generic CFC-beclomethasone inhalers.

The findings from the study highlighted the issue of cost savings. Despite any recent reductions in the prices of Glaxo Wellcome's inhalers, their prices still remained significantly more expensive than the price of comparable Qvar inhalers. The study used price comparisons that were accurate at the time of the study. 3M Health Care stood by the claim that there were significant differences in price between Qvar and the alternatives, based on published clinically comparable doses.

Qvar was the first CFC-free inhaled beclomethasone to be approved in the UK for adults and as such was, *de facto*, the leader for this group of inhalers and others would follow. Therefore the statements that 3M Health Care's product was 'the leader' were accurate and did not imply criticism of other companies or their products.

3M Health Care therefore refuted the allegation that the above statements were in any way misleading and in breach of Clauses 7.2 and 8.1 of the Code.

Conclusion

There had been a centrally generated campaign by 3M Health Care to inform health care professionals, the press and media on the important findings and their cost implications for the NHS from the study. This had been carried out objectively and rigorously to ensure compliance with Clauses 7, 8 and 20 of the Code. 3M Health Care had acted pro-actively in controlling the release of the information and in ensuring that the information was factual and presented in a balanced way. It had also deliberately and consciously avoided statements that would encourage members of the public to ask their doctors to prescribe any specific medicine.

In conclusion, 3M Health Care reiterated its denial of any breach of the Code in any of its activities concerning the media during the dissemination of the findings of the above study. It would certainly not regard any of the activities by 3M Health Care as bringing the industry into disrepute in breach of Clause 2 of the Code.

PANEL RULING

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

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

The Panel noted that the press materials consisted of two press releases, one for the national press headed 'Health Authorities could miss out on saving tens of millions and helping to protect the environment' and the other for the regional and local papers headed 'Health Authorities could be missing out on saving hundreds of thousands of £s'. The national press release stated that health authorities and primary care groups across the UK could save over £56 million by switching to 'an environmentally friendly asthma inhaler produced by 3M Health Care'. The claim was based on new research which examined the cost of switching all patients currently using inhaled steroids to Qvar. The saving would be equivalent to the annual cost of treating coronary heart disease with cholesterol lowering medicines in over 100,000 patients or the annual cost of treating 35,000 patients with Alzheimer's or employing up to 2,418 extra nurses for a year. The press release stated that 'Clinical studies had shown Qvar to be at least as effective, at half the dose, in controlling asthma symptoms as other currently available inhaled steroid treatment'.

The Panel examined the PCG Qvar Cost Projection – Analysis Report. It noted that 3M Health Care used the data as a hypothetical example to indicate, based on simple demographic proportions, the potential financial impact of therapeutic alternatives given an area prescribing profile the same as the example. That this would not be accurate was stated in a specimen letter from 3M Health Care to a health authority which stated that switching to Qvar at recommended doses could save a given sum. Reference was made to the potential saving for the health authority. The Panel noted that the study assessed the cost of switching all patients on inhaled corticosteroids to Qvar. The study report noted that it should be clearly understood that Qvar was only licensed in the 12 years and over age group and had an upper dose limit of 800mcg/day. Some patients could not or would not use a metered dose inhaler and that as Qvar contained a small quantity of ethanol it might not be acceptable to some religious groups.

The Panel noted that the general practitioner had been briefed verbally on the cost research as well as the nature and content of the press releases by the company's public relations agency.

The Panel noted that the general practitioner in question had agreed to give radio interviews and appeared in the BBC Lincolnshire interview with 3M Health Care's medical director. The Panel considered that although he was an independent physician he had been briefed by the company and the company had facilitated his appearance on the programme. It was therefore not possible for 3M Health Care to completely dissociate itself from what he had said during the interview. If 3M Health Care were not responsible then the effect would be for companies to

use independent experts as a means of avoiding the restrictions in the Code.

The Panel first considered the interview broadcast on BBC Lincolnshire. The Panel noted that the basis for the interview was the potential savings to the NHS of switching to Qvar. The Panel noted that during the course of the interview there was only one mention of Qvar by brand name. The Panel considered, however, that even if this one mention of the brand name had not occurred, sufficient information about the product had been given to enable 'the inhaler' to be identified as Qvar. The Panel considered that the interview in effect promoted Qvar to the general public. The medicine was referred to as being safe, effective and competitively priced. Reference was made to the phasing out of CFCs and that patients liked Qvar because by using it they were doing less harm to the environment. Reference was also made to the fact that the same dose gave twice the effect.

The Panel decided that the interview constituted an advertisement to the general public for a prescription only medicine. A breach of Clause 20.1 of the Code was ruled. The Panel also considered that the interview was misleading as the qualifications in the study had not been given. It had been stated in the interview that a total of over £50 million could be saved but the basis of the data had not been explained, ie the data was based on a switch of all patients. No mention had been made in the interview regarding the treatment of costs that might arise from such a switch nor that the data was based on substituting Qvar for all inhaled corticosteroid preparations.

The Panel also considered that the interview was inaccurate with regard to the statement that 'the prices of other inhalers have been slowly rising over the last few months'. This was true in relation to generic inhalers but it was not at all clear in the interview that these were what were being referred to. With regard to Glaxo Wellcome's products these had dropped in price although 3M Health Care submitted that they were more expensive than the price of comparable Qvar inhalers.

The interview would also encourage patients to ask their doctors to prescribe Qvar. The Panel considered that the interview was in breach of Clause 20.2 of the Code and ruled accordingly.

The Panel considered that the alleged breach of Clause 7.2 regarding the price of other inhalers was covered by its ruling of a breach of Clause 20.2. It did not accept that the material was disparaging as alleged and no breach of Clause 8.1 was ruled.

The Panel noted that the medical director had referred to 'the new inhaler'. The product had been available for more than one year. The Panel therefore ruled a breach of Clause 7.9 of the Code.

The Panel considered that its rulings of breaches of Clauses 20.1 and 20.2 also applied to the interview with the general practitioner broadcast on IR Mercury – News.

The Panel did not accept that the matter warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. No breach of Clause 2 was ruled.

Complaint received **14 April 2000**

Case completed **12 June 2000**

CASE AUTH/1017/4/00

PRESCRIBING ADVISER v BOEHRINGER INGELHEIM

Meeting arranged by representative

A hospital prescribing adviser said that he and his wife had been invited to a 'party' at a local Greek restaurant by a representative of Enterprise (Boehringer Ingelheim). He had declined the invitation but the following day the representative had confirmed that the meeting had no educational content and was simply a night out for local health professionals at the expense of the company. The complainant regarded this type of hospitality as unethical and in breach of the Code.

The Panel noted the complainant's statement that the representative had confirmed that the meeting had no educational content and was simply a night out for local health professionals. Boehringer Ingelheim's account of the meeting was quite different in that it stated that the representative had told the complainant that there had not been a speaker at the meeting. The Panel was concerned that the representative had invited the complainant's wife without indicating that she must be a healthcare professional and qualify as a delegate in her own right. The Panel considered that the meeting had limited educational content; a ten minute presentation on two products followed by a round table discussion. The Panel did not accept that the nature of the meeting justified the associated hospitality. In the Panel's view the meeting was inappropriate as it consisted of discussions in a public restaurant, albeit in a section separate from the public area, and the hospitality was not secondary to the main purpose of the meeting. The Panel therefore ruled a breach of the Code. The Panel also considered that the representative, by arranging the meeting, had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach of the Code was also ruled in that regard.

A prescribing adviser at a hospital complained about a meeting which had been organised by a representative of Enterprise (Boehringer Ingelheim Limited).

COMPLAINT

The complainant said that along with his wife he had been invited to a 'party' at a local Greek restaurant by a representative of Enterprise. He declined the invitation but met with the representative the following day when she confirmed that the meeting had no educational content and was simply a night out for local health professionals at the expense of the company.

The complainant regarded this type of hospitality as unethical and a breach of the Code which stated that 'Hospitality must be secondary to the purpose of the meeting'. The complainant was led to believe that other representatives of the same company had provided similar hospitality in the past. He would be grateful for the Authority's assistance in ensuring that such incidents were not repeated.

RESPONSE

Boehringer Ingelheim provided details of the training it gave representatives. The Representative's Contract of Employment with Innovex included the statement that 'It is essential that all representatives abide by the ABPI Code of Practice. In accordance with the Code, Representatives must pass the ABPI exam within two years of joining the pharmaceutical industry. If this is not achieved, disciplinary action will be taken'. Innovex issued a copy of the Code as a supplement to the Contract of Employment. The objectives set out in the Boehringer Ingelheim Initial Training Course Programme included the statement 'By the end of the Initial Training Course you will be able to … exhibit the Professional Standards required by the Company and the ABPI Code of Practice'. On the first day of the Boehringer Ingelheim Initial Training Course there was a plenary presentation by the national sales manager on professional standards and the Code. The presentation emphasised that Boehringer Ingelheim abided by the Code and that the company took pride in this; it stressed the issues covered in Clauses 2, 9.1 and 15.2. The presentation was followed by a syndicate session specifically relating to professional standards and the Code. Each syndicate comprised approximately 10 delegates and was led by a trainer. The objective of the Code section was that 'by the end of the session the delegates will be able to outline the provisions of the Code of Practice that are applicable to Medical Representatives and list and describe the key points that relate specifically to medical representation'. In the session the syndicate leader reviewed the Code and highlighted specific example of situations by using a series of questions (the 'What if …' questions) and referred delegates to the Code to emphasise answers. There were five specific examples of situations that related to Clause 19.1. In addition the delegates were directed to take ownership of reading the Code. Each delegate was issued with a Code in this syndicate session (ie this was the second copy they received since both Boehringer Ingelheim and Innovex issued each new representative with a Code).

Boehringer Ingelheim pointed out that the briefing from Innovex for candidates preparing for the ABPI Medical Representatives Examination contained the statement 'You will also be required to have knowledge of the contents of those clauses of the 1998 ABPI Code of Practice which affect professional representation and also be familiar with the responsibilities of medical representatives in relation to the reporting of Adverse Drug Reactions (leaflet enclosed). These can be found in Clauses 15 to 19, and an additional leaflet on reporting Adverse Drug Reactions will be enclosed with your syllabus'.

The representative who had arranged the meeting had sat the ABPI Medical Representatives Examination

and passed the morning session but at the time of the complaint had still to pass the afternoon session.

In relation to the meeting the subject of the complaint, Boehringer Ingelheim said that telephone invitations were made to a variety of healthcare professionals and these included the complainant. The representative had spoken to the complainant's secretary who asked if partners were invited and she said 'yes' but did not indicate that the partner in question must be a healthcare professional.

Thirteen people replied stating their intention to attend. Ten doctors or medical professionals had attended the meeting. No non-medical people were present. A list of attendees was provided. Three of the GPs who attended were accompanied by their wives each of whom was either a health visitor or a practice nurse. Attendees started arriving at 7.30pm and the last one left around 11.00pm.

The purpose of the meeting was to inform the audience about Mobic and Boehringer Ingelheim's new product, Micardis.

The meeting was held in a section of the restaurant separate from the public area. During the meal there was general discussion about Boehringer Ingelheim's products Micardis and Mobic and at the end of the meal the representative gave a presentation from the front using Boehringer Ingelheim's current detail aids and referring to the printed material distributed to the audience. This presentation lasted approximately ten minutes and was followed by a round table discussion.

The total cost of the meeting was £334.30 (excluding the invitations). This represented a cost per head of £23.88 (including the three people that did not arrive but were charged for).

The representative was employed on a contract basis through Innovex UK. The Enterprise line of Boehringer Ingelheim's field force contained both Boehringer Ingelheim employees and contract employees, both of whom received precisely the same training and instruction. On an operational basis Boehringer Ingelheim did not differentiate between contract and non-contract employees.

Boehringer Ingelheim provided letters from two of the attendees that corroborated some of the above information.

Boehringer Ingelheim stated that the representative and her regional business manager had met with the complainant the day after the meeting. During this interview the complainant had concluded that the meeting had no educational content and was simply a night out for health professionals at the expense of the company. The complainant had asked who had spoken at the meeting and had been told that there had not been a speaker. The complainant's view was that the meeting breached the Code. The representative and her manager tried to explain and clarify that there was no need for an external speaker.

Boehringer Ingelheim submitted that its representative did not breach the Code. It was a presentation of information on Boehringer Ingelheim's products made to healthcare professionals accompanied by hospitality in the form of an inexpensive dinner. This position was confirmed in the two letters from attendees. Boehringer Ingelheim believed that the complainant was misled into thinking that it was anything other than a *bona fide* meeting.

This was the first complaint of this sort that Boehringer Ingelheim had ever received regarding representative conduct. It took strong exception to the insinuation that it was commonplace for its field force to conduct meetings other than in accordance with the Code.

PANEL RULING

The Panel noted the complainant's statement that the representative had confirmed that the meeting had no educational content and was simply a night out for local health professionals at the expense of the company. Boehringer Ingelheim's account of the meeting was quite different in that the representative had told the complainant that there had not been a speaker at the meeting.

The Panel was extremely concerned that when issuing the invitation the representative had invited the complainant's wife without indicating that she must be a healthcare professional and qualify as a delegate in her own right. The supplementary information to Clause 19 stated that hospitality must not extend to spouses and other persons unless that person was a member of the health professions and qualified as a proper delegate or participant in their own right. It thus followed that spouses and other such persons must not be invited. The Panel noted that the spouses that had been invited were two practice nurses and a health visitor and queried whether these qualified as delegates in their own right.

The Panel noted that the Code permitted companies to provide hospitality within certain parameters as set out in Clause 19, which stated that 'The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed the level which the recipients would normally adopt when paying for themselves'. The Panel also noted the supplementary information to Clause 19 which set out certain basic principles for any meeting: the meeting must have a clear educational content, the hospitality associated with the meeting must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion and any hospitality provided must not extend to spouses and other persons unless that person qualified as a proper delegate or participant at the meeting in their own right. Further, the Panel noted that the supplementary information to Clause 19 also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'.

The Panel considered that the meeting had limited educational content; a ten minute presentation on two products followed by a round table discussion. The Panel did not accept that the nature of the meeting justified the associated hospitality. In the Panel's view, the meeting was inappropriate as it consisted of

discussions in a public restaurant, albeit in a section separate from the public area, and the hospitality was not secondary to the main purpose of the meeting. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel also considered that in relation to the requirements of the Code, the representative, by arranging the meeting, had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled.

Complaint received **20 April 2000**

Case completed **20 June 2000**

CASE AUTH/1019/4/00

NOVARTIS v BOEHRINGER INGELHEIM

Promotion of Micardis

Novartis complained about a leavepiece, a journal advertisement, a 'Dear Doctor' letter and a brochure relating to Micardis (telmisartan) issued by Boehringer Ingelheim. The complaint concerned comparisons of Micardis 80mg with the Novartis product valsartan 80mg (Diovan). The leavepiece and the brochure included a bar chart favourably comparing Micardis 80mg with valsartan 80mg in respect to the mean reduction in diastolic (p<0.01) and systolic (p=0.14NS) blood pressure in the final six hours of a dosing interval (18-24 hours). The leavepiece and the brochure also included a bar chart comparing the cost of Micardis 40mg and 80mg with four other products including valsartan 80mg and 160mg. The 'Dear Doctor' letter and the journal advertisement each included a sentence favourably comparing the efficacy in reducing diastolic blood pressure of Micardis 80mg (18-24 hours) with that of valsartan 80mg.

Novartis stated that the bar chart in the leavepiece compared the highest licensed dose of Micardis with that of the recommended starting/maintenance dose of valsartan creating an impression of greater efficacy for Micardis. According to the summaries of product characteristics (SPCs), 80mg of Micardis and 80mg of valsartan were not comparable doses. The graphs and claims based on them represented a misleading comparison to the prescriber. Novartis also had concerns about the 'Dear Doctor' letter announcing the launch of Micardis and its accompanying brochure.

The Panel noted that the recommended dose given in the Micardis SPC was 40mg once daily. Some patients might benefit from a daily dose of 20mg and where target blood pressure was not achieved, the dose could be increased to a maximum of 80mg once daily. The SPC for Diovan stated that the recommended dose was 80mg once daily. The antihypertensive effect was substantially present within two weeks and maximal effects were seen after four weeks. In some patients whose blood pressure was not adequately controlled the dose could be increased to 160mg or a greater decrease might be achieved by adding a thiazide diuretic. The Panel noted that the promotional material compared the highest recommended daily dose of Micardis (80mg) with the lowest recommended daily dose of valsartan (80mg). The comparison was referenced to a study which did not compare any other doses of the products. There was no data comparing Micardis with the higher dose of valsartan.

The Panel considered that the comparison in the material at issue was unfair and a breach of the Code was ruled.

Novartis Pharmaceuticals UK Limited complained about four promotional items for the antihypertensive Micardis (telmisartan) issued by Boehringer Ingelheim Limited. The items in question were a leavepiece (ref MIC00050), a double page journal advertisement (ref MIC00059J), which had appeared in Pulse, a 'Dear Doctor' letter (ref MIC00058C) and a brochure (ref MIC00058B).

The complaint concerned comparisons of Micardis 80mg with the Novartis product valsartan 80mg (Diovan). The leavepiece and the brochure included a bar chart favourably comparing Micardis 80mg with valsartan 80mg in respect to the mean reduction in diastolic (p<0.01) and systolic (p=0.14NS) blood pressure in the final six hours of a dosing interval (18-24 hours). The leavepiece and the brochure also included a bar chart comparing the cost of Micardis 40mg and 80mg with four other products including valsartan 80mg and 160mg. The 'Dear Doctor' letter and the journal advertisement each included a sentence favourably comparing the efficacy in reducing diastolic blood pressure of Micardis 80mg (18-24 hours) with that of valsartan 80mg.

Both telmisartan and valsartan were angiotensin II antagonists.

COMPLAINT

Novartis stated that it had major concerns with regard to the items in question. It believed them to be in breach of the Code. Correspondence with Boehringer Ingelheim had failed to resolve the matter.

The bar chart in the leavepiece compared the highest licensed dose of Micardis with that of the recommended starting/maintenance dose of valsartan creating an impression of greater efficacy for Micardis. Clearly, according to the summaries of product characteristics (SPCs) of both products, 80mg of Micardis and 80mg of valsartan were not comparable doses. The graphs and claims based on them, Novartis therefore believed, represented a misleading comparison to the prescriber. Novartis was aware that the separate price comparison on the same page in question did mention that the usual starting dose of Micardis was 40mg. However as this leavepiece was

aimed at very busy members of the medical profession it was unlikely that they would spare the same length of time, as Novartis had, to read, analyse and fully understand the information provided. Indeed on scanning the information they would have gained a general impression of the comparative data presented which was detrimental to valsartan. This impression would be one of clearly greater efficacy for Micardis at an apparently comparable dose to valsartan.

Novartis stated that it also had concerns about the 'Dear Doctor' letter announcing the launch of Micardis. In the third paragraph of the letter, data on file (study U99-3162) was referenced claiming Micardis 80mg was significantly superior to valsartan 80mg in reducing diastolic blood pressure in the final 6 hours of the dosing interval. Again there was no mention at all of the fact that the two doses presented were not comparable. Therefore this claim represented the same misleading comparison and was clearly in breach of Clause 7.2.

The brochure included a graphical representation of the results from the same study, U99-3162. As with the other mentioned items, there was no mention near to the graph that 80mg Micardis and 80mg valsartan were not comparable doses. The brochure was again aimed at members of the medical profession who would quickly scan the document to gain a general impression. They would not make an association between the efficacy comparison graph and the cost comparison graph, which was actually on a separate page. Therefore the prescriber would be left with the incorrect impression that an 80mg dose of Micardis was equivalent to an 80mg dose of valsartan and that Micardis was more effective.

As previously mentioned, Novartis had alerted Boehringer Ingelheim to its concerns and had invited it to comment on the issues raised. Unfortunately Boehringer Ingelheim had not dealt with this matter to Novartis' satisfaction and these items were still in circulation, continuing to provide a misleading impression to prescribers and were therefore in direct breach of Clause 7.2.

RESPONSE

Boehringer Ingelheim believed that its use of study U99-3162 was not in breach of the Code. The study demonstrated that 80mg of Micardis produced a significantly superior reduction in diastolic blood pressure compared to 80mg of valsartan in the last six hours of the dosing interval ($p<0.01$). The trial compared 80mg of Micardis with 80mg of valsartan as a result of Boehringer Ingelheim's initial intention of marketing Micardis at a single daily dose of 80mg (as had occurred in Canada). This trial represented the only comparative data between Micardis and valsartan, the second most widely prescribed product in the therapeutic class, and as such provided important information for interpretation by potential prescribers. Full details of the trial were available on request to assist clinicians in forming their own conclusions of the data.

In all four of the promotional items cited in the complaint the dosages used in the study were clearly and deliberately stated. It was important to note that no generalised claim of superiority of Micardis over valsartan was made. Furthermore, additional dosage information was made clear in all four of the promotional items in close proximity to the reporting of the results of study U99-3162. Thus, in the leavepiece the 40mg start dose plus start and maintenance dosages of both Micardis and valsartan were shown immediately below in a price comparison chart. In the journal advertisement the preceding sentence clearly stated the dosages of Micardis as 40mg and 80mg. In the 'Dear Doctor' letter the starting dosage for Micardis of 40mg was given prominence within the letter following reports of trial results. On opening the brochure the 40mg Micardis start dose plus start and maintenance dosage information of both products was presented adjacent to the results of study U99-3162. Finally, in interpreting the results of U99-3162 prescribers were likely to look up the dosage of Micardis, a new product, whereas valsartan users would be familiar with its dosage regime.

In summary, Boehringer Ingelheim submitted that: as valsartan was the second most widely prescribed angiotensin II antagonist, it was appropriate to make all comparative data with Micardis available to prescribers; the dosage used in study U99-3162 was clearly stated in the promotion; the promotional materials included non-significant results as well as the significant results of study U99-3162 and no generalised claim of superiority of Micardis over valsartan was made.

In conclusion, Boehringer Ingelheim considered that use of the results of study U99-3162 in its promotion of Micardis was consistent with the provisions of the Code.

PANEL RULING

The Panel noted that the recommended dose given in the Micardis SPC was 40mg once daily. Some patients might already benefit from a daily dose of 20mg and where target blood pressure was not achieved, the dose could be increased to a maximum of 80mg once daily. The SPC for Diovan (Ref Electronic Medicines Compendium) stated that the recommended dose of Diovan was 80mg once daily. The antihypertensive effect was substantially present within two weeks and maximal effects were seen after four weeks. In some patients whose blood pressure was not adequately controlled the dose could be increased to 160mg or a greater decrease might be achieved by adding a thiazide diuretic.

The Panel noted that the promotional material compared the highest recommended daily dose of Micardis (80mg) with the lowest recommended daily dose of valsartan (80mg). The comparison was referenced to study U99-3162 data on file. The study did not compare any other doses of the products. There was no data comparing Micardis with the higher dose of valsartan.

The Panel did not accept the submission that no general claims for superiority were made. The bar chart comparing reductions in diastolic and systolic blood pressures gave the visual impression that

Micardis had greater efficacy than valsartan with regard to both parameters; the difference between the two products in respect of systolic blood pressure was in fact non-significant. The Panel considered that in the brochure, although the heading and the accompanying text only referred to diastolic blood pressure, this was not enough to negate the overall visual given by the bar chart of general superiority for Micardis. The Panel noted that in the detail aid the accompanying text did not refer to diastolic blood pressure and stated 'Continuous ambulatory blood pressure monitoring showed that Micardis 80mg was significantly superior to valsartan 80mg in the last 6 hours of the dosing interval ($p<0.01$)'. In the Panel's view this was a claim for overall antihypertensive superiority of Micardis compared with valsartan.

With regard to the comparability of the doses of Micardis and valsartan, the Panel noted that the bar chart comparing the efficacy of the two did not state that 80mg was the highest recommended daily dose of Micardis but the lowest recommended daily dose of valsartan. The Panel noted the submission that the brochure and detail aid also included a cost comparison chart from which this information could be determined. It was, however, an accepted principle under the Code that misleading claims could not be qualified and put into context by referring to other information printed elsewhere in a piece of promotional literature. The Panel did not accept the submission that additional dosage information was made clear in the 'Dear Doctor' letter and the advertisement both of which contained a claim that Micardis 80mg was more effective than valsartan 80mg in lowering diastolic blood pressure in the final six hours of a dosing interval. Although the letter referred to a starting dose of 40mg for Micardis it did not put the 80mg dose of valsartan into context with respect to its recommended dosage regimen. The advertisement referred to a 40mg dose of Micardis but did not state that this was the starting dose and, like the 'Dear Doctor' letter, it did not refer to the dosage regimen for valsartan.

The Panel considered that the comparison was unfair. The Panel ruled that the leavepiece, the 'Dear Doctor' letter and its accompanying brochure, and the journal advertisement were all in breach of Clause 7.2 of the Code.

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During its consideration of the case, the Panel noted that the brochure sent with the 'Dear Doctor' letter included an offer of a 'Tea for One' teapot and teacup set. The Panel queried whether this met the requirements of Clauses 18.1 and 18.2 that promotional aids cost the company no more than £5 (excluding VAT) and that the item had to be relevant to the recipient's profession. The Panel noted that a coffee mug had been considered to be an acceptable promotional aid provided that it cost the company no more than £5 (excluding VAT). The Panel did not consider that providing a teapot and teacup set was necessarily appropriate. The Panel requested that the matter be taken up with Boehringer Ingelheim in accordance with Paragraph 16 of the Constitution and Procedure for the Authority (Case AUTH/1042/6/00).

Complaint received **25 April 2000**

Case completed **14 June 2000**

CASE AUTH/1020/4/00

COMMUNITY PHARMACIST v CROOKES HEALTHCARE

Balneum Plus Cream journal advertisement

A community pharmacist complained about a journal advertisement for Balneum Plus Cream issued by Crookes Healthcare. The advertisement referred to the product having '3-way action' and 'Anti-Staph' properties. The complainant alleged that the advertisement was misleading as it inferred that Balneum Plus possessed anti-staphylococcal activity.

The Panel noted that the layout of the advertisement added to the impression that the 'Anti-Staph' action was one of the licensed indications. The Panel noted the link between *S. aureus* and eczema and that the action of Balneum Plus was an indirect action and not an antibiotic type of action. The Panel considered that the advertisement did not promote an unlicensed indication but was misleading about the role of *S. aureus*. Insufficient detail had been given. A breach of the Code was ruled.

A community pharmacist, complained about a journal advertisement (ref CHCSK00022) for Balneum Plus Cream (lauromacrogols and urea) which had been issued by Crookes Healthcare Limited and which had appeared, *inter alia*, in The Pharmaceutical Journal and Chemist & Druggist.

The advertisement included a photograph of the product with a circle surrounding the photograph which was broken into three parts alongside which the phrases 'Anti-Staph' 'Relieves dryness' and 'Anti-itch' appeared. The advertisement had also appeared in the medical press.

COMPLAINT

The complainant stated that the advertisement referred to Balneum Plus Cream having a '3-way action' and 'Anti-Staph' properties. The advertisement was misleading in that it clearly inferred that the product possessed anti-staphylococcal activity. Not only was the product not licensed for treatment or prevention of staphylococcal infection, the contra-indications section of the abbreviated product information stated that Balneum Plus Cream '… should not be used to treat … infected skin lesions'. In addition, none of the ingredients possessed antibacterial properties.

RESPONSE

Crookes Healthcare's view was that the 'Anti-Staph' claim would not be appropriate as an indication and it had not regarded it as such. It was, therefore, not inconsistent with the summary of product characteristics (SPC). However, it did believe the claim was capable of substantiation.

Taking the complainant's comments in turn:

(i) It was known that *Staphylococcus aureus* colonised eczematous skin in very large numbers in the absence of clinical infection (Cork 1996). The 'Anti-Staph' claim related to the effect Balneum Plus Cream had been shown to have on the levels of *S. aureus* in atopic eczema patients who were *S. aureus* carriers.

A recent clinical study (Puschmann *et al* 1999) had evaluated the antibacterial effect of Balneum Plus Cream in atopic eczema patients, who were *S. aureus* carriers (n=24). This study demonstrated a significant reduction in total bacteria and *S. aureus* levels. This result correlated with a significant improvement in the clinical condition of the skin. These data supported the 'Anti-Staph' claim. The 3-way action claim was also clearly supported as 'Relieves dryness' and 'Anti-itch' were covered by the current SPC.

(ii) The skin of patients with atopic eczema carried high levels of *S. aureus* in the absence of clinical signs of infection (Cork 1996). The contraindication 'Balneum Plus Cream should not be used to treat infected skin lesions' was not therefore inconsistent with the 'Anti-Staph' claim.

(iii) In the paper by Puschmann *et al* (1999), two possibilities for the reduction in bacteria levels were discussed; the reason could be either a direct effect and/or an indirect effect. It might be a direct result of the formulation of Balneum Plus Cream, since *S. aureus* numbers were significantly reduced on both affected and healthy skin. An indirect effect, due to the galenical properties of the product, was also suggested in association with the improvement of skin condition. Restoration of the skin protective layer increased microbial self-defence, with the relatively smooth skin offering *S. aureus* a reduced capacity for adhesion. Therefore, the reduction in *S. aureus* was not necessarily dependent upon the presence of any particular antibacterial ingredient.

The 'Anti-Staph' claim had been used in promotional items for Balneum Plus Cream since February 1999. Each promotional item had included reference to either Data on File, Crookes Healthcare, 1998, or the published reference Puschmann *et al* (1999).

PANEL RULING

The Panel examined the paper written by Cork (1996) which stated that the skin of patients with atopic eczema carried high levels of *S. aureus* which correlated with the severity of the eczema. *S. aureus* was a major environment trigger in atopic eczema. It released a toxin with superantigenic actions which initiated a vicious circle. Therapy of atopic eczema should aim to break the circle at two points. Treatment could be improved with increased use of complete emollient therapy to restore the epidermal barrier and topical antibiotic/steroid combinations to control inflammation and reduce the numbers of *S. aureus* directly. The *S. aureus* was found in the absence of clinical signs of infection.

The Panel noted that the Puschmann study had evaluated the antibacterial effect of Balneum Plus in 39 atopic patients. After 15 and 29 days of treatment of affected skin a significant reduction in total bacteria and *S. aureus* was shown. On healthy skin, Balneum Plus resulted in a decrease in bacterial count and a significant reduction in *S. aureus* after 29 days. An indirect antibacterial effect due to the galenical properties of Balneum Plus was also suggested in association with the improvement in skin condition. Restoration of the skin protective layer increased microbial self-defence with the relatively smooth skin offering *S. aureus* a reduced capacity for adhesion.

The Panel noted that Balneum Plus cream was indicated for the treatment of pruritus, eczema, dermatitis and scaling skin conditions where an antipruritic and/or hydrating effect was required. It was contraindicated in the treatment of acute erythroderma, acute inflammatory, oozing or infected skin lesions.

The Panel noted that the layout of the advertisement added to the impression that the 'Anti-Staph' action was one of the licensed indications for the product as 'Relieves dryness' and 'Anti-itch' were clearly covered by the indications. The Panel noted the link between *S. aureus* and eczema and noted that the action of Balneum Plus was an indirect action in relation to *S. aureus* and not an antibiotic type of action.

On balance the Panel considered that the impression was that Balneum Plus eliminated *S. aureus* by a direct antibiotic type of mechanism rather than an indirect action as referred to in the Puschmann study. The relevant data was limited to 24 patients. The Panel considered that the advertisement did not promote an unlicensed indication but was misleading about the role of *S. aureus*. Insufficient detail had been given. A breach of Clause 7.2 of the Code was ruled.

Complaint received **27 April 2000**

Case completed **7 June 2000**

CASE AUTH/1021/5/00 *NO BREACH OF THE CODE*

SCHWARZ PHARMA v SCHERING-PLOUGH

Clarityn journal advertisement

Schwarz Pharma complained about a journal advertisement for Clarityn issued by Schering-Plough. It was alleged that the claim 'Clarityn For an unsurpassed performance this summer' was exaggerated, not substantiated and a hanging comparison.

The Panel noted that the advertisement was headed 'Leading the field in hayfever' immediately beneath which was the explanation that leadership was measured by the total number of prescriptions in the UK. In the Panel's view the claim was not a hanging comparison as alleged. In addition, given the heading and its explanation, a reader would assume that Clarityn was being compared with other antihistamines. Nor was the claim exaggerated. A product could be regarded as unsurpassed even if it was in fact equalled though not improved upon by others. The data supplied by Schering-Plough substantiated the claim. No breach of the Code was ruled.

Schwarz Pharma Limited complained about a journal advertisement (ref CLA/00-620) for Clarityn issued by Schering-Plough Ltd.

COMPLAINT

Schwarz was concerned about the advertisement which made the claim 'Clarityn (loratadine) For an unsurpassed performance this summer'.

Schwarz stated that the claim implied that all of the other antihistamines available were no better than Clarityn, and that direct comparison had been made between the products and Clarityn. Schwarz alleged that this claim was exaggerated (Clause 7.8). Schwarz had corresponded with Schering-Plough, copies being provided, and the references supplied to it to support this claim did not contain comparisons with all of the available second-generation antihistamines, and in particular no comparison had been made with mizolastine (Schwarz's product Mizollen). Schwarz believed therefore that the claim was not substantiated (Clause 7.3). In addition, the claim appeared to be a hanging comparative, since it was not stated that with which the medicine was compared.

RESPONSE

Schering-Plough regretted that Schwarz did not consider its original response satisfactory. Schering-Plough explained that it was not aware of the recent transfer of marketing rights of mizolastine to Schwarz and as the company's original letter to Schering-Plough did not make reference to this product Schering-Plough presumed it was a more generic enquiry.

Schering-Plough stated that a review of the available literature comparing mizolastine to loratadine in the treatment of allergic rhinitis did not show any papers which went against the consensus medical opinion that the second-generation antihistamines were of comparable efficacy.

A comprehensive Medline search of all papers related to mizolastine and loratadine identified 16, only one of which was a direct comparison between the two products in allergic rhinitis (Bellioni *et al* 1996). While this paper compared the two products in perennial rather than seasonal allergic rhinitis, the results might have some relevance to the two products in seasonal allergic rhinitis – the topic of the advertisement in question. This study did not find any statistically significant differences in efficacy between mizolastine and loratadine. Schering-Plough noted that though perhaps not directly relevant, it might be of interest to note that the previous marketing right holders of mizolastine, after correspondence with the company, agreed in April 1999 not to use promotional material in the UK containing a claim that mizolastine was clinically superior to loratadine in reducing nasal congestion as this claim was based on a single study, which had a p value of 0.24, far from statistical significance.

In Schering-Plough's original reply to Schwarz it outlined its willingness to receive any information which would change the consensus view reached amongst the medical community that no single antihistamine, including mizolastine, had been demonstrated to be superior to loratadine. Schwarz had chosen not to forward any such material to Schering-Plough.

Schering-Plough noted that Schwarz had complained that the references supplied did not contain comparisons with all of the available second-generation antihistamines. The second-generation antihistamines listed in the May edition of MIMS were acrivastine, cetirizine, fexofenadine, loratadine and mizolastine.

The first review Schering-Plough cited, Slater *et al* (1999), selected the following antihistamines, among others, for review: acrivastine, cetirizine, fexofenadine, loratadine, and mizolastine. The authors concluded, after examining over 150 publications, that 'The large number of comparative studies that have been conducted of second-generation H_1 receptor antagonists in the treatment of seasonal and perennial allergic rhinitis have failed to demonstrate any superiority for one agent over another.' This was the only review article which chose to include mizolastine in its survey. Other reviews of the efficacy of antihistamines came up with the same message, and in their scope covered all the antihistamines mentioned above.

Nightingale (1996) concluded, in a review including terfenadine, astemizole, loratadine, cetirizine, clemastine and placebo, that '… all second-generation antihistamines appear about equally effective … and are similar to first-generation antihistamines'. The conclusion of another review article by Haria *et al* (1994) was that 'In large comparative trials of patients with seasonal allergic rhinitis, short term therapy (2 to 3 weeks) with loratadine at therapeutic doses was significantly superior to placebo, and as effective as azatadine, cetirizine, clemastine, mequitazine or terfenadine.'

A review article by Simons and Simons (1993) concluded: 'In patients with allergic rhinoconjunctivitis, second-generation H_1 antagonists are … comparable in efficacy to each other …'.

The results of all these review articles, based as they were on an overview of the literature of clinical experts, came to the same conclusion. That it was not possible to separate an antihistamine in hayfever (seasonal allergic rhinitis) on the basis of efficacy.

Schering-Plough believed that the claim that no other antihistamine had superior efficacy to loratadine was the balance of medical opinion. The review articles reinforced that an up-to-date evaluation of all the medical evidence on the efficacy of antihistamines had been performed, and the conclusion remained the same.

Schering-Plough noted that with regard to the allegation that the claim was a hanging comparative the advertisement explicitly and implicitly compared loratadine with other antihistamines in the treatment of hayfever. The correspondence from Schwarz clearly demonstrated that it understood this to be the case.

Schering-Plough hoped it had been able to demonstrate the overwhelming medical evidence which suggested that, currently, there was no licensed antihistamine which was demonstrated to surpass loratadine in efficacy.

PANEL RULING

The Panel noted that the advertisement was headed 'Leading the field in hayfever' immediately beneath which was the explanation that leadership was measured by the total number of prescriptions of antihistamines in the UK. The only other claim in the advertisement was 'For an unsurpassed performance this summer'. In the Panel's view the claim for an 'unsurpassed performance' did not amount to a hanging comparison as alleged. In addition, given the heading and its explanation, a reader would assume that Clarityn was being compared with other antihistamines. No breach of Clause 7.2 was ruled.

The Panel did not consider that the claim for an 'unsurpassed performance' amounted to the use of a superlative. The Panel noted that unsurpassed meant that there was nothing better. A product could be regarded as unsurpassed even if it was in fact equalled, though not improved upon by others. No breach of Clause 7.8 was ruled.

The Panel noted that a comparison of mizolastine with loratadine in the treatment of perennial allergic rhinitis had demonstrated that the two products were comparable (Bellioni *et al* 1996). In terms of reducing the total nasal score (sum of nasal pruritus, rhinorrhoea, congestion and sneezing) there was a trend in favour of mizolastine (p=0.09). In terms of reducing the total ocular score (lacrimation, pruritis, conjunctival hyperaemia) there was a trend in favour of loratadine (p=0.07). Mizolastine was more effective than loratadine in reducing the global total score (nasal plus ocular) (p=0.04). The Panel considered that although the study was not in patients with hayfever it had some relevance. The Panel noted the authors' comments that nasal symptomatology was generally more pronounced in perennial than in seasonal allergic rhinitis.

The Panel noted that the most recent comparative review of the second-generation antihistamines (Slater *et al* 1999) included mizolastine. With regard to the treatment of seasonal and perennial rhinitis it was stated that comparative studies had 'failed to demonstrate any superiority for one agent over another'. The authors concluded overall that no single agent offered a superior clinical profile.

The Panel considered that doctors reading the claim 'For an unsurpassed performance this summer' would assume that, with regard to treating hayfever, no other antihistamine was more effective than Clarityn. The literature reviews supported this position and so the Panel considered that the claim had been substantiated. No breach of Clause 7.3 was ruled.

Complaint received **5 May 2000**

Case completed **22 June 2000**

CASE AUTH/1023/5/00

TRINITY v GALEN

Cost comparison chart

Trinity Pharmaceuticals complained about a cost comparison chart produced by Galen. The chart used brand names throughout and compared the prices of Galen's product, Isotard XL, with other brands.

Galen submitted that the chart had been provided by a representative in response to an individual enquiry from a general practitioner and related solely to the subject matter of that enquiry. Galen submitted that the provision of the chart in this way did not constitute promotion under the Code. The chart had been photocopied from the training manual.

The Panel did not accept the submission that the chart was exempt from the Code. The main thrust of the promotion of Isotard XL appeared to be the cost. The chart used other companies' brand names without the prior consent of the proprietors. It was acceptable to include the chart in the representative's briefing material but its provision to a healthcare professional by the representative was not acceptable. A breach of the Code was ruled.

Trinity Pharmaceuticals Ltd complained about a cost comparison chart produced by Galen Limited. The chart compared the prices of Galen's product Isotard XL, with Monomax, Monit SR, Ismo, Imdur, Modisal, Isib and Chemydur. Trinity marketed Monomax SR.

COMPLAINT

Trinity alleged that the chart was in breach of Clause 7.10 of the Code because of the use of other companies' brand names.

RESPONSE

Galen stated that the cost comparison chart formed part of its training package for Isotard XL, a once a day isosorbide mononitrate formulation, which had recently been launched to general practitioners.

Galen stated that in the current climate, reduction of cardiovascular prescribing costs was a key consideration for many GPs, and interest in Isotard XL had centred on the cost benefits it offered compared to its competitors. In this case, Galen's representative had been asked by the GP for a definitive cost comparison of Isotard against other branded isosorbide mononitrate formulations. In response to this request, the representative had photocopied the cost comparison chart from the training manual and passed this on to the GP, without reference to sales management.

Galen's investigation, therefore, indicated that this material was given in response to an individual enquiry from a healthcare professional and related solely to the subject matter of that enquiry ie a cost comparison of branded isosorbide mononitrate formulations. This chart was simply a comparison of packs available and their costs: it was accurate, was not misleading and there were no claims to indicate it was promotional. Galen believed, therefore, that this matter did not constitute promotion under Clause 1.2 of the Code and was therefore not subject to the Code.

However, Galen did recognise that under Clause 7.10 of the Code, 'brand names of other companies' products must not be used unless the prior consent of the proprietors has been obtained', and that the potential for activity which contravened the Code was clear.

Galen was acutely aware of the need to maintain the highest standards with regard to its promotional activities, and the company therefore proposed the following actions which it trusted would be to the satisfaction of both the Authority and the complainant.

Galen provided a copy of a memorandum to its sales force which clearly outlined their responsibilities with regard to use of non-promotional/training resources. Galen had stated that only certified resources should be utilised for promotional purposes; under no circumstances should any training materials be photocopied for healthcare professionals; all information requests should be forwarded to the appropriate product manager at Galen head office. This directive would be backed up with face to face instructions from regional business managers to their teams.

Galen hoped that this would lead to a speedy and satisfactory resolution of this matter. For the record, however, Galen would like to state that had Trinity approached Galen in the first instance, it was certain this matter could have been resolved without having to involve the resources of the Authority.

PANEL RULING

The Panel noted that Cause 1.2 of the Code stated that the definition of promotion did not include replies made in response to individual enquiries from members of the health professions so long as the response related solely to the subject matter of the enquiry, was accurate, did not mislead and was not promotional in nature. In the Panel's view, it was difficult to justify that representatives could reply to such enquiries without it being seen as promotional, given that a representative's role was primarily to promote medicines.

The Panel noted that Clause 7.10 of the Code prohibited the use of brand names of other companies unless the prior consent of the proprietors had been obtained. Clause 15.9 specifically exempted representatives' briefing material from this requirement.

The Panel did not accept the submission that the cost comparison table was exempt from the Code as it had been supplied by the representative in response to a specific request from a healthcare professional. The main thrust of the promotion of Isotard XL appeared to be the cost of the medicine.

It was acceptable to include the chart in the representatives' briefing material but the provision of the chart to a healthcare professional by a representative was not acceptable. Companies should give instructions, clearly differentiating between material which was for training purposes only and that which could be used promotionally. The Panel ruled a breach of Clause 7.10 of the Code.

Complaint received **10 May 2000**

Case completed **13 June 2000**

CASE AUTH/1029/6/00

DIRECTOR v AVENTIS

Tritace journal advertisement

Aventis advised the Authority that an advertisement for Tritace which appeared in the UK edition of The Lancet included an indication not within the UK licence. The company apologised for the appearance of the advertisement which had been a result of errors made by international colleagues.

The Director decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board.

The Panel noted that the advertisement promoted Tritace for an unlicensed indication and a breach of the Code was ruled. The Panel considered that the company's system for approval of promotional material was inadequate. The company had failed to maintain a high standard and a breach of the Code was ruled.

COMPLAINT

Aventis advised the Authority that an advertisement for Tritace (ramipril), which appeared in UK editions of The Lancet (29 April and 13 May), included an indication that was not within the UK licence.

Aventis regretted the transgression and explained that the advertisement was placed in The Lancet and also in three other well respected international journals (New England Journal of Medicine, Circulation and Diabetes Today) by international marketing colleagues based in France.

The development of the advertisement was initiated in November 1999 by the international commercial team of Hoechst Marion Roussel. At this stage the UK product manager was consulted and during the following weeks colleagues pointed out that the advertisement could not be included in the UK print runs of the journals because doing so would represent promotion of an indication not included in the summary of product characteristics (SPC) and would therefore be unacceptable.

In late December the Hoechst Marion Roussel UK product manager, who was in contact with colleagues in Paris, left the UK to take up a post in Australia. However the Paris colleagues did not appreciate this change of responsibility and continued to include him in correspondence in the belief that he would advise them of any issue relevant to UK practices and regulations associated with placing the advertisement. As he did not reply it was assumed he was in agreement with the proposals being made. This situation was compounded because after the product manager's move to Australia his e-mail address was switched to his new location automatically so corporate staff did not receive any electronic indication of his move either.

An additional error occurred when the advertising agency working for Aventis received last minute correspondence from The Lancet, just prior to publication in late April, asking for the UK price for Tritace to be added to the advertisement because, in

the words of The Lancet, it was necessary 'in order to comply with UK regulations'. Regrettably, neither the relevant people in the agency nor in Aventis questioned this request. As a consequence, the belief became established in the international marketing department that with the inclusion of this information requested by The Lancet the advertisement would become acceptable for inclusion in the UK print run.

Aventis stated that the final error in this sorry saga occurred when corporate staff asked the UK to confirm that the prices were correct without explaining the full reason for their request. After receiving confirmation from the UK that 'everything is OK' it was also assumed that this represented acceptance of the advertisement and not just the prices.

Clearly the advertisement should never have appeared in the UK print runs. However, Aventis trusted that it could be seen that its inclusion was not a cynical act designed to mislead physicians and deliberately contravene the regulations, rather it was a sorry catalogue of error, compounded by the human frailty of making assumptions rather than seeking facts and the corroboration of thoughts and ideas.

Aventis took this matter very seriously indeed. As a consequence all international marketing senior managers were being informed of this case and would be reminded of the company policy for staff to obtain the relevant sign-offs for the placement of international advertisements.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board, published in the August 1997 Code of Practice Review.

RESPONSE

Aventis fully understood the implications and deeply regretted the inclusion of the advertisement in The Lancet that was outside the scope of the UK Tritace SPC. Aventis UK took great care to ensure that the company complied with the spirit and letter of the Code and therefore informed the Authority as soon as it became aware of the transgression that had been initiated by its international colleagues. Senior UK and international management had taken steps to ensure that the transgression had been brought to the attention of all relevant colleagues and to re-stress the importance of following the company's own internal procedures. Aventis was confident that this rare slip in its normal high standards would not be repeated.

Aventis acknowledged that the advertisement was a clear breach of Clause 3.2 of the Code and that its high standards had been found wanting and therefore represented a breach of Clause 9.1 of the Code.

PANEL RULING

The Panel noted that the advertisement referred to the results of the HOPE study which compared Tritace, vitamin E and placebo or placebo alone on the incidence of major cardio- and cerebrovascular events in cardiovascular (CV) high risk patients and diabetics aged 55 and over. It was stated that future disability, strokes, infarctions and cardiovascular surgery could be avoided by the use of Tritace in this high risk population. The Panel noted that the indications for Tritace in the SPC were for the treatment of mild to moderate hypertension and in congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides. Tritace had been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

The advertisement, by promoting Tritace for cardio- and cerebroprotection in a general high risk patient population, thus promoted the product for an unlicensed indication and the Panel therefore ruled a breach of Clause 3.2 of the Code.

The Panel noted that Aventis had advised the Authority that the advertisement had appeared. The Panel considered that the company's system for approval of the advertisement was inadequate. The company had failed to maintain a high standard and a breach of Clause 9.1 of the Code was ruled.

Proceedings commenced 1 June 2000

Case completed 23 June 2000

CODE OF PRACTICE REVIEW – AUGUST 2000

Cases in which a breach of the Code was ruled are indexed in **bold type**.

966/1/00	**Lundbeck v SmithKline Beecham**	**'Dear Doctor' letter about Seroxat and citalopram**	**Breaches Clauses 2, 7.7 and 10.1 Four breaches Clause 7.2 Three breaches Clause 8.1**	**Appeal by respondent**	**Page 3**
970/1/00 & 972/1/00	**Parke Davis, Pfizer and Merck Sharp & Dohme v Bayer**	**Lipobay journal advertisement**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 11**
971/1/00	**SmithKline Beecham v Ferring**	**Promotion of Pentasa**	**Breaches Clauses 7.2 and 7.3**	**Appeal by complainant**	**Page 17**
977/2/00	**Solvay Healthcare v Novo Nordisk**	**Kliovance leaflet**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 22**
979/2/00 & 980/2/00	**Wyeth v Eisai and Janssen-Cilag**	**Pariet journal advertisements**	**Breach Clause 7.2**	**Appeal by respondents**	**Page 25**
981/2/00	**Drug Information Pharmacist v Schering Health Care**	**Samples provided by representative**	**Breaches Clauses 15.2, 17.3 and 17.8**	**No appeal**	**Page 28**
982/2/00	**Parke Davis and Pfizer v Merck Sharp & Dohme**	**Promotion of Zocor**	**Two breaches Clause 7.2 Breaches Clauses 7.3, 7.8 and 8.1**	**Appeal by respondent**	**Page 30**
983/2/00	**General Practitioner v Merck Sharp & Dohme**	**Conduct of representative**	**Breaches Clauses 7.2, 7.3 and 15.2**	**No appeal**	**Page 37**
984/2/00	**AstraZeneca v Pfizer**	**Istin detail aid**	**Breaches Clauses 3.2 and 7.7 Ten breaches Clause 7.2 Three breaches Clause 7.3 Two breaches Clause 8.1**	**No appeal**	**Page 38**
989/3/00	**General Practitioner v AstraZeneca**	**Promotion of Losec**	**Breach Clause 15.9**	**No appeal**	**Page 49**
992/3/00	**Wyeth v AstraZeneca**	**Losec leavepieces**	**Breaches Clauses 7.2 and 7.7**	**No appeal**	**Page 51**
994/3/00	**SmithKline Beecham v Lundbeck**	**Cipramil journal advertisement**	**Two breaches Clause 7.2 Breach Clause 7.7**	**No appeal**	**Page 54**
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996/4/00 to 1007/4/00	Prescribing advisor and Primary Care Group Chairman v BASF Pharma, Bristol-Myers Squibb, Ferring, Glaxo Wellcome, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Roche, Schering-Plough, Searle, SmithKline Beecham and Takeda	Article in Sunday Mirror	No breach	No appeals	Page 59
1015/4/00	**Glaxo Wellcome v 3M Health Care**	**Radio broadcasts about asthma inhalers**	**Breaches Clauses 7.9, 20.1 and 20.2**	**No appeal**	**Page 64**
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1019/4/00	**Novartis v Boehringer Ingelheim**	**Promotion of Micardis**	**Breach Clause 7.2**	**No appeal**	**Page 71**
1020/4/00	**Community Pharmacist v Crookes Healthcare**	**Balneum Plus Cream journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 74**
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1029/6/00	**Director v Aventis**	**Tritace journal advertisement**	**Breaches Clauses 3.2 and 9.1**	**No appeal**	**Page 78**