PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 34 NOVEMBER 2001

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.

Material to substantiate claims must be made available

Clause 7.4 of the Code of Practice states that 'Any information, claim or comparison must be capable of substantiation' and Clause 7.5 states that 'Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff'.

It follows, therefore, that everything in an advertisement must be able to be substantiated by material which the company is prepared to supply to health professional enquirers, even if those enquirers are employed by competitor companies.

Companies have on occasion attempted to substantiate claims by material which they regarded as confidential and which they were not prepared to provide to health professionals seeking substantiation. Such a reservation cannot be made. Similarly, copyright problems cannot be used as a valid reason for failure to substantiate. Substantiating materials have to be made available in accordance with the Code. If for any reason they cannot be, then the claim in question cannot be made.

Similar considerations apply to Clause 7.7, a new provision in the 2001 Code, which states that 'When promotional material refers to data on file, the relevant part of this data must be provided without delay at the request of members of the health professions or appropriate administrative staff'.

Public reprimand for GlaxoSmithKline

GlaxoSmithKline has been publicly reprimanded by the ABPI Board of Management as a result of its failure to comply with an undertaking and assurance given previously in relation to an Avandia journal advertisement.

The ABPI Board considered that although GlaxoSmithKline had made some changes to the advertisement, its reaction had been superficial and had not adequately addressed the matter.

Full details can be found at page 17 in this issue of the Review in the report for Case AUTH/1169/3/01.

New Appeal Board Member

The new Constitution and Procedure for the Prescription Medicines Code of Practice Authority, which applies to complaints received on and after 1 July, adds to the Code of Practice Appeal Board 'one member representative of the interests of patients'.

The ABPI Board of Management has appointed to this role Mrs Mary G Baker MBE. Mary Baker worked for the Parkinson's Disease Society for seventeen years and was until recently its chief executive. In June 1992 she was elected as the first President of the European Parkinson's Disease Association and is currently in her fifth term of office.

The holder of many awards and offices, in 2000 she was appointed to the Editorial Board of the BMJ and was awarded the Human Communication International Award, the European Woman of Achievement Award and the first UK Charity Award for Personality of the Year sponsored by Charity Times.

Mary Baker attended her first meeting of the Appeal Board in October and the Authority welcomes her and looks forward to her contribution to its work.

Please circulate the Review

Those receiving the Code of Practice Review at pharmaceutical companies and agencies etc, are reminded that it should be circulated to all those responsible for the preparation or approval of promotional materials and activities. It is the sole source of information about current developments and rulings and can assist companies to stay within the requirements of the Code.

Dating of promotional material

Companies are reminded that Clause 4.9 of the Code of Practice states that 'Promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised'.

The requisite date is the date of preparation or revision of the promotional item as a whole. Instances have arisen where the stated date of preparation was earlier than a date given in the prescribing information or earlier than the dates of quoted references. No separate date for the prescribing information is required, although it can be included.

If any aspect of a promotional item changes, such as amendments to the prescribing information, then a new date for the item and fresh certification are needed. Regardless of the date of preparation or revision, promotional material must be correct and up-to-date when it is posted or given out.

The date of preparation or revision is not required in a journal advertisement because such an advertisement is dated by the date of the journal in which it appears and must be correct and up-to-date at that time.

CODE OF PRACTICE TRAINING

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

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

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

Monday, 7 January

Monday, 25 February

Monday, 18 March

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/1144/2/01

GENERAL PRACTITIONER v SHIRE

Calcichew-D_3 Forte abbreviated journal advertisement

A general practitioner complained that an abbreviated advertisement for Calcichew-D_3 Forte (calcium and vitamin D_3), issued by Shire, promoted the product as a treatment for osteoporosis in the elderly. The advertisement featured a photograph of an older woman and had the headline 'inner strength'. Beneath the product logo was the claim 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly'. Calcichew-D_3 Forte was not indicated for the treatment of osteoporosis but rather only as an adjunct to specific therapy for osteoporosis. The complainant alleged that the marketing was misleading and inappropriate.

The Panel noted that according to its summary of product characteristics (SPC) Calcichew-D_3 Forte was indicated for the treatment and prevention of vitamin D/calcium deficiency, characterised by biochemical markers, particularly in the housebound and institutionalised elderly subjects. It was also licensed for the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia and in other situations requiring therapeutic supplementation of malnutrition.

The advertisement had the headline 'inner strength' and in the bottom right hand corner stated that Calcichew-D_3 Forte was 'the only calcium and vitamin D supplement proven to strengthen bone in the elderly'. In the Panel's view strengthening of bone might be a benefit of treatment with Calcichew-D_3 Forte but such an outcome was not the primary reason to use the product; the reasons to prescribe Calcichew-D_3 Forte, and its licensed indications, were to treat and prevent vitamin D/calcium deficiency or as an adjunct to specific therapy for osteoporosis in situations requiring therapeutic supplementation of malnutrition.

The Panel considered that the indication as stated in the abbreviated advertisement, '… to strengthen bone in the elderly', was misleading and inconsistent with the SPC. Breaches of the Code were ruled.

Upon appeal by Shire, the Appeal Board noted the company's view that calcium/vitamin D deficiency resulted in increased bone loss, particularly in the elderly, and that treatment with Calcichew-D_3 Forte reduced/reversed bone loss ie strengthened bone. The company submitted that this was the primary reason for treatment and that this rationale was widely accepted by clinicians. The Appeal Board noted that after one year's treatment with Calcichew-D_3 Forte of women aged ≥70 years, 80% of whom were institutionalised, bone mineral density (BMD) had increased at all sites compared to baseline but only at the trochanter was the increase statistically significant (p=0.025). The Appeal Board noted that BMD was not a direct measure of bone strength, a more direct measure was fracture rate. BMD was, however, related to bone strength. Some members of the Appeal Board queried whether reversal of bone loss equated with strengthening bone.

The Appeal Board considered that the use of the word 'supplement' in the claim 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly' related the claim to the second indication in the SPC which referred to '... situations requiring therapeutic supplementation of malnutrition'. The first indication in the SPC referred to treatment and prevention of vitamin D/calcium deficiency, particularly in the housebound and institutionalised elderly subjects. The Appeal Board noted that the photograph in the advertisement did not represent the housebound and institutionalised elderly population.

The Appeal Board considered that osteoporosis was a common manifestation of bone loss. Calcichew-D_3 Forte could only be used in osteoporosis as an adjunct to specific therapy in patients who required therapeutic supplementation of malnutrition. The Appeal Board considered that the implication of the advertisement related to the use of the product in osteoporosis. It accepted that this was not stated anywhere in the advertisement. Nevertheless the use of the photograph and reference to 'supplement' in the claim related to the indication for situations requiring supplementation.

In the Appeal Board's view the indication 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly' was inconsistent with the SPC and was misleading. The abbreviated advertisement did not include at least one indication for use consistent with the SPC as required by the Code. The Appeal Board therefore upheld the Panel's rulings of breaches of the Code.

A general practitioner complained about an abbreviated advertisement (ref 003/0084) for Calcichew-D_3 Forte (calcium and vitamin D_3) by Shire Pharmaceuticals Ltd which appeared in Pulse, 24 February. The advertisement featured a photograph of an older woman and had the headline 'inner strength'. Beneath the product logo was the claim 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly'.

COMPLAINT

The complainant stated that the advertisement promoted Calcichew-D_3 Forte as a treatment for osteoporosis in the elderly. The summary of product characteristics (SPC) for Calcichew-D_3 Forte did not indicate it as a preparation for the treatment of osteoporosis but rather only as an adjunct to specific therapy for osteoporosis. The complainant alleged that the marketing was misleading and inappropriate.

When writing to Shire the Authority drew attention to Clauses 3.2, 5.4, 5.5 and 7.2 of the Code.

RESPONSE

Shire pointed out that the advertisement did not mention the word 'osteoporosis' so it would have

helped if the complainant had explained specifically why he felt that the advertisement promoted this medicine as a non-adjunctive treatment for osteoporosis.

Shire stated that a study by Deroisy *et al* (1998) was conducted in a population of 119 female patients at least 70 years of age – 80% of whom were institutionalised. The women were randomised to receive either calcium and vitamin D in one chewable tablet (Orocal, exactly equivalent to Calcichew-D_3 Forte) or calcium and vitamin D taken separately. The patients were treated for one year.

Calcium and vitamin D_3 deficiency were the main causes of bone loss in elderly women. In this study at baseline, the calcium intake of these elderly institutionalised patients was found to be low, serum vitamin D_3 concentrations were lowered, parathyroid hormone (PTH) concentrations raised and alkaline phosphatase concentrations raised. These conditions were those specified for treatment with Calcichew-D_3 Forte in the first part of the licensed indications.

After 12 months' treatment, bone mineral density (BMD) had increased at all sites (significantly so at the trochanter) for Orocal-treated patients. An overall negative change in BMD was observed for patients with separate calcium-vitamin D preparations. The Orocal-treated patients exhibited significant decreases in serum PTH and alkaline phosphatase levels and a significant increase in serum vitamin D_3 levels – results entirely expected following treatment according to the Calcichew-D_3 Forte indications.

Regarding the increase in BMD ('strengthening of bone'), described above in the Deroisy *et al* study, no other calcium and vitamin D supplement (formulated conveniently in one tablet) had demonstrated such an increase. Therefore, the headline in the advertisement was well substantiated – it described a positive documented outcome (not seen with another single supplement) following treatment with Calcichew-D_3 Forte precisely as described in the first part of the licensed indications.

Although an increase in femoral bone density as achieved in this study would be a desirable outcome of treatment of the osteoporotic condition, there was no mention of the word 'osteoporosis' and no claim that Calcichew-D_3 Forte should be used alone as therapy for osteoporosis. The advertisement was therefore not inconsistent with the second part of the licence (use as an adjunct to specific therapy for osteoporosis).

Regarding the term 'inner strength', Shire maintained that this was an uncontentious phrase that was fair, reasonable and consistent with the headline.

Shire stated that the complainant may well have been taken through its detail aid with one of its medical sales representatives, since its GP coverage was extensive. One particularly relevant page from this document carried the same headline statement as the advertisement and clearly illustrated that Calcichew-D_3 Forte was promoted as one of a variety of osteoporosis therapy options. This page demonstrated that Shire recommended lifestyle advice and other medicinal therapies as optional additional therapy to Calcichew-D_3 Forte in elderly patients, within the confines of its licence.

The advertisement specified that any relevant information (which included the above) could be obtained from Shire Pharmaceuticals on request.

Shire submitted that it promoted Calcichew-D_3 Forte in this advertisement according to its marketing authorization and the SPC.

With regard to Clause 5 of the Code, Shire maintained that the headline in the advertisement was consistent with the indications for Calcichew-D_3 Forte. 'Strengthening of bone in the elderly' referred to the correction of increased bone loss in elderly subjects as described in the first item of its therapeutic indications.

With regard to Clause 7.2 of the Code, Shire stated that the headline in the advertisement was factually correct. The supportive evidence detailed above demonstrated that the information, claims and comparisons were accurate, fair, objective and unambiguous. Shire had objectively evaluated and reflected information which was totally up-to-date and did not believe that it had misled the reader in any way with its headline claim.

PANEL RULING

The Panel noted that according to its SPC Calcichew-D_3 Forte was indicated for the treatment and prevention of vitamin D/calcium deficiency (characterised by raised serum alkaline phosphatase levels associated with increased bone loss, raised levels of serum PTH and lowered 25-hydroxyvitamin D), particularly in the housebound and institutionalised elderly subjects. It was also licensed for the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia and in other situations requiring therapeutic supplementation of malnutrition.

The Panel noted that the advertisement had the headline 'inner strength' and in the bottom right hand corner stated that Calcichew-D_3 Forte was 'the only calcium and vitamin D supplement proven to strengthen bone in the elderly'. In the Panel's view strengthening of bone might be a benefit of treatment with Calcichew-D_3 Forte but such an outcome was not the primary reason to use the product; the reasons to prescribe Calcichew-D_3 Forte, and its licensed indications, were to treat and prevent vitamin D/calcium deficiency or as an adjunct to specific therapy for osteoporosis in situations requiring therapeutic supplementation of malnutrition.

The Panel considered that the indication as stated in the abbreviated advertisement, '… to strengthen bone in the elderly', was misleading and inconsistent with the SPC. Breaches of Clauses 3.2, 5.4 and 7.2 were ruled.

During its consideration of this case the Panel was concerned that the claim 'the only calcium and vitamin D supplement proven to strengthen bone in the elderly' might give the impression that this was a benefit of therapy in all elderly patients. The Panel

queried whether this was so. In a previous case concerning a Calcichew-D_3 Forte leaflet, Case AUTH/625/10/97, the Panel had considered that the statement 'Raising serum calcium slows age-associated bone loss' was misleading; supplemental calcium only slowed age-associated bone loss in those patients whose dietary intake was inadequate. The Panel queried whether a similar principle was at issue in the case now before it and requested that Shire be advised of its concerns.

APPEAL BY SHIRE

Shire noted that the complainant stated that the advertisement promoted Calcichew-D_3 Forte as a treatment for osteoporosis in the elderly. In fact, nowhere did the abbreviated advertisement mention the word 'osteoporosis'.

Shire noted that in the Panel's view 'strengthening of bone might be a benefit of treatment with Calcichew-D_3 Forte but such an outcome was not the primary reason to use the product'. The company considered that such an outcome was a clear and major consequence of treatment according to the licensed therapeutic indications - which referred *inter alia* to increased bone loss associated with calcium/vitamin D deficiency, particularly in the housebound and institutionalised elderly. Treatment clearly strengthened bone by preventing or reversing bone loss.

Shire considered that it was within the Code to state major proven clinical benefits of treatment within the licence, particularly when these benefits were widely acknowledged by the clinical community and the links between calcium/vitamin D deficiencies and serious consequences (morbidity and mortality) of bone loss were widely accepted. The company therefore considered that the advertisement was not in breach of Clause 3.2 of the Code, since it was in accordance with the terms of the marketing authorization and not inconsistent with particulars listed in the SPC.

Shire noted that the Panel was concerned that the claim 'the only calcium and vitamin D supplement proven to strengthen bone in the elderly' might give the impression that this was a benefit of therapy in all elderly patients. Shire considered that the Panel's interpretation contrasted with normally accepted conventions regarding claims. For example, a claim that a medicine relieved depression did not imply that all depressed patients would symptomatically improve. No medicine would ever gain a licence if efficacy in 100% of patients was required.

Shire noted that in its initial response to the complaint, it justified the specific relationship between this headline statement (derived from the Deroisy study) and the licensed indications; calcium and vitamin D deficiency were the main causes of bone loss in elderly women. In the Deroisy study at baseline, the calcium intake of these elderly institutionalised patients was found to be low, serum vitamin D_3 concentrations were lowered, PTH concentrations raised and alkaline phosphatase concentrations raised. These conditions were those specified for treatment with Calcichew-D_3 Forte in the first part of the licensed therapeutic indications.

Shire noted that Clause 5.4 of the Code specified that an abbreviated advertisement must contain at least one indication for use consistent with the SPC or data sheet. As stated above, 'strengthening of bone in the elderly' was intimately associated with treatment within the licensed therapeutic indications and was an indisputable general consequence of such treatment. It was therefore Shire's opinion that the advertisement was not in breach of Clause 5.4 of the Code.

The company queried whether a direct quote from the SPC was required under Clause 5.4 or whether headline statements relating to proven benefits of treatment within the licensed therapeutic indications were permitted.

Shire noted that the Panel ruled that the headline statement was misleading. However, this headline was a supportable statement which did not mislead the reader: medical practitioners were fully aware of the firmly established consequence of strengthening of bone in the elderly following administration of calcium and vitamin D to correct calcium/vitamin D deficiency or to treat osteoporosis in combination with other medicine/lifestyle therapies. The company therefore contended that the advertisement was not misleading and did not contravene Clause 7.2 of the Code.

Shire noted that the Panel had alerted it to a previous case, Case AUTH/625/10/97, with a query whether a similar principle was now at issue to that in this previous case. Shire did not agree that the current case was similar. As stated above, the headline statement was fully supportable and not misleading. The statement was derived from a study in which patients at baseline conformed with the Calcichew-D_3 Forte licensed therapeutic indications.

APPEAL BOARD RULING

The Appeal Board noted the company's view that calcium/vitamin D deficiency resulted in increased bone loss, particularly in the elderly, and that treatment with Calcichew-D_3 Forte reduced/reversed bone loss ie strengthened bone. The company submitted that this was the primary reason for treatment and that this rationale was widely accepted by clinicians.

The Appeal Board noted that the Deroisy study examined the effect of one year's treatment with Calcichew-D_3 Forte on bone remodeling markers and bone mineral density (BMD) in women aged ≥70 years, 80% of whom were institutionalised. After 12 months BMD had increased at all sites compared to baseline but only at the trochanter was the increase statistically significant ($p=0.025$). The Appeal Board noted that BMD was not a direct measure of bone strength, a more direct measure was fracture rate. BMD was, however, related to bone strength. Some members of the Appeal Board queried whether reversal of bone loss equated with strengthening bone.

The Appeal Board noted the two indications in the Calcichew-D_3 Forte SPC. One was the treatment and

prevention of vitamin D/calcium deficiency (characterised by raised serum alkaline phosphatase levels associated with increased bone loss, raised levels of serum PTH and lowered 25-hydroxyvitamin D), particularly in the housebound and institutionalised elderly subjects. The other indication was the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia and in other situations requiring therapeutic supplementation of malnutrition.

The Appeal Board considered that the use of the word 'supplement' in the claim 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly' related the claim to the second indication in the product SPC which referred to '... situations requiring therapeutic supplementation of malnutrition'. The first indication in the SPC referred to treatment and prevention of vitamin D/calcium deficiency characterised by biochemical markers, particularly in the housebound and institutionalised elderly subjects. The Appeal Board noted that the photograph in the advertisement did not represent the housebound and institutionalised elderly population.

The Appeal Board considered that osteoporosis was a common manifestation of bone loss. Calcichew-D_3 Forte could only be used in osteoporosis as an adjunct to specific therapy in patients who required therapeutic supplementation of malnutrition.

The Appeal Board considered that the implication of the advertisement related to the use of the product in osteoporosis. It accepted that this was not stated anywhere in the advertisement. Nevertheless the use of the photograph and reference to 'supplement' in the claim related to the indication for situations requiring supplementation.

In the Appeal Board's view the indication 'The only calcium and vitamin D supplement proven to strengthen bone in the elderly' was inconsistent with the SPC and was misleading. The abbreviated advertisement did not include at least one indication for use consistent with the SPC as required by Clause 5.4 of the Code. The Appeal Board therefore upheld the Panel's rulings of breaches of Clauses 3.2, 7.2 and 5.4 of the Code.

Complaint received **26 February 2001**

Case completed **17 August 2001**

CASE AUTH/1151/3/01 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v TAKEDA

Conduct of representative

A general practitioner complained about what a Takeda representative had said when detailing Actos (pioglitazone). The complainant had become aware that doctors were being told that Actos was cheaper than Avandia (GlaxoSmithKline's product). This was true for only a small number of patients.

When the complainant was visited by the Takeda representative he was curious to know what would be said. He indicated he knew a little about Actos. The complainant was concerned that some of what the representative had said was misleading. Firstly, the price comparison, with the higher strength of Avandia, was couched in such a way as to suggest that this was the standard price comparison. Secondly, if favourable NICE guidance on Actos was published local GPs would not automatically be able to prescribe it, as implied. Thirdly, the representative stated that a local hospital consultant was initiating Actos as monotherapy; the complainant eventually managed to ascertain that this was only as part of a clinical trial. To say that a medicine was being used, particularly by specialists, might be a tactic to encourage GPs to prescribe it. The complainant noted that liver function should be monitored regularly in the first year of treatment and periodically thereafter. There was no mention of this monitoring.

The Panel noted that according to Takeda the representative responded accurately to questions about the cost of 30mg Actos and 8mg and 4mg Avandia. Briefing material gave the price range of rosiglitazone and stated that in combination with a sulphonylurea 15mg Actos and 4mg rosiglitazone were comparable in efficacy and price. In combination with metformin it was stated that the maximum dose of rosiglitazone was 8mg (£1.90/£1.95 per day). The maximum dose of Actos was 30mg (£1.32/day). The representative stated that the complainant thought that very few patients treated with rosiglitazone would need the highest dose. The Panel noted that the briefing material mentioned the range of available doses and costs of rosiglitazone. Given the parties' differing accounts it was not possible to determine where the truth lay. No breach of the Code was ruled.

With reference to the publication of a NICE recommendation the complainant had been able to establish that the representative realised that recategorisation of Actos would not be automatic. The representative stated that she had suggested that the prescribing situation might change. There were some differences between the parties' accounts but the Panel considered that the overall impression given that on the publication of a NICE recommendation the prescribing situation might

change, was not unreasonable. No breach of the Code was ruled.

The Panel noted that Actos was indicated in oral combination treatment with either metformin or a sulphonylurea. The complainant stated that it was only after significant questioning that he was able to establish that the monotherapy referred to by the representative was part of a clinical trial and not routine therapy. The representative stated that when asked if Actos was being used, she referred to a local clinical trial. The study was in monotherapy. Again the parties' accounts differed. The Panel was concerned that the representative had referred to the unlicensed use of Actos. Nonetheless it was impossible to determine precisely what was said. No breach of the Code was ruled.

The summary of product characteristics (SPC) referred to the need for liver function tests; the Panel did not consider that the recommendation in the SPC was such that it should always be mentioned when promoting Actos. Liver function monitoring was included in one of the promotional pieces used by the representative but not in the other; it was referred to in the prescribing information in promotional material. Representatives had been trained to discuss the need for liver function monitoring with doctors although Takeda submitted that an opportunity for this had not occurred in the interview in question. In the circumstances no breach of the Code was ruled.

COMPLAINT

The complainant stated that he was concerned that information given to doctors and others by pharmaceutical company representatives was not misleading.

The complainant had become aware that doctors were being given the impression that Takeda's product Actos (pioglitazone) was cheaper than GlaxoSmithKline's product Avandia (rosiglitazone) and was sufficiently concerned at this (as Avandia was cheaper other than for the relatively smaller numbers of patients who were on metformin and had the higher dose of Avandia) to include an item about this in his primary care trust's (PCT) prescribing newsletter. However, he was surprised that despite this one of his partners, having been visited by a Takeda representative, asked him whether he should change his glitazone of choice to Actos as it appeared to be cheaper.

The complainant was then visited by a Takeda representative. The complainant was curious to know, given the above, what she would say to him and was unsure as to whether she knew that he was the PCT's prescribing lead and also sat on the local prescribing forum. The complainant stated that when asked what he knew about Actos he indicated that he knew a little and listened to what she had to say. There were three things that she said about which the complainant was particularly concerned. Firstly, the price comparison was with the higher strength of Avandia, couched in a misleading way suggesting that this was the standard price comparison. Secondly, she said that the National Institute for Clinical Excellence (NICE) was expected to publish guidance on Actos next week and that if it recommended it the local traffic light system for prescribing would change from it being red to a categorisation enabling GPs to prescribe it. Thirdly, she indicated that a local diabetic consultant was initiating prescription of Actos as a monotherapy in diabetic patients.

The complainant stated that he pointed out to the representative that the price comparison was misleading and requested that she inform practices that she had seen and indicated this to previously, that in fact, a more reasonable comparison was with the lower strength of Avandia. The complainant was concerned if other practices had been misled as to an appropriate price comparison. The complainant stated that he requested an undertaking from the representative to contact practices to whom she might have given this impression. She did not give such an undertaking.

With respect to the NICE guidance, the complainant pointed out that it was misleading to say that Actos would automatically be recategorised as it would only be recategorised once the prescribing forum had made a decision so to do and to imply that it would happen automatically was misleading to doctors.

Thirdly, the complainant stated that he eventually managed to obtain the information from the representative that the diabetic consultant prescribing pioglitazone was only doing so as part of a clinical trial. The complainant said that to say that a medicine was being prescribed by other doctors, particularly specialists, might be a tactic to encourage GPs to prescribe new medicines; however, it was misleading to do so when the prescribing was in fact part of a clinical trial and not to say so.

The complainant stated that he had subsequently noted from the literature that liver function tests should be monitored before and then every 2 months for the first 12 months of treatment and periodically thereafter. It was also noted that rarely hepatocellular dysfunction had been experienced. There was no mention of this monitoring. However, when SmithKline Beecham brought out Avandia, even though the complainant understood the company did not have any cases of hepatocellular dysfunction, it was very up front about specifically suggesting the same liver function test monitoring. The complainant stated that if his memory served him correctly, the previous glitazone on the market was withdrawn as a result of liver function test abnormalities.

RESPONSE

Takeda UK Limited stated that it was most concerned that the GP felt he had been given misleading information about pioglitazone from a Takeda representative. It was able to investigate this particularly thoroughly as the representative had informed the company that she had been involved in a difficult meeting before Takeda received the complaint. Takeda did not believe that the representative gave misleading information and it believed that she maintained a high standard of conduct even when she was faced with many difficult challenges from the doctor. During the call the representative used a short leavepiece and the 'Actos – Questions and Answers' booklet.

Cost of Actos

Takeda noted that the GP had stated that doctors had been given the impression that Actos was cheaper than rosiglitazone, and this concerned him. Takeda believed his concern was misplaced.

The representatives for Takeda had no promotional materials which discussed either the cost or efficacy of rosiglitazone and were not being encouraged to discuss the product with doctors.

From the account Takeda had received from its representative the GP asked her for the price of 30mg Actos. The representative responded accurately giving the price for the highest available dose for Actos at £36.96 per month. They also discussed the price of the highest dose of rosiglitazone 8mg, which was described as priced at just over £54 per month. The GP asked for the costs for rosiglitazone 4mg. This was given correctly as £26.60 per month.

Actos was licensed and available at two doses, for the treatment of type 2 diabetes in combination with metformin or sulphonylurea. The range of cost for the two doses 15mg and 30mg was £26.60 - £36.96 for 28 days.

Avandia was available at two doses for the treatment of type 2 diabetes in combination with metformin, and licensed and available at one dose in combination with sulphonylureas. The range of cost for the two doses 4mg and 8mg was £26.60 - £53.20 (or up to £54.60 using the 8mg tablet) for 28 days.

It was relevant to note that in the NICE guidance for Avandia it was assumed that 25% of patients on Avandia required the higher dose giving an average cost of £430 per annum. Similarly in the NICE guidance for Actos the average cost for Actos was assumed to be £414 per annum based on the assumption that equal proportions of patients required the lower and higher doses.

Takeda representatives had received two briefing documents with information about Avandia. The 'Actos Resource folder' was available from November 2000 and the 'Rosiglitazone briefing' was sent to all representatives in December 2000. These gave factual information about the range of prices of the two medicines. The briefing materials did not claim that Actos was cheaper than Avandia.

It was clearly stated in the initial briefing document for the representatives that the highest dose of Actos 30mg would have a relatively small price premium compared to Avandia 4mg in combination with sulphonylurea.

In combination with metformin the situation was different, as Avandia could also be prescribed at the doses of 4mg bd or 8mg od which meant that the maximum costs of the two products were £36.96 for Actos and £53.20 for Avandia for 28 days. In this case if both medicines were prescribed at the top doses Avandia would have the price premium.

Takeda stated that its representative did not set out to make a comparison of Actos 30mg with rosiglitazone 8mg but responded to questions with accurate information.

NICE Guidance and change of local prescribing recommendation

From the account Takeda received from its representative the GP asked if Actos was being prescribed in the area. The representative stated that Actos was not being used locally due to the 'traffic light system' which was in place and that Actos was on a red light. The representative further elaborated on the position with respect to NICE guidance, which was expected within a very short time (just one week after the meeting with the GP) and suggested that she expected that the prescribing situation might change. The GP stated that the NICE guidance would have no effect on the local prescribing of Actos and that it was purely governed by the decision of the health authority and the PCG.

The representative gave accurate information about the expected release of the NICE guidance for Actos and her understanding that if NICE recommended that an agent could be prescribed in the NHS then local guidances would be reviewed. No comment was made about automatic recategorisation of any agent.

Use of Actos as monotherapy

Takeda stated that from the account given by its representative the GP questioned whether Actos was being used. The representative responded that her only information was about patients taking part in clinical trials locally. This clinical trial was of Actos as monotherapy. The GP challenged the representative saying she was being deceitful as she mentioned monotherapy.

Takeda did not believe that this response to a direct question with factual information was misleading.

Liver function tests

Takeda stated that the GP was correct in his understanding of the reasons for the withdrawal of another medicine in this class, and that liver function test monitoring was recommended for this class of agents. The GP believed that there were no cases of hepatocellular dysfunction with Avandia. However, Takeda noted that it was clearly stated in the summary of product characteristics (SPC) for Avandia that isolated cases of hepatocellular dysfunction had been reported although no causal relationship had been established.

Takeda stated that it had been very open and honest about this requirement for monitoring with information about liver function monitoring included in all of the major promotional pieces, eg the Question and Answer booklet that Takeda's representative was carrying. The requirement for liver function monitoring was clearly stated in the prescribing information included with all promotional items, and its representatives had all been trained about the requirements for liver function monitoring and would usually discuss this with a doctor. However in this case the opportunity to discuss this did not arise and the very short leavepiece left with the doctor did not contain this information.

Takeda did not believe that the representative had the opportunity in this call to discuss the liver monitoring.

Takeda did not believe that its representative gave misleading information to the GP and so was not in breach of Clause 7.2 of the Code. In addition Takeda believed that she maintained a high standard of ethical conduct in the meeting and so was not in breach of Clause 15.2 of the Code.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that he stood by his original letter and that he was concerned that in both Takeda's response and the account of the meeting supplied by Takeda, for example, the impression was given that the issue of consultant initiation of Actos as monotherapy was to do with it being monotherapy. It was to do with the representative not making it clear that the situation was one of a clinical trial and not routine prescription, which would clearly have important implications as to whether other prescribers would follow suit as they might if they felt this was being used as standard therapy, but would not be so likely to if they realised that it was a clinical trial. The complainant stated that his clear recollection was that it was only after significant pursuit of this that he was able to establish that this monotherapy use by a local consultant was as part of a clinical trial and not routine therapy.

The complainant reiterated that with respect to the NICE guidance and the local traffic light system, the way that it was stated by the representative came across as if NICE's recommendation would automatically result in a change in the traffic light categorisation of Actos. It was only after specific further questioning that he was able to establish that the representative realised that in fact automatic recategorisation would not take place on publication of NICE guidance but that that guidance would presumably be considered by the prescribing forum if reconsidering the categorisation of Actos at a later date.

With respect to cost the complainant stated that he understood that there had been some work to suggest that there would be proportionately more people on the lower strength of Avandia than the higher strength if Avandia was used, and therefore the overall cost would be lower for Avandia than Actos, and this was somewhat contrary to the impression that the complainant felt he was being given. For example, the routine ladder of treatment would be metformin first followed by the addition of a sulphonylurea followed by substitution of one or other agent with a glitazone. Since more patients would not tolerate metformin than a sulphonylurea (eg renal failure preventing them using it or unacceptable GI symptoms) more patients would end up on the sulphonylurea/glitazone combination than the metformin/glitazone combination. Additionally proportionately many diabetic patients on tablets were overweight and therefore preferentially should stay on metformin than a sulphonylurea. Avandia was not licensed at the higher dose together with sulphonylureas and therefore one should only compare the cost of its lower strength with that of Actos when used in combination with a sulphonylurea. The complainant was not sure that Takeda's response made that clear.

PANEL RULING

The Panel first considered the allegation regarding the price comparison. The complainant stated that the price of Actos had been compared with that of the higher strength of Avandia couched in a misleading way suggesting this was the standard price comparison. According to Takeda the representative responded accurately to questions from the complainant about the cost of 30mg Actos and 8mg and 4mg Avandia.

The Panel noted Takeda's submission that the representatives had no promotional materials which discussed either the cost or efficacy of rosiglitazone. The Panel noted that page 15 of the Actos resource folder (representative's briefing material) beneath a question and answer regarding the cost of Actos stated 'How does this compare to rosiglitazone? Rosiglitazone ranges between 95p - £1.95 per day'. The subsequent section discussed where and how both products could be used in combination with a sulphonylurea and metformin. In combination with a sulphonylurea it was stated that separate studies suggested that 15mg Actos and 4mg rosiglitazone were comparable in efficacy and price. It was noted that there were no direct comparative studies and for a relatively small price premium a greater reduction in HbA1c plus improvements to patients' lipid profiles could be achieved with 30mg Actos. In combination with metformin it was stated that the maximum dose of rosiglitazone was 8mg, at a cost of £1.90/£1.95 per day. The maximum dose of Actos was 30mg at £1.32 per day.

The Panel noted that the parties' accounts differed. The representative's account stated that the complainant appeared to be under the clear impression that the majority of patients treated with rosiglitazone would be maintained on the 4mg dose and that very few patients would need the highest dose. The Panel noted that the briefing material mentioned the range of available doses and costs of rosiglitazone. The Panel considered that given the parties' differing accounts it was not possible to determine where the truth lay. The Panel thus ruled no breach of Clauses 7.2 and 15.2 of the Code on this point.

The Panel then considered the reference to the NICE guidance. The complainant stated that the representative had said that if Actos was recommended by NICE then the local traffic light system for prescribing would change from its being red to a categorisation enabling GPs to prescribe it. In response to a request for further information the complainant stated that after further specific questioning he was able to establish that the representative realised that automatic recategorisation would not take place on publication of the NICE guidance but that the guidance would be considered by the prescribing forum if reconsidering the categorization of Actos at a later date. The representative's account stated that she had suggested that the prescribing situation might change. The Panel noted that there were some differences between the parties' accounts. The Panel considered, however, that the overall impression given, that on the publication of a NICE recommendation the

prescribing situation might change, was not unreasonable. No breach of Clauses 7.2 and 15.2 was ruled.

With reference to the use of Actos as monotherapy, the Panel noted that according to its SPC Actos was indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea. The complainant stated that it was only after significant pursuit of this that he was able to establish that the monotherapy use was part of a clinical trial and not routine therapy. The representative, however, stated that when asked whether Actos was being used she stated that she had been told by a local consultant that some patients were involved in clinical trials. The study was in monotherapy. The complainant had challenged the representative saying she was being deceitful as she mentioned monotherapy. Again, the Panel noted that the parties' accounts differed. The Panel was concerned about the representative's account; the Panel queried whether in response to a question about Actos use the representative's response should have related to the unlicensed use of Actos. Nonetheless the Panel considered that the differences between the parties' accounts were such that it was not possible to determine precisely what was said. No breach of Clauses 7.2 and 15.2 was ruled.

With regard to liver function tests, Section 4.4 of the SPC, monitoring of liver function, stated that there had been rare reports of hepatocellular dysfunction during postmarketing experience. It was recommended that patients underwent periodic monitoring of liver enzymes. The Panel noted Takeda's submission regarding its disclosure of this requirement in all major promotional pieces. Takeda did not believe that the representative had the opportunity to discuss the liver function monitoring. All representatives were trained on this and would usually discuss it with the doctor.

The Panel did not consider that the recommendation in the SPC was such that it should always be mentioned to health professionals when promoting Actos. A judgement had to be made; relevant factors would include the type and nature of any meeting and status of the audience. Liver function monitoring was mentioned in the 'Actos – Questions and Answers' booklet but not in the leavepiece left with the complainant. The Panel noted that liver function monitoring was included in the prescribing information in the promotional material. The Panel noted Takeda's submission that the representatives had all been trained about the requirements for liver function monitoring and would discuss this with a doctor, although this did not happen during the interview with the complainant. In the circumstances the Panel did not consider that there had been a breach of the Code. No breach of Clauses 7.2 and 15.2 was ruled.

Complaint received **27 March 2001**

Case completed **27 July 2001**

CASE AUTH/1164/3/01

ANONYMOUS v ASTRAZENECA

Invitation to a meeting

A letter sent anonymously to the General Medical Council was copied to a newspaper. The letter was critical of a meeting sponsored by AstraZeneca and enclosed a copy of the invitation. The newspaper passed the letter to the Authority which, in accordance with established practice, treated it as a complaint under the Code. The invitation, from a consultant gastroenterologist, was written on hospital headed notepaper and stated:

'Increasingly the optimisation of acid control can be seen to be important in GORD [gastro oesophageal reflux disease]. With the new introduction of Nexium, at a favourable price, comes an opportunity to discuss its indications for use in our patients.

Will you be able to attend a discussion group to altogether reach a consensus on this?'

The invitation stated that AstraZeneca had agreed to sponsor a meal and that the venue would be a local hotel.

The complainant stated that the invitation was to a dinner at an exclusive restaurant to be sponsored by AstraZeneca and it revealed an unethical practice by the company and the consultant to influence the prescribing of Nexium. According to the Code, sponsorship of a meeting by a pharmaceutical company must be for educational purposes and not solely for the promotion of any of its products. Nexium (esomeprazole) was a proton pump inhibitor of a similar structure and effect to Losec (omeprazole) in reducing stomach acid and healing ulcers. With the expiry of Losec's patent, AstraZeneca had effectively relaunched Losec in a double dose under the new name Nexium so that the company maintained its stronghold share of the market. Nexium was more expensive than other proton pump inhibitors available on hospital formularies; the claim that it was cheaper was untrue. AstraZeneca was using various unethical practices to influence doctors in prescribing Nexium and enforcing it on hospital formularies. The correspondent was aware of significant financial contributions made by the company to the funds of two consultant gastroenterologists. There was clear evidence that their unit had been exclusively using Losec rather than other proton pump inhibitors which were as, and in some cases more, effective, and yet substantially cheaper.

The Panel noted the complainant's comments about the financial contributions made by AstraZeneca to the consultant. The Panel noted the schedule of payments provided and the submission that previous fees paid to the consultant were within British Medical Association guidelines and accepted industry practice. The Panel did not consider that the payments were unreasonable. They appeared to be genuine payments for work done. The consultant received no fee for the meeting at issue.

The Panel considered that the letter of invitation was not sufficiently clear about the objectives of the meeting. Overall the meeting had limited educational content which did not justify the associated hospitality. It was principally a discussion between colleagues, chosen by the consultant, who chaired the meeting, as to whether Nexium should be added to the local formulary. The Panel was concerned that AstraZeneca appeared to have had no input with regard to the content and format of, and the invitations to, the meeting. The company's role seemed to be limited to administration and paying for the meal. One representative did attend the meeting. In the Panel's view the hospitality was not secondary to the main purpose of the meeting and was out of proportion to the occasion. The Panel further considered that both the company and representative had failed to maintain high standards. Breaches of the Code were ruled.

In relation to the allegation that the claim that Nexium was cheaper was totally untrue, the Panel noted that the letter of invitation did not state that Nexium was cheaper as alleged by the complainant; rather it referred to the introduction of Nexium at a favourable price. The Director determined that there was no *prima facie* case to answer on this point.

Upon appeal by AstraZeneca, the Appeal Board considered that the meeting was educational. Its purpose was to discuss patient types for whom esomeprazole might be a suitable therapeutic option. New data was presented and acid control in patients with GORD was discussed. The chairman was interested in using Nexium and wished to achieve a consensus view on whether other colleagues might also be interested. The issue of Nexium being on the formulary was also discussed. The Appeal Board considered that the hospitality was secondary to the main purpose of the meeting and the costs, at £38 per head, were not unreasonable. The Appeal Board ruled no breach of the Code in that regard.

The Appeal Board noted that the meeting had been convened at the suggestion of the chairman to provide a forum for discussion. The attendees were senior hospital doctors. The Appeal Board was concerned about the wording of the invitation, it referred to Nexium 'at a favourable price', and by the poor impression given by the statement that AstraZeneca would sponsor a meal. In addition the invitation did not appear to reflect what would be presented or discussed at the meeting. The consultant had dictated the letter of invitation but, given the representative's involvement with the meeting, AstraZeneca was responsible for its content. In such circumstances it was important that representatives were aware of the need to protect their companies from possible breaches of the Code. It would have been helpful if a formal agenda had been produced. The use of hospital paper by the representative was also of concern. This gave the meeting more of an independent appearance than would have been the case if the invitation had been sent on company notepaper. The company representative had sent the letter, provided

hospitality at the meeting and given administrative support.

The Appeal Board decided that the representative had failed to maintain a high standard and upheld the Panel's ruling of a breach of the Code. The Appeal Board did not consider that the company had failed to maintain a high standard and no breach of the Code was ruled in that respect.

A letter sent anonymously to the General Medical Council was copied to a newspaper. The letter was critical of a meeting sponsored by AstraZeneca UK Limited and enclosed a copy of the invitation to it. The newspaper passed the letter to the Authority which, in accordance with established practice, treated it as a complaint under the Code.

The invitation, from a consultant gastroenterologist, was written on hospital headed notepaper and stated:

'Increasingly the optimisation of acid control can be seen to be important in GORD [gastro oesophageal reflux disease]. With the new introduction of Nexium, at a favourable price, comes an opportunity to discuss its indications for use in our patients.

Will you be able to attend a discussion group to altogether reach a consensus on this?'

The invitation went on to state that AstraZeneca had agreed to sponsor a meal for the group and that the meeting would be at an hotel.

COMPLAINT

The anonymous correspondent stated that the invitation was to a dinner at an exclusive restaurant to be sponsored by AstraZeneca and revealed an unethical practice by the company and the concerned consultant to influence the prescribing of Nexium.

The complainant stated that according to the Code, sponsorship of a meeting by a pharmaceutical company must be for educational purposes and not solely for the promotion of any of its products. Nexium (esomeprazole) was a proton pump inhibitor of a similar structure and effect to Losec (omeprazole) in reducing stomach acid and healing ulcers. With the expiry of Losec's patent, AstraZeneca had effectively relaunched Losec in a double dose under the new name Nexium so that the company maintained its stronghold share of the market. This new medicine was more expensive than other proton pump inhibitors available on hospital formularies. The claim made that Nexium was cheaper was totally untrue. Comparing the use of the standard dose of this medicine with others, Nexium was more expensive. AstraZeneca was using various unethical practices to influence doctors in prescribing this medicine and enforcing it on hospital formularies.

Having worked closely with Astra in the past, the correspondent was aware of significant financial contributions made by the company to the funds of two consultant gastroenterologists. There was clear evidence that their unit had been exclusively using Losec rather than other proton pump inhibitors which were as, and in some cases more, effective, and yet substantially cheaper. The correspondent was certain that this case of malpractice required urgent investigation by the GMC.

When writing to AstraZeneca the Authority drew attention to Clauses 2, 9.1, 15.2 and 19 of the Code.

RESPONSE

AstraZeneca stated that the meeting was chaired by the consultant gastroenterologist who had written and sent the invitation to all consultant physicians and surgeons with a specialist interest in gastroenterology within the local area. The purpose of the meeting was a discussion on strategies for the management of upper gastrointestinal disorders. The chairman developed the meeting content and list of delegates to be invited. AstraZeneca sponsored the meeting and the local AstraZeneca hospital representative provided administrative assistance.

The letter of invitation was on hospital headed paper and clearly stated that AstraZeneca sponsored the meeting. Acceptances were sent to the representative who made the arrangements for the meeting. Fourteen consultants accepted the invitation and the meeting was booked for 15 delegates (to include the representative) in a private room. The meal was the standard table d'hôte at £25 per person. Prior to the meeting, the representative sent reminder letters to the delegates. These were on AstraZeneca headed paper and made no mention of any products. Although fourteen invitees had accepted, in the event, only eight attended, including the chairman and the representative. A list of those who were present was provided by AstraZeneca.

The costs of the meeting were: food, 15 x £25 = £375 (the hotel charged for the non-attendees); drinks, £105; overhead projector hire, £30. No honoraria or other payments were made to any of the delegates. No promotional material was distributed at the meeting.

AstraZeneca submitted that this meeting was educational with there being no promotional content. The hospitality offered was secondary to the purpose of the meeting and was at a cost which consultants might reasonably pay for themselves. The invitation to the meeting clearly stated that AstraZeneca sponsored the meeting and no payments were made to any of the delegates for their attendance. AstraZeneca, therefore, submitted that its representative arranged this meeting in a proper and ethical manner in accordance with Clause 15.2 of the Code and that the arrangements for the meeting satisfied all the requirements of Clause 19 of the Code.

AstraZeneca challenged the complainant's view that Nexium was of similar efficacy to Losec. Nexium had been shown to have a superior pharmacokinetic and pharmacodynamic profile compared to Losec; in clinical trials Nexium had demonstrated reduced first pass metabolism, reduced plasma clearance and hence higher systemic bioavailability than Losec. In a study in 36 patients with gastro oesophageal reflux disease (GORD) the area under the plasma concentration-time curve at day 5 of dosing with Nexium 20mg was 80% higher than Losec 20mg, and for Nexium 40mg was five times higher compared to Losec 20mg (both $p<0.0001$).

In acid suppression studies Nexium had demonstrated significantly longer acid suppression compared to Losec (measured over 24 hours at day 5). In a study comparing Nexium 40mg and 20mg with Losec 20mg in GORD patients, Nexium 40mg and 20mg maintained intragastric pH>4 for 16.8 and 12.7 hours respectively, compared to 10.5 hours for Losec 20mg ($p<0.001$ and $p<0.001$ respectively). A further study compared Nexium 40mg with Losec 40mg in 114 patients with GORD; Nexium 40mg maintained intragastric pH for 16.4 hours compared to 14.9 hours for Losec 40mg ($p<0.001$). There was evidence that increased suppression of acidity was beneficial in the healing of reflux oesophagitis; the daily time intragastric pH>4 had been shown to correlate with healing.

Studies in healing of reflux oesophagitis comparing Nexium 40mg with Losec 20mg (respective licensed doses for healing) had shown that significantly more patients were healed at both 4 and 8 weeks with Nexium 40mg. At week 4, Nexium 40mg healed 10% more patients than Losec 20mg (75.9% vs. 64.7%; $p<0.05$). In addition, in healing reflux oesophagitis, Nexium 40mg had demonstrated faster relief from heartburn than Losec 20mg; the time to first period of seven consecutive days without heartburn as recorded by the patient was 5 days with Nexium 40mg compared to 8 days with Losec 20mg ($p<0.001$).

The licensed doses for healing of reflux oesophagitis were the same basic NHS cost (Nexium 40mg and Losec 20mg both cost £28.56 for 28 days). However, since clinical trial data had shown that 10% more patients were healed at 4 weeks with Nexium 40mg than Losec 20mg, there might be cost implications. Nexium was also unique in having a licence for on-demand use in GORD patients without oesophagitis (following initial symptom control). In clinical trials, patients took one dose of Nexium 20mg od on-demand on one-third of the days on average. Nexium 20mg cost £18.50 for 28 days' treatment, which meant that on-demand treatment might cost as little as £6.17 per month (based on clinical trial data). This might be cost effective compared to a continuous Losec regimen in this group of patients.

AstraZeneca provided details of financial contributions made to the two consultant gastroenterologists. Individual payments ranged from £150 to £1000 and were for various item of contracted work, including delivering lectures, chairing meetings and consultancy work. In every case, the fees paid were within British Medical Association guidelines and accepted industry practice.

AstraZeneca was firmly of the view that the arrangements for the meeting, its activities in that meeting and its arrangements with the consultant gastroenterologists and the hospital had, in every case, recognised the special nature of medicines and the professional standing of all concerned. AstraZeneca, therefore, denied any breach of Clause 9.1. Furthermore, it strongly refuted any suggestion that it had, in any way, brought discredit upon or reduced confidence in the pharmaceutical industry and denied a breach of Clause 2.

In response to a request for further information AstraZeneca stated that the meeting was convened as a discussion amongst gastroenterology consultants in the area, at the suggestion of the consultant gastroenterologist, who was interested in using Nexium within his practice in the hospital, but his ability to do so was limited because Nexium was not on the local formulary. The purpose of the meeting was to identify and discuss patient types seen within the area for whom esomeprazole might be a suitable therapeutic option, given its clinical profile. The consultant had new, unpublished data indicating that some patients needed extra-high dose of proton pump inhibitors (PPIs). In these patients cost effectiveness of treatment was a particular issue. The consultant was interested in adopting esomeprazole for use in appropriate patients and wished to achieve a consensus view on whether other colleagues might also be interested in similar adoption. In the event, he also used the meeting as an educational opportunity to discuss acid control in patients with GORD with senior colleagues in hospitals within the area. He also felt that a meeting might offer the opportunity to take a view on whether the clinicians present believed there was a case for making representations for esomeprazole to be added to the local formulary. In the event, the decision was taken at the meeting not to put the product forward for formulary discussion at this stage.

A copy of the slides used by the consultant at the meeting were provided. No formal agenda was produced.

The meeting was scheduled to begin at 7.30pm, however it actually commenced at 7.50pm once the delegates were assembled. The meeting began with the consultant's presentation, this lasted until approximately 8.40pm, at which time dinner was served. Discussion continued throughout the meal and the meeting closed at 9.30pm when all the delegates departed.

A copy of the invoice from the hotel was provided together with a copy of the reminder letter from the representative which reminded invitees to the meeting of its date and time and was printed on AstraZeneca headed paper.

AstraZeneca confirmed that the consultant was not paid an honorarium for his chairmanship of the meeting.

PANEL RULING

The Panel noted that the consultant gastroenterologist who had chaired the meeting had developed the meeting content and the list of delegates to be invited and had sent the invitation to all consultant physicians and surgeons with a specialist interest in gastroenterology within the local area. The invitation, on hospital headed notepaper, stated that AstraZeneca had agreed to sponsor a meal. Acceptances were sent to the representative who made the arrangements for the meeting and also attended the meeting. In response to a request for further information AstraZeneca stated that the meeting was convened, at the suggestion of the chairman, to provide a forum for discussion amongst clinical colleagues as to whether Nexium should be added to the local formulary. The purpose of the

meeting was to identify and discuss patient types within the area for whom Nexium might be a suitable therapeutic option given its clinical profile. The chairman also discussed acid control in patients with GORD. The Panel considered that the arrangements and content of the meeting were such that AstraZeneca was responsible for it under the Code.

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 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. The supplementary information also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'.

The Panel noted that the meeting took place in a private room at a hotel and commenced at 7.50pm with the consultant's presentation which lasted until approximately 8.40pm and was followed by a meal. AstraZeneca submitted that discussion continued throughout the meal. The meeting ended at 9.30pm. The Panel was concerned that no formal agenda had been prepared. There were eight attendees including the chairman and representative; the meal cost £25 per head and drinks a total of £105 (just over £13 per head). The Panel noted that the presentation consisted of 10 slides which discussed the goal of PPI therapy in gastro-oesophagal reflux disease. The third slide stated that 'Currently the high dose PPI should be esomeprazole 40mg a day (or more). High efficacy: cost ratio'. Subsequent slides discussed, *inter alia*, the use of high dose PPI and the plasma concentration of esomeprazole versus omeprazole in GORD patients after five days dosing.

The Panel noted the complainant's comments about the financial contributions made by AstraZeneca to the consultant. The Panel noted the schedule of payments provided. The Panel noted the submission that previous fees paid to the consultant were within BMA guidelines and accepted industry practice. The Panel did not consider that the payments were unreasonable. They appeared to be genuine payments for work done. The Panel noted that the consultant however received no fee for the meeting at issue.

The Panel noted AstraZeneca's response with regard to the stated objectives of the meeting and the status of Nexium on the local formulary. The Panel considered that the letter of invitation was not sufficiently clear about the objectives of the meeting with regard to Nexium. The Panel considered that overall the meeting had limited educational content which did not justify the associated hospitality. The meeting was principally a discussion between colleagues, chosen by the chairman, as to whether Nexium should be added to the local formulary. The Panel was concerned that AstraZeneca appeared to have had no input with regard to the content and format of, and the invitations to, the meeting. The company's role seemed to be limited to administration and paying for the meal. One representative did attend the meeting. In the Panel's view the hospitality was not secondary to the main purpose of the meeting and was out of proportion to the occasion. A breach of Clause 19.1 was ruled.

The Panel then considered the allegation that 'The claim made that Nexium was cheaper was totally untrue'. The Panel noted that the letter of invitation did not state that Nexium was cheaper as alleged by the complainant; rather it referred to the introduction of Nexium at a favourable price. The Director determined that there was no *prima facie* case to answer on this point.

The Panel further considered that both the company and representative had failed to maintain high standards. Breaches of Clauses 9.1 and 15.2 were ruled.

The Panel did not consider that the circumstances warranted a breach of Clause 2 which was used as a sign of particular censure and reserved for such circumstances. No breach of Clause 2 was ruled.

APPEAL BY ASTRAZENECA

AstraZeneca stated that in its view the venue chosen for the meeting was a comfortable, but by no means extravagant or ostentatious hotel. Described by the complainant as an 'exclusive restaurant' indicated there might have been some confusion with another venue with a similar name which was indeed a highly regarded establishment in restaurant circles. The hotel was widely used for many business functions, including pharmaceutical company meetings. It was conveniently located and was easily accessible to the invitees. As would be appropriate for a medical meeting, a private room was used. No separate charge for this was made. There were other hotels in the area which provided more luxurious facilities. AstraZeneca considered this was an appropriate choice of venue for this type of meeting.

The total cost per head for the hospitality provided at the meeting, which comprised dinner and drinks, was £38. AstraZeneca submitted that given the status of the attendees, all (with the exception of its representative) being consultant surgeons or gastroenterologists, dinner at £38 per head was by no means extravagant or beyond what they might expect to pay for themselves. The meal was table d'hôte and in no way exceptional and was accompanied by a modest amount of wine. Pre-dinner drinks were also provided. AstraZeneca noted that in two previous cases concerning a meeting, Cases AUTH/1112/12/00 and AUTH/1113/12/00, the cost of hospitality per head, at just over £40, was ruled by the Panel to be, on balance, not unreasonable. The attendees were general practitioners and pharmacists.

AstraZeneca reiterated that all the invitees at the meeting were senior clinicians and hence exceptionally busy; an evening meeting therefore seemed appropriate in order to optimise attendance.

This being the case, it did not seem unreasonable for dinner to be provided as part of the meeting, at a time at which the attendees would normally eat. This facilitated discussion continuing throughout the evening and was therefore an effective use of time. The principle that hospitality might be provided during a meeting and that discussion or indeed presentation of information might occur whilst refreshments were being consumed, was well-established custom and practice. For example, sales representatives frequently facilitated lunch-time meetings in hospitals and general practices at which lunch was provided and AstraZeneca considered that it was fundamentally no different to facilitate an evening meeting at which a meal was provided.

With regard to the meeting itself, AstraZeneca noted that it had already supplied a copy of the slides used by the consultant and reiterated that the topics under discussion were of significant medical interest to the attendees. The consultant was a leading authority on gastric acid suppression and had introduced a specialised clinic at a local hospital to undertake gastric pH monitoring of patients who were referred with symptoms unresolved by standard management. He presented new and unpublished data concerning a specific group of his patients; this would have been of considerable interest to the clinicians attending. Such patients presented significant issues regarding appropriate management. The consultant, in discussing Nexium as possibly being appropriate for this group, was thus presenting a topic that these doctors would be interested in acquiring further information about and debating. The issue of Nexium being on formulary was highly relevant to the debate, since it would only be possible for the product to be used on an ongoing basis if it were to be accepted on to the local formulary. This was an important issue in management of a long-term chronic condition. The presentation of data, together with questions and discussion, lasted for approximately 50 minutes, after which dinner was served. Further discussion then continued over dinner. The meeting thus lasted for just under two hours, half of which comprised formal presentation and discussion. AstraZeneca submitted that the meeting was scientific and in the broadest sense, educational. Given that the meal lasted for only fifty minutes, it would not be reasonable to describe the occasion as purely social.

AstraZeneca repeated that the consultant was well known and respected in his therapeutic speciality. He was personally known to all of the invitees of the meeting in question, therefore the point that there was not a formal, written agenda, controlled by AstraZeneca, should be viewed in this context. Had a formal agenda existed, it would have been very brief, consisting of the items of the consultant's presentation and discussion. The company did not believe the existence of an agenda would have materially affected the conduct of the meeting or its content. Nor did the company consider that the relatively informal manner in which the meeting was arranged, given the relationship that existed amongst the persons invited, was such as to render the meeting one that was inappropriate for AstraZeneca to have sponsored.

AstraZeneca submitted that it was an accepted principle of the Code that companies might sponsor a wide variety of meetings ranging from small lunch-time meetings in general practice, to very large international symposia. This meeting fell within that continuum of meeting types and as such the company did not consider that, overall, the arrangements were unreasonable.

Given all of the circumstances outlined above, AstraZeneca did not consider that the lack of a formal agenda for the meeting, or the wording of the letter of invitation, amounted to a failure on its part, or that of its representative, to maintain high standards. In AstraZeneca's view, the rulings in this case, if upheld, would seriously undermine the ability of companies in the future to hold valid yet comparatively informal meetings for health professionals; these had been an integral part of accepted industry practice to date and had contributed to successful working relationships between the industry and the NHS.

In summary, AstraZeneca stated that it considered that overall, the hospitality arrangements for the meeting fell well within the acceptable boundaries of the Code. An evening meal was provided at a reasonable cost and at a time when delegates would normally expect to eat their main meal of the day. The meeting was convened for valid scientific and medical reasons. The company thus wished to appeal the ruling of a breach of Clause 19.1. Furthermore, the company considered that the meeting was arranged, in good faith, as a result of the combined efforts of a senior clinician and one of its representatives. The objectives were sufficiently clearly stated in the letter of invitation for these to be understood by those invited. The arrangements for the meeting in general, given all the circumstances outlined, were acceptable and did not warrant a ruling of failure to maintain high standards on the part of the company or its representative. AstraZeneca appealed the ruling of breaches of Clauses 9.1 and 15.2.

AstraZeneca submitted further points having received additional comments from the consultant. The company noted that the Panel's ruling referred to one of the slides presented at the meeting, which stated 'Currently the high dose PPI should be esomeprazole 40mg a day (or more). High efficacy: cost ratio'. The company clarified that this was in fact the last slide to be presented at the meeting itself, not the third, as stated by the Panel. AstraZeneca stated that the copies of the slides submitted with its response were not supplied in the order in which they were presented. A set was enclosed that had been numbered in the correct order of presentation.

AstraZeneca also clarified the point that whilst there was no written agenda for the meeting, the proposed agenda was discussed in detail and agreed between the consultant and the representative. A formal agenda document was not produced. The consultant had indicated that he wished to present new data to the invited consultants concerning his evidence about the need for high dose proton pump inhibitors for some patients with reflux disease. AstraZeneca considered that this was relevant to its position that the meeting was arranged for a serious medical/educational purpose.

At the appeal hearing the AstraZeneca representatives explained that the invitation to the meeting had been dictated by the consultant to the representative who had typed it up at his request on hospital paper. The representative had attended the meeting as an observer and had answered some questions.

APPEAL BOARD RULING

The Appeal Board noted that it was not uncommon for groups of doctors to arrange meetings between themselves, out of normal working hours, to discuss and debate topics of mutual interest. The pharmaceutical industry could facilitate such meetings but arrangements for such meetings had to comply with the Code.

The Appeal Board considered that the meeting was educational. It noted the detailed comments made by the consultant in this regard. The purpose of the meeting was to discuss patient types seen within the area for whom esomeprazole might be a suitable therapeutic option. New data was presented and acid control in patients with GORD was discussed. The chairman was interested in using esomeprazole and wished to achieve a consensus view on whether other colleagues might also be interested. The issue of Nexium being on the formulary was also discussed. The Appeal Board considered that the hospitality was secondary to the main purpose of the meeting and the costs, at £38 per head, were not unreasonable. The Appeal Board therefore ruled no breach of Clause 19.1 of the Code. The appeal on this point was successful.

The Appeal Board noted that the meeting had been convened at the suggestion of the chairman to provide a forum for discussion. The attendees were senior hospital doctors. The Appeal Board was concerned about the wording of the invitation. In particular it was concerned that the invitation referred to Nexium 'at a favourable price' and by the poor impression given by the statement that AstraZeneca would sponsor a meal. In addition the invitation did not appear to reflect what would be presented or discussed at the meeting. The Appeal Board noted that the consultant had dictated the letter of invitation but that given the representative's involvement with the meeting, AstraZeneca was responsible for its content. In such circumstances it was important that representatives were aware of the need to protect their companies from possible breaches of the Code. The Appeal Board considered that it would have been helpful if a formal agenda had been produced. The use of hospital paper by the representative was also of concern. This gave the meeting more of an independent appearance than would have been the case if the invitation had been sent on company notepaper. The company representative had sent the letter, provided hospitality at the meeting and given administrative support.

The Appeal Board decided that the representative had failed to maintain a high standard and upheld the Panel's ruling of a breach of Clause 15.2 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted its ruling that there had been no breach of Clause 19.1. The Appeal Board did not consider that the company had failed to maintain a high standard. No breach of Clause 9.1 of the Code was ruled. The appeal on this point was successful.

* * * * *

During the consideration of this case the Appeal Board considered that it appeared from the presentation at the appeal hearing that the representative had not followed company procedure as the invitation had not been checked by the company. The Appeal Board referred to the Guidelines on Company Procedures relating to the Code of Practice printed in the back of the Code of Practice booklet. These advised that procedures should be in place to ensure that all meetings which were planned were checked to see that they complied with the Code.

The Appeal Board considered that it was important for companies to document arrangements for meetings and they would be well advised to produce formal agendas for all meetings.

Complaint received **9 March 2001**

Case completed **9 October 2001**

CASE AUTH/1169/3/01

SERVIER LABORATORIES/DIRECTOR v GLAXOSMITHKLINE

Breach of undertaking

Servier Laboratories alleged that an advertisement for Avandia (rosiglitazone) issued by SmithKline Beecham Pharmaceuticals was in breach of the undertaking given in relation to Case AUTH/1084/10/00. The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

Servier noted that in Case AUTH/1084/10/00 the Panel had considered that 'the journal advertisement failed to make it clear that the product was indicated for use as an add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the advertisement was that Avandia could be used in any patient with type 2 diabetes'. The Panel had ruled that this was misleading and in breach of Clause 7.2 of the Code. Servier noted that three amendments had been made to the advertisement: the visual had changed; the headline had changed; and a flash had been added to the corner with the statement 'NICE has recommended the use of Avandia in combination with oral monotherapy (metformin or sulphonylurea) for specific groups of patients with type 2 diabetes'. In Servier's view, this did not address the concerns 'of patients inadequately controlled on maximal doses' and notes of this kind could not be used to correct the overall misleading impression of the advertisement.

The Panel noted that following its ruling in Case AUTH/1084/10/00, GlaxoSmithKline had amended its advertising. It was a question of whether the amendment was sufficient with regard to the ruling in the previous case.

The background colour of the new advertisement was pink. In the top right-hand corner was the quote 'I think we can now move forward in type 2 diabetes with every confidence'. In the top left-hand corner, in a yellow triangular flash, was the statement that 'NICE has recommended the use of Avandia in combination with oral monotherapy (metformin or sulphonylurea) for specific groups of patients with type 2 diabetes'.

Avandia was licensed for oral combination treatment of type 2 diabetes in patients with insufficient glycaemic control despite maximal tolerated dose of either metformin or sulphonylurea, in combination with metformin in obese patients, in combination with a sulphonylurea in patients who were intolerant to or in whom metformin was contraindicated. The Panel considered that the licensed indications had not been made clear. The prominent unqualified claim 'I think we can now move forward in type 2 diabetes with every confidence' was inadequate given the restrictions on the use of Avandia. The overall impression was that Avandia could be used in any patient with type 2 diabetes but that NICE only recommended its use in certain patients.

The material at issue in this case was not the same as the material at issue in the previous case. The Panel considered that nonetheless GlaxoSmithKline had failed to comply with the undertaking given in the previous case. A breach of Clause 21 of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board noted the company's submission that there was a difference between the NICE guidance and the product's licensed indication. The Appeal Board considered that despite the addition of the brief reference to the NICE guidance, the advertisement did not sufficiently qualify or explain the product's licensed indication. It appeared that the NICE guidance had been used as a further endorsement of the product and not as a way of alerting prescribers to the restrictions on its use. No attempt had been made to identify the group of patients for whom Avandia was licensed and thus GlaxoSmithKline had failed to comply with the undertaking given in the previous case. The breach of Clause 21 was upheld.

The Appeal Board was concerned that the amendments to the advertisement were such that they exacerbated the points which gave rise to the previous ruling in Case AUTH/1084/10/00. The company appeared to have disregarded the previous ruling which had required it to make it clear that the product was not licensed for use in all patients with type 2 diabetes; the company had instead referred to the NICE recommendations which were not wholly consistent with the licensed indications. The Appeal Board considered that this was a serious matter. The conduct of the company was such that the Appeal Board decided to report the company to the ABPI Board of Management.

The ABPI Board felt that although GlaxoSmithKline had made some changes to its advertising, the reaction had been superficial and had not addressed the needs of the ruling. In these circumstances the Board felt it appropriate to express its concern by issuing a reprimand to the company with subsequent publication in the Code of Practice Review.

Servier Laboratories Ltd complained about an advertisement (ref 10/00:AVAD00129f) for Avandia (rosiglitazone) which had been placed by SmithKline Beecham Pharmaceuticals in Doctor on 15 March. Servier alleged that the advertisement was in breach of the undertaking given in relation to Case AUTH/1084/10/00.

The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

COMPLAINT

Servier Laboratories noted that in Case AUTH/1084/10/00 the Panel had considered that 'the journal advertisement failed to make it clear that the product was indicated for use as an add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the advertisement was that Avandia could be used in any patient with type 2 diabetes'. The Panel had considered that this was misleading and in breach of Clause 7.2 of the Code.

Servier noted that three amendments had been made to the advertisement: the visual had changed; the headline had changed; and a flash had been added to the corner with the statement 'NICE has recommended the use of Avandia in combination with oral monotherapy (metformin or sulphonylurea) for specific groups of patients with type 2 diabetes'.

In Servier's view, this did not address the concerns 'of patients inadequately controlled on maximal doses' and, in any case, notes of this kind could not be used to correct the overall misleading impression of the advertisement.

RESPONSE

GlaxoSmithKline noted that Servier referred to three amendments made to the advertisement in question. The first two changes (of visual and headline) were unrelated to the original upheld complaint (Case AUTH/1084/10/00). The third amendment was made in response to the finding of the Panel that the original journal advertisement failed to make it clear that the product was indicated for use as add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea.

The amendment in question consisted of a triangular flash, measuring approximately 13 x 11.5 x 5.5cm on a page of approximately 39.5 x 28cm, and thus representing some 2% of the area of the page as a whole. The background colour of the flash was an eye-catching yellow, and it contained the following text: 'NICE has recommended the use of AVANDIA [in approximately 14 point type] in combination with oral monotherapy (metformin or sulphonylurea) for specific groups of patients with type 2 diabetes' [in approximately 10 point type]. The statement was referenced to the NICE Technology Appraisal Guidance Number 9.

GlaxoSmithKline believed that this amendment fully complied with the Panel's ruling on this issue by clearly and prominently indicating that Avandia was not licensed for use in *any* patient with type 2 diabetes, the substance of Servier's original complaint. Servier did not dispute – at least as far as the indicated patient population was concerned – the accuracy of the three major straplines included in the advertisement ('fighting insulin resistance'; 'defending beta-cells'; 'sustaining control'), and these straplines, taken in conjunction with the prominent reference to the NICE ruling and the prescribing information, could not, in GlaxoSmithKline's opinion, be considered to be in any way misleading.

The indications for Avandia as stated in the summary of product characteristics (SPC)were as follows:

'Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea: in combination with metformin only with obese patients; in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.'

Likewise, the NICE Technology Appraisal Guidance No.9 stated:

'1.1 Rosiglitazone is effective at reducing blood glucose when added to oral monotherapy (metformin or sulphonylurea) for patients who have inadequate control of blood glucose on these conventional agents alone.

1.2 Patients with inadequate blood glucose control on oral monotherapy (metformin or sulphonylurea) should first be offered metformin and sulphonylurea combination therapy, unless there are contraindications or tolerability problems.

1.3 Patients who are unable to take metformin and sulphonylurea combination therapy, and patients whose blood glucose remains high despite adequate trial of this treatment, should be offered rosiglitazone combination therapy as an alternative to injected insulin.

1.4 The combination of rosiglitazone plus metformin is preferred to rosiglitazone plus sulphonylurea, particularly for obese patients. Rosiglitazone plus sulphonylurea may be offered to patients who show intolerance to metformin or for whom metformin is contraindicated.'

GlaxoSmithKline believed that it would be both impractical and unreasonable to require such complex guidelines to be included as part of the strapline(s) of an advertisement; nor was there any requirement in the Code that every nuance of the SPC or NICE guidance be included in the main body. The primary requirement was that the advertisement as a whole should not be misleading. GlaxoSmithKline contended that the prominence of the yellow flash (which could not be considered to be a footnote), drawing attention to the fact that Avandia was only currently recommended for specific groups of patients, was fully in compliance with this requirement.

GlaxoSmithKline therefore maintained that this advertisement was not in breach of Clause 7.2 of the Code and nor, inasmuch as it complied with the prior ruling of the Panel, was it in breach of Clause 21.

PANEL RULING

The Panel noted that following its ruling in Case AUTH/1084/10/00, GlaxoSmithKline had amended its advertising. It was a question of whether the amendment was sufficient with regard to the Panel's ruling in the previous case that the journal advertisement failed to make it clear that Avandia was indicated for use as add on therapy for patients

inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the previous advertisement was that Avandia could be used in any patient with type 2 diabetes. The advertisement had been ruled to be misleading in breach of Clause 7.2 of the Code.

Turning to the advertisement now before it, the Panel noted that the background colour of the new advertisement was pink. In the top right-hand corner was the quote 'I think we can now move forward in type 2 diabetes with every confidence'. In the top left-hand corner, in a yellow triangular flash, was the statement that 'NICE has recommended the use of Avandia in combination with oral monotherapy (metformin or sulphonylurea) for specific groups of patients with type 2 diabetes'.

The Panel noted that Avandia was licensed for oral combination treatment of type 2 diabetes in patients with insufficient glycaemic control despite maximal tolerated dose of either metformin or sulphonylurea, in combination with metformin in obese patients, in combination with a sulphonylurea in patients who were intolerant to or in whom metformin was contraindicated. The Panel considered that the licensed indications had not been made clear. The prominent unqualified claim 'I think we can now move forward in type 2 diabetes with every confidence' was inadequate given the restrictions on the use of Avandia. The more detailed information about the NICE recommendation was not sufficient to counter the inadequate claim. The overall impression was that Avandia could be used in any patient with type 2 diabetes but that NICE only recommended its use in certain patients.

The Panel noted that the material at issue in this case was not the same as the material at issue in the previous case. The Panel considered that nonetheless GlaxoSmithKline had failed to comply with the undertaking given in the previous case. A breach of Clause 21 of the Code was ruled. The Panel considered that its ruling of a breach of Clause 21 covered the allegation of a breach of Clause 7.2 of the Code.

The Panel noted that in cases where a breach of undertaking had been ruled a breach of Clause 2 was often ruled. Clause 2 was used as a sign of particular censure and was reserved for such circumstances. The Panel noted that the advertisement had been amended, the amendment had been ruled to be inadequate. The Panel decided that the circumstances did not warrant a ruling of a breach of Clause 2 and no breach was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that the grounds for its appeal rested on three points.

1 There existed many current journal advertisements for products with licence restrictions in which such restrictions were not mentioned in the body of the text of the advertisement, but solely in the prescribing information. The company representative provided examples of such advertisements at the appeal. The company thus contended that it was a common and hitherto accepted practice; and that it would be unreasonable and impractical to include every detail of every SPC restriction in the body of an advertisement, especially where the restrictions themselves were as complex as they were for the glitazones. Alternatively, if the Avandia advertisement was in breach of the Code, it must also be accepted that a significant number of other currently published advertisements were equally in breach.

2 GlaxoSmithKline stated that it maintained that the strapline of the advertisement in question, 'I think we can now move forward in type 2 diabetes with every confidence', did not, in itself, imply that Avandia was therefore suitable for all diabetes patients. The statement was neutral. One could well complete it with the phrase '… given that Avandia is now available for the treatment of diabetic patients who are inadequately controlled on monotherapy and are unsuitable for traditional combination therapy, thus delaying or avoiding the need for treatment with insulin', although such an addition would render the strapline rather unwieldy! The company contended that the overall impression of the advertisement was not necessarily that Avandia might be used in any patient with type 2 diabetes, especially when the prominent yellow flash drawing the reader's attention to the licence restrictions was taken into consideration.

3 GlaxoSmithKline stated that it considered that the addition of the yellow flash was an adequate representation of the Avandia licence restrictions. The NICE recommendations were fully in line with the SPC restrictions for Avandia. The flash explicitly stated that Avandia was recommended only in combination with oral monotherapy, and then only in specific groups of patients. Which groups of patients might be gleaned from the adjacent prescribing information. Again, the company considered that it would be impractical to specify, in the body text of a general advertisement, that Avandia was licensed 'for oral combination treatment of type 2 diabetes in patients with insufficient glycaemic control despite maximal tolerated doses of either metformin or sulphonylurea: in combination with metformin in obese patients; or in combination with a sulphonylurea in patients intolerant to metformin or in whom metformin is contraindicated'. While the company accepted the general principle that the inclusion of prescribing information did not exempt promotional material from complying with other provisions of the Code, it considered that the yellow flash in conjunction with the prescribing information was a sufficient and adequate indication of the licence restrictions for Avandia.

GlaxoSmithKline therefore contended that the advertisement was not in breach of Clause 21 of the Code, inasmuch as the amendments made since the original ruling of a breach of Clause 7.2 were in compliance with the dictates of that original ruling.

At the appeal hearing the representative acknowledged that point 1.4 of the NICE guidance advocated a wider use of rosiglitazone than the SPC. Point 1.4 stated that 'The combination of rosiglitazone plus metformin is preferred to rosiglitazone plus

sulphonylurea, particularly for obese patients. Rosiglitazone plus sulphonylurea may be offered to patients who show intolerance to metformin or for whom metformin is contraindicated'. Conversely the indication for Avandia in the SPC stated that the product was to be given in combination with metformin only in obese patients and that it was to be given in combination with a sulphonylurea only in patients who showed intolerance to metformin or for whom metformin was contraindicated. The first part of point 1.4 of the NICE guidance was thus less emphatic about the use of rosiglitazone and metformin in obese patients than the SPC.

APPEAL BOARD RULING

The Appeal Board noted GlaxoSmithKline's submission that there was a difference between the NICE guidance and the product's licensed indication. The Appeal Board noted that the yellow flash was prominent and the text within was designed to catch the reader's eye. The Appeal Board considered that despite the addition of the brief reference to the NICE guidance, the advertisement did not sufficiently qualify or explain the product's licensed indication. It appeared that the NICE guidance had been used as a further endorsement of the product and not as a way of alerting prescribers to the restrictions on its use. The Appeal Board considered that no attempt had been made to identify the group of patients for whom Avandia was licensed and thus GlaxoSmithKline had failed to comply with the undertaking given in the previous case. The Panel's ruling of a breach of Clause 21 was upheld. The appeal was unsuccessful.

The Appeal Board was further concerned that the amendments to the advertisement at issue were such that they exacerbated the points which gave rise to the previous ruling in Case AUTH/1084/10/00. The Appeal Board was concerned that the company appeared to have disregarded the previous ruling which had required it to make it clear that the product was not licensed for use in all patients with type 2 diabetes; the company had instead referred to the NICE recommendations which were not wholly consistent with the licensed indications. The Appeal Board considered that this was a serious matter. The conduct of the company was such that the Appeal Board decided to report the company to the ABPI Board of Management in accordance with Paragraph 11.1 of the Constitution and Procedure for the Authority.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board felt that although GlaxoSmithKline had made some changes to its advertising, the reaction had been superficial and had not addressed the needs of the ruling. In these circumstances the Board felt it appropriate to express its concern by issuing a reprimand to the company with subsequent publication in the Code of Practice Review.

Complaint received	**22 March 2001**
PMCPA proceedings completed	**5 July 2001**
ABPI Board proceedings completed	**11 September 2001**

CASE AUTH/1173/4/01

PAEDIATRICIAN v FERRING

Desmotabs leavepiece

A paediatrician was concerned that a Desmotabs (desmopressin) leavepiece, issued by Ferring, gave a falsely optimistic picture of the success rate (71%) in the treatment of childhood nocturnal enuresis. This figure referred to improvement rather than complete success. No mention was made of the age groups in which desmopressin might be indicated or of alternative treatments. While accepting that 71% might show a reduction in the number of wet nights, total night-time dryness was seen in far fewer.

The Panel noted that Desmotabs were indicated for the treatment of primary nocturnal enuresis in children (from 5 years of age) and adults (up to 65 years of age). A dose of 200mcg should be taken at bedtime and only if needed should the dose be increased to 400mcg. The need for continued treatment should be reassessed after 3 months by means of a period of at least a week without Desmotabs. Desmospray (desmopressin nasal spray) had the same licensed indication although the doses to be given were one tenth of those of Desmotabs ie 20-40mcg.

The front page of the leavepiece featured two photographs of two boys aged about 8 or 9 years. Pages 2 and 3 of the leavepiece related to the use of Desmotabs in children; headlines referred to 'chronic childhood disorders' and a 'child's self-esteem' and pie charts depicting results from Riccabona *et al* and Butler *et al* stated the age of patients included in the studies as 5-19 years and 8-16 years respectively. In the Panel's view it was clear that the leavepiece related to the use of Desmotabs in children aged at least 5, a patient population for which it was indicated. The claim on the front page 'Up to 71% of patients achieve long term dryness' was referenced to a study by Riccabona *et al*. Enuretic children were treated with 20mcg desmopressin spray and titrated to 40mcg (maximum 50mcg) after 2 days if the child had not become dry within 48 hours. The maximum dosage was maintained for at least 4-6 weeks. After 4 weeks of complete dryness the dosage was reduced by 10mcg initially, and after each additional 4 dry weeks, by a further 10mcg; medication was stopped only after 4 dry weeks at 10mcg. Results showed that 71% of children achieved complete dryness with no relapses, remaining dry with no further treatment. The mean duration of therapy was 28 weeks and the mean dose of desmopressin was 30mcg.

Literature reviewed by Moffatt *et al* focussed mainly on short-term efficacy. Results from 18 randomized controlled trials showed that only 24.5% of subjects achieved short-term dryness. One study of desmopressin responders showed that 21% of subjects who had achieved dryness on medication maintained dryness 12 weeks after stopping therapy. A study by Stenberg and Läckgren evaluated the efficacy of long-term oral desmopressin. Results showed that during the first of two 12 week treatment periods 48% of patients were full responders (≤1 wet night/week) and in the second 12 week period 53% were full responders; only 7 (29%) patients were completely dry at the end of the study although 2 years post-treatment 17 (71%) of the 24 patients were completely dry. A study by Uygur *et al* showed that at the end of an initial two-week dose titration period 41 (63%) children were completely dry on 20 or 40mcg desmopressin spray. Complete (totally dry) and partial (1 or 2 wet nights) responders entered a two-week double-blind phase followed by six months of desmopressin treatment. Among 50 patients treated for 6 months 76% achieved total dryness. Overall, during the 6-month period 58% of patients were completely dry.

Overall the Panel did not consider that the literature supported the claim for Desmotabs that 'Up to 71% of patients achieve long term dryness'. The literature contained studies which used either desmopressin oral tablets or nasal spray. The Panel queried whether the route of administration affected response. The large review by Moffatt *et al* showed that desmopressin treatment was successful in a significantly smaller proportion of patients than 71%. Subsequent studies included relatively small numbers of patients (Stenberg and Läckgren and Uygur *et al*) or used dosing schedules and long continued treatment periods not licensed in the UK (Riccabona *et al* and Uygur *et al*). Although the Panel noted that the claim referred to 'Up to 71%' it considered that most readers would assume that the balance of the evidence was such as to suggest that 71% of patients would achieve long-term dryness which was not so. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

Upon appeal by Ferring, the Appeal Board considered most readers would assume that the claim 'Up to 71% of patients achieve long term dryness' meant that they could expect almost three quarters of all of their enuretic patients to achieve long term dryness on Desmotabs. In that context the Appeal Board noted that any percentage success rate claimed should refer to an intention-to-treat population. The figure of 76% of patients reported to be completely dry by Uygur *et al* referred to a sub-group of 50 patients who entered a 6 month period and not to the initial 65 who entered the study. 58.5% of the total patient population achieved complete dryness. Similarly the Hjalmas *et al* paper reported on a subgroup of 242 patients who were entered for up to four blocks of 3 month treatment periods. The intention to treat cohort was 393.

The Appeal Board noted that the study cited in support of the claim, Riccabona et al, used a more aggressive dose titration schedule than that detailed in the Desmospray summary of product characteristics (SPC). Riccabona *et al* increased the dose of desmopressin from 20mcg to 40mcg if a child had not become dry within 48 hours. The SPC stated that only if needed should the dose be increased from 20mcg to 40mcg. Riccabona *et al* also allowed a maximum dose of 50mcg to be used whereas the maximum dose referred to in the SPC

was 40mcg. In addition, medication in the study was only stopped after a patient had been dry for four weeks. The mean duration of therapy was 28 weeks. The SPC, on the other hand, stated that the need for continued treatment should be reassessed after 3 months by means of one week without treatment. The study did not use Desmospray in accordance with its UK SPC and the Appeal Board questioned the applicability of the results to UK practice. Variations in dose titration, maximum dose and length of treatment might affect efficacy.

The Appeal Board noted that primary nocturnal enuresis spontaneously resolved in many patients, particularly children, over time. At the appeal hearing the representatives had referred to a figure of 15%. Long-term studies were thus performed against the background of a shifting baseline and it was difficult to determine whether a patient became dry because of desmopressin therapy or because of spontaneous resolution of their condition. Overall the Appeal Board did not consider that the balance of the evidence was such as to support the claim 'Up to 71% of patients achieve long term dryness'. The claim was referenced to a study in which desmopressin was not used according to the UK SPC. The Appeal Board considered that the claim was misleading and could not be substantiated. The Panel's ruling of breaches of the Code was upheld.

A paediatrician complained about a leavepiece (ref E/166/07/00) for Desmotabs (desmopressin) issued by Ferring Pharmaceuticals Ltd. The front cover of the leavepiece featured the claim 'Up to 71% of patients achieve long term dryness'. The claim was referenced to Riccabona *et al* (1998).

COMPLAINT

The complainant stated that as a community paediatrician working in the field of childhood continence she had come to value the appropriate use of desmopressin in the treatment of childhood nocturnal enuresis. She was concerned that recent advertising by Ferring gave a falsely optimistic picture of the success rate (71%) when used for the treatment of nocturnal enuresis. This figure referred to improvement rather than complete success. No mention was made in the literature of the age groups in which desmopressin might be indicated or of alternative treatments.

Nocturnal enuresis was a common developmental feature in many children, more prevalent in boys. The complainant, and many others, considered that the first line of treatment should be an enuresis alarm used from seven years of age. Surveys suggested that between 70% and 75% of children achieved dryness in five to twelve weeks (Doleys 1977, Forsyth and Butler 1989). In the under sevens behavioural methods alone could be of great help. In this younger age group medication should be reserved for exceptional cases where social circumstances and/or parental intolerance made a trial of medication appropriate.

Desmopressin clearly had a place in treatment of the older child when alarm use had failed. In the complainant's experience, the 71% success rate claimed was to be questioned. While accepting that this number might show a reduction in the number of wet nights, total night-time dryness was seen in far fewer (24.5%, Moffatt *et al* 1993). Having criticised Ferring's advertising the complainant had to reassert that she used desmopressin widely, both alone and in combination with other treatments. She considered it a very safe medication to use and felt that it had an important place in the treatment of enuresis, particularly in the older child.

When writing to Ferring the Authority drew attention to Clauses 7.2 and 7.3 of the Code.

RESPONSE

With regard to the allegation that recent advertising gave a falsely optimistic picture of the success rate (71%), Ferring referred to the study cited in support, Riccabona *et al*. This study investigated 155 children with symptoms of primary nocturnal enuresis (PNE) with a mean age of 8 years with a range of 5-19 years and found that 110 patients (71%) achieved complete dryness with no relapses and remained dry without treatment. The mean duration of therapy for these patients was 7 months, with a minimum of 3 months and a maximum of 2 years.

The complainant incorrectly stated that this figure of 71% was an improvement rate, not complete success, and was therefore misleading. This was not the case because the quoted figure of 71% did refer to patients who were completely dry, which was complete success. The figure for the combined group of partial and full responders quoted in that study was 85%.

This result was not isolated or at odds with other publications where long-term treatment had been studied. Stenberg and Läckgren (1993) investigated the use of oral desmopressin in the treatment of PNE and found that two years post treatment 71% of patients remained completely dry. The dose regime in that study involved a two week dose titration period, following which the patients were treated for two 12 week periods with a two week observation period after each treatment period.

It was important to distinguish between short-term response rates and the success that could be achieved following treatment of longer duration, and this was well illustrated in the review by Moffatt *et al* which was quoted by the complainant. This paper was a review of 18 papers, the vast majority of which discussed the short-term use of desmopressin for the treatment of PNE. The longest study in this review, Rittig *et al* (1989), where the duration of treatment was just over 5 months (161 days) showed that 24/28 (85.7%) patients achieved complete dryness. This supported the benefits of the long-term use of desmopressin.

There were two facets to desmopressin treatment. One was its use for short-term cover; Uygur *et al* (1997) showed that after a two week period of dose titration, 63% of patients became completely dry, this underlined the usefulness of desmopressin for holidays and stays away from home. The second was long-term treatment where, as the evidence outlined above showed, up to 71% of patients could achieve lasting dryness with long-term desmopressin treatment.

With regard to the complainant's view that no mention was made in the literature of the age groups in which desmopressin might be indicated, Ferring stated that both the graphs in the piece showing treatment success rates clearly showed the age range of patients in both studies. In Riccabona *et al* the mean age was 8 years with a range of 5-19 years and in Butler *et al* (1998) the mean age was 11.8 years with a range of 8-16 years.

Desmotabs were licensed for use in children (from 5 years of age) and adults (up to 65 years of age) who had normal urine concentrating ability. This was stated in the prescribing information given on the reverse of the piece.

The chart on the second page showing the prevalence of bedwetting also included only patients in the licensed age range from 5 years of age.

With regard to the failure to mention alternative treatments, Ferring submitted that it was not comparing desmopressin with alarms or behavioural treatments. It was outlining the benefits of long-term treatment with desmopressin.

Ferring noted that the complainant stated that she considered that enuresis alarms should be the first line therapy in children from the age of 7. This was her opinion and might also be the opinion of other doctors. However, Desmotabs and Desmospray were both licensed for the treatment of PNE in children from the age of 5. As would be seen in the summaries of product characteristics (SPCs) these products were not restricted to second line use for their approved indications. The products were indicated for first line therapy in adults and children from the age of 5 years and many doctors prescribed them as such. Desmotabs and Desmospray had an important advantage over alarms for many patients in that they could have an immediate effect and might be more suitable where there were conditions making alarm use difficult, such as room sharing or parental intolerance. Alarms were not recommended for children under 7 years of age.

Ferring confirmed that the leavepiece would be given to doctors after the representative had detailed Desmotabs. Copies would also have been made available on Ferring Desmotabs stands at various conferences and meetings.

PANEL RULING

The Panel noted that Desmotabs were indicated for the treatment of PNE in children (from 5 years of age) and adults (up to 65 years of age) with normal urine concentrating ability. A dose of 200mcg should be taken at bedtime and only if needed should the dose be increased to 400mcg. The need for continued treatment should be reassessed after 3 months by means of a period of at least a week without Desmotabs. Desmospray (desmopressin nasal spray) had the same licensed indication although the doses to be given were one tenth of those of Desmotabs ie 20-40mcg.

The front page of the leavepiece featured two photographs of two boys aged about 8 or 9 years. Pages 2 and 3 of the leavepiece related to the use of Desmotabs in children; headlines referred to 'chronic childhood disorders' and a 'child's self-esteem' and pie charts depicting results from Riccabona *et al* and Butler *et al* stated the age of patients included in the studies, 5-19 years and 8-16 years respectively. In the Panel's view it was clear that the leavepiece related to the use of Desmotabs in children aged at least 5, a patient population for which it was indicated.

The claim on the front page 'Up to 71% of patients achieve long term dryness' was referenced to a study by Riccabona *et al*. Enuretic children (n=155) were treated with 20mcg desmopressin spray and titrated to 40mcg (maximum 50mcg) after 2 days if the child had not become dry within 48 hours. The maximum dosage was maintained for at least 4-6 weeks. After 4 weeks of complete dryness the dosage was reduced by 10mcg initially, and after each additional 4 dry weeks, by a further 10mcg; medication was stopped only after 4 dry weeks at 10mcg. Results showed that 71% of children achieved complete dryness with no relapses, remaining dry with no further treatment. The mean duration of therapy was 28 weeks and the mean dose of desmopressin was 30mcg.

The literature reviewed by Moffatt *et al* focussed mainly on short-term efficacy. Results from 18 randomized controlled trials (n=689) showed that only 24.5% of subjects achieved short-term dryness. One study of desmopressin responders showed that 21% of subjects, who had achieved dryness on medication, maintained dryness 12 weeks after stopping therapy.

The study by Stenberg and Läckgren evaluated the efficacy of long-term oral desmopressin (n=24). Results showed that during the first of two 12 week treatment periods 48% of patients were full responders (≤ 1 wet night/week) and in the second 12 week period 53% were full responders; only 7 (29%) patients were completely dry at the end of the study although 2 years post-treatment 17 (71%) of the 24 patients were completely dry.

The study by Uygur *et al* showed that at the end of an initial two-week dose titration period 41 (63%) children were completely dry on 20 or 40mcg desmopressin spray. Complete (totally dry) and partial (1 or 2 wet nights) responders entered a two-week double-blind phase followed by six months of desmopressin treatment. Among 50 patients treated for 6 months 76% achieved total dryness. Overall, during the 6-month period 58% of patients were completely dry.

Overall the Panel did not consider that the literature supported the claim for Desmotabs that 'Up to 71% of patients achieve long term dryness'. The literature contained studies which used either desmopressin oral tablets or nasal spray. The Panel queried whether the route of administration affected response. The large review by Moffatt *et al* showed that desmopressin treatment was successful in a significantly smaller proportion of patients than 71%. Subsequent studies included relatively small numbers of patients (Stenberg and Läckgren and Uygur *et al*) or used dosing schedules and long continued treatment periods not licensed in the UK (Riccabona *et al* and Uygur *et al*). Although the Panel noted that the claim

referred to 'Up to 71%' it considered that most readers would assume that the balance of the evidence was such as to suggest that 71% of patients would achieve long-term dryness which was not so. The Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

APPEAL BY FERRING

Ferring stated that the key point to consider in this case was what level of efficacy could be substantiated for the treatment of primary nocturnal enuresis with Desmotabs following long-term treatment as opposed to short-term treatment. The company did not dispute the complainant's contention that using short-term treatment, as studied in the majority of the papers reviewed by Moffat *et al*, one would not expect 71% of patients to achieve total dryness. However, Ferring emphasised that it was not making claims on the benefits of short-term treatment in the leavepiece. Following treatment with Desmotabs in clinical trials of at least six months' duration, the number of patients achieving dryness dramatically increased and this was the basis of the claims in the leavepiece, which the company firmly believed could be fully substantiated.

Ferring stated that the leavepiece clearly related to the benefits that could be expected from long-term treatment with Desmotabs. The heading for the pie charts on page 3 was '% dry after long-term desmopressin treatment' and the pie charts were each labelled with the treatment periods applicable to each study ('Mean treatment period – 7 months' and 'Treatment period – 6 months'). The dosing schedule below the pie charts also reflected long-term treatment, including the three monthly drug free assessment week, which was used to check if patients who were dry on treatment still needed to continue with Desmotabs or whether they had achieved permanent dryness.

Within the patient population treated with Desmotabs for primary nocturnal enuresis, there would be a number of distinct groups; non responders, partial responders who had improved on treatment, but not achieved full dryness, responders who had achieved full dryness whilst on treatment, but relapsed when treatment was withdrawn, and responders who had achieved full dryness whilst on treatment and remained dry when treatment was withdrawn.

The claim that 'Up to 71% of patients achieve long term dryness' was based on the number of responders achieving full dryness in clinical trials of at least six months' duration, whether on or off treatment. This percentage therefore included patients who remained dry without the need for further treatment and those who still needed to take Desmotabs to remain dry, because they reverted to wetting the bed when treatment was stopped.

There were two aims in treating primary nocturnal enuresis. The short-term aim was to provide immediate relief from the symptoms to allow the patient to stay away overnight or to go on holiday. The immediate effects of Desmotabs were reflected in the rates of total dryness reported in the review by Moffat *et al*, as described by the Panel in its ruling. Moffat did not report the proportion of partial responders in the studies that were reviewed. It should also be noted that no meta-analysis was possible for the studies reviewed because of insufficient information on patient selection criteria, so only qualitative information was presented.

Ferring stated that the second aim in treating primary nocturnal enuresis was to achieve long-term dryness and this was the approach that the company was promoting in this leavepiece. The proportion of patients achieving this goal could be improved through long-term treatment with Desmotabs and in some cases this would necessitate prolonged use of Desmotabs to maintain dryness. This was because the condition did not resolve in a small proportion of patients; indeed, it was believed that approximately 1% of adults regularly continued to wet the bed. A number of long-term studies reported results that were entirely consistent with the claim that 71% of patients could achieve long-term dryness and Ferring considered the figure to be fully representative of published clinical trials studying the long-term efficacy of desmopressin. Some of these publications were discussed below.

Ferring noted that in its ruling, the Panel raised several concerns.

1 Whether the route of administration affected the response

The basis on which oral formulations of desmopressin were licensed was on the equivalence of response in patients and there were no clinically relevant differences in efficacy reported between nasal and oral administration. Fjellstad-Paulsen *et al* (1987) found that 20mcg intranasally was as effective as 200mcg orally in the treatment of primary nocturnal enuresis. Another study, Janknegt *et al* (1997), in patients who had previously responded to intranasal desmopressin, showed no significant difference in efficacy for 20mcg desmopressin administered intranasally and 200 or 400mcg oral desmopressin.

The intranasal and oral routes of administration were therefore considered to be equivalent. The use of oral desmopressin predominated because many patients preferred to take a tablet than use a nasal spray.

2 The large review by Moffat *et al* showed that desmopressin treatment was successful in a significantly smaller proportion of patients than 71%

Ferring noted that the complainant had referred to a 1993 review paper by Moffat *et al*, which showed that desmopressin treatment was successful in a significantly smaller proportion of patients than 71%.

The paper by Moffat *et al* was a review of 18 studies the latest of which was published in 1990. 17 of the 18 trials reviewed were concerned only with short-term use (range of duration of treatment was 2 to 12 weeks). In these studies, where the data allowed, the percentage of patients achieving total dryness was in the range of 10.3% to 58.3%. This appeared to be in line with the known initial rate of response to

desmopressin. In the review of all 18 studies Moffat quoted an average of 24.5% of patients becoming totally dry. This proportion was still greater than the expected annual spontaneous remission rate of 15%. The variation of response rates within these publications probably reflected different patient inclusion and selection criteria, and for this reason, a meta-analysis was considered to be inappropriate.

There was just a single study investigating longer-term use reviewed by Moffat *et al* (Rittig *et al*). This was a trial where the duration of treatment with intranasal desmopressin was up to 161 days (23 weeks) in 34 patients. In the initial titration period of this study, 6 non responders were identified and excluded from the long-term treatment period, during which 24/34 became totally dry whilst on therapy (70% of the initial population of 34 patients). 6 (21%) of these patients remained dry off treatment. These results were in extremely close agreement with the 71% reported in the Riccabona study quoted in the leavepiece.

In the conclusions of his review, Moffat stated that the literature focused on short-term efficacy, and that the true role of desmopressin would be known when more comparisons with other treatments were conducted focusing on long-term outcomes.

3 Subsequent studies included relatively small numbers of patients (Stenberg and Lackgren and Uygur *et al*) or used dosing schedules and long continued treatment periods not licensed in the UK (Riccabona *et al* and Uygur *et al*)

In a later paper, from 1997, Moffat stated that evidence on long-term use was accumulating and he referred to a study by Hjalmas *et al* (1995). In this study 242 patients were treated for up to a year with desmopressin with three-month treatment periods separated by a week off therapy, which was consistent with the current SPC for Desmotabs. If the patient had one wet night during this week they began another three-month period. This was repeated twice more if necessary equating to a maximum of 4 three-month periods of treatment followed by a week off treatment. If a patient was not 100% dry after a year they were randomised to either abrupt withdrawal or a tapered dose reduction. 31% of the patients were dry in one of the four week periods off therapy and stopped treatment. 7% of the patients became dry in time when they were randomised to either abrupt withdrawal or a tapered dose period. 31% of the patients who were never dry had a >90% reduction in the number of wet nights whilst receiving medication.

These results showed that 38% of the patients achieved total dryness off treatment. A further 31% achieved a full response whilst on treatment. This was defined as a reduction in the number of wet nights of more than 90% over baseline and represented patients who wet the bed 0, 1 or 2 nights in 28, depending on the severity of their initial symptoms. By this criterion, a patient who initially wet the bed every night could wet the bed no more than 2/28 nights to achieve a reduction of >90% and could therefore be considered to be effectively dry in comparison to their initial symptoms. Ferring noted that this study was substantially larger than any single study within the earlier review by Moffat *et al*, discussed above.

Uygur *et al* (1997) in a study of 65 subjects found that after the initial dose titration period the percentage of patients totally dry whilst treated with desmopressin was 63%. This underlined the usefulness of desmopressin for holidays and stays away from home. 50 children then entered a 6 month period. During this period 38 of the 50 patients (76%) were completely dry. After the six months were completed the 50 patients were observed for 14 further nights off treatment. During this time 25 of the 50 patients (50%) remained totally dry. The Panel had noted that six months' continuous treatment as used in this study was not licensed in the UK. The SPC stated that the need for continued treatment should be reassessed after 3 months by means of a treatment free period of one week. If bedwetting recurred during this period, desmopressin could be used again. There was no other requirement for reinstating treatment and there was no restriction within the SPC regarding the total length of treatment, in segments of three months. There was no evidence that the omission of the one-week treatment free period in this study affected the results.

Lackgren *et al* (1998) investigated oral desmopressin in the treatment of severe nocturnal enuresis in 25 subjects. Patients were treated for two 12-week periods with a 2 week observation period after each period. During the two treatment periods, 48% and 53% of patients were completely dry and in the final observation period, 35% were completely dry off treatment. In long-term follow up after the study, it was found that 7 of the patients had continued with long-term desmopressin and 6 of these became dry. Within 2 years, 15/25 (60%) patients were dry off treatment.

Riccabona *et al* (1998) using long-term intranasal desmopressin and a withdrawal schedule showed that 71% of 155 patients achieved complete dryness without relapse after a mean duration of treatment of 28 weeks. The dosing schedule allowed doses of up to 50mcg, which was outside the range of 20 - 40mcg approved for Desmospray although the average dose was 30mcg, which was within the licensed range. During the long-term treatment, the dose was titrated downwards in 10mcg increments when the patient had maintained dryness for 4 weeks so that the highest dose was not important in the eventual efficacy results. It should be noted that this study was also substantially larger than any single study within the earlier review by Moffat *et al*, which was discussed above.

Stenberg and Lackgren treated 24 patients with Desmotabs for two twelve week periods separated by a two week observation period. In the two twelve week periods 48% and then 53% of the patients were full responders, no more than 1 wet night per week. At the end of the study 38% of patients remained having 1 or less wet episodes per week. A follow up 2 years after the end of treatment showed 17 patients were dry (71%). Although this was a small study, it showed good agreement with the results of Riccabona *et al* and confirmed the equivalent efficacy of oral and intranasal desmopressin.

In conclusion, Ferring stated that the claim 'Up to 71% of patients achieve long term dryness' could be fully substantiated. The company had demonstrated the equivalence of intranasal and oral desmopressin and showed that published long-term clinical trials were in close agreement with the figure of 71% of full responders, who became dry either on or off treatment. The two studies by Hjalmas *et al* and Riccabona *et al* were substantially larger than any of the earlier studies reviewed by Moffat *et al*, of which 17 of 18 studies involved only short-term treatment. The single long-term study by Rittig *et al*, which was included in the review by Moffat, also agreed with the claim, reporting 70% of patients achieving total dryness. There was no evidence that small deviations from the dosing schedules within the UK could have materially affected the results of the studies by Riccabona *et al* or Uygur *et al* or their applicability to clinical practice within the UK.

The leavepiece was clear that the claim related to long-term treatment and was therefore not misleading in the light of the publications discussed above which fully substantiated the claim. In four of the six published long-term trials lasting six months or more 71% or more of patients achieved long term dryness using the optimum dose.

APPEAL BOARD RULING

The Appeal Board considered most readers would assume that the claim 'Up to 71% of patients achieve long term dryness' meant that they could expect almost three quarters of all of their enuretic patients to achieve long term dryness on Desmotabs. In that context the Appeal Board noted that any percentage success rate claimed should refer to an intention-to-treat population. The figure of 76% of patients reported to be completely dry by Uygur *et al* referred to a sub-group of 50 patients who entered a 6 month period and not to the initial 65 who entered the study. 58.5% of the total patient population achieved complete dryness. Similarly the Hjalmas *et al* paper reported on a subgroup of 242 patients who were entered for up to four blocks of 3 month treatment periods. The intention to treat cohort was 393.

The Appeal Board noted that the study cited in support of the claim, Riccabona *et al*, used a more aggressive dose titration schedule than that detailed in the Desmospray SPC. Riccabona *et al* increased the dose of desmopressin from 20mcg to 40mcg if a child had not become dry within 48 hours. The SPC stated that only if needed should the dose be increased from 20mcg to 40mcg. Riccabona *et al* also allowed a maximum dose of 50mcg to be used whereas the maximum dose referred to in the SPC was 40mcg. In addition, medication in the study was only stopped after a patient had been dry for four weeks. The mean duration of therapy was 28 weeks. The SPC, on the other hand, stated that the need for continued treatment should be reassessed after 3 months by means of one week without treatment. The study, therefore, did not use Desmospray in accordance with its UK SPC and the Appeal Board questioned the applicability of the results to UK practice. Variations in dose titration, maximum dose and length of treatment might affect efficacy.

The Appeal Board noted that the natural history of primary nocturnal enuresis was such that the condition spontaneously resolved in many patients, particularly children, over time. At the appeal hearing the representatives had referred to a figure of 15%. The Appeal Board noted that long-term studies were thus performed against the background of a shifting baseline and it was difficult to determine whether a patient became dry because of desmopressin therapy or because of spontaneous resolution of their condition.

Overall the Appeal Board did not consider that the balance of the evidence was such as to support the claim 'Up to 71% of patients achieve long term dryness'. The claim was referenced to a study in which desmopressin was not used according to the UK SPC. The Appeal Board considered that the claim was misleading and could not be substantiated. The Panel's ruling of breaches of Clauses 7.2 and 7.3 was upheld. The appeal was unsuccessful.

During its consideration of this appeal, the Appeal Board noted that page three of the leavepiece contained the headline 'Nothing Works Faster to Keep Them Dry'. The Appeal Board considered that this was ambiguous and could be taken to mean that no treatment at all worked faster than desmopressin. The Appeal Board requested that Ferring's attention be drawn to its concerns.

Beneath the headline was the heading '% Dry after long term desmopressin treatment' and beneath this were two pie charts, one depicting the results from Riccabona *et al* and the other depicting the results from a study by Butler *et al* (1998). Just over half of the Butler *et al* pie chart was shaded blue with the figure 54.8% written in it. The Appeal Board noted, however, that the study by Butler *et al* was a structured withdrawal programme. Each night children either took medication (desmopressin or imipramine) or used an enuresis alarm according to a pre-determined schedule. The study was thus not a simple evaluation of the efficacy of desmopressin. The impression given by the leavepiece, however, was that the 54.8% success rate reported was due to treatment with desmopressin alone, which was not so. The Appeal Board requested that Ferring be advised of its concerns in this regard.

Complaint received **4 April 2001**

Case completed **10 August 2001**

CASE AUTH/1179/4/01

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Seroxat mailing

A general practitioner complained about a Seroxat (paroxetine) mailing sent by SmithKline Beecham. The first page read 'For those that feel an extra 2p a day is far too much for all that 'Seroxat' has to offer …'. The phrase '… here's a little something to tide you over' appeared on page two around a two pence coin which was stuck to the mailing.

The complainant found the mailing very offensive and demoralising. He was continually being pressed to reduce his costs and alleged that the advertisement offended doctors who were trying hard to deliver a quality of service on a budget. The crude way in which money was being offered was very insulting and the complainant asked whether he could take this as some sort of reason to see a SmithKline Beecham representative. The complainant worked very hard to manage all his patients, using his knowledge of both their medical and social circumstances. He had tried various treatments in his patients who suffered from depression and, in his experience and that of colleagues, they did not all work every time in every patient. To suggest that 'Seroxat is a logical choice for first time success with new patients' was incorrect according to the clinical experience of himself and his colleagues.

The Panel considered that the claim 'For those that feel an extra 2p a day is far too much for all that 'Seroxat' has to offer … here's a little something to tide you over', together with an actual two pence coin, denigrated prescribing decisions. The mailing was likely to cause offence and failed to maintain high standards. A breach of the Code was ruled as acknowledged by GlaxoSmithKline. The Panel did not consider that the provision of a two pence coin would amount to an inducement to prescribe, supply, administer or buy Seroxat and nor would it be seen as an inducement to gain an interview or as a fee for an interview. No breach of the Code was ruled in this respect.

The claim 'Seroxat is a logical choice for first time success with new patients' appeared as the final claim on a page listing Seroxat's licensed indications above four bullet points which discussed efficacy, speed of action, safety profile and cost. The Panel noted the submission that the claim was based on extensive clinical studies and more than 70 million patient treatments worldwide which had established Seroxat as an effective and generally well-tolerated treatment. The claim did not state that Seroxat was the logical choice, but merely a choice, thereby implying that other choices were available. The Panel did not consider the claim unacceptable in this regard. The complainant's view was that the medications did not all work every time in every patient. One interpretation of the claim was that Seroxat was one of a group of medicines that would always work first time in every new patient; it could also be interpreted as recommending Seroxat as a first line treatment. On balance the Panel considered that the claim was misleading as it was not clear what was meant and it could be interpreted as a claim for 100% success with Seroxat in new patients. A breach of the Code was ruled which was appealed by GlaxoSmithKline.

The Appeal Board considered that the meaning of the claim was unclear. It might be interpreted as referring to a reasonable chance of success of first line treatment in new patients. Equally it might be read as stating or implying that treatment with Seroxat was successful in every new patient. Whilst the Appeal Board noted that the audience would not expect a medicine to have a 100% success rate, it considered that to state or imply such a success rate in promotional material was unacceptable. The Appeal Board further considered that the claim would not be read in isolation but would be considered within the context of the page as a whole. Immediately beneath the claim, at the bottom of the page, was the product logo with the strapline 'Make a difference that everybody notices'. The Appeal Board considered that the layout of the page was such that the claim, which appeared in an emboldened red type face, would be inextricably linked to the strapline, which was in red italics. The Appeal Board considered that the strapline compounded the misleading impression given by the claim at issue. The Appeal Board upheld the Panel's ruling of a breach of the Code.

A general practitioner complained about a four page Seroxat (paroxetine) mailing (ref ST:ML0002) sent by SmithKline Beecham Pharmaceuticals.

The first page read 'For those that feel an extra 2p a day is far too much for all that 'Seroxat' has to offer …'. The phrase '… here's a little something to tide you over' appeared on page two around a two pence coin which was stuck to the mailing.

COMPLAINT

The complainant found the mailing very offensive and demoralising. He was continually being pressed to reduce his costs and alleged that the advertisement offended doctors who were trying hard to deliver a quality of service on a budget. The complainant stated that it was very insulting in the crude way in which money was being offered, and asked whether he could take this as some sort of reason to see a representative from this particular company.

The complainant worked very hard to manage all his patients using his knowledge of the patient's circumstances, both medical and social, before deciding to treat their particular illness. He had tried various treatments in his patients who suffered from depression and, in his experience and that of colleagues, the medications did not all work every time in every patient. To suggest, as this item did that, 'Seroxat is a logical choice for first time success with new patients' was incorrect according to the clinical experience of himself and a number of his colleagues.

When writing to GlaxoSmithKline the Authority drew attention to Clauses 2, 7.2, 9.1 and 15.3 of the Code.

RESPONSE

GlaxoSmithKline regretted that the complainant was distressed by this mailing, finding it 'offensive and demoralising'. It was in no way its intention to cause offence and GlaxoSmithKline now realised that the wording of this piece was open to misinterpretation. It fully recognised the professional standing of the complainant and wished to reassure him that its aim was to maintain high standards of all materials and activities as recognition of the special nature of medicines and prescribers. GlaxoSmithKline apologised to the complainant for the offence that was caused and accepted that a breach of Clause 9.1 of the Code had occurred.

GlaxoSmithKline fully acknowledged the financial pressures upon doctors when managing patients and it was the intent of the mailing to highlight this issue. The issue of antidepressant cost had always been present and was raised in 1999 with a series of promotions referring to financial differences in the prescribing of selective serotonin reuptake inhibitors. It was this line of promotion that led to this mailing. Although the method of highlighting this issue was direct, it was an accurate and objective representation of the monetary differences between a citalopram 20mg tablet (57 pence) and a Seroxat 20mg tablet (59 pence) based on MIMS Dec 2000. The mailing highlighted the wide breadth of licensed indications for which Seroxat was prescribed, including depressive illness, panic disorder, obsessive compulsive disorder, social phobia and most recently post traumatic stress disorder. Conversely, the licensed indications for citalopram were more limited and included only depressive illness and panic disorder. This wider range of indications for Seroxat was put forward as a justification for the small cost difference when compared to citalopram.

The complainant also suggested that the offer of 2p might be viewed as an inducement to gain an interview. The inappropriate wording for the professional recipients was in no way meant to be a reflection upon the readers of this mailing and the intent of the two pence coin was to physically highlight the financial difference in the prescribing of Seroxat to citalopram. GlaxoSmithKline did not believe that 2p could be seen as an inducement to prescribe Seroxat and therefore did not consider that a breach of Clause 18.1 of the Code had occurred. This direct approach of attaching a two pence coin to the mailing in order to highlight the difference between prescription costs of Seroxat and citalopram, was not intended, nor did GlaxoSmithKline believe it could be interpreted as, payment to the reader to gain an interview. While it appreciated that the wording was not ideal, it did not believe that there had been a breach of Clause 15.3 of the Code.

GlaxoSmithKline stated that the claim 'Seroxat is a logical choice for first time success with new patients' was placed at the end of the mailing as a summary statement relating to the information presented above it. This statement represented the wide spectrum of disorders in which Seroxat was licensed for use along with its established safety profile and rapid onset of action. It in no way instructed the reader that Seroxat was the only medicine of choice for first time success with new patients, but merely that after assessment of the current information, it was seen to be a reasonable choice. Appropriate prescription of Seroxat rested upon the professional judgement of the treating physicians and their clinical management plan. GlaxoSmithKline believed that Seroxat was a logical choice for first time success with new patients based on extensive clinical studies and more than 70 million patient treatments worldwide which had established Seroxat as an effective and generally well-tolerated treatment. GlaxoSmithKline did not believe that this claim was misleading nor in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that Clause 9.1 required that all material and activities must recognize the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained.

The Panel considered that the claim 'For those that feel an extra 2p a day is far too much for all that 'Seroxat' has to offer … here's a little something to tide you over', together with an actual two pence coin, denigrated prescribing decisions. The Panel considered that the mailing was likely to cause offence and failed to maintain high standards. A breach of Clause 9.1 was ruled as acknowledged by GlaxoSmithKline.

The Panel did not consider that the provision of a two pence coin would amount to an inducement to prescribe, supply, administer or buy Seroxat. No breach of Clause 18.1 was ruled. Nor did the Panel consider that the provision of the two pence coin as part of a mailing would be seen as an inducement to gain an interview or as a fee for an interview. No breach of Clause 15.3 of the Code was ruled.

The Panel then considered the claim 'Seroxat is a logical choice for first time success with new patients' which appeared as a final claim on page 3. This page listed Seroxat's licensed indications above four bullet points which discussed Seroxat's efficacy, speed of action, safety profile and cost. The Panel noted GlaxoSmithKline's submission that the claim was based on extensive clinical studies and more than 70 million patient treatments worldwide which had established Seroxat as an effective and generally well-tolerated treatment. The Panel noted that the claim did not state that Seroxat was the logical choice, but merely a choice, thereby implying that other choices were available. The Panel did not consider the claim unacceptable in this regard. The Panel further noted the complainant's view that the medications did not all work every time in every patient. One interpretation of the claim was that Seroxat was one of a group of medicines that would always work first time in every new patient. The claim could also be interpreted as recommending Seroxat as a first line treatment.

On balance the Panel considered that the claim was misleading as it was not clear what was meant and it could be interpreted as a claim for 100% success with Seroxat in new patients. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2.

During its consideration of this case the Panel noted that the first mention of the product name, Seroxat, was on the first page of the mailing. In the Panel's view this was the most prominent display of the brand name and in accordance with Clause 4.2 of the Code the non-proprietary name should have appeared immediately adjacent to this display of the brand name. The non-proprietary name was given on page three of the mailing. The Panel requested that GlaxoSmithKline be advised of its concerns.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that the Panel noted that the claim did not state that Seroxat was the logical choice, but merely a choice, thereby implying that other choices were available. The Panel did not consider the claim unacceptable in this regard. The Panel further noted the complainant's view that the medications did not all work every time in every patient. One interpretation of the claim was that Seroxat was one of a group of medicines that would always work first time in every new patient. However, GlaxoSmithKline believed that this interpretation was not within acceptable range of interpretations and hence invalid. Seroxat was one of several selective serotonin reuptake inhibitors (SSRIs) available on the market that were used to treat patients suffering from depression and several other associated disorders. It was common medical knowledge that no medication was successful in every new patient for which it was prescribed and the view of one practice should not be taken as the indication of the outcomes experienced by thousands of other doctors. More importantly, however, was that no interpretation of any medicine success statements could incorporate 100% as an outcome of success and this applied not only to the words used in the claim, but also to its competitors' claims, examples being 'simply effective', 'not just emerging from depression...' and 'antidepression not antipatient'. In terms of initial face validity of the claim, the interpretation largely rested on the word 'for' linking Seroxat as a logical choice of antidepressant with a positive outcome in new patients. From a semantic point of view, the preposition 'for' as defined in the Oxford dictionary was 'in support or favour of, with a view to, in order to obtain' which indicated intent, but was not an absolute. The words 'would always' stated an absolute, which did not accurately represent the word 'for' and should not therefore be used in any interpretation of the claim.

Depression was a complex disease consisting of many overlapping conditions and patients presented to their doctor in different ways. The different presentations of depression were often masked, making diagnosis difficult in the primary care setting. Epidemiological studies confirmed that some degree of comorbidity was usual among patients suffering depression, with about 60% of them having a concurrent anxiety disorder. It was clear that comorbidity denoted a group of patients with more severe symptoms, greater impairment, poorer outcome and higher risk of suicide than those with either condition alone. Hence, it was these comorbid affective disorders that must be recognised and treated appropriately and it was here especially, that Seroxat had an important role to play. Not only did Seroxat possess an established safety profile and offered recognised efficacy with a rapid onset of action, but it was one of the most studied in comorbid disorders and it had the most licensed indications of all the SSRIs. As such, Seroxat had been used for many years as a first line treatment for a broad range of depressive illnesses especially those with overlapping symptoms.

GlaxoSmithKline stated that it was inherent in the practice of medicine that no medication was a success in every patient. However, clinicians continued to strive to attain as much first time success in treating patients as possible. In the treatment of depression and certain anxiety disorders, Seroxat was one antidepressant to be considered when striving to maximise the success rate. In short-term clinical trials in patients suffering depression, paroxetine produced clinical improvements that were significantly greater than those with placebo and similar to those achieved with other agents, including tricyclic antidepressants, maprotiline, nefazodone and the SSRIs fluoxetine, fluvoxamine and sertraline.

GlaxoSmithKline stated that the evidence presented, showed that the claim, and hence the mailing, was not in breach of Clause 7.2 of the Code, as it accurately indicated that Seroxat might offer the physician first time success in new patients and was not an absolute statement.

APPEAL BOARD RULING

The Appeal Board considered that the meaning of the claim was unclear; it could be interpreted in a number of ways. It might be interpreted as referring to a reasonable chance of success of first line treatment in new patients. Equally it might be read as stating or implying that treatment with Seroxat was successful in every new patient. Whilst the Appeal Board noted that the audience would not expect a medicine to have a 100% success rate it considered that to state or imply such a success rate in promotional material was unacceptable. The Appeal Board further considered that the claim would not be read in isolation but would be considered within the context of the page as a whole. Immediately beneath the claim, at the bottom of the page, was the product logo with the strapline 'Make a difference that everybody notices'. The Appeal Board considered that the layout of the page was such that the claim, which appeared in an emboldened red type face, would be inextricably linked to the strapline, which was in red italics. The Appeal Board considered that the strapline compounded the misleading impression given by the claim at issue. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

Complaint received **27 April 2001**

Case completed **9 August 2001**

ANONYMOUS v BRISTOL-MYERS SQUIBB and SANOFI-SYNTHÉLABO

Arrangements for meeting

An anonymous complainant stated that Bristol-Myers Squibb's sales force promoted the company's products by flouting the Code. An example of this was that a general practitioner's practice manager was paid to give a live musical performance to entertain local GPs in a restaurant on Friday, 27 April. Apparently lots of food and drink would be provided, all paid for by Bristol-Myers Squibb as well as the singers. There might be other pharmaceutical companies involved.

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

The Panel noted that the meeting was held for a large, self-formed group of local GPs that met regularly, traditionally at a local restaurant, for medical education followed by dinner. At the doctors' request the meeting in question was jointly sponsored by Bristol-Myers Squibb and Sanofi-Synthélabo. The meeting lasted from 7pm until 10.30pm and included a 45 minute presentation from a local expert clinician on the use of anti-platelet therapy in the management of stroke. There was a further 15-20 minutes for questions before dinner. The Panel noted an inconsistency in the companies' responses; the first response implied that the entire meeting was held in a private room in the restaurant whilst subsequent information clearly stated that the doctors moved from the meeting room into the restaurant after the formal part of the meeting had finished. The Panel noted that the restaurant provided musical entertainment for its diners.

The meeting in question did have a clear educational content and the costs involved were not excessive. The meeting was attended by health professionals only. In the Panel's view, however, the hospitality provided was not secondary to the main purpose of the meeting. The meeting lasted three and a half hours; there was just over one hour of education followed by dinner in an open restaurant which provided live music. The Panel considered it unlikely that, in such surroundings, academic discussion would continue over dinner and in its view the balance of the meeting was such that it was mainly a social event and a breach of the Code was ruled. The Panel ruled that the representative involved in organising the meeting had thus not maintained high standards and nor had the companies and breaches of the Code were ruled. The Panel further considered that the impression created by the meeting brought discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel's rulings were appealed by Bristol-Myers Squibb and Sanofi-Synthélabo.

The Appeal Board expressed its concern that it was not until the companies had decided to appeal that they had interviewed the representatives. Information supplied to the Panel had come from a sales manager who had not attended the meeting. The Appeal Board noted that it had been supplied with further particulars and detail additional to those supplied to the Panel.

The Appeal Board noted that the local representatives had booked the restaurant and had verbally invited the GPs. It further noted that, although there was a large number of attendees, there were no formal invitations issued. The Appeal Board's view was that invitations should have been issued. An aide-mémoire was given to remind doctors about the meeting but no copy of that document was provided, nor had the companies referred to, or supplied a copy of, the invitation to the speaker. The Appeal Board considered that, for a meeting of this size, involving a prestigious speaker, there should have been better documentation and recording of the arrangements. In addition the companies should have provided copies of all the relevant documentation in their response to the complaint; they had been asked by the Authority to provide full details of the event.

The Appeal Board noted that the meeting had a clear educational content. The speaker was a national opinion leader and his presentation lasted about an hour. There was also an opportunity for attendees to discuss the topic with the speaker. The Appeal Board considered that the hospitality provided was secondary to the main purpose of the meeting, it was appropriate and not out of proportion to the occasion. No breach was ruled in that regard. The Appeal Board considered that high standards had been maintained although it noted its concerns with regard to the fact that there had been no formal invitation to the meeting and its view that there should have been better documentation and records kept. No breach was ruled in that regard. The Appeal Board did not consider that the impression created by the meeting brought discredit upon the pharmaceutical industry. No breach of Clause 2 was ruled.

An anonymous complaint consisting of a single sheet of A4 paper headed 'Stop press stop press stop press' was received.

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

COMPLAINT

The complaint stated that Bristol-Myers Squibb's sales force had started promoting the company's products by flouting the industry's code and against all ethics. A blatant example of this was that a general practitioner's practice manager was paid to give a live musical performance to entertain local GPs in a restaurant on Friday, 27 April. Apparently lots of food and drink would be provided, all paid for by

Bristol-Myers Squibb as well as the singers. There might be other pharmaceutical companies involved.

The material stated that this would be a great scoop for the media to expose all the unethical tricks that Bristol-Myers Squibb got up to; it would be great if some reporters were to turn up at the restaurant with photographers.

In writing to Bristol-Myers Squibb the Authority requested that it considered the provisions of Clauses 2, 9.1, 15.2 and 19.1 of the Code.

RESPONSE FROM BRISTOL-MYERS SQUIBB

Bristol-Myers Squibb stated that the meeting in question was jointly sponsored by it and Sanofi-Synthélabo. The company noted that the presentation of the complaint was unorthodox and the complaint itself extremely disparaging. Bristol-Myers Squibb stated that the complainant did not appear to be in possession of the full facts or to be familiar with the Code. In view of the anonymous nature of the complaint the company accepted that the Authority must proceed on the complainant's behalf. Bristol-Myers Squibb stated that it had taken steps to investigate the source of these alarmist allegations and to avoid precipitating a further such attack. The company gave its assurance that there had been no change in policy and it continued to take the Code, and its reputation as an ethical research organisation, extremely seriously. Having reviewed the facts surrounding the event in question the company was satisfied that there had been no breach of the Code.

Bristol-Myers Squibb explained that a group of local Asian GPs had formed a group that met regularly for medical education followed by dinner. The meetings were usually sponsored by a pharmaceutical company and had traditionally been held in a private room in a particular Indian restaurant. On 27 April the meeting was held at a different restaurant, as the doctors had become dissatisfied with their usual venue.

The meeting was organised by experienced local Bristol-Myers Squibb representatives and was approved by their area business manager. All had passed their ABPI examination and attended refresher courses. All representatives received written training instructions on the provision of hospitality for health professionals.

Bristol-Myers Squibb stated that the meeting was attended by health professionals only. An attendee list was provided and comprised around 65 GPs, 2 practice nurses and 3 pharmacists. At the doctors' request the meeting was sponsored jointly by Bristol-Myers Squibb and Sanofi-Synthélabo as was customary under the terms of the companies' joint venture agreement. The meeting was held in a private room between 7.00pm-10.30pm in the restaurant. There was no room rental charge.

The meeting comprised of an educational lecture followed by dinner. A local clinical expert in the management of stroke in the elderly, gave a presentation entitled 'Anti-platelet therapy in the management of stroke' which lasted 45 minutes with a further 15-20 minutes for questions. The speaker's honorarium of £200 was paid jointly by Bristol-Myers Squibb and Sanofi-Synthélabo.

After the educational meeting an evening meal was provided costing £17.25 per person. Drinks were also paid for although these comprised mainly soft drinks as the majority of the doctors in attendance did not drink alcohol.

Bristol-Myers Squibb stated that the Indian musicians employed by the restaurant formed part of its standard entertainment for its diners. The entertainment was not commissioned or paid for by Bristol-Myers Squibb or Sanofi-Synthélabo. Bristol-Myers Squibb considered that the entertainment was culturally appropriate for the restaurant and the group of doctors in attendance.

There were no exhibition stands at the meeting and no involvement of other pharmaceutical companies. There were no promotional materials of any kind at the meeting. The chairman of the group acknowledged sponsorship of the meeting by Bristol-Myers Squibb and Sanofi-Synthélabo.

Bristol-Myers Squibb stated that it considered that high standards had been maintained throughout and that there had been no breaches of Clauses 9.1, 15.2, 16.3 or 19.1. Consequently there had been no breach of Clause 2 of the Code.

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On receipt of Bristol-Myers Squibb's response it was clear that Sanofi-Synthélabo was also involved in the meeting arrangements. Sanofi-Synthélabo later confirmed that the initial response from Bristol-Myers Squibb was on behalf of both companies.

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FURTHER INFORMATION FROM BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHÉLABO

With regard to the entertainment the companies confirmed that after selecting a restaurant and inviting the doctors, the representative learned that there would be entertainment at the restaurant. The practice manager was not involved in the selection or booking of the venue for the meeting. The restaurant, which regularly provided musical entertainment, commissioned and paid for the music itself and neither company was involved in this arrangement or payment. The companies could not answer questions about the involvement of the practice manager in the choice/provision of the entertainment as neither company was involved in this but confirmed that the practice manager had no part in the arrangements of the sponsored meeting.

Bristol-Myers Squibb and Sanofi-Synthélabo stated that the entertainment was proceeding in the restaurant when the doctors moved from the meeting room into the restaurant after the lecture, and continued intermittently throughout the evening.

PANEL RULING

The Panel noted that the meeting was held for a large,

self-formed group of local GPs that met regularly for medical education followed by dinner. The meetings were traditionally held at a local restaurant. At the doctors' request the meeting in question was jointly sponsored by Bristol-Myers Squibb and Sanofi-Synthélabo. The meeting lasted from 7pm until 10.30pm and included a 45 minute presentation from a local expert clinician on the use of anti-platelet therapy in the management of stroke. There was a further 15-20 minutes for questions after which the doctors had dinner. The Panel noted that there was an inconsistency in the companies' responses regarding the arrangements for dinner. The first response implied that the entire meeting was held in a private room in the restaurant while the further information clearly stated that the doctors moved from the meeting room into the restaurant after the formal part of the meeting had finished. The Panel noted that the restaurant provided musical entertainment for its diners.

Clause 19.1 of the Code stated, *inter alia*, that companies were permitted to provide appropriate hospitality in association with scientific and promotional meetings but that such hospitality had to be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed that level which recipients would normally adopt when paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information to Clause 19.1 further added, *inter alia*, that meetings must have a clear educational content. The impression that was created by the arrangements for any meeting must be kept in mind. Meetings organised for groups of doctors which were of a wholly or mainly social nature were unacceptable.

The Panel noted that the meeting in question did have a clear educational content and that the costs involved were not excessive. The meeting was attended by health professionals only. In the Panel's view, however, the hospitality provided was not secondary to the main purpose of the meeting. The meeting lasted three and a half hours; there was just over one hour of education followed by dinner in an open restaurant which provided live music. The Panel considered it unlikely that, in such surroundings, academic discussion would continue over dinner and in its view the balance of the meeting was such that it was mainly a social event and a breach of Clause 19.1 of the Code was ruled. The Panel considered that the representative involved in organising the meeting had thus not maintained high standards and nor had the companies and breaches of Clauses 9.1 and 15.2 of the Code were ruled. The Panel further considered that the impression created by the meeting brought discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHÉLABO

Bristol-Myers Squibb and Sanofi-Synthélabo stated that the meeting had a clear educational objective and this was the primary focus of the meeting.

The objective of the meeting was to assist GPs in preparing to implement the recently published National Service Framework for the Older Person (NSF) (March 2001). The NSF included recommendations and standards for the management of stroke. A meeting that aimed to help GPs to update their knowledge and expertise in stroke management and provide guidance on current best practice was expected to be highly relevant to the intended audience. The guest speaker was an expert in stroke medicine of national acclaim. The subject of his presentation was the role of 'Anti-platelet therapy in the management of stroke'. Details of his professorial commitments, positions held on prominent UK professional organisations and publications were provided.

The meeting proved to be very popular, attracting one of the largest audiences for an event of this kind in this region. Bristol-Myers Squibb and Sanofi-Synthélabo believed this to be due to the meeting's topical nature and prestigious guest speaker. The educational value of the meeting was confirmed in independent written testimonies that the companies had obtained from GPs at the meeting. These also confirmed that the presentation stimulated much academic discussion over dinner.

The meeting was not only for local GPs, doctors from surrounding areas also attended. The companies would dispute the impression formed by the Panel that this meeting was more like a social event.

It was usual for dinner to be provided at an evening meeting. For convenience the meeting was held at a restaurant that could also provide a meeting room able to accommodate 60-80 people. Arrangements with the restaurant were confined solely to the price per head for the buffet dinner and use, free of charge, of the private room. It was by coincidence that musical entertainment was provided on the evening of 27 April and the written testimony from the restaurant confirmed this.

The educational part of the meeting was held in a private room. The companies stated that in their initial response they had failed to elaborate that dinner was served in the main restaurant. It was assumed that it would be understood that as the meeting was held at a restaurant, guests would dine in the main dining area. The companies apologised for any confusion. The meeting began late and there was a delay between the end of the educational session and the meal during which time several GPs left. All the guests left by around 10.30-11.00pm and this was possibly later than if the meeting had run to time. The companies considered the hospitality to have been in proportion to the educational content of the meeting.

The musicians, comprised of a singer, who by coincidence was a practice manager at one of the local GP practices, and two other instrumentalists, set up to play in the private room after the educational part of the meeting had finished. Their music began at around 10.30pm and they played intermittently. They were not visible to the doctors who were seated at the furthest possible distance from the private room (a copy of the restaurant floor plan was provided). The

written testimonies from doctors stated that the music was barely audible in the restaurant. The music did not cause any disturbance to conversation over dinner and written testimony supported this. Few, if any GPs would have known to expect any musical entertainment at the restaurant.

With regard to Clauses 9.1 and 15.2 the companies stated that the focus of the meeting was primarily educational. The hospitality arrangements were modest and proportionate. The companies did not consider that the meeting could have caused any offence to attendees and that high standards were maintained throughout.

With regard to Clause 2, Bristol-Myers Squibb and Sanofi-Synthélabo did not believe that the meeting had brought discredit upon the pharmaceutical industry either by the impression created or by the event itself. The companies would be happy for the details of the meeting to be widely known because they believed the event to have been entirely reputable. The anonymous complaint was misleading and untrue.

The companies considered that the ruling of a breach of Clause 2 had been excessively severe and requested that it be considered, particularly in the light of the rulings made in previous cases. For example, Case AUTH/1017/4/00, in which local GPs were taken out to a Greek restaurant and the only educational content of the evening was a 10 minute presentation by the representative from a detail aid. The presentation took place in the main restaurant rather than a private room. This case did not attract a ruling on Clause 2. The companies also cited the following: Case AUTH/1017/4/00; Case AUTH/732/6/98; Case AUTH/637/11/97 and Case AUTH/632/10/97 noting that all of these cases involved a ruling of a breach of Clause 19.1 but no ruling of a breach of Clause 2.

At the appeal hearing itself the representatives stated that the companies' initial response had been based upon a sales manager's account of events. The sales manager had not attended the meeting. It was only in preparing their appeal that the companies had interviewed the sales representatives involved. The representatives also submitted that, although no formal invitations had been issued, invitees to the meeting were given an aide-mémoire, copies of which were not provided.

APPEAL BOARD RULING

The Appeal Board expressed its concern that it was not until the companies had decided to appeal in this case that they had interviewed the representatives involved in organising the meeting. Information supplied to the Panel had come from a sales manager who had not attended the meeting. The Appeal Board noted that it had been supplied with further particulars and detail additional to those supplied to the Panel.

The Appeal Board noted that the local representatives had booked the restaurant and had verbally invited the GPs. It further noted that, although there was a large number of attendees, there were no formal invitations issued in relation to the meeting. The Appeal Board's view was that invitations should have been issued. The representatives had submitted that an aide-mémoire was given to remind doctors about the meeting but no copy of that document was provided, nor had the companies referred to, or supplied a copy of, the invitation to the speaker. The Appeal Board considered that, for a meeting of this size, involving a prestigious speaker, there should have been better documentation and recording of the arrangements. In addition the companies should have provided copies of all the relevant documentation in their response to the complaint; they had been asked by the Authority to provide full details of the event.

The Appeal Board noted that it was not unusual for doctors to form their own group, members of which would meet regularly for medical education followed by dinner. In such instances, where a group was inviting sponsorship from a company, as opposed to a company holding a meeting and inviting doctors of its choosing, companies must be careful to ensure that all of the arrangements complied with the Code.

The Appeal Board noted that the meeting in question had a clear educational content. The speaker was a national opinion leader in the management of stroke and his presentation lasted about an hour. There was also an opportunity for doctors at the meeting to discuss the topic with the speaker. The Appeal Board considered that the hospitality provided was secondary to the main purpose of the meeting, it was appropriate and not out of proportion to the occasion. No breach of Clause 19.1 was ruled. The Appeal Board considered that high standards had been maintained, although it noted its concerns with regard to the fact that there had been no formal invitation to the meeting and its view that there should have been better documentation and records kept. No breaches of Clauses 9.1 and 15.2 were ruled. The Appeal Board did not consider that the impression created by the meeting brought discredit upon the pharmaceutical industry. No breach of Clause 2 was ruled. The appeal was successful on all matters.

Complaint received **30 April 2001**

Case completed **26 July 2001**

CASE AUTH/1188/5/01

ROCHE v KNOLL

Reductil journal advertisements

Roche complained about two journal advertisements for Reductil (sibutramine) issued by Knoll. Reductil was licensed for use as adjunctive therapy within a weight management programme for patients with obesity. One advertisement featured a grid of small photographs each of which was of an obese person's torso dressed only in underclothes. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' and 'Colerectal cancer'. The other advertisement also featured a grid of small photographs, this time of plates of leftovers from a meal each one labelled 'Love it and leave it'. Both advertisements referred to Reductil enabling patients to achieve medically beneficial weight loss.

Roche alleged that the prescribing information was deficient as there was no mention that the product should be withdrawn in patients who did not respond adequately to therapy; nor was there any mention that Reductil should only be given for periods of up to one year.

The Panel noted that there was an increased risk of adverse events if Reductil therapy was continued in non-responders. In the Panel's view such information should have been included in the prescribing information. Similarly prescribers should have been made aware that Reductil should only be given for up to one year. A breach of the Code was ruled.

Roche alleged that the inclusion of photographs of obese patients associated with a listing of co-morbid conditions, together with the claim 'medically beneficial weight loss', implied that Reductil had a beneficial effect on all of these conditions which was inaccurate and misleading.

The Panel considered that the advertisement clearly promoted Reductil as an anti-obesity agent. The strapline beneath the product logo was 'Helps obese patients control their eating'. The text described Reductil as 'a new effective aid to weight loss' and stated that the product enabled patients to 'achieve medically beneficial weight loss'. The Panel considered that the grid of photographs would be seen as depicting the profiles of patients who presented with obesity and, in its view, osteoarthritis, gout etc would be seen by the reader as co-morbid conditions, not as the reason to prescribe Reductil. The Panel did not consider that the advertisement implied that treatment with Reducil would have a beneficial effect on these conditions as alleged. The Panel did not consider that the advertisement was inaccurate or misleading in this regard. No breach of the Code was ruled. Upon appeal by Roche the Appeal Board considered that the advertisement did imply that Reductil had a beneficial effect on the co-morbid conditions listed as alleged. A breach of the Code was ruled.

Roche alleged that the claim 'Reductil has no embarrassing GI [gastrointestinal] side effects', which appeared in both advertisements, was not an accurate or balanced summary of the side effect profile for the product; the summary of product characteristics (SPC) included a number of GI side effects.

The Panel considered that the claim would be read in the context of other anti-obesity agents. Within the context of the GI side effects associated with Xenical (Roche's product) those associated with Reductil ie loss of appetite, constipation, nausea and haemorrhoid aggravation were not embarrassing. The Panel did not consider that the claim was inaccurate or unbalanced as alleged. No breach of the Code was ruled. Upon appeal by Roche the Appeal Board considered that embarrassment was a personal feeling; although some of the GI side effects caused by Reductil might not be obvious to anyone else, the patient might still be embarrassed about them. There was no data to show that patients were not embarrassed. The Appeal Board considered that the claim had not been substantiated by clinical evidence. Breaches of the Code were ruled.

Roche Products Ltd complained about two advertisements for Reductil (sibutramine) (refs ETH 2921/12/00a and ETH 2980/04/01b), issued by Knoll Limited, which appeared in GP magazine, 25 May 2001. Reductil was licensed for use as adjunctive therapy within a weight management programme for patients with obesity. One of the advertisements (ref ETH 2921/12/00a) was a double page spread which featured a grid (9 x 10) of small photographs each of which was of an obese person's torso; each person was dressed only in underclothes. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' and 'Colorectal cancer'. The second advertisement (ref EH 2980/04/01b) was a single A3 page again featuring a grid (7 x 7) of small photographs, this time of plates of leftovers from a meal each one labelled 'Love it and leave it'. Both advertisements referred to Reductil 'enabling patients to achieve medically beneficial weight loss'.

Roche marketed Xenical (orlistat).

1 Prescribing information

COMPLAINT

Roche alleged that the prescribing information for Reductil did not provide 'a succinct statement of the information in the summary of product characteristics or data sheet relating to the dosage and method of use relevant to the indications quoted in the advertisement …' as required in Clause 4.2. There was no mention in the prescribing information that 'treatment must be discontinued in patients who have not responded adequately ie whose weight loss stabilises at less than 5% of their initial bodyweight or whose weight loss within 3 months after starting therapy has been less than 5% of their initial bodyweight'. There was also no mention of the fact that Reductil 10mg/15mg should only be given for

periods up to one year. A copy of the Reductil summary of product characteristics (SPC) was provided.

RESPONSE

Knoll noted that Clause 4.2 of the Code required 'a **succinct statement** of the information in the SPC or data sheet relating to **the dosage** and **method of use** relevant to the indications quoted in the advertisement' (emphasis added). It did not ask that the relevant part of the SPC be reproduced verbatim. Knoll submitted that its prescribing information did exactly that by detailing the two doses of the product, how to employ the higher dose, the exact circumstances and conditions for administration of the medicine (… adjunctive therapy within a weight management programme… may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone…). Discontinuation of Reductil for therapeutic failure was so obvious that, whilst of interest, was neither required by Clause 4.2, nor a sensible inclusion given the need to be succinct. Similarly the maximum period of administration was neither 'dosage' nor 'method of use'. Knoll stated that it considered that its prescribing information achieved the right balance between 'use' and 'safety/toleration' types of information and that the addition of lengthy statements on the obvious fact that any medicines not producing the desired therapeutic effect should be discontinued would be entirely inappropriate.

PANEL RULING

The Panel noted that the Reductil SPC gave details of when the product should be withdrawn due to an inadequate response or lack of response. The SPC stated that non-responders were at a higher risk of undesirable effects. It was also stated that Reductil should only be given for up to one year; data on its use for over one year was limited.

The Panel noted that the prescribing information did not refer to any of the above. There were adverse implications with regard to patient tolerability if Reductil therapy was continued in non-responders. In the Panel's view that information was such that reference should have been made to it in the prescribing information to alert the prescriber to the increased risk of undesirable effects. Similarly the Panel considered that prescribers should have been made aware that Reductil should only be given for up to one year.

Clause 4.2 of the Code listed the components parts of prescribing information; Clause 4.1 stated that the information listed in Clause 4.2 must be provided. The Panel considered that by not referring to the above, the prescribing information did not provide important information relevant to the use of Reductil. A breach of Clause 4.1 was ruled.

2 Photographs of patients in association with labels referring to co-morbid conditions

COMPLAINT

Roche considered that the inclusion of photographs of obese patients associated with a listing of co-morbid conditions, including osteoarthritis, colorectal and breast cancer, hypertension and type 2 diabetes, together with the claim of 'medically beneficial weight loss', implied that Reductil had beneficial effects on all of these conditions. Roche was not aware of any evidence to support these claims and alleged that they were therefore both inaccurate and misleading in breach of Clause 7.2 of the Code.

RESPONSE

Knoll acknowledged that the double page advertisement used the repeated images of obese people labelled with some of the diseases and syndromes associated with obesity. The labelling was to ensure that readers understood that the company did not advocate the use of Reductil for cosmetic reasons; rather it was legitimate medical reasons which underlay any decision to treat obesity. Put simply it was an acceptable way to depict the seriousness of obesity as a disease (something that was not generally recognised yet in the UK) and only that.

Knoll noted that its SPC referred to obesity related co-morbid factors in Section 4.1 to define the therapeutic indications for Reductil and the penultimate paragraph of Section 4.2 detailed how the clinical course of obesity co-morbid conditions should inform treatment decisions. In the last paragraph of Section 5.1 beneficial outcomes to associated risk factors were given. The company considered that these sections of its SPC gave ample justification for use of co-morbid conditions when communicating with health professionals.

Knoll stated that together these facts made it difficult for it to understand the complaint. Clearly the company was entirely within its SPC, as well as ethically responsible, in its attempts to guide the reader to the medical reasons for treating obesity and overweight.

Knoll noted that the final point made by Roche was regarding the use of the phrase 'medically beneficial weight loss'. Knoll disputed that use of this phrase implied that it claimed that Reductil had beneficial effects on all of the conditions referred to above. The company had carefully separated the depiction of the seriousness of obesity as a disease by using small lettering and embedding the various conditions amongst the images of obese people and it consciously and deliberately separated these from the text on what Reductil did.

Knoll considered that Reductil's ability to produce weight loss was not in contention by Roche. Of course not all degrees of weight loss were medically meaningful (eg by virtue of being too small). Knoll stated that it had qualified the degree of weight loss achievable by use of Reductil as 'medically beneficial' to indicate that it lay in the range of weight loss that had been found to be associated with medical benefits (ie of the order of 5% - 10% of initial weight). This was widely accepted and the guidelines issued by the Royal College of Physicians was one of the many sources where this was mentioned. A copy of the guidelines was provided; Knoll stated that it would

provide other sources if required. The company submitted that the use of the phrase 'medically beneficial weight loss' was readily understood to mean just this, that in no way could it be understood to imply a claim that Reductil cured or benefited all the obesity co-morbid conditions.

PANEL RULING

The Panel considered that the Reductil advertisement clearly promoted the product as an anti-obesity agent. The strapline beneath the product logo was 'Helps obese patients control their eating'. The text described Reductil as 'a new effective aid to weight loss' and stated that the product enabled patients to 'achieve medically beneficial weight loss'. The Panel considered that the grid of photographs would be seen depicting the profiles of patients who presented with obesity. In the Panel's view, osteoarthritis, gout and reflux oesophagitis etc would be seen by the reader as co-morbid conditions, not as the reason to prescribe Reductil. The Panel did not consider that the advertisement implied that Reductil would have a beneficial effect on these conditions as alleged. The Panel did not consider that the advertisement was inaccurate or misleading as alleged. No breach of Clause 7.2 was ruled.

APPEAL BY ROCHE

Roche noted that the Panel considered that 'the grid of photographs would be seen depicting the profiles of patients who presented with obesity' and that the 'conditions illustrated would be seen by the reader as co-morbid conditions, not as the reason to prescribe Reductil'. However, Roche believed that the statement partially overlying these photographs that 'Thanks to Reductil, enough is enough' implied that Reductil could have a direct effect on the co-morbid conditions illustrated. This might be the implication to the reader, particularly when taken in conjunction with the other advertisement forming part of this promotional campaign and which was running concurrently. This illustrated plates of food with the caption 'Love it and leave it'. It was clear that the intention was to link the overlying statement, 'Thanks to Reductil, enough is enough', with these illustrations. It was reasonable therefore to assume that the company believed that the illustrations in both advertisements would be associated with the statement, implying a direct effect of Reductil on the illustrated co-morbidities. Roche believed therefore that this was a clear breach of Clause 7.2 which required that claims must not mislead either directly or by implication.

Roche noted that Knoll claimed to have 'carefully separated the depiction of the seriousness of obesity as a disease by using small lettering and embedding the various conditions amongst the images of obese people' and to have 'consciously and deliberately separated these from the text on what Reductil does'. However, the statement 'Thanks to Reductil, enough is enough' overlaid the illustrations in both the double and single page executions of the advertisements in this current campaign. Clearly Knoll would have been aware of this when it responded to the complaint.

Roche further noted that in its response Knoll stated that its SPC referred to obesity related co-morbid risk factors in Section 4.1 to define the therapeutic indications, and that the penultimate paragraph of Section 4.2 detailed how the clinical course of obesity co-morbid conditions should inform treatment decisions. In the last paragraph of Section 5.1 beneficial outcomes to associated risk factors were given and Knoll believed these parts of the SPC provided ample justification for use of co-morbid conditions when communicating with health professionals. However, the SPC referred to obesity related risk factors, such as type 2 diabetes or dyslipidaemia in Section 4.1. Section 4.2 referred to improvements in lipid profile in dyslipidaemic patients and in glycaemic control of type 2 diabetes. The beneficial outcomes referred to in Section 5.1 also related to type 2 diabetes and dyslipidaemia. Amongst the many co-morbidities highlighted in Knoll's promotional campaign were stroke, hypertension, cardiovascular disease and sweating. It was interesting to note that a history of stroke, coronary artery disease, congestive cardiac failure, tachycardia, peripheral arterial occlusive disease, arrhythmias and inadequately controlled hypertension were all listed as contraindications in the same SPC while sweating and cardiovascular symptoms were listed amongst the frequent undesirable effects.

Following discussions with the Medicines Control Agency (MCA) between March and July 1999, Roche undertook to clarify the relationship between weight loss and any resulting improvement in co-morbidities in all promotional materials. The Panel's decision suggested that there was clear disparity between the positions of the MCA and the Authority on this matter.

SCOPE OF THE APPEAL

The Authority informed Roche that it considered that the reasons for the appeal went beyond the scope of the original complaint.

In its original complaint Roche had stated that the inclusion of photographs of obese patients associated with a listing of co-morbid conditions, together with the claim of 'medically beneficial weight loss', implied that Reductil had beneficial effects on all of these conditions. Roche stated that it was not aware of any evidence to support these claims, which were therefore both inaccurate and misleading.

The first two paragraphs of Roche's appeal gave further reasons as to why Roche considered that this was so. In the third paragraph, however, reference was made to the view that some of the co-morbidities listed were contraindications to, or might be exacerbated by, Reductil therapy. As this point was not part of Roche's original complaint it had not been considered by the Panel.

Roche stated in reply that it believed that the information provided in the third paragraph supported its belief that there was a breach of Clause 7.2 stating that '… claims … must be accurate, balanced, fair, objective and unambiguous and must be based on up to date evaluation of all the evidence

and reflect this evidence clearly. They must not mislead either directly or by implication'.

It was misleading to include co-morbidities where Reductil not only had not demonstrated benefit as a result of use of the medicine, but indeed might have a detrimental effect. As stated in Roche's original letter, there would appear to be no evidence to support the claim of 'medically beneficial weight loss' in relation to all these co-morbidities.

In response, the Authority repeated that the view that some of the co-morbidities listed were contraindications to, or might be exacerbated by, Reductil was not part of the original complaint. They were not given as reasons as to why the material was alleged to be in breach of the Code and were not therefore considered by the Panel. The point was considered on the narrow grounds in the allegation and the Panel had ruled that the advertisement did not imply that Reductil would have a beneficial effect on these conditions.

The wider grounds, ie that the product was contraindicated with certain conditions, was the subject of a separate complaint [Case AUTH/1197/6/01].

RESPONSE FROM KNOLL

Knoll stated that it was apparent that Roche had sought to extend the original scope of its complaint and it agreed with the Authority's comments to Roche on the matter.

FURTHER COMMENTS FROM ROCHE

Roche had no further comments.

APPEAL BOARD RULING

The Appeal Board considered that, in its appeal, Roche had sought to widen the scope of its original complaint. The Appeal Board thus decided that its consideration of the matter should be restricted to the grounds of the original complaint and the reasons for appeal which related to the original complaint. The Appeal Board noted that the wider grounds of Roche's appeal ie that the product was contraindicated in certain conditions had been the subject of a separate complaint (Case AUTH/1197/6/01). Knoll had accepted the Panel's rulings of breaches of the Code in that case and a new advertisement, which did not refer to any co-morbid conditions, had been produced.

With regard to the case now before it (Case AUTH/1188/5/01) the Appeal Board considered that the advertisement did imply that Reductil had a beneficial effect on the co-morbid conditions listed as alleged. The Appeal Board was not aware of any evidence that this was so. The advertisement was therefore misleading and a breach of Clause 7.2 was ruled.

The appeal on this point was successful.

3 Claim 'Reductil has no embarrassing GI [gastrointestinal] side effects'

This claim appeared in both advertisements.

COMPLAINT

Roche alleged that the claim was in breach of Clauses 7.2 and 7.7 of the Code as it did not reflect an accurate or balanced summary of the side effect profile of Reductil; the SPC for Reductil included a number of GI side effects. The company had written to Knoll requesting supporting evidence that these effects were in no way embarrassing.

RESPONSE

Knoll submitted that a current SPC (especially one as recently approved as Reductil's) reflected available evidence on safety and tolerability. The following GI side effects were listed in the Reductil SPC: loss of appetite; constipation; nausea and haemorrhoid aggravation. These were obviously not embarrassing. Furthermore it was important to point out that in the obesity area embarrassing GI side effects appeared to be an important issue as another leading medication was reported to be associated with flatulence and diarrhoea (sometimes accompanied by anal leakage and clothes soiling). Thus in this context it was necessary and legitimate to point out the absence of embarrassing GI side effects without any fear of misinterpretation or the need to demonstrate the few GI side effects of Reductil as being non-embarrassing.

Knoll stated that both generally, as well as specifically in the context of this disease area, the information given by the phrase 'Reductil has no embarrassing GI side effects' did reflect available evidence, and was entirely accurate, balanced and fair information in this respect.

PANEL RULING

The Panel noted that there were only three anti-obesity agents on the market in the UK (ref June 2000 MIMS) methylcellulose, Reductil and Xenical. During the first year of treatment with Xenical adverse GI reactions commonly associated with therapy were, *inter alia*, oily spotting from the rectum (27% of patients), flatus with discharge (24% of patients), faecal urgency (22% of patients) and faecal incontinence (8% of patients). The incidence of such events decreased with prolonged use of the product (ref Xenical SPC, Electronic Medicines Compendium). The Panel considered that some of these GI side effects would be seen as embarrassing.

The Panel considered that the claim would be read within the context of other anti-obesity agents. Within the context of the GI side effects associated with Xenical, those associated with Reductil ie loss of appetite, constipation, nausea and haemorrhoid aggravation, were not embarrassing. The Panel thus did not consider that the claim that 'Reductil has no embarrassing GI side effects' was inaccurate or unbalanced as alleged. No breach of Clauses 7.2 and 7.7 was ruled.

APPEAL BY ROCHE

Roche noted that the Panel considered that the claim would be read within the context of other anti-obesity agents and alleged that 'within the context of GI side effects associated with Xenical, those associated with Reductil ie loss of appetite, constipation, nausea and

haemorrhoid aggravation were not embarrassing'. Roche believed this to be a subjective assessment by the Panel and on this basis felt a similar case could be made that symptoms of uncontrollable itching, blood loss and faecal staining sometimes associated with haemorrhoid aggravation (a frequent side effect of Reductil) were embarrassing. Roche was surprised that the Panel did not appreciate such effects of haemorrhoid aggravation. Having requested substantiation by clinical experience of the claim that 'Reductil has no embarrassing GI side effects', Roche still awaited a response from Knoll's medical department. Should no clinical evidence of this claim be forthcoming, Roche believed this was a clear breach of Clause 7.7 which required that 'claims about side effects must reflect available evidence or be capable of substantiation by clinical experience'.

It should also be noted that the GI side effects associated with the use of Xenical were under the patient's control by appropriate dietary modification as acknowledged in the recent NICE guidelines (March 2001) which stated that 'these effects encourage patients to limit fat intake'. This was clearly an important factor in dietary re-education and long-term weight control. It would be noted from the Reductil SPC that 'obesity management should include dietary and behavioural modification …. This integrated approach is essential for a lasting change in eating habits and behaviour …'.

Further, on the basis of the Panel's ruling many of the cardiovascular, psychological and neurological side effects associated with the use of Reductil could be subjectively described as 'upsetting', 'inconvenient' or even 'dangerous'. Roche believed, therefore, that comparisons of a subjective nature would set a precedent within the promotion of medicines. For example, on the basis of the Panel's ruling, it could be said that Reductil caused 'embarrassing flushing', 'frightening tachycardia', 'worrying palpitations', 'disconcerting dry mouth', 'distressing insomnia' etc. This type of knocking copy could lead to discredit and a reduction in confidence in the pharmaceutical industry which surely would breach Clause 2. Roche believed that implied criticism of competitive products by use of subjective judgement was contrary to the spirit of the Code.

Certainly, it seemed that focussing only on gastrointestinal side effects, when use of Reductil was frequently associated with cardiovascular, CNS, skin and sensory undesirable effects, did not represent a fair and balanced presentation of the evidence. Further, if the aim was to compare with Xenical, Roche believed this was a breach of Clause 7.2 which required that '… comparisons must be accurate, balanced, fair, objective and unambiguous'. Given that only GI events were compared (by implication), this was unbalanced and the reference to 'embarrassing' side effects was clearly not an objective assessment.

SCOPE OF THE APPEAL

The Authority informed Roche that here again it considered that the reasons for the appeal went beyond the scope of the original complaint.

In its original complaint Roche had alleged that the claim did not reflect an accurate or balanced summary of the side effect profile of Reductil; the SPC for Reductil included a number of GI side effects. Roche had written to Knoll requesting supporting evidence that these effects were in no way embarrassing.

The fourth paragraph of Roche's appeal on this matter extended its complaint as it further alleged that only focussing on GI side effects was unbalanced as Reductil was frequently associated with other types of adverse events. Again, as this issue was not included in Roche's original complaint, it was not one on which the Panel had ruled.

Roche stated in reply that, as stated in its original letter, it believed that 'Reductil has no embarrassing GI side effects' was neither accurate or balanced. Roche still awaited, as indicated previously, a response to its request for supporting data, to validate the accuracy of the statement, but the SPC for Reductil, in Roche's opinion, clearly demonstrated why such claims were not balanced.

In response, the Authority accepted that Roche alleged in its original complaint that the claim did not reflect an accurate or balanced summary of the side effect profile of Reductil. This was expanded by a reference to GI side effects and a request for supporting evidence that these were in no way embarrassing. It appeared to the Panel that the allegation related to the embarrassing nature of the GI side effects and not that the material was misleading as other side effects had not been mentioned, as stated in Roche's letter of appeal.

RESPONSE FROM KNOLL

Knoll stated that it was apparent that Roche had sought to extend the original scope of its complaint and it agreed with the Authority's comments to Roche on the matter.

FURTHER COMMENTS FROM ROCHE

Roche had no further comments.

APPEAL BOARD RULING

The Appeal Board again considered that, in its appeal, Roche had sought to widen the scope of its original complaint. The Appeal Board thus decided that its consideration of the matter should be restricted to the grounds of the original complaint and the reasons for appeal which related to the original complaint.

The Appeal Board considered that embarrassment was a personal feeling; although some of the GI side effects caused by Reductil might not be obvious to anyone else, the patient might still be embarrassed about them. There was no data to show that patients were not embarrassed. The Appeal Board considered that the claim 'Reductil has no embarrassing GI side effects' had not been substantiated by clinical evidence. Breaches of Clauses 7.2 and 7.7 were ruled.

The appeal on this point was successful.

Complaint received **29 May 2001**

Case completed **8 October 2001**

CASE AUTH/1190/5/01

PRACTICE MANAGER v TRINITY

Conduct of representative

A practice manager complained about the manner in which a representative from Trinity had gained access to the surgery. The complainant was telephoned and asked if a named person, representing the local primary care group (PCG) prescribing adviser, could come and do an audit. The name of Trinity was not mentioned and the complainant's understanding was that this was a PCG run project. The person named in the telephone call was given access to the surgery's computer database and it was not until he was leaving that it became apparent that he was a pharmaceutical representative.

The Panel considered that it was incumbent upon representatives to ensure that the people they spoke to knew immediately that they were company representatives. By not introducing himself when he first met the complainant by means of a company business card, and by opening the interview with a reference to the PCG, the representative had misled as to his identity and that of the company he represented. The Panel considered that the representative had failed to maintain a high standard of ethical conduct. Breaches of the Code were ruled.

Clause 2, which stated that activities associated with promotion must not bring discredit upon or reduce confidence in the pharmaceutical industry, was used as a sign of particular censure and reserved for such circumstances. The Panel considered that the circumstances did not warrant such a ruling and no breach of that clause was ruled.

A practice manager complained to Trinity Pharmaceuticals Ltd about the manner in which one of its representatives had gained access to the surgery. The letter of complaint was copied to the Authority.

COMPLAINT

The complainant explained that she was contacted by telephone and asked if a named person representing the local primary care group (PCG) prescribing adviser could come to do an audit in relation to a project on reducing the cost of prescribing modified release drugs. During the conversation the name of Trinity was not mentioned, and the complainant stated that her understanding was that this was a PCG run project like others in which the surgery took part. The person named in the telephone call was therefore given access to the surgery's computer database in the mistaken belief that he was from the PCG. The complainant stated that she did not realise that he was a pharmaceutical representative until he was leaving, when he produced promotional material about the project and about the company.

The complainant stated that it was not her practice's policy to grant access to its database to anyone other than practice and healthcare staff and PCG/health authority auditors, for reasons of patient confidentiality. Neither did the surgery wish to find itself in breach of the Data Protection Act.

The complainant stated that the practice would therefore like the immediate return of any disks or paperwork which might contain information about its patients, with a guarantee that no copies had been retained by Trinity. The practice would like the representative to complete, sign and return a confidentiality statement which it gave to all visitors to the practice who did not belong to the above mentioned groups of personnel.

When writing to Trinity the Authority requested that it consider the requirements of Clauses 2, 9.1, 15.2 and 15.5 of the Code.

RESPONSE

Trinity explained that the PCG prescribing adviser had been seen on numerous occasions by another of its medical representatives and was now broadly supportive of practices within her area switching over to the Trinity range of modified release products. The prescribing adviser had asked this second representative to work with all practices within the PCG and to clarify to those practices the savings which could be made if that practice took a decision to switch over to the Trinity range of products. This particular PCG area overlapped geographically onto the territory of the first representative, so consequently he was asked to cover relevant practices within his territory and to explain the benefits of switching key products over to the Trinity portfolio.

Trinity noted that the key issue here was that upon the involvement of the first representative, he visited the complainant's practice and on this occasion failed to introduce himself by means of a company business card – which was strictly against company guidelines.

The complainant alleged that the representative misled the practice into believing that he was working directly on behalf of the PCG. However the representative claimed that although he opened the interview by stating that he had the support of the local PCG, he made it quite clear that he was employed as a Trinity representative and in addition left a company sales aid and an umbrella clearly branded as 'Trinity Pharmaceuticals'.

Trinity submitted that the representative was then allowed to discuss details of the initiative which resulted in the practice agreeing to undertake a practice audit. The practice audit involved looking at numbers of patients and at no time were any confidential personal patient details accessed, nor were any details removed from the practice.

Trinity stated that the representative had been formally reprimanded following his failure to adhere to company policy – which was the cause of the confusion created with the practice manager. The second representative had contacted the PCG

prescribing adviser again and a new agreement had been formalised between the PCG and Trinity which would allow the second representative to work directly with those practices falling within the geography of her own territory. For those practices which fell within the first representative's territory, it had been agreed that the second representative would personally introduce him and full company procedure would be followed. The first representative had formally apologised to the practice for the misunderstanding caused and in addition all company personnel had been strongly reminded of correct company procedure.

In response to a request for further information Trinity confirmed that the initial telephone call to the practice was made by the first representative. As far as was known he stated that he had been working with the PCG in question although on arrival at the surgery he presented a Trinity business card to the complainant. The representative was given access to the computer database but the audit performed was an anonymous one, only giving details of patient numbers (no individual patient details were revealed).

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that with regard to her letter of complaint to Trinity, she had received no written response or acknowledgement from the company. The representative signed the confidentiality statement which she had enclosed in her letter, and had returned it to her in person and apologised for the misunderstanding. He had said that in his original telephone call to her he had told her that he was from a pharmaceutical company. The complainant stated that she had no recollection of pharmaceutical companies being mentioned and that if she had known that he was a representative when he made his original call, she would have referred him on to one of the GPs who normally saw representatives. The complainant stated that she was entirely under the impression that he was from the PCG. She believed that hers was not the only practice which was under this impression, otherwise she would have given him the benefit of the doubt and thought that she had simply misinterpreted the contents of his original call.

The complainant noted that Trinity stated that the representative had presented a business card on arrival. He certainly did not do this. He was given a desk and computer on which to do his audit. The complainant stated that she was quite busy at the time and being totally under the impression that he was from the PCG she left him to get on with the audit. The audit did not take long but when the representative was about to leave the complainant noticed that he was not wearing an identification badge which members of the PCG usually wore when they visited. When the complainant asked him where his badge was he said that he had a business card in his car, and this was the first inkling that she had that he was not from the PCG. He went out to fetch a business card but returned without one because he had none left. The representative brought in three company umbrellas and some promotional material about his project. The complainant stated that the promotional information should really have been presented to her or the GPs before the representative came to do the audit. Had he done that, no misunderstanding would have arisen.

The complainant stated that she had to accept Trinity's word that the audit was anonymous. This was the main cause of her anxiety as the practice would not like to be seen to be in breach of patient confidentiality.

PANEL RULING

The Panel noted that the complainant claimed that the representative had not made it clear when he introduced himself to her that he was employed by a pharmaceutical company; the complainant was under the impression that he was from the PCG.

The Panel noted that there was an inconsistency in Trinity's response with regard to the way in which the representative introduced himself. In its initial response Trinity stated that the representative had not introduced himself by means of a company business card. He had opened the interview by stating that he had the support of the local PCG although Trinity stated that he made it quite clear that he was a company representative. Following a request for further information Trinity again stated that the representative referred to working with the PCG but that he did give a business card to the complainant upon arrival at the surgery.

The Panel considered that it was difficult to tell exactly what had happened with regard to the representative's use of a business card given that the company's response was inconsistent. The complainant maintained that no business card was given to her. Trinity had stated that the representative had been formally reprimanded for his failure to adhere to company policy which the Panel assumed was his failure to introduce himself by means of a company business card. Bearing in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint, the Panel considered that, on the balance of probability, no business card had been offered when the representative had first met the complainant.

The Panel considered that it was incumbent upon representatives to ensure that the people they spoke to knew immediately that they were company representatives. By not introducing himself at the outset by means of a company business card, and by opening the interview with a reference to the PCG, the representative had misled as to his identity and that of the company he represented. A breach of Clause 15.5 was ruled. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and a breach of Clause 15.2 was ruled.

The Panel considered that the possible breach of Clause 9.1 was covered by its ruling of a breach of Clause 15.2 of the Code. The Panel noted that Clause 2, which stated that activities associated with promotion must not bring discredit upon or reduce

confidence in the pharmaceutical industry, was used as a sign of particular censure and reserved for such circumstances. The Panel considered that the circumstances did not warrant such a ruling.

In the Panel's view there was no complaint about the audit itself. The Panel noted that no patient details had been accessed by the representative. No rulings were made with regard to the audit.

During its consideration of this case the Panel noted that Clause 18.2 of the Code stated that gifts in the form of promotional aids had to be relevant to the practice of the recipient's profession or employment. The representative had given the practice three umbrellas. The Panel queried the relevance of an umbrella to the practice of medicine and to the employment of a practice manager. The Panel requested that its concerns be drawn to Trinity's attention.

Complaint received **30 May 2001**

Case completed **6 August 2001**

CASES AUTH/1192/6/01 and AUTH/1193/6/01 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v PROCTER & GAMBLE and AVENTIS PHARMA

Actonel mailing

A general practitioner complained about a package he had received from Procter & Gamble and Aventis Pharma as part of the companies' promotion of Actonel (risedronate) for the treatment of established postmenopausal osteoporosis. The package consisted of a 2.5cm deep cardboard box which was a little larger than A4 size. The top face of the box was headed 'Multifunctional Electronic Calendar Offer' in large red letters; to the left was a picture of the electronic calendar branded with the Actonel product name. The face of the box featured an 'X-ray' of an alarm clock, which included space for the postal address, and the phrase 'Alarm Bells are Ringing...'; the bottom right hand corner was marked 'URGENT' in large red letters.

The complainant noted that the package was marked 'URGENT' in bold red letters measuring 1.5cm high and the word was 5cm long. Enclosed was a glossy brochure for a non-essential, expensive medicine. The complainant noted that he was also invited to win an electronic calendar and that, ironically, the package was posted second class. As a busy GP the complainant considered that only urgent things should be marked as urgent. For pharmaceutical companies to send unsolicited mail advertising their products as urgent was highly irresponsible and a dangerous practice.

The Panel considered that the wording and design on the front face of the box would make it unlikely that recipients would think that it had come from an official source. Clear reference was made to a 'Multifunctional Electronic Calendar Offer' and a picture of the electronic calendar included the Actonel product logo. The box was glossy and colourful. Given the overtly promotional appearance of the package the Panel did not consider that the use of the word 'Urgent' was unacceptable. Once opened the content of the box clearly promoted Actonel. The Panel did not consider that the mailing failed to recognise the special nature of medicines or the professional standing of the recipients. Whilst bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint, the Panel did not consider that the mailing would cause offence to the majority of its recipients. The Panel did not consider that the promotional nature of the mailing had been disguised. The Panel ruled no breach of the Code.

A general practitioner complained about a package he had received from Procter & Gamble Pharmaceuticals, UK Ltd and Aventis Pharma Ltd as part of the companies' promotion of Actonel (risedronate) for the treatment of established postmenopausal osteoporosis. The package consisted of a 2.5cm deep cardboard box which was a little larger than A4 size. The top face of the box was headed 'Multifunctional Electronic Calendar Offer' in large red letters; to the left was a picture of the electronic calendar branded with the Actonel product name. The face of the box featured an 'X-ray' of an alarm clock, which included space for the postal address, and the phrase 'Alarm Bells are Ringing...'; the bottom right hand corner was marked 'URGENT' in large red letters.

COMPLAINT

The complainant noted that the package was marked 'URGENT' in bold red letters measuring 1.5cm high and the word was 5cm long. Enclosed was a glossy brochure for a non-essential, expensive medicine, a bisphosphonate which helped prevent post-menopausal women's bones from thinning. The complainant noted that he was also invited to win an electronic calendar and that, ironically, the package was posted second class.

The complainant stated that as a busy GP he received numerous letters and other messages daily. It was essential to prioritise the urgency of these. He considered that only urgent things should be marked

as urgent. For instance, at Christmas he received a fax from his local public health department marked 'urgent' notifying him of a case of meningococcal meningitis. This undoubtedly was of immediate urgency. For pharmaceutical companies to send unsolicited mail advertising their products as urgent was highly irresponsible and a dangerous practice. The complainant stated that he had written to the companies in the strongest terms but had heard nothing in two weeks (perhaps they were not treating it as urgent!).

When writing to Procter & Gamble and Aventis, the Authority requested that they bear in mind the requirements of Clauses 9.1 and 10.1 of the Code.

RESPONSE

Procter & Gamble and Aventis Pharma submitted a joint response and stated that they considered that the material in question was clearly a promotional piece. In that context, the use of the word 'Urgent' was acceptable as it referred to the need for urgent treatment of women at risk of further vertebral fractures.

The outside of the mailer was clearly identifiable as a promotional item from a pharmaceutical company: it was colourful, and the brand name of the product (accompanied by the generic name and the dose form) appeared prominently at the top of the piece as well as the words 'Multifunctional Electronic Calendar Offer'. In particular, the companies considered that the word 'Offer' was very unlikely to appear on any non-promotional correspondence. For these reasons, they did not consider that the mailer was likely to be misunderstood to be a communication from an official source such as a health authority or hospital. Procter & Gamble and Aventis stated that it was certainly not their intention to cause any such misunderstanding. Therefore, with regard to Clause 10.1, the companies did not believe that the outside of the mailer in any way implied that the contents were non-promotional.

The respondents submitted that the remainder of the outside of the mailer was, understandably, designed to raise a doctor's interest in the more detailed information inside the package. The phrases 'Alarm bells are ringing...' and 'Urgent' next to an X-ray of an alarm clock were all intended to convey a sense of urgency, which was explained further within the mailer itself. On the front page of the brochure, the word 'OSTEOPOROSIS' was most prominent on the page; in fact the specific treatment population, established postmenopausal osteoporosis, was the first wording at the top of the page. The reason for urgency and the X-ray and clock imagery were included because osteoporosis was not perceived by health professionals to be a condition requiring urgent intervention. However, there was recent data showing 1 in 5 postmenopausal women with established osteoporosis fractured again within one year of sustaining an incident vertebral fracture (Lindsay 2001) and the subsequent risk increased with each prevalent fracture (Cooper 2000). There were also recent data highlighting the increased mortality associated with vertebral fractures (Kado 1999; Center 1999), challenging the belief that only hip fractures were responsible for osteoporosis-related deaths. Together, these findings were changing the perception of osteoporosis; once seen as a slowly developing condition, it was now recognised that the rapid progression of the disease from the initial vertebral fracture had significant clinical importance. Once a woman had suffered a vertebral fracture, use of a rapidly acting therapy could help prevent a cascade of subsequent fractures. In fact, Lindsay stated that 'The increased fracture risk in the immediate period following a fracture demonstrates the urgency of identification and intervention for this segment of the population'.

Procter & Gamble and Aventis explained that mailers were designed to be read by a busy doctor, so this message of urgency in preventing the next fracture must be conveyed succinctly. All of the wording and imagery used intended to do this, starting with the 'Alarm Bells are Ringing...' and 'Urgent' wording, continuing through the X-ray and clock imagery, and then in the '1 in 5' statement in the brochure concerning women who had already had a fracture (ie those suffering from established postmenopausal osteoporosis). With regard to Clause 9.1, the companies did not believe that this message of urgency was likely to cause offence to the majority of the audience.

In summary, the companies believed that this mailer was clearly a promotional piece and the use of the word 'Urgent' was acceptable in this context.

Procter & Gamble and Aventis regretted that the complainant did not receive a prompt response to his initial letter. This was due to a delay in receiving the letter, which had been sent to the mailing company. As soon as the companies were aware of his letter they replied and a copy of the letter was provided. Procter & Gamble and Aventis stated that they had already worked with the mailing company to put procedures in place to ensure that in future, any replies that were intended for either company were identified and forwarded promptly.

PANEL RULING

The Panel considered that the wording and design on the front face of the box would make it unlikely that recipients would think that it had come from an official source. Clear reference was made to a 'Multifunctional Electronic Calendar Offer' and a picture of the electronic calendar included the Actonel product logo. The box was glossy and colourful. Given the overtly promotional appearance of the package the Panel did not consider that the use of the word 'Urgent' was unacceptable. Once opened the content of the box clearly promoted Actonel. The Panel did not consider that the mailing failed to recognise the special nature of medicines or the professional standing of the recipients. Whilst bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint, the Panel did not consider that the mailing would cause offence to the majority of its recipients. The Panel did not consider that the promotional nature of the mailing had been disguised. The Panel ruled no breach of Clauses 9.1 and 10.1 of the Code.

During its consideration of this case the Panel noted the size of the cardboard package – 2.5cm deep and approximately 2cm larger all round than A4. Inside was a four page A4 brochure, a four page A5 brochure and a pen. The size and form of the package was such that it would be too large for a standard letterbox. The Panel queried whether the package met the requirements of Clause 9.6 of the Code which stated *inter alia* that extremes of size of promotional material must be avoided. The package was much larger than that necessary for sending the contents. The Panel requested that its concerns in this regard be conveyed to the companies.

Complaint received **13 June 2001**

Case completed **27 July 2001**

CASE AUTH/1194/6/01

ASTRAZENECA v NOVARTIS

Femara mailing

AstraZeneca complained about a Femara (letrozole) mailing produced by Novartis. The claim 'More potent than anastrozole [AstraZeneca's product Arimidex] at suppressing oestrogen in advanced breast cancer patients' appeared half way down a page headed 'Femara – clear advantages in early and advanced breast cancer'. Immediately beneath the heading were claims for Femara versus tamoxifen based on the results of a clinical trial. AstraZeneca noted that the claim in question, however, was referenced to a small pharmacology study and that there were no head-to-head clinical comparisons of letrozole and anastrozole. In the absence of such data the claim for superior potency was of no clinical relevance and therefore misleading by implication. AstraZeneca also alleged that the claim *per se* was misleading because any significant differences between letrozole and anastrozole with regard to suppressing oestrogen in breast cancer patients could not, in the absence of supporting clinical data, be extrapolated to infer a significant difference in clinical efficacy. In addition no statistically significant differences in oestradiol suppression had been shown (oestradiol was the target hormone to manipulate in breast cancer) in the study of only 12 patients.

The Panel did not accept Novartis' submission that because the claim was presented in a different style and format to those above it, readers would know that it was not related to clinical efficacy. It was assumed that promotional material related to the clinical situation unless it was clearly stated otherwise. The Panel considered that within the context in which it appeared the claim implied that letrozole was more clinically effective than anastrozole which was misleading. A breach of the Code was ruled.

The Panel considered that the difference in oestrogen suppression between the products was relevant although, as ruled above, it could not be extrapolated to infer a difference in clinical efficacy. Reference to oestrogen suppression was not unacceptable given that the Femara summary of product characteristics also referred to oestrogen suppression. In the circumstances the small size of the study was not considered a problem; the data had been widely accepted. The Panel did not consider that the reference to oestrogen instead of oestradiol and the size of the study made the claim misleading as alleged. No breach of the Code was ruled.

AstraZeneca UK Limited complained about a Femara (letrozole) mailing (ref FEM/01/09) produced by Novartis Pharmaceuticals Limited and sent to medical and clinical oncologists. The mailing announced that Femara was now the first hormone therapy licensed for first-line (preoperative) treatment of advanced breast cancer. AstraZeneca marketed Arimidex (anastrozole). Both letrozole and anastrozole belonged to a class of medicines known as aromatase inhibitors.

Page 3 of the mailing was headed 'Femara – clear advantages in early and advanced breast cancer'. Immediately below the heading were claims for Femara versus tamoxifen based on the results of a clinical trial. The claim in question 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients' appeared half way down the page and was the first of three comparing Femara with other therapies for breast cancer.

COMPLAINT

AstraZeneca noted that the claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients', although misreferenced, was based on a small (n=12) pharmacology study (Geisler *et al* 2000) which compared the effects of letrozole and anastrozole on hormonal levels of oestradiol, oestrone and oestrone sulphate. There were however no direct head-to-head clinical comparisons of letrozole and anastrozole to substantiate the clinical relevance of this potency claim which was being used to support the heading 'Femara – clear advantages in early and advanced breast cancer'. In fact there were no clinical trials which compared letrozole with anastrozole and according to Hamilton and Piccart (1999), 'Without direct comparison, the best third-generation aromatase inhibitor at a clinical level remains undefined'.

AstraZeneca noted that in marked contrast, the heading to page 2 of the mailing, 'Femara – proven superior to tamoxifen as first-line therapy in advanced breast cancer', was clearly supported with entirely

clinical comparative data. Specifically, the superiority of letrozole over tamoxifen was supported by data on the widely accepted clinical endpoints of time to progression, time to treatment failure, objective response and clinical benefit. The reader could then reasonably expect to see similar clinical endpoint data to support the heading to page 3. However, as already alleged above, a misleading potency claim was being used to support the heading.

AstraZeneca noted that Clause 7.2 of the Code stated that companies should take particular care when using claims for superior potency which 'are generally meaningless and best avoided unless they can be linked with some practical advantage'. In this instance AstraZeneca was of the opinion that, in the absence of any comparative clinical data for letrozole and anastrozole, this potency claim was of no clinical relevance and therefore was misleading by implication. AstraZeneca therefore alleged a breach of Clause 7.2 of the Code.

Secondly, AstraZeneca stated that the claim misled directly for the following reasons:

- Any significant differences observed between letrozole and anastrozole with regard to suppressing oestrogen in breast cancer patients could not, in the absence of supporting clinical data, be extrapolated to infer a significant difference in clinical efficacy.
- No actual statistically significant differences in the levels of suppression of oestradiol, the major active oestrogenic steroid (Santen 1987) and therefore the target hormone to manipulate in breast cancer (Klijn *et al* 2001 and Santen 1989), were actually shown. The only statistically significant differences were shown for the suppression of oestrone and oestrone sulphate levels. Unlike oestradiol, oestrone sulphate was unable to bind to oestrogen receptors and therefore stimulate tumour growth (Purohit 1999).

For the above two reasons, AstraZeneca believed this potency claim, *per se*, to be misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Novartis stated that the mailing had been designed for, and was exclusively sent to, medical and clinical oncologists who were highly specialised medical professionals and formed a specialist user group for the company's products. Oncology was a highly specialised and complex area of medicine and the clinicians using the various products were clearly experts in their field.

Novartis stated that the mailing represented a summary of the key data regarding the first-line metastatic use of Femara versus tamoxifen. On page three, in addition to representing the preoperative data for early and local advanced breast cancer, the mailing summed up relevant new and existing data on Femara. The bottom half of page three summarised data which did not relate to the new indications. It was at this point where Novartis introduced the potency of letrozole on its target enzyme, aromatase, and its subsequent effects on oestrogen suppression which had been evaluated in comparison to anastrozole. Studies with other comparative compounds as baseline were planned or ongoing. The distinction between these two areas was clearly differentiated by a change in copy format through the lack of bullet points, a different typeface and paragraph setting for the data not relating to the new indications. Novartis therefore disagreed with AstraZeneca that there was any intent to mislead the expert readership.

Novartis noted that the page at issue was headed 'Femara – clear advantages in early and advanced breast cancer'. This claim highlighted the fact that in preoperative patients Femara was a more effective alternative to tamoxifen and this was qualified by two bullet point pieces of text. A similar heading and bullet point format was used on page two to support the heading 'Femara – proven superior to tamoxifen as first-line therapy in advanced breast cancer'.

The main purpose of the item was to highlight the new indications in first-line therapy. This was emphasised on the front page of the item. The data outlined on page two and the top part of page three highlighted the data supporting these two new indications.

The claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer' was referenced to Dowsett's presentation at the European Breast Cancer Conference 2000 at which for the first time oestrogen suppression data and aromatase inhibition data were presented together in Europe. It was thus not incorrectly referenced and a copy of the abstract was provided.

Novartis noted that Dowsett and Geisler were co-authors of the same study; AstraZeneca's case of inaccurate referencing was thus refuted.

With regard to the study in question and AstraZeneca's contention of the small sample size, Novartis noted that the study size was consistent with the purpose and statistically powered to show greater potency in oestrogen suppression. It would have been unethical to include more than the required number of patients.

The design had been chosen by the world's leading experts in aromatase measurement and oestrogen determination. The study design and its data had on several occasions been peer reviewed and published. It had also been provisionally accepted by the Journal of Clinical Oncology (the world's leading peer reviewed oncology publication). The senior authors as well as other leading authorities in the field of aromatase inhibition were prepared if necessary to provide statements to this effect. Novartis also noted that AstraZeneca had collaborated in the past with the same group to produce similar data for anastrozole employing the same methodology (Geisler *et al* 1996).

Novartis stated that the claim only referred to potency and not clinical efficacy. The claim of superior potency in oestrogen suppression was by no means associated to a clinical efficacy claim. The word potent was printed in red to raise the reader's awareness to this fact. The potency of the medicine on its target enzyme aromatase and its subsequent effects on

oestrogen suppression which had been evaluated in comparison to anastrozole were clearly relevant if one discussed targeted therapy in cancer.

Novartis repeated that the clinicians who would have received the mailing were experts in their field and disagreed that all data presented should require similar clinical endpoints. Novartis was confident that health professionals involved in the use of such products would be able to interpret the statements in the way in which they were intended and would find the interpretation suggested by AstraZeneca too far removed from clinical practice.

The misquoting of Clause 7.2 by AstraZeneca to support its complaint appeared to be made from a position in order to legitimise the complaint. This clause when properly quoted stated that 'claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage'.

Novartis therefore did not consider that a complaint under Clause 7.2 was appropriate as no claim had been made in relation to comparative weights in relation to potency.

Novartis believed the AstraZeneca suggestion to be inappropriate in its claim that the pharmacological effect on the target enzymes for this class of medicines were meaningless given that they had performed and co-authored studies to this effect themselves.

Novartis did not consider that it had breached Clause 7.2 as alleged.

Novartis stated that the results of the study by Geisler *et al* were first presented in a peer-reviewed abstract accepted for presentation as a poster at the Annual Meeting of the American Society of Clinical Oncology (ASCO) meeting in May 2000. The results and statements about the data were taken from this peer-reviewed abstract and were accurate and scientifically and medically sound. The authors concluded 'Letrozole achieves more complete aromatase inhibition and plasma oestrogen suppression than anastrozole in postmenopausal women'. The study was subsequently presented at several other international meetings and had been provisionally accepted by the Journal of Clinical Oncology for publication. Oestradiol in the circulation was a composite of conversions of androgen and oestrone sulphate to oestradiol. This formed the basis of sustained work from several laboratories on the inhibition of the sulphatase enzyme as a therapeutic modality for reducing circulating oestradiol.

In fact, oestrone and oestrone sulphate were the major components in the circulation of postmenopausal women by either weight and/or percentage. From the Geisler abstract, it was clearly evident that oestrone sulphate was the largest component of the three oestrogens measured followed by oestrone and oestradiol in that order.

Furthermore, the inability to show significance in oestradiol reduction might be more accurately related to the fact that the detection threshold of the current diagnostic tests was limited. In the similar study sponsored by AstraZeneca employing the same method it was found that: 'Plasma levels of E2 (oestradiol) and E1 (oestrone) were measured with sensitive methods previously validated in our laboratories. However, owing to the low levels of these oestrogens (mean concentration of plasma E2 and E1 of about 20 and 75 pmol/l) in post-menopausal women it remains difficult to detect >90% suppression of these oestrogens from pretreatment levels. On the other hand, the oestrogen conjugate E1S (oestrone sulphate) is found in much higher concentrations than E2 and E1 in post-menopausal women'.

In summary, and consistent with conclusions drawn from previous studies, the senior authors of the study in question (Loenning and Dowsett), the peer-reviewed Journal of Clinical Oncology, other leading experts in the field and Novartis considered that the study, as presented, fully supported the claim made in its conclusion: 'Letrozole achieves more complete aromatase inhibition and plasma oestrogen suppression than anastrozole in postmenopausal women'. This view was further supported by the references cited above.

Novartis therefore rejected AstraZeneca's allegation of a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim in question 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients' appeared half way down a page headed 'Femara – clear advantages in early and advanced breast cancer'. Immediately beneath the heading to page three were claims for Femara versus tamoxifen which related to results from a clinical trial. The Panel did not accept the submission that because the claim in question was presented in a different style and format to the claims above it, readers would know that the claim was not related to clinical efficacy. The claims below the claim in question were claims for superior efficacy and for an equal or superior safety profile compared to the identified comparators. The Panel noted that it was assumed that promotional material related to the clinical situation unless it was clearly stated otherwise.

The Panel noted that the cited study was a double-blind cross-over comparison of letrozole and anastrozole in 12 postmenopausal women with metastatic breast cancer. Patients received 6 weeks' therapy with each treatment option. The study showed that letrozole was a more potent suppressor of plasma oestrogen levels than anastrozole; differences had been shown for the suppression of oestrone and oestrone sulphate in favour of letrozole compared to anastrozole. There was no difference between letrozole and anastrozole with regard to oestradiol suppression. The authors did not extrapolate the results to the clinical situation. It was noted that a study comparing the clinical effects of letrozole and anastrozole as second-line therapy in metastatic breast cancer was expected to report in 2001.

The Panel considered that within the context in which it appeared the claim for greater potency for letrozole

at suppressing oestrogen compared to anastrozole implied that letrozole was more clinically effective. The style and layout of the page did not negate this impression. The Panel considered that this was misleading as alleged and a breach of Clause 7.2 was ruled. In that regard the Panel considered it irrelevant that the claim did not refer to potency by weight.

With regard to the second allegation which referred to the size of the study and the fact that the study showed no statistically significant differences in the level of suppression of oestradiol, the Panel noted Novartis' submission that the study size was consistent with the purpose of the study. The Panel noted that the claim referred to a greater suppression of oestrogen. Section 5.1 of the Femara summary of product characteristics (SPC) stated that in postmenopausal women (the patient population for whom the product was indicated) oestrogens were mainly derived from the action of the aromatase enzyme, which converted adrenal androgens, androstenedione and testosterone, to oestrone and oestradiol. In patients with advanced breast cancer a daily dose of 0.1 to 5mg Femara suppressed plasma concentration of oestradiol, oestrone and oestrone sulphate in all patients treated. With doses of 0.5mg and higher many values of oestrone and oestrone sulphate were below the limit of detection in the assays indicating that high oestrogen suppression was achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

The Panel noted that the mechanistic goal of breast cancer therapies was to reduce the amount of oestradiol acting locally on the tumour and that after the menopause the amount of testosterone produced by the adrenal gland and converted peripherally to oestradiol was negligible (Santen 1989). The Panel noted Novartis' submission that the detection threshold of current diagnostic tests was limited. The reference cited in support of the claim in question had shown no significant difference between letrozole and anastrozole in the suppression of oestradiol.

The Panel considered that differences in oestrogen suppression between the products, although relevant, could not be extrapolated to infer a difference in clinical efficacy. This was covered by the ruling already made. The reference to oestrogen suppression was not unacceptable given the information in the SPC. The Panel did not consider that in the circumstances the small size of the study was a problem; the data had been widely accepted. The Panel did not consider that the reference to oestrogen instead of oestradiol and the size of the study made the claim misleading as alleged. No breach of Clause 7.2 was ruled in that regard.

Complaint received **13 June 2001**

Case completed **25 July 2001**

CASE AUTH/1195/6/01

VOLUNTARY ADMISSION BY BAYER

Conduct of representatives

Bayer voluntarily advised the Authority of activities on the part of certain of its representatives which had come to light.

One of its representatives had brought to Bayer's attention activities that his team were being asked to participate in with which they were not comfortable. Bayer had immediately suspended the regional business manager responsible and carried out a full investigation, including interviewing all the employees within the region as well as certain GPs and practice staff. Bayer's investigations were complete and the regional business manager had been dismissed. Two representatives had also left the company. The activities involved the use of unapproved promotional material, breaches of patient confidentiality and the taking of pin prick samples of blood by representatives.

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

The Panel considered that Bayer had acted responsibly when the matters had been brought to its attention. It seemed inequitable that a company which took the correct steps and informed the Authority about what had happened might be in a worse position than a company which attempted to hide any wrongdoing. Nevertheless the matters were serious and the Appeal Board's advice had to be followed. Companies were responsible for the activities of their representatives even if they were acting contrary to the instructions which they had been given.

The Panel noted that two booklets issued by the company had been amended and used by the regional business manager. One booklet headed 'Change of Heart Programme Practice Effective Prescribing' described a computer based system that analysed prescribing and identified areas where costs could be reduced without ignoring other prescribing parameters. The booklet set out the agreements for carrying out an audit. The other booklet was headed 'Change of Heart practice effective prescribing' and featured a section headed 'The treatment' followed by the suggestion that patients not currently controlled on their existing statin dose be titrated to cerivastatin (Bayer's product Lipobay) where appropriate. Participants were to sign an agreement to proceed with the clinic and the prescribing revisions.

The Panel considered that the regional business manager had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. Neither document had been certified by Bayer. A breach of the Code was ruled as acknowledged by Bayer.

The Panel considered that the second booklet linked the provision of the audit to the switching of patients to Lipobay. The supplementary information of the Code stated that medical and educational goods and services which would enhance patient care and benefit the NHS could be provided. This must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. By linking the audit to the prescribing of Lipobay the arrangements as described amounted to an inducement to prescribe Lipobay. A breach of the Code was ruled.

The Panel noted that representatives had had access to patient details, albeit at the request of the practices. This was not specifically prohibited by the 1998 edition of the Code but was in the Panel's view totally unacceptable. The Panel considered that the activities of the regional business manager and of the representatives meant that they had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. A breach of the Code was ruled as acknowledged by Bayer.

The Panel noted that representatives had, with the permission of a practice nurse and general practitioner, taken blood samples (finger-pricks) from patients during cholesterol screening clinics. The Panel considered that this was unacceptable. It noted that Bayer instructed representatives that the finger-prick procedure had to be carried out by medical professionals only and not by Bayer personnel. The Panel considered that the representatives had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. A breach of the Code was ruled as acknowledged by Bayer.

The Panel noted that Clause 2 of the Code was used as a sign of particular censure and reserved for such circumstances. The Panel noted that the employees had acted contrary to Bayer's instructions. On discovering the activities Bayer had taken action. The regional business manager had been dismissed and two representatives had left and Bayer had volunteered the information to the Authority. Nevertheless the regional business manager had produced and used unapproved material which had linked the audit to prescribing Bayer's product. Representatives had been given access to patient details and some had taken finger-prick blood samples. Taking all the circumstances into account the Panel considered that despite the action taken by Bayer the activities of the regional business manager and the representatives had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

Bayer plc, Pharmaceutical Division, voluntarily advised the Authority about representative activities that had come to light.

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

Bayer stated that a representative had brought to Bayer's attention certain activities that his team were being asked to participate in with which they were not comfortable. Bayer immediately suspended the regional business manager responsible and carried out a full investigation including interviewing all the employees within the region involved as well as certain GPs and practice staff. Bayer's investigations were complete and the regional business manager had been dismissed. Two representatives had also left the company.

There were three activities at issue.

1 The use of unapproved promotional material

Two pieces of promotional material had been issued to staff by the regional business manager.

2 Breaches of patient confidentiality

Three representatives had been given access by practice staff to patients' names, addresses and telephone numbers.

3 Taking of blood samples (finger-pricks)

Three representatives had been involved in taking pin-prick samples of blood at cholesterol clinics albeit under the supervision of a practice nurse. Bayer stated that at no time did the representatives present themselves as qualified to take the blood samples although in several cases the nurse concerned asked the patient's permission. Bayer did not believe that the representative's identity was made known to the patients.

* * * * *

The Director decided that the matters raised were potentially serious and had to be taken up and dealt with as a formal complaint.

Bayer was asked to consider the requirements of Clauses 2, 9.1, 14, 15.2 and 18.1 of the Code.

RESPONSE

Bayer stated that it had brought this matter to the Authority's attention because it voluntarily acknowledged breaching the Code. It accepted that it was responsible for the behaviour and conduct of employees and had taken decisive action concerning the individuals involved in these transgressions and indeed, as a consequence had reinforced its company conduct policy for its representatives. The company was naturally very disappointed that these three individuals behaved in the manner described and wished to reassure the Authority that it took this matter very seriously.

1 Use of unapproved promotional material

Bayer stated that two promotional items were put together by the regional business manager without head office awareness, involvement and approval. This was in direct contravention of Bayer's published company policy.

Bayer stated that all field-generated letters and materials required approval by the regional business manager, the sales manager and the medical operations department. Such a system had been working well for many years.

Bayer believed that it had acted in a proper and appropriate manner as soon as it became aware of this activity. The regional business manager concerned was immediately suspended and the matter fully investigated. This involved senior members of staff formally interviewing all the representatives in the region involved and members of the two practice surgeries that became involved in the actual audit initiative. The materials had since been destroyed. One item was published but never used.

Bayer stated that a single practice did comment on the use of the other item but was assured that such an item and indeed activity, was not sanctioned by the company and that the regional business manager and representative were acting without company approval and endorsement.

Bayer submitted that its decisive action was therefore a credit to its ethical standing in the industry and exemplified its integrity and high sense of moral value. By reporting this incident and engaging in open and candid dialogue it believed it had acted properly with the industry's best interest at heart. The immediate action regarding these three individuals, who were operating outside company policy and the Code, had not brought discredit upon the industry. Bayer thus, submitted that it had not breached Clause 2 of the Code.

With regard to Clause 9.1, Bayer accepted that the two items did not recognise the special nature of medicines or the professional standing of the audience and might have caused offence. It reiterated that the items were produced by a single region for local use without the express knowledge and endorsement of the company. The two items were immediately destroyed (during the first week of March 2001). Bayer accepted that the items were in breach of Clause 9.1 of the Code.

Similarly, it accepted that the two items were not approved according to the internal policy and sign-off procedure. The regional business manager was acting on his own initiative and despite his seniority was clearly negligent in the administration of his duties. Moreover, he wilfully misled his team into believing the materials to be company approved. Bayer therefore accepted a breach of Clause 14 of the Code.

Bayer also accepted that it had breached Clause 15.2 of the Code. However, it would like to reassure the Authority that it was fully conversant with the Code and provided copies to all representatives during their first week with the company. During this week all representatives were required to attend a training session devoted to the Code where company standards for behaviour and conduct were discussed together with policy on what was expected of them. Clear company guidelines had long been published regarding unauthorised materials production and the route for approval of *ad hoc* items. Bayer considered it important to point out to the Authority that the training was fully comprehensive and that documentation on the company's policy was available for consultation by any representative on an electronic database accessible day or night.

2 Audit procedure and breaches of patient confidentiality

Bayer stated that the 'Change of Heart Programme' was designed to assist in the identification of patients at risk of heart disease in general practice. Like many other pharmaceutical companies Bayer facilitated the running of a coronary heart disease risk clinic in surgeries. This involved the loan of a Cholestech machine to the practice nurse for measuring cholesterol levels (via a finger-prick blood sample taken by the practice nurse), the provision of surgery posters advertising the clinic, guidance notes, and personal diaries for patients to record their blood pressure and cholesterol levels. Bayer stated that it made it quite clear in its briefing notes that representatives could not link the offer of this service to prescriptions of any product. The briefing notes stated 'With specific reference to Change of Heart, this means that you cannot make a link between the offering of services (eg the Cholestech LDX) and the request for prescriptions of any of our products.'

As previously mentioned, three representatives were given access to patient names and addresses in order to invite them to attend the risk clinic. This was at the explicit request of the practices. The representatives concerned complied with this request, acting in good faith to support the audit programme. In addition, three representatives were present during the actual screening clinic.

Bayer believed that it had acted in a proper and appropriate manner as soon as it became aware of this matter. It did not accept that it was in breach of Clause 2 for similar reasons to those given in point 1.

Bayer accepted that it had breached Clause 9.1 of the Code. The activity, as carried out by the regional business manager and representatives concerned, was not sanctioned or approved by the company. Furthermore, the activity was not submitted for company approval via the route for such field-based items/activities. Moreover, the activity clearly breached patient confidentiality.

Bayer also accepted that the regional business manager's and representatives' conduct was substandard and below that which was acceptable under the Code and below the high standards that Bayer expected. Bayer thus accepted that there was a breach of Clause 15.2 of the Code.

Bayer accepted that representatives having access to confidential patient information breached the guidelines on the provision of medical and educational goods and services issued by the Authority and published in the Code of Practice Review, November 1999. These guidelines had since been incorporated in the 2001 edition of the Code under the supplementary information to Clause 18.1. Notwithstanding the fact that the new Code would be enforced from September 2001, Bayer accepted that the representative's activities breached the Code.

3 Taking blood samples (finger-pricks)

Bayer stated that three representatives (including a trainee representative in her first week on territory) took blood samples (finger-pricks) from patients during cholesterol screening clinics in two practices. In all three instances this had been agreed with the explicit knowledge of the practice nurse and general practitioner. The practice was aware that the representatives were not medically qualified and took steps to evaluate their finger-pricking technique to ensure that it was acceptable before the start of the clinics. The practice had confirmed that, in most cases, the representative was introduced to the patient as not being medically qualified and that the patient's consent was obtained before blood was extracted via a finger-prick for use in the Cholestech machine.

As before, Bayer believed that it had acted appropriately and did not consider that its actions could be considered to bring the industry into disrepute. It did not accept that it was in breach of Clause 2 for similar reasons to those given in point 1 above.

Bayer stated that its briefing document clearly stated that representatives must not take blood samples themselves, 'Even though this is only a finger-prick procedure, it must be carried out by medical professionals only and not by Bayer personnel'.

Bayer accepted that its usual high standards were compromised by this activity however, because it was sanctioned by both practices, Bayer did not believe that it caused specific offence. The practice nurses from both practices wholly supported the representative's involvement in the running of the clinics and specifically the taking of blood via finger-prick for the Cholestech machine. During the disciplinary process two of the representatives and the regional business manager involved left the company. Nonetheless such an activity contravened Bayer's own policy as well as the Code and Bayer accepted breaches of Clauses 9.1 and 15.2.

Again, Bayer accepted that this activity breached the guidelines on medical and educational goods and

services. Bayer accepted that the representative's activities breached the Code.

As requested a copy of an email to representatives reminding them of their responsibilities in terms of fully complying with the Code and highlighting the specific areas relating to the discovery of the above transgressions was provided. Bayer stated that it had strengthened its specific training relating to the provision of such services.

Bayer reiterated that it considered this matter to be very serious indeed and was very disappointed in the conduct of the four individuals involved.

Finally, Bayer asked that the Authority take into account the fact that it had voluntarily brought this matter to the Authority's attention in the spirit of its commitment to adhere to its tenets.

PANEL RULING

The Panel noted that Bayer had voluntarily provided the information about the conduct of its representatives. It appeared that the company had thoroughly investigated the matters and had taken action. A regional business manager and two representatives had left the company. The Panel considered that Bayer had acted responsibly when the matters had been brought to its attention. It did seem inequitable that a company which took the correct steps and informed the Authority about what had happened might be in a worse position than a company which attempted to hide any wrongdoing. Nevertheless the matters were serious and the Appeal Board's advice had to be followed. Under Clause 15.10 of the Code companies were responsible for the activities of their representatives even if they were acting contrary to the instructions which they had been given.

1 Use of unapproved promotional material

The Panel noted that two booklets issued by the company had been amended and used by the regional business manager. Bayer had not provided details about the differences between the company version and the amendments made by the regional business manager. The first booklet headed 'Change of Heart Programme Practice Effective Prescribing' described a computer based system that analysed prescribing. The programme was described as identifying areas where costs could be reduced without ignoring other prescribing parameters. The booklet set out the agreements for carrying out an audit and mention was made of prescribing amendments as detailed 'on the sheets at the back of this folder' (copies of the sheets had not been provided). The second booklet was headed 'Change of Heart practice effective prescribing'. This included a section headed 'The treatment' followed by the suggestion that patients not currently controlled on their existing statin dose be titrated to cerivastatin (Bayer's product Lipobay) where appropriate. Participants were to sign an agreement to proceed with the clinic and the prescribing revisions.

The Panel considered that the regional business manager had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled as acknowledged by Bayer.

The Panel noted that neither document had been certified by Bayer as required by Clause 14.1 of the Code. It considered that this was covered by its ruling of a breach of Clause 15.2 of the Code.

2 Audit procedure and breaches of patient confidentiality

The Panel considered that the second booklet linked the provision of the audit to the switching of patients to Bayer's product Lipobay. The supplementary information to Clause 18.1 of the Code stated that medical and educational goods and services which would enhance patient care and benefit the NHS could be provided. This must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. By linking the audit to the prescribing of Lipobay the arrangements as described amounted to an inducement to prescribe Lipobay. A breach of Clause 18.1 of the Code was ruled.

The Guidance on the provision of medical and educational goods and services published in the Code of Practice Review, November 1999 clearly stated that representatives should not be involved if the goods and services required patient contact. Representatives could provide administrative support in relation to the provision of a screening service but must not be present during the actual screening. Companies were required to ensure that patient confidentiality was maintained at all times. At the time of the activities in question the Guidance was separate from the Code. It had been included in the supplementary information to Clause 18.1 of the 2001 edition of the Code which came into operation on 1 July.

The Panel noted that representatives had had access to patient details, albeit at the request of the practices. This was not specifically prohibited by the Code but was in the Panel's view totally unacceptable.

The Panel considered that the activities of the regional business manager and of the representatives meant that they had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled as acknowledged by Bayer.

3 Taking blood samples (finger-pricks)

The Panel noted that representatives had, with the permission of the practice nurse and general practitioner, taken blood samples (finger-pricks) from patients during cholesterol screening clinics. The Panel considered that this was unacceptable. It noted that Bayer instructed representatives that the finger-prick procedure had to be carried out by medical professionals only and not by Bayer personnel.

The Panel considered that the representatives had not maintained a high standard of ethical conduct and complied with all the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled as acknowledged by Bayer.

4 Clauses 2 and 9.1

The Panel considered that a possible breach of Clause 9.1 was covered by its rulings of breaches of Clause 15.2.

With regard to Clause 2 of the Code, the Panel noted that it was used as a sign of particular censure and reserved for such circumstances. The Panel noted that the employees had acted contrary to Bayer's instructions. On discovering the activities Bayer had taken action. The regional business manager had been dismissed and two representatives had left and Bayer had volunteered the information to the Authority. Nevertheless the regional business manager had produced unapproved material which had been used in the field. The material had linked the audit to prescribing Bayer's product. Representatives had been given access to patient details and some had even taken finger-prick blood samples. Taking all the circumstances into account the Panel considered that despite the action taken by Bayer the activities of the regional business manager and the representatives brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

Proceedings commenced 19 June 2001

Case completed 20 August 2001

CASE AUTH/1196/6/01

GLAXOSMITHKLINE v AVENTIS PHARMA

Nasacort journal advertisement

GlaxoSmithKline complained about a journal advertisement for Nasacort (triamcinolone nasal spray). It featured the statement 'Special delivery for those hard to reach places' beneath a depiction of a bottle of Nasacort being dropped by a parachute labelled 'thixotropic' and read 'An intranasal steroid produces optimal effects if it gets where it's needed, and stays where it's needed'. Subsequent text referred to delivery to the target tissues and concluded that '… thixotropic Nasacort stays where it's sprayed'. GlaxoSmithKline marketed Flixonase (fluticasone nasal spray). Both Nasacort and Flixonase were for use in seasonal and perennial allergic rhinitis.

GlaxoSmithKline alleged that the claim 'Nasacort has superior deposition in the nasal turbinates than fluticasone. So it gets straight to the nasal mucosa and concentrates in the target tissues' implied that Nasacort was clinically superior to Flixonase, that the prime site of action of intranasal corticosteroids was the nasal turbinates and that deposition of spray elsewhere in the nasal cavity was clinically irrelevant.

GlaxoSmithKline stated that the reference cited in support of the implied claim of superiority was a non-comparative, single-dose study of the deposition of radio-labelled fluticasone nasal spray conducted in six healthy volunteers, without assessment of clinical parameters. Another study examined the deposition of a single dose of radio-labelled triamcinolone nasal spray. In these separate studies comparable levels of deposition throughout the nasal passages were achieved, when the results for different parts of the nasal passages were summated. In addition, there was no evidence to support the claim concerning Nasacort 'So it gets straight to the nasal mucosa and concentrates in the target tissues'. This claim was thus not only misleading, but also lacked clinical relevance, as comparative studies showed no significant differences in efficacy between Nasacort and Flixonase in the treatment of rhinitis. The claim was based on the implication that the clinical efficacy of intranasal corticosteroids was due to direct deposition on the nasal turbinates (and that presumably deposition in other areas of the nasal cavity did not contribute to clinical efficacy). There was no evidence to support this assumption. Clinical data found no significant difference between Nasacort and Flixonase in terms of nasal obstruction, a symptom that might be expected to correlate strongly with inflammation and swelling of the turbinates. This suggested that any claimed difference in deposition on the turbinates rather than the nasal mucosa as a whole was not clinically relevant. The advertisement also included the claim that '… 85% of Nasacort is delivered to the target tissues'. According to the poster from which this claim was derived 'target tissues' must include both the nasal cavity and the turbinates. Based on the same poster the delivery of fluticasone to the same 'target tissues' was between 78% and 84%. GlaxoSmithKline alleged that the claim of superiority of Nasacort over Flixonase based on deposition data was misleading and at odds with the clinical data.

The Panel considered that the claim at issue implied that Nasacort produced superior clinical outcomes compared with fluticasone. There was no direct comparative clinical data. The cited studies were non-comparative and related to deposition data in healthy volunteers with no assessment of clinical parameters. It was not made clear that the data was derived from human volunteer studies and nor was it demonstrated that the data was of clinical significance. The Panel considered the claim misleading as alleged and a breach of the Code was ruled.

GlaxoSmithKline stated that use of the word 'special' in the claim 'Special delivery for those hard to reach places' suggested special merit for Nasacort

in relation to all other treatments for hay fever. This was an exaggerated, all-embracing claim that was not supported by available evidence. No evidence was provided to support the claim that the delivery of Nasacort conferred any special benefits. The word 'thixotropic' on the parachute suggested special relevance. However, there was evidence to show that thixotropy was not a property unique to Nasacort. While it had been demonstrated that other aqueous intranasal corticosteroid sprays, as well as Nasacort, were also thixotropic, for all sprays there was no significant thixotropic recovery, ie return of increased viscosity, in the short term (within 5 minutes) and only partial recovery within hours. This suggested that thixotropy was not the controlling factor in determining duration of nasal deposition, rather it was the high viscosity present in all sprays even after the structure breakdown caused by spraying a dose into the nose. This was consistent with other findings which concluded that 'increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal spray preparations'.

The Panel considered that Aventis had submitted no evidence to demonstrate that thixotropy was a property unique to Nasacort and no clinical evidence to show the association between this property and delivery to the target tissues. The Panel considered the claim implied special merit in relation to the delivery of Nasacort and its thixotropic qualities and was thus exaggerated as alleged. A breach of the Code was ruled.

GlaxoSmithKline complained about an advertisement (ref NAS246031) for Nasacort (triamcinolone nasal spray) which appeared in Doctor, 5 April 2001. The advertisement stated that further information was available from Aventis Pharma Ltd. The advertisement featured the statement 'Special delivery for those hard to reach places' beneath a depiction of a bottle of Nasacort being dropped by a parachute labelled 'thixotropic'. The advertisement read 'An intranasal steroid produces optimal effects if it gets where it's needed, and stays where it's needed'. Subsequent text referred to delivery to the target tissues and concluded that '… thixotropic Nasacort stays where it's sprayed'.

GlaxoSmithKline marketed Flixonase (fluticasone nasal spray). Both Nasacort and Flixonase were for use in seasonal and perennial allergic rhinitis.

1 Claim 'Nasacort has superior deposition in the nasal turbinates than fluticasone. So it gets straight to the nasal mucosa and concentrates in the target tissues'

COMPLAINT

GlaxoSmithKline alleged that the claim implied that Nasacort consequently produced superior clinical outcomes compared with Flixonase and that the prime site of action of intranasal corticosteroids was the nasal turbinates, and that deposition of spray elsewhere in the nasal cavity was clinically irrelevant.

With regard to the implied claim of superiority of Nasacort over Flixonase, the poster presentation by Berridge *et al* (1998) cited in support of this claim was a non-comparative, single-dose study of the deposition of radio-labelled fluticasone nasal spray. It was conducted in six healthy volunteers, without assessment of clinical parameters, and with no direct comparison of deposition between Nasacort and Flixonase. The paper by Berridge *et al* (1998), cited as reference 2, separately examined the deposition of a single dose of radio-labelled triamcinolone nasal spray. In these separate studies, comparable levels of deposition throughout the nasal passages were achieved, when the results for different parts of the nasal passages were summated.

GlaxoSmithKline stated that, in addition, there was no evidence to support the claim concerning Nasacort: 'So it gets straight to the nasal mucosa and concentrates in the target tissues'. Pennington *et al* (1998) did not support the claim that Nasacort 'concentrates in the target tissues' as it referred to the slowness of loss of nasally deposited hydroxypropyl methylcellulose sprays in proportion to their viscosities. Indeed, this study did not include Nasacort and was performed several years before this formulation of Nasacort was available.

This claim was thus not only misleading, but also lacked clinical relevance, as studies that had compared the clinical efficacy of Nasacort and Flixonase (Bartal *et al* 2000 and Malone *et al* 2000) showed no significant differences in efficacy between the products in the treatment of rhinitis.

Further, the claim was based on the implication that the clinical efficacy of intranasal corticosteroids was due to direct deposition on the nasal turbinates (and that presumably deposition in other areas of the nasal cavity did not contribute to clinical efficacy). There was no evidence to support this assumption. Clinical data from Bartal *et al* found no significant difference between Nasacort and Flixonase in terms of nasal obstruction, a symptom that might be expected to correlate strongly with inflammation and swelling of the turbinates. This suggested that any claimed difference in deposition on the turbinates rather than the nasal mucosa as a whole was not clinically relevant.

Further, it was worth noting that the advertisement also included the claim that '85% of Nasacort is delivered to the target tissues'. According to the poster by Berridge *et al* (from which this claim was derived), 'target tissues' must include both the nasal cavity and the turbinates. Indeed, based on the Berridge poster the delivery of fluticasone to the same 'target tissues' was between 78% and 84%.

GlaxoSmithKline alleged that the claim of superiority of Nasacort over Flixonase based on deposition data was misleading, at odds with the clinical data, and therefore in breach of Clause 7.2 of the Code.

RESPONSE

Aventis Pharma stated that the claim was not of stated or implied superior clinical outcomes compared with fluticasone. The statement referred only to superior deposition of Nasacort in the turbinates.

The definition of target tissues was explained in the paper by Berridge *et al* which stated that 'The frontal

cavity and the turbinates (the majority of the divided passages through which air is filtered and humidified during passage through the nasal airway) are the most important target regions, and they become inflamed during allergic rhinitis'. There was no implied or stated claim in the advertisement that the turbinates were the only target tissue for intranasal delivery.

Furthermore, this reference stated that 'Deposition of the majority of the dose on the target tissues was immediate' and that 'The majority of the dose was retained in the target area'. This was supported by the definition provided by GlaxoSmithKline that thixotropy was the 'property of becoming temporarily liquid when shaken, stirred etc and returning to a gel state on standing'. Furthermore, as indicated by Pennington *et al*, the solution viscosity might provide a means of prolonging the therapeutic effect of nasal preparations. Therefore Aventis considered that the claim 'It gets straight to the nasal mucosa and concentrates in the target tissues' was justified.

Aventis did not consider the claim to be in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel did not accept Aventis' submission that the claim at issue did not imply superior clinical outcomes compared with fluticasone. The claim was preceded by the statement that 'An intranasal steroid produces optimal effects if it gets where it's needed, and stays where it's needed,' followed by a reference to the delivery of Nasacort to the target tissues. The Panel considered that the context of the advertisement was such that the claim implied that Nasacort's superior deposition in the nasal turbinates and thus concentration in target tissues was such that it was more efficacious than fluticasone.

The Panel noted that the supplementary information to Clause 7.2 in relation to the use of data derived from *inter alia* healthy volunteers stated that care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The claim was referenced to a poster presentation by Berridge *et al*, a paper by Berridge *et al* and Pennington *et al*. In their poster Berridge *et al*, presented a study which was designed to use positron tomography (PET) scans to measure the distribution and kinetics of a fluticasone nasal spray for the treatment of allergic rhinitis for comparison with other formulations in healthy volunteers. The results showed, *inter alia*, 18% deposition on the inferior turbinates which peaked at around 23% at 3 minutes post-inhalation. Superior turbinates received less than 1% of the dose. Turbinate deposition dropped rapidly to 10% at 30 mins and 5% at 3 hours. It was stated that these results contrasted heavily with the authors' previous work with Nasacort which showed 50% of dose deposited on the turbinates, 17% on the superior portion and a maximum of 35% in the nasal cavity. The authors concluded that PET was an effective tool for regional quantitative evaluation and comparison of inhaled drug delivery and kinetics.

The Panel noted that there was no assessment of clinical parameters or direct comparison with Nasacort.

The paper by Berridge *et al* was a pilot study performed to demonstrate the effectiveness of PET scans for drug development and to determine the human biodistribution and kinetics of Nasacort. The purpose of the study was limited to demonstration of the ability of PET to provide this unique type of information and to function effectively for measurement of dose delivery and pharmacokinetics. It was not intended to address clinical use and effectiveness or to assess the delivery system. The study population comprised four healthy female volunteers. The authors stated that triamcinolone was distributed rapidly into the turbinate and sinus areas after administration and this direct *in vivo* evaluation in three healthy volunteers was a more reliable indicator of its performance than inferences drawn from extensive *in vitro* experiments. The authors concluded that the study showed effective deposition of drug into the target tissues and demonstrated that the clearance of drug from the target areas was slow enough to allow significant amounts of drug to be present for at least several hours.

Pennington *et al* assessed the influence of solution viscosity on nasal spray deposition and clearance in eight healthy volunteers and indicated that increasing solution viscosity might provide a means of prolonging the therapeutic effect of nasal spray preparations. The areas of the deposition sites, however, were not statistically different for all solutions.

The Panel considered that the claim at issue implied that Nasacort produced superior clinical outcomes compared with fluticasone. There was no direct comparative clinical data. The cited studies were non-comparative and related to deposition data in healthy volunteers with no assessment of clinical parameters. It was not made clear that the data was derived from human volunteer studies nor was it demonstrated that the data was of clinical significance. The Panel considered the claim misleading as alleged. A breach of Clause 7.2 was ruled.

2 Claim 'Special delivery for those hard to reach places'

COMPLAINT

GlaxoSmithKline stated that use of the word 'special' to describe the delivery of Nasacort suggested special merit for Nasacort in relation to all other treatments for seasonal allergic rhinitis. This was an exaggerated, all-embracing claim that was not supported by available evidence. There was no evidence provided to support the claim that the delivery of Nasacort conferred any special benefits.

The word 'thixotropic' on the parachute suggested special relevance. However, there was evidence to show that thixotropy was not a property unique to Nasacort. Eccleston *et al* (2000) demonstrated that other aqueous intranasal corticosteroid sprays, Flixonase (fluticasone), Beconase (beclomethasone) and Nasonex (mometasone), as well as Nasacort, were also thixotropic. However, this investigation also

reported that, for all sprays, there was no significant thixotropic recovery, ie return of increased viscosity, in the short term (within 5 minutes) and only partial recovery within hours. This suggested that thixotropy was not the controlling factor in determining duration of nasal deposition, rather it was the high viscosity present in all sprays even after the structure breakdown caused by spraying a dose into the nose. This was consistent with the findings of Pennington *et al* which concluded that 'increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal spray preparations'.

GlaxoSmithKline also noted that there was no evidence that the delivery of Nasacort resulted in any clinical advantages over Flixonase. As stated under point 1 above, Bartal *et al* and Malone *et al* showed no significant differences in clinical efficacy between the products in the treatment of rhinitis. Further both products were licensed for once daily administration.

GlaxoSmithKline alleged that the use of the word 'special' to describe the delivery of Nasacort was both exaggerated and suggested special merit in breach of Clause 7.8 of the Code.

RESPONSE

Aventis stated that by nature of its formulation, Nasacort was thixotropic; this property differentiated the delivery of Nasacort from other compounds and therefore provided a special property. In the advertisement the parachute was labelled 'thixotropic' and the words 'special delivery' referred to the delivery of a thixotropic agent to the target tissues and its retention there. Aventis cited the paper by Berridge *et al*.

PANEL RULING

The Panel noted Aventis' submission that special delivery related to the delivery of a thixotropic agent to the target tissues and its retention there and that the thixotropic nature of Nasacort differentiated it from other compounds.

The Panel noted that Ecclestone *et al* was an *in vitro* study which compared the rheological profiles of Beconase, Nasacort, Flixonase and Nasonex. The authors stated that corticosteroid nasal spray suspensions were generally formulated to be thixotropic as they required high apparent viscosity at rest to inhibit particle sedimentation but should thin down significantly when shear was applied (eg by shaking the container) to redispose the drug before use. The authors concluded that all the nasal spray suspensions were shear thinning and thixotropic to different degrees. Although the correlation of such *in vitro* experiments with the *in vivo* situation must be approached with extreme caution the absence of significant thixotropic recovery at short times (5 minutes) for all sprays implied that thixotropy was not necessarily the controlling factor but rather it was the high viscosities present in all four sprays even after structure breakdown. The Panel also noted the findings of Pennington *et al*. The Panel noted that Aventis referred to the paper by Berridge *et al* in its response and noted its comments on the study and use of *in vitro* data generally at point 1 above. The Panel considered that Aventis had submitted no evidence to demonstrate that thixotropy was a property unique to Nasacort and no clinical evidence to show the association between this property and delivery to the target tissues. The Panel considered the claim implied special merit in relation to the delivery of Nasacort and its thixotropic qualities and was thus exaggerated as alleged. A breach of Clause 7.8 was ruled.

Complaint received **19 June 2001**

Case completed **21 August 2001**

CASE AUTH/1197/6/01

PRIMARY CARE GROUP PRESCRIBING ADVISER v KNOLL

Reductil journal advertisement

A primary care group prescribing adviser complained about an advertisement for the anti-obesity medicine Reductil, issued by Knoll. The advertisement featured a grid of small photographs of obese people's torsos. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' etc. The complainant alleged that several of the medical conditions so quoted were at odds with the summary of product characteristics (SPC) and was concerned that the advertisement suggested that Reductil might be prescribed to groups of patients in whom it would not be safe.

In the Panel's view the overall impression given by the advertisement was that Reductil could be used, without further consideration, in a wide range of obese patients which was not so. Some of the patient types shown ie 'Stroke' 'Cardiovascular disease' were clearly contraindicated, while others eg 'Ovarian cancer' 'Breast cancer' would require an assessment of concomitant treatment before Reductil could be started. Patients with hypertension would need careful monitoring as Reductil could exacerbate their condition. The Panel thus considered that the advertisement was inconsistent with the particulars listed in the Reductil SPC and a breach of the Code was ruled. The Panel was concerned that the advertisement might encourage doctors to prescribe Reductil for those patients who should not be so treated and therefore compromised patient safety. The Panel considered that such advertising brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

A primary care group (PCG) prescribing adviser complained about an advertisement issued by Knoll Limited for Reductil (sibutramine) (ref ETH 2921/12/00g) which had appeared in the medical and pharmaceutical press. The advertisement featured a grid (7 x 7) of small photographs each of which was of an obese person's torso; each person was dressed only in underclothes. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' and 'Colorectal cancer'. Reductil was licensed for use as adjunctive therapy within a weight management programme for patients with obesity.

COMPLAINT

The complainant referred to the labels beneath the photographs and alleged that several of the medical conditions quoted were at odds with the summary of product characteristics (SPC) and the prescribing information as follows:

- Hypertension: Reductil was contraindicated in patients with a BP > 145/90mmHg. Although treatment targets for hypertensive patients were below this, a significant proportion of patients did not reach them. Thus Reductil would not be suitable in most of these patients.
- Stroke: Reductil was contraindicated in cerebrovascular disease.
- Cardiovascular disease: Reductil was contraindicated in patients with coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, tachycardias or other arrhythmias. This in combination with the hypertension restrictions would be likely to rule out a large proportion of patients in this group.
- Breathlessness was a symptom/sign of heart failure, another contraindication.
- Ovarian, colorectal and breast cancers: dexamethasone was a commonly prescribed antinauseant in patients with malignancies. Reductil was cautioned for use with dexamethasone. These patients were also likely to be receiving opiate analgesics, several of which were also cautioned with Reductil.

The complainant recognised that the advertising was perhaps meant to suggest that if these patients lost weight they might not go on to suffer from the conditions named, as opposed to them being current morbidities, however this was certainly not clear from the advertisement. The complainant was concerned that the advertisement suggested that Reductil might be prescribed to groups of patients in whom it would not be safe.

When writing to Knoll the Authority asked it to consider the provisions of Clauses 2, 3.2, 7.7 and 9.1 of the Code.

RESPONSE

Knoll stated that it was difficult to know precisely exactly what the complaint was. The complainant appeared to suggest that, because of the inclusion of the names of co-morbid conditions amongst the images of obese people, there was a suggestion that Reductil should be prescribed for conditions for which it was clearly contraindicated (as shown on the prescribing information, an integral part of the advertisement). It was important to note that although the complainant feared this for other readers of the advertisement, he or she did not reach this conclusion. This at the very least diminished the validity of the complaint. In other words on the evidence provided by the complainant the risk of misunderstanding of the advertisement appeared not to be present.

Knoll acknowledged that it used the repeated images of obese people and some of the diseases and syndromes associated with obesity. The company did the latter to ensure that readers understood that it did

not advocate the use of Reductil for cosmetic reasons; rather it was legitimate medical reasons which underlay any decision to treat obesity that the company wanted to bring to their attention. Put simply it was an acceptable way to depict the seriousness of obesity as a disease (something as yet that was not generally recognised in the UK) and only that. Indeed Knoll believed that by using co-morbid conditions amongst the images of obese people the company had been ethically responsible in its attempts to guide the reader to the medical, rather than cosmetic, reasons for treating obesity and overweight.

With regard to Clause 2 Knoll stated that it would be perverse if its conscious attempt to direct the reader to the ethical side of obesity treatment was to be misinterpreted and bring to it accusation under this clause. Knoll did not accept that its advertisement breached Clause 2 of the Code.

Knoll stated that as indicated above the inclusion of the various co-morbidities of obesity was carefully placed amongst the images of obese people to emphasize why obesity was not a cosmetic but a medical issue, which merited the readers' attention. The SPC referred to obesity related co-morbid factors in section 4.1 to define the therapeutic indications and in the penultimate paragraph of section 4.2 it gave details of how the clinical course of obesity co-morbid conditions should inform treatment decisions. In the last paragraph of section 5.1 beneficial outcomes to associated risk factors were given. Knoll noted that through the advertisement it had not discussed this subject or made any claim on the relevance to these; let alone the complainant's assertion that the company sought to have people treating patients in the face of clear contraindications. Knoll did not accept that its advertisement breached Clause 3.2 of the Code.

Knoll stated that it was at a slight loss as to why the Authority had directed it to look at Clause 7.7 which related *inter alia* to information and claims about side effects and use of the word 'safe' when the complaint appeared to be about the fear that readers might think that the inclusion of several obesity related conditions within the images of obese people might be misinterpreted to advocate treatment or prevention of these by Reductil. Knoll considered that its advertisement did not breach this clause of the Code.

Knoll noted that although the complainant appeared to fear that other people might misinterpret the advertisement and thereby disregard the clear contraindications to the use of Reductil, the company did not perceive either that offence was taken or indeed that its standards were questioned. As the company had indicated above it was precisely because of its desire to maintain the very highest ethical standards in the context of less than ideal level of knowledge about obesity in the health professions, that it directed the reader to the medical rather than the cosmetic side of obesity and overweight. Knoll did not accept that its advertisement in any way breached Clause 9.1 of the Code.

PANEL RULING

The Panel considered that most readers would assume that the grid of photographs, together with their labels, represented a typical group of obese patients and the co-morbid conditions with which they might present.

The Reductil SPC listed a number of contraindications including history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischaemic attack (TIA)). In that regard the Panel noted that some of the photographs in the advertisement were labelled 'Stroke' and 'Cardiovascular disease'; 'Breathlessness' could be a symptom of heart failure. In the Panel's view the advertisement thus implied that Reductil could be used in some obese patients for whom, because of co-morbid conditions, it would be contraindicated. Some of the photographs were labelled 'Hypertension' and the Panel noted that inadequately controlled hypertension was also a contraindication to therapy. In addition section 4.4 of the SPC, 'Special warnings and special precautions for use', stated that blood pressure and pulse rate should be monitored in all patients on Reductil as it had caused clinically relevant increases in blood pressure in some patients. Section 4.8, 'Undesirable effects', stated, *inter alia*, that raised blood pressure/ hypertension was a frequent (1-10%) side effect; prescribers were also told that if they wished to use Reductil in patients with hypertension they should read the sections of the SPC detailing contraindications and special warnings and precautions for use.

Some of the photographs were labelled 'Ovarian cancer', 'Colorectal cancer' and 'Breast cancer.' The Panel noted that dexamethasone could be used to prevent the nausea associated with cytotoxic therapy. Section 4.5 of the Reductil SPC which detailed interactions, included the warning that dexamethasone might accelerate sibutramine metabolism although this had not been studied experimentally. Thus while an interaction with dexamethasone was a possibility the Panel questioned how many patients in practice would simultaneously receive cytotoxic therapy and be treated for obesity. Section 4.5 of the SPC also included the warning that serotonin syndrome, a serious interaction, might occur in rare cases in connection with the simultaneous use of Reductil and certain opioids. In that regard the Panel noted that opioids were often prescribed for patients with cancer-related pain. Again the Panel questioned how many cancer patients would be concomitantly prescribed opioid analgesics and be treated for obesity but noted that the interaction that might occur with Reductil was serious.

In the Panel's view the overall impression given by the advertisement was that Reductil could be used, without further consideration, in a wide range of obese patients which was not so. Some of the patient types shown ie 'Stroke' 'Cardiovascular disease' were clearly contraindicated, while others eg 'Ovarian cancer' 'Breast cancer' would require an assessment of concomitant treatment before Reductil could be started. Patients with hypertension would need careful monitoring as Reductil could exacerbate their condition. The Panel thus considered that the advertisement was inconsistent with the particulars

listed in the Reductil SPC and a breach of Clause 3.2 was ruled. The Panel considered that the alleged breach of Clause 7.7 of the Code was covered by this ruling. The Panel was concerned that the advertisement might encourage doctors to prescribe Reductil for those patients who should not be so treated and therefore compromise patient safety. The Panel considered that such advertising brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **19 June 2001**

Case completed **13 August 2001**

CASE AUTH/1198/6/01 *NO BREACH OF THE CODE*

MEDIA/DIRECTOR v WYETH

Sponsorship of primary care group guidelines

An article in GP referred to a general practitioner demanding the suspension of the entire board of the Brighton and Hove Primary Care Group (his local PCG). The GP stated that the PCG had obtained sponsorship from individual pharmaceutical companies whose products had then been mentioned exclusively in guidelines to GPs. The GP claimed that as a result Wyeth took 77% of the local market in medicines for treating stomach ailments in 2000. Wyeth had refuted this figure and stated that its market share had increased over the past two years from 46.5 to 49.7%. The GP stated that information came from questioning at a meeting called by the PCG to discuss guidelines in the treatment of dyspepsia. The meeting was sponsored by Wyeth. The GP had written to the other companies and seven had said that they had not been approached by the PCG for information on their products or to assist in drawing up guidelines. The GP's view was that in drawing up guidelines the whole field had to be looked at, not just one company. This was not an ethical approach.

The article stated that Wyeth had been offering an audit tool free to PCGs all over the country to help GPs review their prescribing practice in line with guidance from the National Institute for Clinical Excellence (NICE). Wyeth believed the process was appropriate and transparent.

The GP did not believe that sponsorship was necessary for developing such guidelines but even if it was needed it should be sought from a broader range of companies.

A subsequent article had appeared in GP and referred to the fears that the use of pharmaceutical companies in primary care initiatives carried serious risks. The GP alleged that the PCG had misused sponsorship by allowing single companies to promote themselves in presentations to GPs and then issuing guidelines that mentioned only that company's products. The PCG had declined to comment while the health authority inquiry proceeded.

The Constitution and Procedure for the Authority was such that public criticisms of the industry were taken up and dealt with as complaints under the Code.

The Panel noted the submission from Wyeth that the selection of lansoprazole as the PCG's proton pump inhibitor of choice was made independently by the PCG prior to any approach to Wyeth for sponsorship of the PCG proposed audit. Wyeth had provided funding for the audit. The Panel considered that this was not necessarily unacceptable. The supplementary information to the Code permitted the provision of medical and educational goods and services which would enhance patient care or benefit the NHS. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. The audit tool had been agreed between the PCG and an independent third party prior to Wyeth's involvement. The payments were made without any pre-condition as to the outcome of the audit or the prescribing recommendation of the PCG. Each practice was at liberty to select whichever proton pump inhibitor it wished in accordance with the practice's policy. The 'Drug Choices' document stated that if a proton pump inhibitor other than lansoprazole was prescribed, its licensed indications should be checked.

The Panel noted that the meeting invitation clearly stated that the evening was sponsored by Wyeth. The company had paid £500 for room hire and refreshments. Two stands had been made available. Wyeth had been asked to provide certain documents and a folder for the Guidelines. The documents provided by Wyeth had been published papers and articles by NICE and Bandolier. These had been presented in card folders with a summary of the article printed on the front and prescribing information for Zoton (lansoprazole) on the back. The folder contained information from 'Drug Choices' based on current clinical cost effectiveness. The 'Guidelines for the Management of Dyspepsia' referred to types of medicine to be used eg H2 antagonist, PPI etc. Some medicines were named.

The Panel noted that the GP article was inaccurate.

The Panel considered that there was no evidence that the arrangements between the PCG and Wyeth were unacceptable. The Guidelines' recommendation to use Wyeth's product lansoprazole had been finalised before the audit was carried out. Practices were free to use other products provided the licensed indications were checked.

The arrangements for the meeting were not unacceptable. The hospitality was secondary to the main purpose of the meeting which was educational. The article had not commented on this aspect.

Overall the Panel considered that, in relation to the criticisms in the article that the sponsorship had been obtained from Wyeth, whose products had been mentioned exclusively in guidelines to GPs, there had been no breach of the Code.

COMPLAINT

An article in GP, 22 June 2001, referred to a general practitioner demanding the suspension of the entire board of the Brighton and Hove Primary Care Group (his local PCG). The GP stated that the PCG had obtained sponsorship from individual pharmaceutical companies whose products had then been mentioned exclusively in guidelines to GPs. The GP claimed that as a result Wyeth took 77% of the local market in medicines for treating stomach ailments in 2000. Wyeth had refuted this figure and stated that its market share had increased over the past two years from 46.5 to 49.7%. The GP stated that information came from questioning at a meeting called by the PCG to discuss guidelines in the treatment of dyspepsia. The meeting was sponsored by Wyeth. The GP had written to the other companies and seven had said that they had not been approached by the PCG for information on their products or to assist in drawing up guidelines. The GP's view was that in drawing up guidelines the whole field had to be looked at not just one company. This was not an ethical approach.

The article stated that Wyeth had been offering an audit tool free to PCGs all over the country to help GPs review their prescribing practice in line with guidance from the National Institute for Clinical Excellence (NICE). Wyeth believed the process was appropriate and transparent.

The GP did not believe that sponsorship was necessary for developing such guidelines but even if it was needed it should be sought from a broader range of companies.

The article stated that the East Sussex, Brighton and Hove Health Authority was conducting an investigation.

A subsequent article had appeared in GP, 29 June, and referred to the fears that the use of pharmaceutical companies in primary care initiatives carried serious risks. The GP alleged that the PCG had misused sponsorship by allowing single companies to promote themselves in presentations to GPs and then issuing guidelines that mentioned only that company's products. The PCG had declined to comment while the health authority inquiry proceeded.

The Constitution and Procedure for the Authority was such that public criticisms of the industry were taken up and dealt with as complaints under the Code.

In writing to Wyeth attention was drawn to the requirements of Clauses 2, 9.1 and 18.1 of the Code.

The Panel noted that the GP had been notified that the matter was being considered in relation to the requirements of the Code. He had subsequently written to state that he had no complaint about any pharmaceutical company and that his complaint centred on approaches made to pharmaceutical companies by the PCG at the instigation of the PCG.

The GP was informed that as the articles were in the public domain and there was an implication that Wyeth had not acted ethically, then the matter had to be considered under the Code.

RESPONSE

Wyeth stated that the GP article of 22 June contained several statements attributed to the GP that related to Wyeth, the majority of which were based upon incorrect assumptions.

Wyeth stated that the upper gastrointestinal (GI) prescribing audit, the Guidelines for the Management of Dyspepsia and the discussion meeting held to launch the Guidelines were each initiated by the PCG. Further, the selection of lansoprazole as the PCG's proton pump inhibitor (PPI) of choice was a decision made independently by the PCG's prescribing sub-committee. Furthermore, this decision was made prior to any approach being made to Wyeth for sponsorship of the PCG's proposed audit.

Audit

Wyeth stated that having decided to carry out GI audits, the PCG tendered for, and subsequently selected, an independent third party to undertake them. Wyeth became involved following this selection when the third party, on the authority and recommendation of the PCG, approached Wyeth to provide supplementary funding to help carry out the proposed audit. Wyeth agreed to provide funding for the audit, the first phase of which ran from May 2000 to April 2001.

The audit tool used was agreed between the PCG and the third party prior to Wyeth's involvement. Wyeth had no input into either its content or format. Wyeth provided funding but the payments were made without any pre-condition as to the outcome of the audit or the prescribing recommendation of the PCG. Wyeth's payments were made directly to the third party.

Although lansoprazole was the PCG's proton pump inhibitor of choice, this was not proscriptive. As Wyeth understood it, when undertaking the audit review programme, each practice was at liberty to select whichever PPI it wished in accordance with the practice's policy.

Guidelines and discussion meeting

Wyeth stated that at the end of the first phase of the audit, the PCG approached Wyeth to fund a meeting called by the PCG to discuss its Guidelines for the Management of Dyspepsia. Wyeth agreed to fund the evening meeting. However, Wyeth had had no role (financial or otherwise) in the creation of the Guidelines.

The meeting to launch the Guidelines was arranged by the PCG, with invitations sent out by the Chair of

the Prescribing Committee. The invitation letter clearly stated that the evening was sponsored by Wyeth and that a 'Guidelines Information Pack' would be available. The meeting was held on 4 May 2001 at the PCG selected local Nuffield Hospital (Wyeth helped to make the arrangements to hold the meeting there). The meeting was attended by approximately 45 GPs, two local consultant gastroenterologists, a health authority pharmaceutical adviser, 2 PCG prescribing/pharmaceutical advisers and 4 Wyeth representatives. The chair of the PCG Prescribing Sub-Committee chaired the meeting.

Wyeth stated that the PCG arranged the food and beverages, which were also provided by the hospital. Wyeth provided £500 sponsorship for the room hire and provision of food and beverages for the attendees. Wyeth had two tabletop stands adjacent to the registration desk at the start of the evening (Zoton/Efexor and 'Support in Primary Care') and a further HRT product related tabletop stand in the dining room later on. Two of the four Wyeth representatives were invited by the PCG pharmaceutical adviser to sit in on the meeting, albeit at the back of the room, but they took no active part in the proceedings.

The meeting lasted approximately two hours (PGEA accredited) and involved the PCG prescribing adviser outlining the audit programme and associated savings of approximately £180,000, the two local consultant gastroenterologists reviewing the Guidelines and a discussion on medicine choices as outlined in a PCG handout. It was restated that whilst lansoprazole was the PCG's PPI of choice due to its wide range of licensed indications, alternatives could be prescribed with the proviso that their licensed indications should be checked.

Each GP was given a 'Guidelines Information Pack' which had been assembled by the PCG. Contained within the pack was:

1 The Guidelines for the Management of Dyspepsia printed on a laminated card.

2 A sheet headed 'Drug Choices' which listed the current PCG acid suppressant drug choices and the PCG's rationale for these choices. Under the heading 'Proton pump inhibitors' it stated 'lansoprazole is the PPI of choice within Brighton and Hove PCG as it has a wide range of licensed indications. If a different PPI is prescribed, its licensed indications should be checked'.

3 Supplementary sheets depicting the relative costs of 28 days of treatment.

4 A sheet outlining the doses and licensed indications for each of the PPIs (omeprazole, lansoprazole, pantoprazole and rabeprazole).

5 Reprints of the following items:

- NICE 'Guidance on the use of Proton Pump Inhibitors in the Treatment of Dyspepsia'
- Bandolier article entitled 'Treatment effectiveness and costs in reflux disease'
- Reprints of articles relating to upper GI prescribing reviews.

Wyeth stated that items 1 - 4 were all prepared by the PCG without any Wyeth involvement. The items listed in 5 were supplied by Wyeth in response to a request from the PCG – these were items that Wyeth provided regularly to PCGs in its pack of material relating to the 'Upper GI Review Solutions'. Further, the PCG also asked Wyeth if it could supply folders in which to distribute its Guidelines documents. In response to this request Wyeth supplied its 'Upper GI Review Solutions' folder and the Guidelines documents were distributed in this. A copy of the Guidelines pack distributed by the PCG was provided.

GP article

Turning to the GP article itself:

1 The article stated that '... Brighton and Hove PCG had obtained sponsorship from individual pharmaceutical companies, whose products had then been mentioned exclusively in guidelines to GPs'. Wyeth was named as one of the companies.

In response Wyeth stated that it had provided sponsorship for the PCG's audit exercise only and provided no sponsorship for the Guidelines creation process. The Guidelines written by the PCG did not exclusively refer to Wyeth's products.

2 The article accurately quoted the GP stating that a meeting called by the PCG to discuss guidelines on the treatment of dyspepsia had been sponsored by Wyeth.

3 The article quoted the GP stating that 'If you are going to develop guidelines you have to look at the whole field, not limit it to one pharmaceutical company. It is not an ethical approach'. This was said in the context of providing assistance to draw up the Guidelines. As indicated previously, Wyeth did not assist the PCG in drawing up the Guidelines.

4 The article stated that the GP had said that he did not believe sponsorship was necessary for developing Guidelines but even if it was needed it should be sought from a broader range of companies. Wyeth stated again that it did not sponsor the PCG's exercise to draw up Guidelines.

With regard to Clause 2 of the Code, Wyeth stated that, for the reasons above, it did not accept that its activities brought discredit upon or reduced confidence in the pharmaceutical industry. Wyeth's activities in connection with the PCG audit, Guidelines and associated meeting had all been in accordance with the Code. Wyeth provided sponsorship for the PCG's third party audit exercise without pre-condition and at the request of the PCG. Wyeth had no involvement in the creation or sponsorship of the PCG's Guidelines. Wyeth sponsored a meeting associated with the Guidelines but did so in accordance with the provisions of Clause 19 of the Code.

With regard to Clause 9.1 of the Code, Wyeth submitted that it adopted a high standard in relation to its activities with the PCG and recognised the special nature of medicines and the professional standing of the audience.

Wyeth submitted that it had complied fully with the requirements of Clause 18.1. It had provided sponsorship of the PCG's third party audit exercise without pre-condition and at the request of the PCG. Wyeth offered no inducement to any member of the PCG to prescribe, supply, administer or buy any medicine. Wyeth's sponsorship of the audit exercise was agreed through a third party and not with the PCG and the audit was conducted by the PCG's chosen third party in accordance with a protocol agreed between the PCG and that third party. The selection of lansoprazole as the PCG's proton pump inhibitor of choice was a decision made independently by the PCG's prescribing sub-committee and prior to any approach being made to Wyeth to sponsor the PCG's proposed audit.

With regard to Clause 19.1, Wyeth submitted that the hospitality provided at the PCG Guidelines meeting was appropriate and was secondary to the purpose of the meeting. The hospitality provided was not out of proportion to the occasion and the cost was at an acceptable level. Wyeth's sponsorship of the meeting was disclosed to all attendees in the invitation to the meeting sent out by the PCG.

PANEL RULING

The Panel noted the submission from Wyeth that the selection of lansoprazole as the PCG's proton pump inhibitor of choice was made independently by the PCG prior to any approach to Wyeth for sponsorship of the PCG proposed audit. Wyeth had provided funding for the audit. The Panel considered that this was not necessarily unacceptable. The supplementary information to Clause 18.1 of the Code permitted the provision of medical and educational goods and services which would enhance patient care or benefit the NHS. The provision of such goods or services must not be done in such a way as to be a inducement to prescribe, supply, administer or buy any medicine. The audit tool had been agreed between the PCG and the independent third party prior to Wyeth's involvement. The payments were made without any pre-condition as to the outcome of the audit or the prescribing recommendation of the PCG. Each practice was at liberty to select whichever proton pump inhibitor it wished in accordance with the practice's policy. The 'Drug Choices' document stated that if a proton pump inhibitor other than lansoprazole was prescribed, its licensed indications should be checked.

The Panel noted that the meeting invitation clearly stated that the evening was sponsored by Wyeth. The company had paid £500 for room hire and refreshments. Two stands had been made available. Wyeth had been asked to provide certain documents and a folder for the Guidelines. The documents provided by Wyeth had been published papers and articles by NICE and Bandolier. These had been presented in card folders with a summary of the article printed on the front and prescribing information for Zoton on the back. The folder contained the card folders with the articles as well as information from 'Drug Choices' based on current clinical cost effectiveness. The 'Guidelines for the Management of Dyspepsia' referred to types of medicine to be used eg H2 antagonist, PPI etc. Some medicines were named, for example the COX2 inhibitors, the NSAIDs were listed together with an indication of risk of GI complications. The recommended triple therapy of *H Pylori* eradication was mentioned in detail.

The Panel noted that the GP article was inaccurate. Sponsorship activities had to meet the requirements of the supplementary information to Clause 18.1 of the Code.

The Panel considered that there was no evidence that the arrangements between the PCG and Wyeth were unacceptable. The Guidelines' recommendation to use Wyeth's product lansoprazole had been finalised before the audit was carried out. Practices were free to use other products provided the licensed indications were checked.

The arrangements for the meeting were not unacceptable. The hospitality was secondary to the main purpose of the meeting which was educational. The article had not made a comment on this aspect.

Overall the Panel considered that, in relation to the criticisms in the article that the sponsorship had been obtained from Wyeth, whose products had been mentioned exclusively in guidelines to GPs, there had been no breach of Clause 18.1 of the Code. Nor had there been any breach of Clauses 9.1 and 2.

Proceedings commenced 26 June 2001

Case completed 24 August 2001

SCHERING-PLOUGH and GENERAL PRACTITIONER v SCHWARZ PHARMA

'Dear Doctor' letter detailing previous Code of Practice rulings

Schering-Plough and a general practitioner complained about a 'Dear Doctor' letter sent by Schwarz Pharma which gave details of adverse rulings made in Case AUTH/1172/3/01 in which Schwarz had complained about the promotion of NeoClarityn by Schering-Plough. Schering-Plough alleged that inclusion of the statement 'Schwarz Pharma also market a non-sedating antihistamine' constituted disguised promotion for Schwarz's product Mizollen in a letter which purported to give information on a recent ruling. Schering-Plough noted that there was no prescribing information for Mizollen included in the letter. The general practitioner objected to a pharmaceutical company airing its laundry in this way, wasting GPs' time with triumphalism of the worst kind.

With regard to Schering-Plough's complaint, the Panel considered that the letter was promotional for Mizollen although the product was not mentioned by either its brand name or its generic name. Reference was made to its indication, a claim that it was non-sedating was made and the letter made critical comment about the promotion of a competitor product. The Panel considered that prescribing information for Mizollen should have been included and accordingly ruled a breach of the Code. The Panel considered that the letter constituted disguised promotion and a further breach of the Code was ruled.

With regard to the general practitioner's complaint, the Panel considered it was not in itself a breach of the Code to advertise by way of reference to previous rulings made under the Code. No breach of the Code was ruled.

Schering-Plough Ltd and a general practitioner complained about a 'Dear Doctor' letter (ref M12S 1985/June 01 RMS4627 9762) sent to GPs by Schwarz Pharma Limited. The letter was headed 'Desloratadine promotion – ruling by Prescription Medicines Code of Practice Authority (PMCPA)' and gave details of some of the rulings made in Case AUTH/1172/3/01 in which Schwarz had complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough. Readers were told that promotional material for desloratadine had been considered to be in breach of the Code of Practice in eight separate instances. The letter summarised the most important points of the ruling. These being an unsupported potency claim, misleading strapline and overstating the anti-inflammatory effect. The letter stated that the licence holder was now obliged to replace, amend or qualify all of these claims. The penultimate paragraph stated 'Schwarz Pharma also market a non-sedating antihistamine, hence our interest in maintaining promotional standards in this therapeutic area'.

Schwarz marketed Mizollen (mizolastine).

Case AUTH/1199/6/01

COMPLAINT

Schering-Plough noted that the 'Dear Doctor' letter purported to be about a recent ruling by the PMCPA. However the statement 'Schwarz Pharma also market a non-sedating antihistamine' was clearly designed to increase awareness and interest in Mizollen with the aim of promoting its 'prescription, supply, sale or administration' making the letter promotional in intent.

Schering-Plough had two objections to the letter: it promoted Mizollen but did not contain prescribing information as required by Clause 4; by pretending to be an informational piece, it constituted disguised promotion, in breach of Clause 10.

Schering-Plough considered that, rather than the letter being an altruistic attempt by Schwarz, borne out of its 'interest in maintaining promotional standards in this therapeutic area', this was a case of disguised promotion, which did the industry harm.

RESPONSE

Schwarz Pharma submitted that the 'Dear Doctor' letter was not in breach of the Code. The aim of the letter was to ensure that GPs had an up-to-date, factual account of the PMCPA ruling. At no time was promotion the company's intent; its antihistamine product was not mentioned, and no promotional claims were made.

Schwarz did not consider that the letter was promotional. No mention was made of its product, either by generic or brand name. The letter was a '...factual, accurate, informative announcement...' (Clause 1). No product claims were made and it had been written and presented in a non-promotional style. High standards of accuracy were adhered to. No complaint had been lodged against the content of the letter.

The purpose of the statement 'Schwarz Pharma also market a non-sedating antihistamine, hence our interest in maintaining promotional standards in this therapeutic area' was to comply with the spirit of the Code. Schwarz noted that Clause 9.9 required companies to declare their involvement in sponsorship on other materials (whether they were promotional or not) and the company considered that it would be more ethical to admit that it had a vested interest in this therapy area. Schwarz stated that it did not pretend to altruism but, since it had a minimal market-share, there were several other products that might benefit more than its own if its letter affected GP prescribing habits.

Schwarz stated that the supplementary information to Clause 9.7 stated that a reply paid card '...should not bear both the name of the medicine and information as to its usage but may bear one or the other'. This was the basis upon which the Code decided whether a reply paid card was 'promoting to the general public'. Schwarz noted that its letter did not bear the name of its medicine. It made no statements at all about its product, other than to state its therapeutic indication. Therefore, by the standards of the Code, it did not constitute promotion.

The letter was posted directly to GPs. The company's medical representatives were not involved in its distribution. At no time did it encourage doctors '...to prescribe, supply, administer, recommend or buy...' Mizollen.

In answer to Schering-Plough's specific complaints Schwarz stated that since the letter was not promotional, it did not require prescribing information. It was therefore not in breach of Clause 4. The letter was also not 'pretending' to be an informational piece – it was one. It was therefore not disguised promotion.

Schwarz noted that the Authority had previously stated that reporting these matters was not in itself a breach of the Code, but that it was the manner in which it was done which was important (Case AUTH/442/7/96). Schwarz considered that the letter was a purely factual, accurate announcement to GPs, countering claims that had been ruled to be misleading. Many GPs might have continued to prescribe on the basis of these claims. They would now be able to judge which antihistamine to choose based on more accurate information.

Schwarz stated that the letter did nothing to promote its product, it merely refuted unsubstantiated claims made by Schering-Plough. Since Schwarz was by no means the main or only competitor, this did not constitute indirect promotion.

The company considered that by making doctors aware of the industry's attempts to improve the information it provided, Schwarz was actually helping to improve the reputation of the pharmaceutical industry. Attempting to hide this sort of information from the medical profession would only reinforce its belief that the information the industry delivered was not to be trusted.

PANEL RULING

The Panel noted that Case AUTH/442/7/96 had been the first case concerning the use by one company (in this instance Parke Davis) of material detailing instances where another company (Janssen-Cilag) had been ruled to be in breach of the Code. The case had concerned a journal advertisement.

In Case AUTH/442/7/96 the Panel had first considered whether the advertisement came within the scope of the Code. It noted that Parke Davis claimed that the advertisement was not promotional for its product Neurontin (gabapentin). Three products were referred to in the advertisement by generic name, lamotrigine, gabapentin and topiramate. The Panel noted that the advertisement included both a product name, gabapentin, and an indication 'refractory partial epilepsy'. The Panel concluded that the advertisement was a form of promotion of gabapentin and was therefore within the scope of the Code. The Panel noted that even if the advertisement had only reproduced the ruling it would still have been subject to the Code in that it made critical comment about the promotion of a competitor product. The Panel considered that prescribing information for Neurontin should have been included and had accordingly ruled a breach of Clause 4.1 of the Code. The Code did not recognise the concept of corrective advertisements as a special category which did not need prescribing information.

With regard to the question of the concept of the advertisement, that was to say making use of rulings on Code of Practice complaints in promotional material, the Panel did not consider that this was barred by the Code. Decisions on completed cases were in the public domain, being published in the Code of Practice Review which was issued quarterly by the Authority and was available to anyone. It seemed to the Panel to be an unwarranted limitation on freedom of speech to say that, as a matter of principle, use could not be made of Code of Practice rulings in promotional material, particularly in a case where a company considered that its interests had been damaged by activities of another which had been ruled to have breached the Code. Case reports were not usually reported in medical publications and therefore the medical profession knew little, if anything, about them. It was difficult to see why reference to published cases in promotional material should in itself be held to bring the industry into disrepute.

The Panel had noted that if the industry wanted to prevent reference being made to Code of Practice rulings in promotional material, then consideration would have to be given to amending the Code to specifically prevent such use.

The case had gone on to appeal. The Appeal Board considered that the advertisement was clearly promotional in nature and that prescribing information for Parke Davis' product Neurontin (gabapentin) should accordingly have been included. It had not been given. The Appeal Board had therefore upheld the Panel's ruling of a breach of Clause 4.1.

In relation to the general principle of whether promotional material could refer to rulings under the Code of Practice, the Appeal Board was of the opinion that this was not in itself contrary to the Code. Clearly the way in which it was done could breach the Code and the Appeal Board considered that in such advertisements great care must be taken to ensure fairness and exactitude.

Turning to the case now before it, Case AUTH/1199/6/01, the Panel considered that the letter was promotional for Schwarz's product Mizollen, although the product was not mentioned by either its brand name or its generic name. Reference was made to its indication, a claim that it was non-sedating was given and the letter made critical comment about the promotion of a competitor product. The Panel considered that prescribing

information for Mizollen should have been included and accordingly ruled a breach of Clause 4.1 of the Code. The Panel considered that the letter constituted disguised promotion. The Panel therefore ruled a breach of Clause 10.1 of the Code.

Case AUTH/1201/7/01

COMPLAINT

The general practitioner took issue with the fact that a pharmaceutical company should choose to air its laundry in this way, wasting GPs' valuable time with triumphalism of the worst kind.

In considering this matter the Authority asked Schwarz to bear in mind the provisions of Clause 9.1 of the Code.

RESPONSE

Schwarz did not believe that the letter was in breach of the Code. The aim was to ensure that GPs had an up-to-date, factual account of the PMCPA ruling. A deliberate decision was made not to mention Schering-Plough, as it had no desire to be disparaging. Schwarz was not 'airing dirty laundry'; it was giving GPs information that clearly related to evidence based prescribing.

Information that helped GPs to make sound clinical decisions based on facts should not be regarded as a 'waste of GPs' valuable time'. The information in the letter was undeniably relevant to GPs, who treated the bulk of allergic disease. No information was included in the letter that did not relate to GPs' treatment of allergy. They were previously given inaccurate information (as agreed by the PMCPA) about the advantages of prescribing desloratadine. Schwarz had only supplied them with facts.

This information could make a real difference to a doctor's patients. Safety and efficacy issues were involved. What could be more important to a doctor in their choice of treatments? Taking hypothetical situations based on the three corrections noted in the letter:

a) Claim '40 times more potent than Clarityn'; lack of effect was a recognised adverse event, as the patient continued to suffer from their symptoms. If a patient had tried loratadine and this did not treat their symptoms, would a GP have offered desloratadine, mistakenly believing it was '40 times more potent'?

b) Claim 'Clarityn with extra clout'; Schwarz queried whether a GP would have mistakenly considered that desloratadine's safety profile and interactions were the same as loratadine's when prescribing to people with other health problems or medications?

c) Claim 'Comparable IL-8 inhibition to a steroid'; Schwarz questioned whether a GP would inadequately treat a patient with severe allergic symptoms, believing that: 'I don't need to give steroids to this patient because desloratadine has a comparable anti-inflammatory effect'?

Schwarz submitted that evidence based medicine was based on facts. The claims referred to in the letter could have resulted in treatment decisions being made without correct clinical information. Schwarz suggested that the letter was therefore in the best interests of GPs and their patients.

With reference to Clause 9.1, Schwarz believed that high standards had been maintained. Schering-Plough was found in breach of the Code eighteen times in Case AUTH/1172/3/01. The 'most important parts of the ruling' were selected because these claims could result in poor clinical practice. This was in recognition of the professional standing of the recipients. Only information that could make a difference to rational prescribing of medicines was included.

Naturally, Schwarz regretted any offence that the letter might have caused. However, given the clinical relevance of the information, and the factual, accurate and informative way in which it was presented, it did not agree that it constituted a breach of the Code.

Schwarz believed that this response addressed the GP's concerns. It considered that the complaint was unjustified.

PANEL RULING

The Panel noted its comments made in Case AUTH/1199/6/01 about the concept of making use of rulings on Code of Practice complaints in promotional material and considered that they applied to this case, Case AUTH/1201/7/01.

Turning to Case AUTH/1201/7/01, the Panel considered that the letter was promotional for Schwarz's product Mizollen, although the product was not mentioned by either its brand name or its generic name. Reference was made to its indication and a claim that it was non-sedating was given and the letter made critical comment about the promotion of a competitor product. The Panel considered it was not in itself a breach of the Code to advertise in this way. It was difficult to see why reference to previous decisions in promotional material should in itself be unacceptable. The Panel did not consider that the distribution by Schwarz of details about rulings made about Schering-Plough's promotional materials under the Code was unacceptable and no breach of Clause 9.1 of the Code was ruled.

Case AUTH/1199/6/01

Complaint received **29 June 2001**

Case completed **1 August 2001**

Case AUTH/1201/7/01

Complaint received **2 July 2001**

Case completed **7 August 2001**

ANONYMOUS v LUNDBECK

Attendance of general practitioner's wife at a company sponsored meeting

An anonymous complainant alleged that a general practitioner was accompanied by his wife to a meeting in Seville and the costs were met by Lundbeck. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

The Panel noted that the supplementary information to the Code provided, *inter alia*, that any hospitality must not extend to spouses unless that person was a member of the health professions and qualified as a proper delegate or participant at the meeting in their own right. The Panel noted that Lundbeck had not invited the GP's wife to the meeting and nor had it incurred any expenditure in relation to her travel or accommodation. The Panel had no evidence before it to suggest that the company had provided any hospitality to the GP's wife. Indeed the company had been unaware of her presence in Seville. No breach of the Code was ruled.

COMPLAINT

An anonymous general practitioner telephoned the Authority and stated that a general practitioner had recently attended a meeting in Seville organised by Lundbeck Limited. The complainant was concerned that the general practitioner's wife had attended the meeting and that the costs were paid by Lundbeck.

* * * * *

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

When writing to Lundbeck the Authority requested that it consider the requirements of Clauses 2, 9.1 and 19.1 of the Code.

* * * * *

RESPONSE

Lundbeck stated that it was surprised to have received such a complaint as it had a standard policy of not inviting/paying for accompanying non-medical persons to any meeting organised by the company. The company policy for any meeting was that all invited delegates were not only medically qualified but qualified for attendance in their own right.

Lundbeck provided a copy of the 'generic' invitation to the meeting in Seville. The invitation contained the paragraph 'We would like to stress that we are unable to extend our invitation to include partners whether or not they are medically qualified. This ensures that all parties meet the requirements of the ABPI Code of Practice.'

Lundbeck confirmed that the general practitioner attended a meeting organised by Lundbeck International. He was invited on his own and was provided with return air travel with single room occupancy provided by Lundbeck in Seville. Lundbeck stated that on receipt of the complaint it contacted the general practitioner who confirmed that his wife had accompanied him to Seville having made private arrangements for travel and accommodation (unknown to Lundbeck). Lundbeck enclosed a letter of confirmation to this effect from the general practitioner. The company was also aware that the general practitioner's former partner in practice was also at the symposium and that this doctor was disgruntled by the appearance of the other's wife in Seville whom he misunderstood to have been taken by Lundbeck. The company assumed this to be the source of the complaint.

Lundbeck concluded that the complaint had most probably arisen due to a grievance between two former partners in general practice, and a misinterpretation by one of them. Lundbeck stated that it had a strict company policy on attendance at meetings, which was adhered to in this case and the company denied a breach of the Code.

PANEL RULING

The Panel noted that the supplementary information to Clause 19.1 provided, *inter alia*, that any hospitality must not extend to spouses unless that person was a member of the health professions and qualified as a proper delegate or participant at the meeting in their own right. The Panel noted that Lundbeck had not invited the GP's wife to the meeting and nor had it incurred any expenditure in relation to her travel or accommodation. The Panel had no evidence before it to suggest that the company had provided any hospitality to the GP's wife. Indeed the company had been unaware of her presence in Seville. No breach of Clauses 2, 9.1 and 19.1 of the Code was ruled.

Complaint received **27 June 2001**

Case completed **23 July 2001**

CASE AUTH/1202/7/01

PHARMACIST v KNOLL

Reductil journal advertisement

A pharmacist complained about a journal advertisement for Reductil (sibutramine) issued by Knoll. Reductil was licensed for use as adjunctive therapy within a weight management programme for patients with obesity. The advertisement featured a grid of small photographs each of which was of an obese person's torso; each person was dressed only in underclothes. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' and 'Colorectal cancer'.

The complainant found the advertisement in extremely bad taste. The depiction of half dressed, obese bodies was not appealing to look at and could be perceived as being offensive to people of a larger stature.

The Panel noted that all promotional materials and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. The advertisement had appeared in the pharmaceutical press and the Panel accepted that some people might consider it to be in bad taste. The Panel considered, however, that it was unlikely to cause offence to the majority of those who would see it. No breach of the Code was ruled.

The prominent claim 'Thanks to Reductil enough *is* enough' appeared in a highlighted box which blanked out some of the small photographs. In the bottom right-hand corner of the box was the picture of a plate of leftovers from a meal. The complainant noted that there were a number of complications listed under each photograph such as 'Sleep apnoea', 'Breast cancer', 'Hypertension'. The advertisement implied, due to the positioning of the claim 'Thanks to Reductil, enough is enough', that, as a result of taking Reductil and reducing obesity, patients would also have reduced incidence of the complications listed. This was misleading as there were no references listed on the advertisement to indicate whether patients had reduced morbidity from the complications listed as a result of taking Reductil. The complainant noted that, in addition, Reductil was contraindicated in patients with congestive heart failure, history of coronary artery disease and peripheral arterial occlusive disease. One of the side effects of taking Reductil was raised blood pressure, which could subsequently lead to cardiovascular disease and stroke. The complications listed, and the implication that Reductil was reducing the incidence of all of these conditions, was inaccurate, misleading and incapable of substantiation.

The Panel considered that the advertisement clearly promoted Reductil as an anti-obesity agent. The strapline beneath the product logo was 'Helps obese patients control their eating'. The text described Reductil as 'a new effective aid to weight loss' and stated that the product enabled patients to 'achieve medically beneficial weight loss'. The Panel considered that the grid of photographs would be seen as depicting the profiles of patients who presented with obesity and, in its view, 'Hypertension', 'Breast cancer', and 'Type 2 diabetes' etc would be seen by the reader as co-morbid conditions. The Panel did not consider that the advertisement implied that treatment with Reductil would lead to a reduced incidence of these conditions as alleged. The Panel did not consider that the advertisement was inaccurate or misleading in this regard. No breach of the Code was ruled.

The complainant had also raised the issue that some of the co-morbid conditions were contra-indications to therapy with Reductil or, as in the case of hypertension, might be exacerbated by such treatment. This issue had been previously considered in Case AUTH/1197/6/01. In Case AUTH/1197/6/01 the Panel had noted that the Reductil summary of product characteristics (SPC) listed a number of contraindications, including history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischaemic attack). In that regard the Panel noted that some of the photographs in the advertisement were labelled 'Stroke' and 'Cardiovascular disease'; 'Breathlessness' could be a symptom of heart failure. In the Panel's view the advertisement thus implied that Reductil could be used in some obese patients for whom, because of co-morbid conditions, it would be contraindicated. Some of the photographs were labelled 'Hypertension' and the Panel noted that inadequately controlled hypertension was also a contraindication to therapy. In addition the SPC stated that blood pressure and pulse rate should be monitored in all patients on Reductil as it had caused clinically relevant increases in blood pressure in some patients, and that raised blood pressure/hypertension was a frequent (1-10%) side effect. Prescribers were also told that if they wished to use Reductil in patients with hypertension they should read the sections of the SPC detailing contraindications and special warnings and precautions for use.

In Case AUTH/1197/6/01 the Panel's view had been that the overall impression given by the advertisement was that Reductil could be used, without further consideration, in a wide range of obese patients which was not so. Some of the patient types shown were clearly contraindicated. Patients with hypertension would need careful monitoring. The Panel thus considered that the advertisement was inconsistent with the particulars listed in the Reductil SPC and a breach of the Code was ruled. The Panel was concerned that the advertisement might encourage doctors to prescribe Reductil for those patients who should not be so treated and therefore compromise patient safety. Such advertising brought discredit upon, and reduced confidence in the pharmaceutical industry.

Turning to the case now before it, Case AUTH/1202/7/01, the Panel considered that the allegations were covered by its rulings in the previous case and breaches of the Code were ruled.

The complainant considered that the claim 'Reductil has no embarrassing GI side effects and is easy to comply with' was inaccurate. The prescribing information listed constipation and haemorrhoid aggravation as very frequent (>10%) and frequent (1-10%) side effects respectively. These side effects could be considered as embarrassing and hence affect compliance. It was not clear whether the compliance was easier due to the lack of embarrassing GI side effects or whether Reductil was a medicine which patients found it easy to comply with. If the former was the case, this claim should be substantiated, of which there was no evidence.

In the Panel's view the claim in question was for two separate benefits of Reductil; no embarrassing GI side effects and easy compliance with therapy. The Panel did not consider that the claim meant that as a consequence of no embarrassing GI side effects Reductil was easy to comply with. The Panel thus did not consider that the claim was misleading as alleged and ruled no breach of the Code.

A pharmacist complained about an advertisement issued by Knoll Limited for Reductil (sibutramine) (ref ETH 3044/6/01j) which appeared in The Pharmaceutical Journal in June. Reductil was licensed for use as adjunctive therapy within a weight management programme for patients with obesity. The advertisement featured a grid (6 x 5) of small photographs each of which was of an obese person's torso; each person was dressed only in underclothes. Beneath each photograph was a label such as 'Type 2 diabetes', 'Sweating', 'Gout' and 'Colorectal cancer'.

1 Taste

COMPLAINT

The complainant stated that she found the advertisement in extremely bad taste. The depiction of half dressed, obese bodies was not appealing to look at. In one instance, it was difficult to detect whether the photograph shown was male or female and could be perceived as being offensive to people of a larger stature. A breach of Clause 9.1 of the Code was alleged.

RESPONSE

Knoll was sorry if its advertisement had been found by the complainant to be in bad taste. It was certainly not the company's intention to publish anything in bad taste, let alone an advertisement where it clearly sought to portray a balanced but positive view of both its product and the company. In obesity there appeared to exist a state somewhat akin to learned helplessness. Health professionals appeared to have become conditioned to reject any possibility of influencing matters to the good because of their general inability (until recently) to do so, coupled with a history of mishaps with several anti-obesity agents and in the context of a stubbornly persistent private, largely cosmetic, slimming industry. Knoll considered that its advertisement in combining the reality of the images of obese and overweight people with the conditions that obesity was associated with challenged the hitherto conventional wisdom of ignoring obesity, dismissing it as a self inflicted condition that did not merit the health professional's attention. Rather than being in bad taste, the company considered that its advertisement was ethical in guiding the reader to the medical, and not the cosmetic, side of obesity treatment. Knoll asked that its advertisement be compared with any from the cosmetic obesity industry where presumably 'good taste' images of half clad young non obese people, usually women, were used. The advertisement was clearly and specifically aimed at health professionals and aimed to lead them to question their current beliefs about obesity treatment. Images of obese people were used; these might not be appealing to the complainant but should not surprise other health professionals such as nurses and doctors. According to the National Audit Office, over half of all women and almost two thirds of men in England were either overweight or obese. Obesity and overweight were associated with a range of co-morbidities which were likely to make such people more frequent users of health services and, appealing or not, the images in the advertisement were not uncommon amongst those faced by health professionals every day. Indeed they might well represent the norm for users of health services.

Knoll noted that the complainant found it difficult to distinguish as to whether a photograph shown was of a male or of a female and stated that this was simply a reflection of the condition depicted. That this could be perceived as being offensive to people of larger stature Knoll did not understand and strongly disputed.

Finally Knoll submitted that although the images were half-naked the partial nudity was neither gratuitous nor offensive in the context of depicting obesity to a health professional.

Knoll stated that in summary, although it regretted that the advertisement appeared to have caused offence in this case, it considered that in the context of where and how the images were used this should not be so. Knoll did not accept that its advertisement breached Clause 9.1 of the Code.

PANEL RULING

The Panel noted the requirement of Clause 9.1 of the Code that all promotional materials and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence.

The advertisement had appeared in the pharmaceutical press and the Panel accepted that some people might consider it to be in bad taste. The Panel considered, however, that it was unlikely to cause offence to the majority of those who would see it. No breach of Clause 9.1 was ruled.

2 Claim 'Thanks to Reductil enough *is* enough'

This prominent claim appeared in a highlighted box which blanked out 8 (4 x 2) of the small photographs. In the bottom right-hand corner of the box was the picture of a plate of leftovers from a meal.

COMPLAINT

The complainant noted that there were a number of complications listed under each photograph such as 'Sleep apnoea', 'Breast cancer', 'Hypertension'. The advertisement implied, due to the positioning of the claim 'Thanks to Reductil, enough is enough', that as a result of taking Reductil and reducing obesity, patients would also have reduced incidence of hypertension, breast cancer, type 2 diabetes and other complications listed. This was misleading as there were no references listed on the advertisement to indicate whether patients had reduced morbidity from the complications listed as a result of taking Reductil.

The complainant noted that in addition, Reductil was contraindicated in patients with congestive heart failure, history of coronary artery disease and peripheral arterial occlusive disease. One of the side effects of taking Reductil was raised blood pressure, which could subsequently lead to cardiovascular disease and stroke. The complications listed and the implication that Reductil was reducing the incidence of all of these conditions was inaccurate, misleading and incapable of substantiation. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Knoll stated that it did not consider it appropriate to address the issue of substantiation. The company did not make any claim that Reductil should be used in any of these conditions or indeed that weight reduction effected by Reductil would lead to any reduction in morbidity from any of these conditions.

The advertisement used the repeated images of obese people and some of the diseases and syndromes associated with obesity. The latter was done to ensure that readers understood that the company did not advocate the use of Reductil for cosmetic reasons; rather it was legitimate medical reasons which underlay any decision to treat obesity that the company wanted to bring to their attention. Put simply it was an acceptable way to depict the seriousness of obesity as a disease (something that was not generally recognised yet in the UK) and only that. Knoll considered that by the use of the co-morbid conditions amongst the images of obese people it had been ethically responsible in its attempts to guide the reader to the medical, rather than cosmetic, reasons for treating obesity and overweight.

Knoll stated that '...enough is enough' simply indicated the mode of action of Reductil, which was to enhance satiety (resulting in smaller portions of food being consumed). This was emphasised by the use of the plate with the unfinished meal immediately adjacent and within the specific area occupied by the claim 'enough is enough'. Knoll referred to the Reductil summary of product characteristics (SPC) for mode of action support and substantiation.

Knoll stated that in summary it had taken a lot of care to keep the obesity plus co-morbidities area of the advertisement distinct from the 'mode of action' area, to avoid any possible misunderstanding. The company considered that, given the mode of action of Reductil, '...enough is enough' was a perfectly acceptable line to use. The link between this line and the mode of action of Reductil was evident by use of the half full plate immediately adjacent to it. The company did not claim any effect on the clinical course of obesity co-morbidities, but thought that the latter indicated that obesity was a condition that merited health professionals' attention. The company considered that it was taking an ethical approach to the treatment of obesity and did not accept that the advertisement was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that the Reductil advertisement clearly promoted the product as an anti-obesity agent. The strapline beneath the product logo was 'Helps obese patients control their eating'. The text described Reductil as 'a new effective aid to weight loss' and stated that the product enabled patients to 'achieve medically beneficial weight loss'. The Panel considered that the grid of photographs would be seen depicting the profiles of patients who presented with obesity. In the Panel's view, 'Hypertension', 'Breast cancer', and 'Type 2 diabetes' etc would be seen by the reader as co-morbid conditions. The Panel did not consider that the advertisement implied that treatment with Reductil would lead to a reduced incidence of these conditions as alleged. The Panel did not consider that the advertisement was inaccurate or misleading in this regard. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant had also raised the issue that some of the co-morbid conditions were contra-indications to therapy with Reductil, or as in the case of hypertension, might be exacerbated by such treatment. This issue had been previously considered in Case AUTH/1197/6/01.

In Case AUTH/1197/6/01 the Panel had noted that the Reductil SPC listed a number of contraindications including history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischaemic attack). In that regard the Panel noted that some of the photographs in the advertisement were labelled 'Stroke' and 'Cardiovascular disease'; 'Breathlessness' could be a symptom of heart failure. In the Panel's view the advertisement thus implied that Reductil could be used in some obese patients for whom, because of co-morbid conditions, it would be contraindicated. Some of the photographs were labelled 'Hypertension' and the Panel noted that inadequately controlled hypertension was also a contraindication to therapy. In addition section 4.4 of the SPC, 'Special warnings and special precautions for use', stated that blood pressure and pulse rate should be monitored in all patients on Reductil as it had caused clinically relevant increases in blood pressure in some patients. Section 4.3, 'Undesirable effects', stated, *inter alia*, that raised blood pressure/ hypertension was a frequent (1-10%) side effect; prescribers were also told that if they wished to use Reductil in patients with hypertension they should read the sections of the SPC detailing

contraindications and special warnings and precautions for use.

In Case AUTH/1197/6/01 the Panel's view was that the overall impression given by the advertisement was that Reductil could be used, without further consideration, in a wide range of obese patients which was not so. Some of the patient types shown ie 'Stroke' 'Cardiovascular disease' were clearly contraindicated. Patients with hypertension would need careful monitoring as Reductil could exacerbate their condition. The Panel thus considered that the advertisement was inconsistent with the particulars listed in the Reductil SPC and a breach of Clause 3.2 was ruled. The Panel considered that the alleged breach of Clause 7.7 of the Code was covered by this ruling. The Panel was concerned that the advertisement might encourage doctors to prescribe Reductil for those patients who should not be so treated and therefore compromise patient safety. The Panel considered that such advertising brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel's rulings had been accepted by Knoll.

Turning to the case now before it, Case AUTH/1202/7/01, the Panel considered that the alleged breaches of Clauses 7.2 and 7.3 of the Code were covered by its rulings in the previous case. Breaches of Clauses 7.2 and 7.3 were ruled.

3 Claim 'Reductil has no embarrassing GI side effects and is easy to comply with'

COMPLAINT

The complainant considered that the claim was inaccurate since the prescribing information listed constipation and haemorrhoid aggravation as very frequent (>10%) and frequent (1-10%) side effects respectively. These side effects could be considered as embarrassing and hence affect compliance. It was not clear whether the compliance was easier due to the lack of embarrassing GI side effects or whether Reductil was a medicine which patients found it easy to comply with. If the former was the case, this claim should be substantiated, of which there was no evidence. Breaches of Clauses 7.2 and 7.3 of the Code were alleged.

RESPONSE

Knoll noted that the relevant sentence used in the advertisement was 'Reductil has no embarrassing GI side effects and is easy to comply with, enabling patients to...'. The company considered that any unbiased observer would agree that no link was made between the lack of embarrassing GI side effects and ease of compliance. They simply sat consecutively in a list. The company did not state that 'Reductil has no embarrassing GI side effects and is therefore easy to comply with,...' or that 'Reductil has no embarrassing GI side effects and hence is easy to comply with,...' or that 'Because Reductil has no embarrassing GI side effects it is easy to comply with,...'. Knoll simply gave a list of important features of its medicine. Knoll referred to the Reductil SPC for ample substantiation of ease of use as Reductil was a tablet that could be taken once a day with or without meals.

Knoll submitted that a current SPC (especially one as recently approved as Reductil's) reflected available evidence on safety and toleration. The following GI side effects were listed in section 4.8: loss of appetite; constipation; nausea; haemorrhoid aggravation. These were obviously not embarrassing. Furthermore it was important to point out that in the obesity area obviously embarrassing GI side effects appeared to be an important issue as another leading medication was reported to be associated with 'oily spotting from the rectum, flatus with discharge, faecal urgency, fatty/oily stool, oily evacuation, increased defecation and faecal incontinence'. Thus in this context it was necessary and legitimate to point out the absence of embarrassing GI side effects without any fear of misinterpretation or the need to demonstrate the few GI side effects of Reductil as being non embarrassing.

Clearly both generally, as well as specifically in the context of obesity, the information given by the phrase 'Reductil has no embarrassing GI side effects' reflected available evidence, and was entirely accurate, balanced and fair information in this respect.

Knoll rejected the allegation that its advertisement was in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

In the Panel's view the claim in question was for two separate benefits of Reductil; no embarrassing GI side effects and easy compliance with therapy. The Panel did not consider that the claim meant that as a consequence of no embarrassing GI side effects Reductil was easy to comply with. The Panel thus did not consider that the claim was misleading as alleged and ruled no breach of Clauses 7.2 and 7.3 of the Code.

Complaint received **2 July 2001**

Case completed **13 September 2001**

CASE AUTH/1203/7/01

WYETH/DIRECTOR v ORGANON LABORATORIES

Breach of undertaking

Wyeth alleged that Organon Laboratories was in breach of the undertaking and assurance that it had given in Case AUTH/1147/2/01 in that it was continuing to claim that Zispin was over 25% cheaper than venlafaxine (Wyeth's product Efexor).

The Panel noted that the material at issue in the previous case had included a claim that Zispin was over 25% cheaper than venlafaxine. The material now at issue, a leavepiece, included a cost comparison chart which illustrated the same price difference. The Panel considered that although different to the claim in Case AUTH/1147/2/01, the cost comparison was similarly misleading and sufficiently similar for it to be caught by the undertaking given in the previous case. Organon had thus failed to comply with its undertaking and a breach of the Code was ruled.

The Panel considered that an undertaking was an important document. Companies must have procedures in place to ensure compliance with undertakings. Material ruled in breach of the Code must be withdrawn forthwith. The leavepiece in question had been used eight days after the undertaking in Case AUTH/1147/2/01 had been signed and two months after stocks of it had been exhausted. The Panel queried whether it was reasonable to assume that, after two months of no stock, all copies of the leavepiece had actually been used. There would be a time difference between a representative ordering the item and using it. The continued use of a claim previously ruled in breach of the Code brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

COMPLAINT

Wyeth, the complainant in Case AUTH/1147/2/01, complained that Organon Laboratories Ltd was continuing to claim that Zispin was more than 25% cheaper than venlafaxine (Wyeth's product Efexor). In Case AUTH/1147/2/01 the Panel had considered that such a claim was unfair and misleading given that it was based on weighted average costs and weighted average doses. The Panel considered that most readers would assume that the more than 25% difference related to the cost of treating typical patients which was not so. A breach of the Code was ruled which was upheld on appeal by Organon. Organon had signed the form of undertaking and assurance on 13 June and stated that the claim would not be used after 14 June.

Wyeth now drew attention to a leavepiece which was used by Organon at a meeting on 21 June in which it was stated that, compared to venlafaxine at a cost of £30, Zispin would cost £8.31 less which was over 25% cheaper.

Wyeth stated that use of material that should have been withdrawn appeared to constitute a Clause 2 complaint. Furthermore Wyeth alleged that Organon had breached its undertaking, in breach of Clause 21, and that the claim was again misleading in breach of Clause 7.2 of the Code.

RESPONSE

Organon Laboratories stated that in Case AUTH/1147/2/01 it had signed an undertaking that the offending advertisement and related materials would no longer be distributed. As part of that undertaking the company specified that advertising materials would last be used on 14 June 2001. That undertaking was complied with fully for the company's journal advertising campaign. However investigations following receipt of the current complaint revealed that an additional affected piece of promotional material was not withdrawn.

Organon explained that the promotional item in question was fairly old (date of production December 2000) and had been out of stock for the last two months. Prior to that time representatives were only able to order limited quantities and most copies had been used and distributed before the date of the final decision on Case AUTH/1147/2/01 became available. However it appeared now that a few copies of the leavepiece remained available and were inadvertently used during the meeting in question. Organon stated that all remaining copies had now been destroyed.

Organon stated that it appreciated that a review of its procedures for complying with undertakings was essential. This had been done and additional checks and safeguards were now in place to ensure that any future undertakings, when given, were fully complied with. Organon was confident that such problems would not arise in future.

Organon expressed its regret that this incident occurred, and gave its assurance that all steps necessary had been taken to ensure that there were no recurrences.

PANEL RULING

The Panel noted that the material now at issue was not the same as that at issue in Case AUTH/1147/2/01. In Case AUTH/1147/2/01 the claim in question was 'Did you know ZISPIN is over 25% cheaper than venlafaxine?' which had appeared in a journal advertisement. The material now at issue was a leavepiece which contained a cost comparison chart showing that compared to the monthly cost of venlafaxine (£30), Zispin cost £8.31 less ie Zispin was over 25% cheaper than venlafaxine. The Panel considered that, although different to the claim in Case AUTH/1147/2/01, the cost comparison now at issue was similarly misleading and sufficiently similar for it to be caught by the undertaking given in the previous case. Organon had thus failed to comply with its undertaking. The leavepiece was distributed in June and so was in use when the 1998 edition of the Code of Practice was in operation; the Panel therefore ruled a breach of Clause 21. The Panel considered that its ruling of a breach of Clause 21 covered the allegation of a breach of Clause 7.2 of the Code.

The Panel considered that an undertaking was an important document. It required companies to provide details of the action taken and the date of the final use of the materials ruled in breach. Companies must have procedures in place to ensure compliance with undertakings. Material ruled in breach of the Code must be withdrawn forthwith.

The Panel noted that the leavepiece had been used eight days after the undertaking in Case AUTH/1147/2/01 had been signed. It had been produced in December 2000 and representatives had been able to order limited quantities of the leavepiece up until about May 2001 when stocks of the item had been exhausted. The company had thus assumed that all copies of the leavepiece had been used by the time it had signed its undertaking in Case AUTH/1147/2/01 in mid June 2001.

The Panel noted that although Organon had had procedures in place to ensure compliance with the undertakings, these had not been wholly adequate.

On receipt of the current complaint Organon had reviewed its procedures and found it necessary to add further checks and safeguards. The leavepiece had been used two months after stocks of it had become exhausted. The Panel queried whether it was reasonable to assume that, after two months of no stock, all copies of the leavepiece had been actually been used by the representatives. There would be a time difference between a representative ordering the item and using it. The Panel considered that the continued use of a claim previously ruled in breach of the Code brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel noted that Organon had stated that all necessary steps had been taken to ensure that there were no recurrences.

Complaint received **3 July 2001**

Case completed **10 August 2001**

CASE AUTH/1206/7/01

HOSPITAL PHARMACIST v ELAN PHARMA

Conduct of representative

A hospital pharmacist complained about an Elan Pharma representative who had visited the operating theatres informing staff that the pharmacy department had a bulk trial supply of Elan's product Ultiva (remifentanil) which could be used for any procedure. The complainant's name was quoted as the person organising supplies to be placed in the theatre cupboards. None of this information was true. Following a request for further information the complainant explained that it had recently been agreed to allow the use of Ultiva for cardiothoracic surgery. Elan explained that the hospital had previously only allowed the product to be used in neurosurgery.

The complainant stated that the representative also met with one of the hospital consultants and when the consultant mentioned that he would use Ultiva on one patient that afternoon, the representative replied 'It would be a good test of the system'. It appeared that the representative hoped that by using the complainant's name no queries would be raised about the change in hospital policy on Ultiva usage. The complainant was extremely annoyed and upset by the fact that her name had been used by the representative to substantiate lies and was sure that the company would not endorse this kind of practice.

The Panel noted that the parties' accounts of what took place when the representative visited the operating theatres differed. It was difficult in such cases to know what exactly transpired between the parties. The Panel considered that in a hospital department where a representative might interact with several staff it could be difficult for any one person to know what the representative had said to the others. In this regard the complainant had provided supporting statements from two other members of staff.

Elan did not dispute the fact that the representative had misunderstood the nature of the agreement regarding Ultiva usage. With regard to the representative's use of the complainant's name, the Panel considered that given Elan's version of the agreement, that an anaesthetist could contact the complainant to discuss cases but would only be able to use Ultiva after approval, the representative had referred to the complainant by name. The statement from the senior operating department assistant was clear on this point. The Panel noted Elan's submission that on no occasion did the representative use the complainant's name to endorse the use of Ultiva.

The Panel considered that by misunderstanding the nature of the agreement, and in the process referring to the complainant by name, the representative had not maintained a high standard of conduct and ruled a breach of the Code.

A hospital pharmacist wrote to Elan Pharma Limited about the conduct of one of its representatives. The letter was copied to The Association of the British Pharmaceutical Industry which forwarded it to the Authority to be dealt with as a complaint under the Code.

COMPLAINT

The complainant stated that an Elan representative had visited the operating theatres at a local hospital informing staff that the pharmacy department had a bulk trial supply of Ultiva (remifentanil). He told the theatre staff that the supplies could be used for any

procedure. The representative quoted the complainant's name as the person organising supplies to be placed in the cupboards on the theatres. None of this information was true.

The representative also met with one of the hospital consultants the same day and when the consultant mentioned that he would use Ultiva on one patient that afternoon, the representative replied 'It would be a good test of the system'. It appeared that the representative hoped that by using the complainant's name no queries would be raised about the change in hospital policy on Ultiva usage.

The complainant was extremely annoyed and upset by the fact that her name had been used by the representative to substantiate lies and was sure that the company would not endorse this kind of practice from its representatives.

RESPONSE

Elan Pharma explained that its representative organised a promotional meeting to discuss Ultiva, an opoid analgesic licensed for use during anaesthesia. Thirteen anaesthetists, including eight consultants, attended the meeting. Senior pharmacists were also invited and the complainant attended. The Drugs and Therapeutics Committee at the hospital currently approved the use of Ultiva for neurosurgical procedures only. Some anaesthetists at the meeting expressed an interest in using Ultiva in other procedures and this led to a discussion between themselves and the complainant on how this might be achieved. The representative understood the outcome of this discussion to be that Ultiva would be made available for a six-month trial period for non-neurosurgical procedures. The understanding was that an anaesthetist could contact the complainant to discuss cases, but would only be able to use Ultiva after approval. It was clear, however, that the representative misunderstood the nature of the agreement reached.

Elan stated that its representative communicated this procedure to other anaesthetists in the hospital in the belief that the complainant was in full agreement. On no occasion did he use the complainant's name to endorse the use of Ultiva and he made it clear in all his dealings with customers that any additional use of Ultiva should be discussed with and approved by pharmacy. No commercial gain for Elan or material loss to the hospital could have resulted from this misunderstanding, as there was no possibility of additional use of Ultiva without the full knowledge and agreement of the pharmacy department.

Elan stated that its representative had clearly acted in good faith and did not knowingly mislead or misrepresent at any time. Despite the misunderstanding, he maintained a high standard of ethical conduct and complied with all relevant requirements of the Code. However, the company understood how the complainant came to be annoyed and upset and it apologised for this and any inconvenience caused.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant confirmed that she had attended the promotional meeting in April at which a number of anaesthetists involved in cardiothoracic procedures expressed an interest in trialing Ultiva for a period of three to six months to allow them to assess its efficacy. The complainant stated that she suggested that the way forward would be for the anaesthetist to write to her requesting the use of Ultiva. This request would be forwarded to the Drugs and Therapeutic Committee as the final decision was left with it. The discussion about a possible trial only related to cardiothoracic surgery and not the whole of surgery.

The complainant stated that she found the representative's misunderstanding of what had been discussed hard to believe. Firstly, she did not have the authority to agree to a six-month trial so she would not have used any language implying that a trial could start. Secondly, the consultant anaesthetists had demonstrated that they had understood the discussions as they had written to her formally requesting the hospital to purchase Ultiva for a trial period in cardiothoracic surgery, but had not tried to use the product as it had not yet been agreed by the Drugs and Therapeutics Committee.

One consultant anaesthetist had been using Ultiva on a 'named patient' basis for certain cases, thus contacting the complainant about each patient prior to use. The complainant certainly would not want this to become common practice with other anaesthetists for every potential patient as she did not have the time available to deal with this procedure and she most certainly did not indicate this as the way forward at the meeting.

With regard to the use of the complainant's name by the representative, the senior operating department assistant involved was adamant that it was used, as she had not previously heard of the complainant, and made a note against the name as the person to be contacted. The complainant provided two statements, one from the senior operating department assistant and another from a consultant anaesthetist, both reporting the course of events. The statement from the senior operating department assistant confirmed that the representative did use the complainant's name and that contrary to Elan's response the representative specifically stated that the complainant had sanctioned the use of Ultiva and was actively trying to put it into all the medicine cupboards. The consultant anaesthetist stated that the representative had told him that he had spoken to the complainant and that Ultiva was available for his use for certain cases for approximately six months and that the complainant would be able to issue the Ultiva provided the appropriate forms were filled in.

The complainant agreed that there was no material loss to the hospital, but a considerable amount of her time and that of other colleagues, an anaesthetic consultant, a senior operating department assistant and two senior pharmacy technicians, was wasted when they should have been dealing with more important duties.

The complainant stated that according to the senior operating department assistant, there was a trainee from Elan accompanying the representative during his visit in July. The trainee was never introduced so

her name was not known. The complainant noted that Elan had made no reference to her in its response even though she would have been an essential witness to the conversation that took place. The complainant understood, however, that asking her for a statement could place her in a difficult position.

PANEL RULING

The Panel noted that the parties' accounts of what took place when the representative visited the operating theatres differed. The Panel observed that it was difficult in such cases to know what exactly transpired between the parties. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel considered that in a hospital department where a representative might interact with several staff it could be difficult for any one person to know what the representative had said to the others. In this regard the Panel noted that, following a request for further information, the complainant had provided supporting statements from two other members of staff.

The Panel noted that it had been alleged that the representative had misunderstood the nature of the agreement regarding the limited use of Ultiva within the hospital. Furthermore, that when telling other staff about the agreement, as he understood it, the representative had used the complainant's name in the hope that no queries would be raised regarding the change in policy on the use of Ultiva. The Panel noted that Elan did not dispute the fact that the representative had misunderstood the nature of the agreement. With regard to the representative's use of the complainant's name, the Panel considered that given Elan's version of the agreement, that an anaesthetist could contact the complainant to discuss cases but would only be able to use Ultiva after approval, the representative had referred to the complainant by name. The statement from the senior operating department assistant was clear on this point. The Panel noted Elan's submission that on no occasion did the representative use the complainant's name to endorse the use of Ultiva.

The Panel considered that by misunderstanding the nature of the agreement, and in the process referring to the complainant by name, the representative had not maintained a high standard of conduct and ruled a breach of Clause 15.2 of the Code.

Complaint received **16 July 2001**

Case completed **6 September 2001**

CASE AUTH/1208/7/01 *NO BREACH OF THE CODE*

PRESCRIBING ADVISER v SCHERING HEALTH CARE

Promotion of Mirena

A primary care group prescribing adviser stated that he had attended a training meeting for community pharmacists supported by Schering Health Care at which there had been a stand displaying posters for Mirena and Levonelle-2. After the meeting, one of the complainant's colleagues was talking to the company's representative about hormone replacement therapy (HRT) and the representative was extolling the virtues of Mirena (levonorgestrol) as a means of providing a progestogen for post-menopausal women with an intact uterus. The complainant alleged that such use was outside the terms of the marketing authorization for Mirena, which was licensed solely for contraception.

The Panel noted that the representative had been asked a question about combining contraception with HRT. Schering Health Care had stated that the enquirer was possibly to undertake some audit work for the health authority with one project on Mirena and the other on HRT. Schering Health Care stated that the representative made it clear that Mirena did not have a licence for HRT but had gone on to mention that some local consultants had decided to add oestrogen where a perimenopausal woman already had Mirena fitted for contraception. The Panel acknowledged that contraception/HRT was a complex area of medicine and that representatives might well be asked questions about unlicensed uses of their company's medicines. In the Panel's view it was reasonable that representatives should know about the unlicensed uses of the medicines they promoted. Requests for information regarding such use, however, were best referred to the company for an answer to avoid the representative promoting outside the licence or promoting unlicensed medicines.

In cases like this it was difficult to establish exactly what was said between the parties. The matter was raised via a question and Schering Health Care had stated that the representative made it clear that Mirena did not have a licence for HRT. It was always difficult to know in which direction a conversation was heading. It would have been preferable if the representative had not referred to unlicensed local use and as soon as the issue of HRT had been raised had advised the enquirer that the matter would be referred to medical information. Nevertheless, on balance, the Panel did not consider that the representative had promoted the product for an unlicensed indication and no breach of the Code was ruled.

A primary care group prescribing adviser complained about the conduct of a representative from Schering Health Care Limited in relation to Mirena (levonorgestrel).

COMPLAINT

In July the complainant had attended a training meeting for community pharmacists with refreshments provided by Schering Health Care. At this meeting, the company's representative had erected a stand displaying posters for Mirena and Levonelle-2. After the meeting, one of the complainant's colleagues was talking to the representative about hormone replacement therapy (HRT) and the representative was extolling the virtues of Mirena as a means of providing a progestogen for post-menopausal women with an intact uterus. The complainant stated that such use was outside the terms of the marketing authorization for Mirena, which was licensed solely for contraception. A breach of the Code was alleged.

RESPONSE

Schering Health Care stated that the training meeting was one of a series of four supported by the company for the pharmacists' Prescribing Group Direction (PGD) for Levonelle-2 in the area.

The representative advised that at the end of the meeting, whilst she was clearing up, she was approached by one of the meeting participants, a CPPE tutor for the area and a community pharmacist, who was also possibly to undertake certain audit work for the health authority with one project concerning the prescribing of Mirena and another project on HRT.

The conversation between the representative and the tutor commenced with a general discussion on Mirena and its use for contraception locally and the representative was also able to clarify some confusion over the licensing of Mirena for menorrhagia.

The conversation continued on the use of Mirena for the older woman who still needed effective contraception and the effect of progestogen on the uterus. When the issue of combining effective contraception with HRT was raised by the tutor, the representative made it clear to her that Schering Health Care did not have a licence for HRT, but mentioned that some consultants locally had made a decision to add oestrogen where a perimenopausal woman already had a Mirena system fitted for contraception depending on the hormonal needs of the woman.

When the tutor mentioned that she might possibly be undertaking an audit on HRT for the health authority, the representative advised that she was not an HRT expert and proposed that one of the HRT representatives should contact her to discuss the issues.

The representative had advised that the health authority's prescribing adviser might have overheard a part of the conversation. Whatever was overheard, the complaint was silent on the detail. Schering Health Care would challenge the image which the complainant was attempting to create by describing the representative as 'extolling the virtues of Mirena'. This misrepresented the nature of the conversation between the tutor and the representative, which the representative submitted amounted to a certain extent to a personal private discussion.

In one-to-one exchanges it was sometimes difficult to determine what exactly transpired between the parties and, in this instance, it was not even a primary participant in the conversation who had complained. It seemed to Schering Health Care that, in any event, it was not necessary to investigate exactly what was said, although the company did not consider that the representative had said anything for which she could be criticised, as she was responding to an individual enquiry from a health professional and such replies were excluded from the Code by Clause 1.2.

FURTHER COMMENTS FROM THE COMPLAINANT

Whilst accepting most of the company's response, the complainant took issue with the charge that the nature of the conversation had been misrepresented. In a public forum it was extremely difficult for a representative to have a 'personal private discussion'. The representative was working for the company and as such anything said relating to one of her employer's products must be considered promotional.

PANEL RULING

The Panel noted that the representative had been asked a question about combining contraception with HRT. Schering Health Care stated that the representative made it clear that Mirena did not have a licence for HRT but had gone on to mention that some local consultants had decided to add oestrogen where a perimenopausal woman already had Mirena fitted for contraception.

The Panel noted that Clause 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 did not accept Schering Health Care's submission that the conversation amounted to a personal private discussion. The representative had been promoting Mirena at the meeting and had been asked a question by one of the attendees.

The Panel acknowledged that contraception/HRT was a complex area of medicine and that representatives might well be asked questions about unlicensed uses of their company's medicines. In the Panel's view it was reasonable that representatives should know about the unlicensed uses of the medicines they promoted. Requests for information regarding such use, however, were best referred to the company for

an answer to avoid the representative promoting outside the licence or promoting unlicensed medicines.

In cases like this it was difficult to establish exactly what was said between the parties. The matter was raised via a question and Schering Health Care had stated that the representative made it clear that Mirena did not have a licence for HRT. It was always difficult to know in which direction a conversation was heading. It would have been preferable if the representative had not referred to unlicensed local use and as soon as the issue of HRT had been raised had advised the enquirer that the matter would be referred to medical information. Nevertheless, on balance, the Panel did not consider that the representative had promoted the product for an unlicensed indication and no breach of Clause 3.2 of the Code was ruled.

Complaint received **18 July 2001**

Case completed **5 October 2001**

CASE AUTH/1209/7/01

PRESCRIBING ADVISER v TRINITY

Prescribing support service

The prescribing adviser to a primary care trust complained that a booklet issued by Trinity and entitled 'Concept Your Questions Answered' was misleading. Concept was a prescribing support service offered by Trinity which provided a systematic, practice based review of repeat medication. The service was claimed to be a rapid and effective way of achieving rational prescribing.

The complainant alleged that the statement 'Discounts to chemists may increase, but these discounts are not passed on to the surgery. In other words, as costs to pharmacy decrease, costs to the practice remain consistently high' was quite clearly not true. A discount was deducted from the NHS remuneration to pharmacy contractors which reflected the discounts they obtained; the level was determined by national discount enquiries. This was to ensure that pharmacy contractors did not profit by these discounts. The discount was therefore to the benefit of the NHS and was passed on to the practices in the calculations made by the Prescription Pricing Authority in monitoring GP practice expenditure against their indicative prescribing budget.

The Panel noted that there had been a previous case which was of relevance, Case AUTH/938/10/98. No breach of the Code had been ruled on appeal. With regard to the case now before it, Case AUTH/1209/7/01, the Panel considered that the statement at issue was similar to that at issue in the previous case. The remuneration of pharmacists was complicated and the statement did not reflect the whole picture. The booklet was, however, aimed at GP practices. For the purpose of managing an individual practice's prescribing costs the Panel considered that the statement was factual, accurate and not misleading. No breach of the Code was ruled.

With regard to the statement 'Bioequivalence and/or therapeutic equivalence means no patient consultations are generally required', the complainant stated that the reason for encouraging GPs to prescribe modified release preparations by brand name was because of bioinequivalence between these products. It was important that patients were assessed and monitored before and after switching brands of modified release preparations.

The Panel noted that the British National Formulary (BNF) Number 41, March 2001, stated in its 'Guidance on prescribing' that in general generic names should be used except where bioavailability problems were so important that patients should always receive the same brand; in such cases the brand name should always be used. In the case of some modified release products, eg diltiazem, the relevant section of the BNF was preceded with the statement 'Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed'. The Panel noted that Trinity agreed with the general principle of prescribing modified release preparations by brand but submitted that its products had proven bio or therapeutic equivalence to the brand leader. The inference from this was that if a patient was receiving a brand leader and was switched to the Trinity product then, as stated, 'Bioequivalence and/or therapeutic equivalence means no patient consultations are generally required'. For sustained release diltiazem there were, however, thirteen modified release preparations listed in the BNF. Trinity claimed its product to be bio or therapeutically equivalent to the brand leader. Patients could thus be stabilized on a modified release preparation of diltiazem that was not the brand leader and therefore possibly not equivalent to the Trinity product; a patient consultation would be required if a switch to Trinity's product were to occur. The Panel noted that for other Trinity products, eg verapamil sustained release tablets, bioinequivalence between brands was not highlighted as a problem in the BNF. The Panel considered that the statement did not give enough information about when a patient consultation would be required and was misleading in that regard. A breach of the Code was ruled.

The complainant questioned what was meant by the term 'brand leader' in the statement 'Trinity Pharmaceuticals guarantees significantly lower prices than the brand leader(s)'. If the Trinity product became the brand leader, how could the company make its product cheaper than itself? The complainant noted that the price of Angitil XL was not 'significantly lower' than the prices of Slozem or Zemtard, potential 'brand leaders'.

In the Panel's view the statement meant that any Trinity product cost significantly less than the brand leader. Only Trinity marketed Tanatril (imidapril); the Trinity brand of imidapril was thus the brand leader. In addition Trinity marketed Brexidol tablets (piroxicam 20mg) which at £12.22 for 30 tablets (ref MIMS July 2001) was significantly more expensive dose for dose than the originating brand, and presumably brand leader, Feldene. The Panel thus considered that the statement was not true for all of Trinity's products. A breach of the Code was ruled.

The complainant alleged that the statement 'Modified Release (MR, CR, SR, Retard) products available from more than one supplier are not included in the Drug Tariff' was not true as verapamil 240mg SR tablets were included in the current Drug Tariff (July 2001). These were produced by Dexel, Trinity and Knoll.

Trinity had stated that the statement was true – with the exception of verapamil 240mg SR tablets for some reason. Some time ago it was decided not to list modified release products in the Drug Tariff, instead such products would be charged at list price to the prescriber. The inclusion of verapamil 240mg within the Drug Tariff was thus not in line with other modified release products.

The Panel noted that verapamil 240mg SR tablets were available from more than one supplier and were included in the Drug Tariff. The statement in the booklet was therefore not true. A breach of the Code was ruled.

A prescribing adviser to a primary care trust complained about statements made in a booklet, issued by Trinity Pharmaceuticals Ltd entitled 'Concept Your Questions Answered' (ref TR 269 – August 2000). Concept was a prescribing support service offered by Trinity which provided a systematic, practice based review of repeat medication. The service was claimed to be a rapid and effective way of achieving rational prescribing. The complainant alleged that the booklet was misleading and referred to Clause 7.2 of the Code.

1 Statement 'Discounts to chemists may increase, but these discounts are not passed on to the surgery. In other words, as costs to pharmacy decrease, costs to the practice remain consistently high'

COMPLAINT

The complainant stated that this was quite clearly not true. A discount was deducted from the NHS remuneration to pharmacy contractors (Drug Tariff July 2001, page 5 Clause 6A); this reflected the discounts obtained by pharmacy contractors and the level was determined by national discount enquiries. This was to ensure that pharmacy contractors did not profit by these discounts.

The discount was therefore to the benefit of the NHS, and was passed on to the practices in the calculations made by the Prescription Pricing Authority in monitoring GP practice expenditure against their indicative prescribing budget.

RESPONSE

Trinity stated that contrary to the statement made by the complainant, the fact was that retail pharmacists did profit from competitive purchasing despite the discount deduction from the NHS remuneration to pharmacy contractors.

Whilst the company agreed that the discount might benefit the NHS as a whole, it did not believe this was passed down to surgery level – instead the discount was calculated as a percentage of the total value of medicines dispensed, it was not calculated by individual line. Consequently the surgery would be charged at either the modified release product list price or (in the case of non-modified release products) at the generic Drug Tariff price.

Trinity stated that in the case of a modified release product being dispensed, unless the prescription had been specifically branded then the pharmacist was free to dispense any brand of modified release product and the full NHS cost of the brand would be attributed to the GP's prescribing costs, regardless of any discounts available to the pharmacist. It might therefore transpire that a modified release product sold to the retail pharmacist at a large discount by a generic manufacturer might be the product with by far the highest list price – the GP was charged this high list price!

Trinity noted that this matter had some similarity with a previous case, Case AUTH/938/10/99. However, the promotional piece was changed following discussion and agreement with the Panel and the Code of Practice Appeal Board ruling; the Appeal Board noted that the statement made in the previous case was 'factual, accurate and not misleading and no breach of Clause 7.2 was ruled'.

PANEL RULING

The Panel noted that in a previous case, Case AUTH/938/10/98, consideration was given to the statement 'Any discount received by a pharmacist is not transferred to a GP's prescribing costs. In other words, additional profit for the pharmacist could mean additional cost to the surgery'. This statement appeared in a booklet produced by Trinity in support of its modified release preparations.

Ruling in Case AUTH/938/10/98

Panel Ruling
The Panel noted that discounting was a long established part of wholesalers' and manufacturers' normal business practices. Pharmacists were able to negotiate discounts on purchases of medicines. The Prescription Pricing Authority calculated

reimbursement costs of the medicines dispensed according to the full NHS price of branded medicines or the Drug Tariff price for generic medicines. The overall benefit to the pharmacist of negotiating discounts was reduced by a system of claw back whereby a lump sum was deducted from the calculated reimbursement cost.

The Panel considered that the statement 'In other words, additional profit for the pharmacist could mean additional cost to the surgery' did not represent the whole picture. No mention had been made of the claw back. The booklet was too simplistic and in the Panel's view gave the impression that pharmacists could benefit directly from additional cost to the surgery. The Panel considered that the booklet was misleading in this regard. It was also disparaging to pharmacists. Breaches of Clauses 7.2 and 8.2 were ruled.

Appeal by Trinity
At the Appeal Board hearing Trinity's representative stated that the message could have been worded more subtly. The company would not use the point negatively and the document would be reprinted without the last sentence. The representative decided not to appeal the Panel's ruling of a breach of Clause 8.2 of the Code.

Appeal Board Ruling
The Appeal Board noted that the statement 'Any discount received by a pharmacist is not transferred to a GP's prescribing costs. In other words, additional profit for the pharmacist could mean additional cost to the surgery' was factual, accurate and not misleading. No breach of Clause 7.2 was ruled.

The appeal on this point was thus successful.

The Appeal Board noted that the representative had accepted the Panel's ruling of a breach of Clause 8.2 of the Code.

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The Panel noted that neither it nor the Appeal Board had agreed with Trinity as to how its promotional literature should be changed in the light of the ruling made in Case AUTH/938/10/98. The Authority could only give companies informal advice about such matters but if a complaint were received about a piece upon which the Authority had advised it would, nonetheless, proceed in the usual way.

Turning to the case now before it, Case AUTH/1209/7/01, the Panel considered that the statement 'Discounts to chemists may increase, but these discounts are not passed on to the surgery. In other words, as costs to the pharmacy decrease, costs to the practice remain consistently high' was similar to that at issue in the previous case. The remuneration of pharmacists was complicated and the statement did not reflect the whole picture. The booklet was, however, aimed at GP practices. For the purpose of managing an individual practice's prescribing costs the Panel considered that the statement was factual, accurate and not misleading. No breach of Clause 7.2 was ruled.

2 Statement 'Bioequivalence and/or therapeutic equivalence means no patient consultations are generally required'

COMPLAINT

The complainant stated that the reason for encouraging GPs to prescribe modified release preparations by brand name was because of bioinequivalence between these products. The BNF (41, March 2001) stated that 'Different versions of modified-release preparations may not have the same clinical effect'. It was therefore important that patients were assessed and monitored before and after switching brands of modified release preparations.

RESPONSE

Trinity stated that whilst it agreed with the complainant's comment that 'the reason for encouraging GPs to prescribe modified release preparations by brand name is because of bioequivalence between these products' – and indeed different versions of modified release preparations might be bioinequivalent, Trinity had proven bio or therapeutic equivalence to the brand leader. Consequently by prescribing a Trinity modified release brand, not only would GPs save money against their prescribing budget but they could also take comfort in the fact that Trinity's products were bio or therapeutically equivalent to the brand leader – unlike many other MR brands which could have a list price higher than the brand leader and be bioinequivalent. If a GP was to prescribe an MR product generically there were no guarantees which product would be dispensed.

PANEL RULING

The Panel noted that the British National Formulary (BNF) Number 41, March 2001, stated in its 'Guidance on prescribing' that in general generic names should be used except where bioavailability problems were so important that patients should always receive the same brand; in such cases the brand name should always be used. In the case of some modified release products, eg diltiazem, the relevant section of the BNF was preceded with the statement 'Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed'. The Panel noted that Trinity agreed with the general principle of prescribing modified release preparations by brand but submitted that its products had proven bio or therapeutic equivalence to the brand leader. The inference from this was that if a patient was receiving a brand leader and was switched to the Trinity product then, as stated, 'Bioequivalence and/or therapeutic equivalence means no patient consultations are generally required'. For sustained release diltiazem, there were, however, thirteen modified release preparations listed in the BNF. Trinity claimed its product only to be bio or therapeutically equivalent to the brand leader. Patients could thus be stabilized on a modified release preparation of diltiazem that was not the brand leader

and therefore possibly not equivalent to the Trinity product; a patient consultation would be required if a switch to Trinity's product were to occur. The Panel noted that for other Trinity products eg verapamil sustained release tablets, bioinequivalence between brands was not highlighted as a problem in the BNF. The Panel considered that the statement did not give enough information about when a patient consultation would be required and it was misleading in that regard. A breach of Clause 7.2 was ruled.

3 Statement 'Trinity Pharmaceuticals guarantees significantly lower prices than the brand leader(s)'

COMPLAINT

The complainant questioned what was meant by the term 'brand leader'. If the Trinity product became the brand leader, how could the company make its product cheaper than itself?

The complainant noted the following prices from the Chemist and Druggist Monthly Price List (June):

Angitil XL (Trinity) 240mg	£10.15 (28 caps)
Angitil XL (Trinity) 300mg	£9.22 (28 caps)
Slozem (Merck) 240mg	£8.20 (28 caps)
Slozem (Merck) 300mg	£8.50 (28 caps)
Zemtard XL (Galen) 240mg	£8.20 (28 caps)
Zemtard XL (Galen) 300mg	£8.50 (28 caps)

The complainant stated that it could thus be seen that the prices for these Trinity products were not 'significantly lower' than potential 'brand leaders'.

RESPONSE

Trinity explained that the brand leader was the brand (for that particular molecule) which possessed the highest market share. This was typically the originating brand. Trinity MR brands were not the brand leader for any of its products and if it were to become brand leader then it would obviously qualify its statement.

Using the diltiazem examples listed by the complainant, Tildiem was the brand leader (annual turnover May 2000 to May 2001 was £19,091,500) and the pro-rata price comparisons between the brand leader and the Trinity equivalent brand justified the statement, that Trinity had a significantly lower price than the brand leader. The annual sales value of Slozem was £894,300, whilst that of Zemtard was £183,900. Trinity submitted that the latter two products hardly qualified as potential 'brand leaders' when compared to the turnover of Tildiem.

PANEL RULING

The Panel noted that the statement 'Trinity Pharmaceuticals guarantees significantly lower prices than the brand leader(s)' appeared as the only statement on page 4 of the booklet. In the Panel's view the statement would be assumed to apply to all of Trinity's products. There was no indication on page 4 that the statement only related to modified release products. Although the booklet referred to modified release products on pages 9 to 12, there was nothing in the preceding pages to indicate that it related solely to such products. In the Panel's view the statement on page 4 would be read as meaning that any Trinity product cost significantly less than the brand leader.

The Panel noted that only Trinity marketed Tanatril (imidapril); the Trinity brand of imidapril was thus the brand leader. In addition Trinity marketed Brexidol tablets (piroxicam 20mg) which at £12.22 for 30 tablets (ref MIMS July 2001) was significantly more expensive dose for dose than the originating brand, and presumably brand leader, Feldene capsules (28 x 20mg – £6), Feldene dispersible tablets (28 x 20mg – £9.75) or Feldene Melt (28 x 20mg – £9.83). The Panel thus considered that the statement was not true for all of Trinity's products. A breach of Clause 7.2 was ruled.

4 Statement 'Modified Release (MR, CR, SR, Retard) products available from more than one supplier are not included in the Drug Tariff'

COMPLAINT

The complainant stated that this was clearly not the case as verapamil 240mg SR tablets were included in the current Drug Tariff (July 2001). These were produced by Dexel, Trinity and Knoll.

RESPONSE

Trinity stated that the statement was true - with the exception of verapamil 240mg SR tablets for some reason. Some time ago the Pharmaceutical Services Negotiating Committee in conjunction with the Department of Health took a decision not to list modified release products in the Drug Tariff, deciding that such products would be charged at list price to the prescriber. The inclusion of verapamil 240mg within the Drug Tariff was thus not in line with other modified release products. It might be that the Prescription Pricing Authority/Pharmaceutical Services Negotiating Committee were unaware of competition within the market. Trinity would make some enquiries and to seek to clarify this anomalous situation.

PANEL RULING

The Panel noted that verapamil 240mg SR tablets were available from more than one supplier and were included in the Drug Tariff. The statement that modified release products available from more than one supplier were not included in the Drug Tariff was therefore not true. A breach of Clause 7.2 was ruled.

Complaint received **18 July 2001**

Case completed **28 August 2001**

CASE AUTH/1211/7/01

PFIZER v MERCK SHARP & DOHME

Promotion of Zocor

Pfizer complained about a journal advertisement and two leavepieces for Zocor (simvastatin) issued by Merck Sharp & Dohme. Pfizer supplied Lipitor (atorvastatin).

The advertisement featured a photograph of a couple dancing in front of a large neon sign which read 93%. The neon sign had an arrow which pointed down to the only claim on the advertisement '93% of CHD patients in the GOALLS* study achieved LDL-C targets with ZOCOR at the starting dose'. The claim was referenced to the National Service Framework (NSF) for Coronary Heart Disease (CHD) and to the GOALLS (Getting to appropriate LDL-C Levels with Simvastatin) study.**

Pfizer alleged that the claim was misleading and exaggerated for three reasons. Firstly it was unclear from the claim what the starting dose was in order to achieve the results demonstrated. There were two different starting doses for Zocor; patients with coronary heart disease (CHD) should be started on 20mg whereas those with hyperlipidaemia should be initiated on 10mg per day. This might lead the reader to assume that CHD patients could reach the same target as in the GOALLS study on a starting dose of only 10mg, whereas the benefit was only seen in those taking 20 to 80mg. This information could only be obtained from the prescribing information. Secondly, the claim of 93% of CHD patients achieving LDL-C targets was exaggerated. There was no specification of what the LDL-C targets were and it gave the impression that it encompassed all LDL-C targets as set by different national and international guidelines for the management of hyperlipidaemia. The LDL-C target set by the Joint European Taskforce (≤ 3.0mmol/l) was very different from those set by the US National Cholesterol Education Program (NCEP, ≤ 2.6mmol/l). In addition, the targets set in the UK by the NSF were totally different (total cholesterol at 5mmol/l or LDL-C at 3mmol/l, or by 30% whichever was the greater). Thirdly, although two asterisks were included above the word 'targets' – the explanation was provided in tiny font size at the bottom of the page that it referred to the 'NSF target for LDL-C ≤ 3mmol/l'. However, the GOALLS study only looked at the LDL-C targets as set out by the European guidelines. This target at LDL-C < 3mmol/l could not be extrapolated to that of the NSF's targets. Therefore the information was extrapolated incorrectly and was misleading.

The Panel noted that the claim clearly defined the patient population to which it referred. The advertisement did not refer to a 10mg dose and the prescribing information clearly stated that the recommended starting dose for CHD patients was 20mg a day. The Panel did not consider that readers would be misled into assuming that the results referred to in the claim could be achieved using a 10mg starting dose. The claim referred to the GOALLS study and the percentage of patients which achieved LDL-C targets. In the Panel's view most readers would assume that the LDL-C targets referred to were those set in the GOALLS study. The Panel did not consider that the claim gave the impression that the LDL-C targets referred to encompassed all LDL-C targets as set by different national and international guidelines for the management of hyperlipidaemia or that the claim was exaggerated as alleged. One of the key efficacy parameters set in the GOALLS study was the percentage of patients achieving European LDL-C targets ie ≤ 115mg/dl (3mmol/l). In the claim, however, the term 'LDL-C targets' was asterisked to a footnote which read 'NSF target for LDL-C: < 3mmol/l'. The NSF CHD guidelines actually stated that cholesterol should be lowered either to <5mmol/l (LDL-C <3mmol) or by 30% whichever was greater. The Panel thus considered that the LDL-C targets set in the GOALLS study were not those referred to in the footnote. The NSF LDL-C target as stated in the footnote was not that as stated in the actual NSF for CHD. The Panel considered that the advertisement was misleading in this regard and ruled a breach of the Code.

A four page leavepiece was entitled 'Rapid benefits of early statin-based intervention in CHD patients'. Page 2 was headed 'Survival benefits of early intervention' below which was a graph which depicted the benefits of a number of different types of intervention compared to no intervention in the acute period following myocardial infarction (MI). Page 3 was headed 'Four sound reasons why ZOCOR should be your first-line statin'. Below this heading were claims relating to efficacy, cost, HDL and outcomes.

The claim 'The recent GOALLS† study has reinforced the benefit of early statin intervention: 93% of CHD patients achieved NSF cholesterol targets‡ after receiving ZOCOR 20mg for six weeks' appeared below the graph on page 2 which depicted the survival benefits of different interventions post-MI. Pfizer stated that according to the published paper the GOALLS study did not demonstrate that 93% of CHD patients on 20mg Zocor achieved a target of LDL-C ≤ 3mmol/l after 6 weeks; this was achieved after 14 weeks of treatment. The published study did not provide data on the number of patients who reached a target of LDL-C ≤ 3mmol/l at week 6. This had been extrapolated from the design of the study. Patients who were not at the pre-defined target of 2.6mmol/l at weeks 6 and 10 were titrated from 20mg onwards to 40mg and subsequently to 80mg. By the end of the study at week 14, there were 92.7% of patients who reached an LDL-C target of ≤ 3mmol/l at 20mg of simvastatin. However, one could not extrapolate that all patients on 20mg Zocor who achieved this pre-defined target of LDL-C at week 14 were the same number who achieved the target at week 6. Pfizer stated that in order to claim that 93% of CHD patients in the GOALLS study achieved NSF cholesterol targets after 20mg, one had to demonstrate that LDL-C was lowered to ≤ 3mmol/l or by 30% whichever was the greater. This was not demonstrated in the study. The mean baseline LDL-C level for patients entered in the study was**

3.7mmol/l. Although 93% of the patients achieved an LDL-C reduction to ≤ 3mmol/l, this constituted an LDL-C reduction of around 23% only. Furthermore, the study showed that only 72.5% of patients achieved an LDL-C reduction to ≤ 2.6mmol/l, which constituted a reduction around 30%. According to the NSF, the greater reduction of 30% was acceptable here and not just a reduction to an LDL-C level of 3mmol/l. Therefore, the claim for 93% of patients achieving the NSF cholesterol target was exaggerated. The study did not assess the patients according to the NSF targets for cholesterol reduction (as defined above). It was designed to assess the effectiveness and safety of Zocor in achieving LDL-C targets as recommended by the US NCEP and the European guidelines (Joint Task Force of European Societies on Coronary Prevention). Once again, the findings from the study had been extrapolated to the targets set by the NSF. Although the European guidelines' LDL-C target might be similar to that of the NSF, it was not clear from the claim which cholesterol target was achieved. Instead the claim implied that both the total cholesterol target of ≤ 5mmol/l and the LDL-C ≤ 3mmol/l target were achieved.

Pfizer noted that the claim was written as a second bullet point below the heading 'Survival benefits of early intervention'. Such juxtaposing misled the reader into thinking that the GOALLS study had demonstrated outcome in morbidity and mortality in CHD patients treated with 20mg of Zocor. Pfizer alleged that the claim was ambiguous, misled by implication, was incapable of substantiation and was all-embracing.

The Panel noted that the claim stated that the GOALLS study had shown that 93% of CHD patients achieved NSF cholesterol targets after 6 weeks' therapy with Zocor 20mg. A footnote below the claim stated that the NSF targets were defined as total cholesterol < 5mmol/l: LDL-C < 3mmol/l. The Panel noted its comments above with regard to the differences between the targets set in the GOALLS study, the NSF targets as stated by Merck Sharp & Dohme and the official NSF targets. The aim of the GOALLS study was to evaluate the effectiveness of Zocor in achieving LDL-C goals as recommended by US and European guidelines. The study design was such that all eligible patients received Zocor 20mg/day for the first 6 weeks. After that time, patients with an LDL-C >2.6mmol/l (the US target level) had their dose doubled to 40mg: patients with an LDL-C ≤ 2.6mmol/l remained on 20mg/day. At week 10 all patients were reassessed, those whose LDL-C remained >2.6mmol/l despite an increase in dose to 40mg had their dose of Zocor further increased to 80mg/day for the final four weeks of treatment. Patients who had originally stayed on the 20mg dose but whose LDL-C had now increased to >2.6mmol/l had their dose increased to 40mg/day. There was no provision for doses of Zocor to be decreased.

The Panel considered, therefore, that those patients who were taking 20mg Zocor at the end of the study (week 14) must have achieved the target of LDL-C ≤ 2.6mmol/l at week 6 and retained that level at week 10. With regard to the European target a table in the published paper showed that 92.7% of patients received 20mg Zocor. The Panel considered that to claim that 93% of patients achieved target lipid levels on the starting dose after 6 weeks was not misleading or exaggerated as alleged. No breach of the Code was ruled in that regard. The Panel noted, however, that the targets that the 93% of patients were claimed to have achieved were those of the NSF. The NSF targets were to lower total cholesterol to < 5mmol/l (LDL-C below 3mmol/l) or by 30% whichever was greater. These were not the targets set in the GOALLS study; patients in the GOALLS study were titrated to absolute LDL-C targets, not to a percentage change from initial LDL-C levels. The 30% lowering of LDL-C required by the NSF target meant that patients would not be titrated to a single LDL-C level; target LDL-C would be individualised according to LDL-C levels at the start of treatment. The Panel considered that in this regard the claim was misleading and exaggerated and ruled a breach of the Code.

The Panel noted the claim stated that the GOALLS study had reinforced the benefit of early statin intervention. The claim appeared on a page headed 'Survival benefits of early intervention' and below a graph showing the benefit, in terms of improved survival, of statin therapy post-MI. The Panel noted that Zocor was indicated in CHD, in patients with a plasma cholesterol level of 5.5mmol/l or greater to reduce the risk of mortality; reduce the risk of coronary death and non-fatal myocardial infarction; reduce the risk for undergoing myocardial revascularisation procedures and to slow the progression of coronary atherosclerosis. The Panel was concerned that the 'benefits' referred to in the claim might be assumed by some readers to be the 'survival benefits' referred to in the heading. The GOALLS study did not have any mortality or outcome data. Nevertheless, on balance it did not consider that readers would be misled into thinking that the GOALLS study had demonstrated outcome in morbidity and mortality in CHD patients. The claim was qualified by reference to cholesterol targets. The Panel considered that the results of the GOALLS study were relevant to the issue of early intervention in that they showed that lipid levels were lowered within a few weeks of therapy. Given the relevance of the data and the licensed indications for Zocor, the Panel decided that, on balance, the juxtaposing of the heading and the claim was not misleading as alleged.

The claim 'Efficacy: Zocor has powerful efficacy across all lipids, with many patients reaching target at starting doses' appeared on page 3 of the leavepiece below the heading 'Four sound reasons why Zocor should be your first-line statin'. Pfizer alleged that to indicate that many patients could reach target was all-embracing as it implied that the majority of all different types of patients with dyslipidaemia would reach a 'pre-specified target' (which was also unclear). The GOALLS study showed that the starting dose of 20mg could achieve the LDL-C target ≤ 3mmol/l only in patients with CHD and not at a starting dose of 10mg for hyperlipidaemic patients without established CHD.

In addition, 'reaching target' suggested that all different types of targets (eg US, NCEP, JBR and NSF etc) were achievable by prescribing Zocor. The 'starting doses' of Zocor had not been listed anywhere on the same page. Exaggeration in this fashion was clearly intended to mislead the reader.

The leavepiece was entitled 'Rapid benefits of early statin-based intervention in CHD patients' and so the Panel considered that most readers would assume that all of the claims in the piece related to CHD patients unless otherwise stated. The claim referred to 'starting doses'. There was only one starting dose for Zocor for CHD and this was 20mg per day. On balance the Panel considered that the claim in question would be taken to be a general claim about the efficacy of Zocor in CHD, ie that many such patients would achieve clinically relevant target lipid levels at the starting dose. In that regard the Panel considered it unnecessary to quantify 'many', specify the targets set or to state the starting dose for CHD patients. The Panel did not consider that the claim was misleading or exaggerated as alleged.

The claim 'HDL: Zocor increases HDL more than atorvastatin' was the third of the 'Four sound reasons why Zocor should be your first-line statin'. Pfizer noted that the claim was substantiated by only two clinical studies (Crouse *et al* 1999 and Jones *et al* 1998) but had omitted consideration of several other comparative studies which demonstrated equivalence or no difference between Zocor and atorvastatin in raising HDL-C. Recto *et al* (2000) demonstrated in a study with 258 patients that atorvastatin 10mg and 20mg increased HDL-C by 8.1% and 8.5% compared with Zocor 20mg and 40mg which increased HDL-C by 8.7% and 9.3% which was not statistically significant (p=0.407). In another study conducted by Farnier *et al* (1997) atorvastatin 10mg increased HDL-C by 5.7% compared to Zocor 10mg at 2.2% (not statistically significant) and to Zocor 20mg at 3.0% (also not statistically significant). Dart *et al* (1997) looked at the effects of Zocor 10-20mg compared to atorvastatin 10-20mg and found no difference in the increase in HDL-C (of 7%) in both groups. Finally, a large meta-analysis of 25 clinical studies evaluated the effects of treatment on HDL-C levels across the dose range of atorvastatin 10-80mg, Zocor 10mg and pravastatin 20mg. The results showed that atorvastatin increased HDL-C to a range between 6.7% and 8.6%, where Zocor had a similar increase of 7.6% (Nawrocki *et al* 2000). Pfizer alleged that the claim disparaged atorvastatin, was inaccurate, unfair, and did not reflect the evidence appropriately.

The Panel considered that readers would assume that the claim 'Zocor increases HDL more than atorvastatin' meant that such an effect was generally observed across the dose range. Jones *et al*, however, reported a statistically significant difference only when comparing the 40mg doses of each medicine. There was a mean percent change from baseline of 9.6 for simvastatin 40mg and 4.8 for atorvastatin (p=0.05). Using 20mg doses of each, however, the mean percent change was 5.2 for simvastatin and 5.1 for atorvastatin 20mg. Crouse *et al* (n=846) reported an advantage for Zocor in terms of increasing HDL-C levels which was particularly evident at the higher doses in patients with low HDL-C at baseline. The study stated that there was a statistically significant difference between simvastatin and the corresponding dose of atorvastatin. Results were given for simvastatin 40mg and 80mg and atorvastatin 20mg and 40mg. Recto *et al* (n=258) and Farnier *et al* (n=272) showed no advantages for Zocor compared with atorvastatin in terms of raising HDL-C. An abstract from Otvos *et al* (2000) showed that in terms of raising HDL-C levels there was no significant difference between doses of atorvastatin 20mg and Zocor 40mg. Zocor 80mg, however, raised HDL-C significantly more than atorvastatin 40mg (p= <0.0001). Branchi *et al* showed differences between 20mg simvastatin and 10mg atorvastatin. Illingworth showed differences at higher doses. The Panel queried whether these data were available when the leavepiece was issued and used. The Panel considered that the claim was a strong one and while some studies had shown at high doses that Zocor increased HDL-C more than atorvastatin the data at lower doses was not as clear cut. On balance the Panel considered that the claim was misleading and exaggerated and ruled a breach of the Code. A similar claim in the second leavepiece was also ruled in breach. The Panel did not consider that the claim disparaged atorvastatin as alleged.

The front cover of the second leavepiece featured a photograph of a couple dancing in front of a large neon sun ray with 80mg in its centre. The Zocor product logo with the strapline '20, 40, 80mg Increase the power, not the price' was at the bottom of the front cover and also at the bottom of pages 1, 3 and 4; the prescribing information was printed on page 2. On page 3 were '6 powerful reasons to choose Zocor as your first-line statin'. The back page of the leavepiece asked 'How much are you paying for your statin?' and featured a table showing the costs of 10, 20, 40 and 80mg each of Zocor and atorvastatin.

The claim 'Many CHD patients will reach NSF targets (LDL-C < 3mmol/l) using starting doses of Zocor' was given as one of the six reasons to choose Zocor as a first-line statin. Pfizer stated that it was unclear from the claim what the 'starting doses' were for Zocor in order for CHD patients to achieve their NSF targets defined as LDL-C < 3mmol/l. The NSF targets had not been fully defined – it should be a total cholesterol target of < 5mmol/l or LDL-C < 3mmol/l or by 30% whichever was the greater. In order to claim that 93% of CHD patients in the GOALLS study achieved NSF cholesterol targets after 20mg, one had to demonstrate that LDL-C was lowered to ≤ 3mmol/l or by 30% whichever was the greater (according to the NSF guidelines). This was not demonstrated in the study. The mean baseline LDL-C level for patients entered in the study was 3.7mmol/l. Although 93% of the patients achieved an LDL-C reduction to ≤ 3mmol/l, this constituted an LDL-C reduction of around 23% only. Furthermore, the study showed that only 72.4% of patients achieved an LDL-C reduction to ≤ 2.6mmol/l, which constituted a reduction of around 30%. According to

the NSF, the greater reduction of 30% was acceptable here and not just a reduction to an LDL-C level of 3mmol/l. Therefore, the claim for 93% of patients achieving the NSF cholesterol target was exaggerated. According to the SPC, there were two different starting doses for Zocor; 20mg/day for CHD patients and 10mg/day for those with hyperlipidaemia. This might lead the reader into assuming that CHD patients could reach their NSF targets on a starting dose of only 10mg, whereas the benefit was only seen in those taking 20 to 80mg of Zocor.

The Panel noted that the claim in question did not quantify 'many' and nor did it refer to the GOALLS study specifically. The claim in question was referenced to the National Service Framework for Coronary Heart Disease, March 2000, Data on file and a paper by Smith *et al* (1999). The data on file was preliminary data from the GOALLS study. The Panel noted its comments above that it was not misleading or exaggerated to claim that 93% of patients in that study achieved target lipid levels (LDL-C ≤ 3mmol/l) on the starting dose of Zocor after 6 weeks' therapy. The study by Smith *et al* showed that 35% of patients receiving Zocor 10mg daily achieved the LDL-C target (≤ 2.6mmol/l). In the Panel's view a starting dose of 20mg would be expected to result in a larger percentage of patients achieving target lipid levels. The Panel considered that there was data to show that many CHD patients on a starting dose of Zocor would achieve an LDL-C < 3mmol/l as claimed. In that respect the Panel did not consider that the claim was misleading or exaggerated as alleged. The claim defined the NSF targets as LDL-C < 3mmol/l. The Panel noted that the NSF targets were to lower cholesterol by achieving a total cholesterol ≤ 5mmol/l or LDL-C ≤ 3mmol/l, or by 30% whichever was the greater. The claim had, therefore, wrongly defined the NSF targets and was thus misleading in that respect. A breach of the Code was ruled. With regard to the issue of starting doses the Panel noted that although the claim in question referred specifically to CHD patients there was nothing else in the leavepiece to suggest that it related solely to that patient group. Although the strapline throughout the leavepiece referred only to 20, 40 and 80mg of Zocor, the cost comparison included the 10mg dose. In the absence of any indication to the contrary the Panel considered that some readers might assume that the lowest dose, 10mg, was a suitable starting dose for CHD patients. The Panel considered that within the context in which it appeared, the claim was misleading as alleged. A breach of the Code was ruled.

The cost comparison table on the back page of the leavepiece gave the cost of 10, 20, 40 and 80mg each of Zocor and atorvastatin; the 20, 40 and 80mg strengths of Zocor all cost the same. Increasing strengths of atorvastatin were increasingly expensive. Pfizer noted that the table compared the 28 days' treatment costs between atorvastatin and Zocor (dose ranges from 10-80mg). Such a comparison was meaningless as like had not been compared with like. For example, the efficacy of Zocor 10mg was not the same as that of atorvastatin 10mg in terms of lowering LDL-C or total cholesterol. Atorvastatin on a mg for mg basis had been shown in numerous studies to reduce LDL-C and/or total cholesterol more than Zocor (Jones *et al*, Farnier *et al*). The cost for a 28 day pack of 80mg atorvastatin was £47.04 and not £94.08. This change in price had been published since December 2000. Pfizer alleged that the table was misleading directly and by implication. It also contained the wrong price for 80mg atorvastatin.

The Panel accepted that the table was designed to show the price structure of Zocor and atorvastatin but noted that the supplementary information to the Code stated that valid comparisons could only be made where like was compared with like. It followed therefore that a price comparison should be made on the basis of the equivalent dosage requirement for the same indication. The Panel noted that it was stated that 'This table does not imply that equal mg doses of these drugs possess equal life saving, HDL-raising or cholesterol-lowering properties'. Nonetheless the Panel considered that some readers would assume that the milliequivalent doses of Zocor and atorvastatin were also clinically equivalent and that to achieve a particular clinical effect it was always less expensive to prescribe Zocor. The Panel considered that on balance the cost comparison would be read as implying a comparison of efficacy. Like was not compared with like and a breach of the Code was ruled.

The Panel noted that, on the launch of atorvastatin 80mg, the cost comparison had become outdated; it had been based on the cost of 2 x 40mg tablets which was £94.08. Atorvastatin 80mg tablets, however, were introduced at the same price as the 40mg tablets ie £47.04. The first mention of the product in MIMS had been in February 2001. Merck Sharp & Dohme had been in communication with Pfizer about the matter in January and on 30 January agreed to have new material briefed in by the end of February and all existing material withdrawn by the end of March. The Panel noted that the leavepiece in question had been withdrawn in February. The Panel was concerned that Merck Sharp & Dohme was prepared to leave material in circulation despite being aware that certain price comparisons were misleading. Once a company knew that material was inaccurate, for whatever reason, the material should be withdrawn forthwith; companies should not wait until new material had been made available. Merck Sharp & Dohme had proposed in January that all existing material would be out of circulation by the end of March. In the Panel's view such a proposal was unacceptable. The Panel noted that the leavepiece had been withdrawn in February. On balance, however, the Panel considered that given Merck Sharp & Dohme's comments about withdrawing material the balance of probability was that it had not been withdrawn forthwith ie as soon as the company knew that the cost comparison was inaccurate. A breach of the Code was ruled.

Pfizer Limited complained about three pieces of promotional literature for Zocor (simvastatin) issued by Merck Sharp & Dohme Limited. Pfizer marketed Lipitor (atorvastatin).

This complaint was considered under the requirements and procedures of the 2001 edition of the Code with the exception of point C. It was assumed that the clause numbers cited by Pfizer referred to the 1998 edition. These were changed in the Panel's rulings on points A and B to refer to the 2001 edition.

A Journal advertisement (eg ref 02-02 ZCR.01.GB.70031D)

Pfizer did not provide a copy of the journal advertisement but referred to the above reference number. The advertisement provided by Merck Sharp & Dohme had the reference number 04-02 ZCR.01.GB.70031.Ba.

The A3 advertisement featured a photograph of a couple dancing in front of a large neon sign which read 93%. The neon sign had an arrow which pointed down to the only claim on the advertisement '93% of CHD patients in the GOALLS* study achieved LDL-C targets** with ZOCOR at the starting dose'. The claim was referenced to the National Service Framework (NSF) for Coronary Heart Disease (CHD) and to the GOALLS (Getting to appropriate LDL-C Levels with Simvastatin) study.

Claim '93% of CHD patients in the GOALLS* study achieve LDL-C targets with ZOCOR at the starting dose'**

COMPLAINT

Pfizer alleged that the claim was misleading and exaggerated for three reasons.

Firstly it was unclear from the claim what the starting dose was in order to achieve the results demonstrated from the study. There were two different starting doses for Zocor according to its summary of product characteristics (SPC). Patients with coronary heart disease (CHD) should be started on 20mg whereas those with hyperlipidaemia should be initiated on 10mg per day. This might lead the reader into assuming that CHD patients could reach the same target as in the GOALLS study on a starting dose of only 10mg, whereas the benefit was only seen in those taking 20 to 80mg of simvastatin. This information could only be obtained from the prescribing information at the bottom of the advertisement.

Secondly, the claim of 93% of CHD patients achieving LDL-C targets was an exaggerated one. There was no specification of what the LDL-C targets were and it gave the impression that it encompassed all LDL-C targets as set by different national and international guidelines for the management of hyperlipidaemia. The LDL-C target set by the Joint European Taskforce (≤ 3.0mmol/l) was very different from those set by the US National Cholesterol Education Program (NCEP, ≤ 2.6mmol/l). In addition, the targets set in the UK by the NSF were totally different (total cholesterol at 5mmol/l or LDL-C at 3mmol/l, or by 30% whichever was the greater).

Thirdly, although two asterisks were included above the word 'targets' – the explanation was provided in tiny font size at the bottom of the page that it referred to the 'NSF target for LDL-C ≤ 3mmol/l'. However, the GOALLS study only looked at the LDL-C targets as set out by the European guidelines. This target at LDL-C < 3mmol/l could not be extrapolated to that of the NSF's targets which were to lower cholesterol by achieving a total cholesterol ≤ 5mmol/l or LDL-C ≤ 3mmol/l, or by 30% whichever was the greater. Therefore the information was extrapolated incorrectly and was misleading.

In view of the above Pfizer considered the context in which the claim was made was misleading by implication, including the use of small font size to link to the reference. This latter point was acknowledged by Merck Sharp & Dohme (in intercompany correspondence), that the layout of the note and the NSF targets should be clarified further. Pfizer alleged that the claim breached Clauses 7.2 and 7.8 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it was made perfectly clear in large red print that the patients referred to were CHD patients. As stated by Pfizer, the starting dose of 20mg for CHD patients was clearly stated in the Zocor SPC. This was clarified further when explaining the term GOALLS, an asterisk was adjacent to the name and in the explanation it clearly stated the dose in the study 'Zocor 20-80mg'.

Merck Sharp & Dohme submitted that the claim that '93% of CHD patients achieved LDL-C targets' was not exaggerated. Adjacent to the word targets were two asterisks which linked to a note explaining the NSF target (LDL-C < 3mmol/l). In the course of the GOALLS study 93% of patients achieved an LDL-C target of < 3mmol/l by taking Zocor 20mg. Merck Sharp & Dohme stated that because the study did not look at percentage changes in LDL-C levels it did not include this in the wording so as not to mislead readers.

Merck Sharp & Dohme provided a copy of intercompany correspondence to show that it had noted Pfizer's comments about the size and clarity of the NSF note which the company considered was further clarified by the link to the reference. Whilst Merck Sharp & Dohme did not agree with Pfizer's comments it would review the layout next time the advertisement was revised.

PANEL RULING

The Panel noted that the claim '93% of CHD patients in the GOALLS* study achieved LDL-C targets** with ZOCOR at the starting dose' clearly defined the patient population to which it referred. The advertisement did not refer to a 10mg dose and the prescribing information clearly stated that the recommended starting dose for CHD patients was 20mg a day. The Panel did not consider that readers would be misled into assuming that the results referred to in the claim could be achieved using a 10mg starting dose. No breach of Clause 7.2 was ruled.

The claim referred to the GOALLS study and the percentage of patients which achieved LDL-C targets.

In the Panel's view most readers would assume that the LDL-C targets referred to were those set in the GOALLS study. The Panel did not consider that the claim gave the impression that the LDL-C targets referred to encompassed all LDL-C targets as set by different national and international guidelines for the management of hyperlipidaemia. The Panel did not consider that the claim was exaggerated as alleged. The relevant clause in the 2001 Code was Clause 7.10. No breach of Clause 7.10 was ruled.

The Panel noted that one of the key efficacy parameters set in the GOALLS study was the percentage of patients achieving European LDL-C targets ie ≤ 115mg/dl (3mmol/l). In the claim, however, the term 'LDL-C targets' was asterisked to a footnote which read 'NSF target for LDL-C: < 3mmol/l'. The NSF CHD guidelines actually stated that serum cholesterol should be lowered either to less than 5mmol/l (LDL-C to below 3mmol) or by 30% whichever was greater. The Panel thus considered that the LDL-C targets set in the GOALLS study were not those referred to in the footnote. The NSF LDL-C target as stated in the footnote was not that as stated in the actual NSF for CHD. The Panel considered that the advertisement was misleading in this regard and ruled a breach of Clause 7.2 of the Code.

B Leavepiece (ref 11-01 ZCR.GB.70410M.73m)

This four page leavepiece dated November 2000 was entitled 'Rapid benefits of early statin-based intervention in CHD patients'. Page 2 was headed 'Survival benefits of early intervention' below which was a graph which depicted the benefits of a number of different types of intervention compared to no intervention in the acute period following myocardial infarction (MI). Page 3 was headed 'Four sound reasons why ZOCOR should be your first-line statin'. Below this heading were claims relating to efficacy, cost, HDL and outcomes.

1 Claim 'The recent GOALLS† study has reinforced the benefit of early statin intervention: 93% of CHD** patients achieved NSF cholesterol targets‡ after receiving ZOCOR 20mg for six weeks'

This claim appeared below the graph on page 2 which depicted the survival benefits of different interventions post-MI.

COMPLAINT

Pfizer stated that according to the published paper the GOALLS study did not demonstrate that 93% of CHD patients on 20mg Zocor achieved a target of LDL-C ≤ 3mmol/l after 6 weeks of treatment; this was achieved after 14 weeks of treatment. The published study did not provide data on the number of patients who reached a target of LDL-C ≤ 3mmol/l at week 6. This had been extrapolated from the design of the study. Patients who were not at the pre-defined target of 2.6mmol/l at week 6 and 10, were titrated from 20mg onwards to 40mg and subsequently to 80mg. By the end of the study at week 14, there were 92.7% of patients who reached an LDL-C target of ≤ 3mmol/l at 20mg of simvastatin. However, one could not extrapolate that all patients on 20mg Zocor who achieved this pre-defined target of LDL-C at week 14 were the same number who achieved the target at week 6.

Pfizer stated that in order to claim that 93% of CHD patients in the GOALLS study achieved NSF cholesterol targets after 20mg, one had to demonstrate that LDL-C was lowered to ≤ 3mmol/l or by 30% whichever was the greater. This was not demonstrated in the study. The mean baseline LDL-C level for patients entered in the study was 3.7mmol/l. Although 93% of the patients achieved an LDL-C reduction to ≤ 3mmol/l, this constituted an LDL-C reduction of around 23% only. Furthermore, the study showed that only 72.5% of patients achieved an LDL-C reduction to ≤ 2.6mmol/l, which constituted a reduction around 30%. According to the NSF, the greater reduction of 30% was acceptable here and not just a reduction to an LDL-C level of 3mmol/l. Therefore, the claim for 93% of patients achieving the NSF cholesterol target was exaggerated.

Pfizer stated that the study did not assess the patients according to the NSF targets for cholesterol reduction (as defined above). It was designed to assess the effectiveness and safety of Zocor in achieving LDL-C targets as recommended by the US NCEP and the European guidelines (Joint Task Force of European Societies on Coronary Prevention). Once again, the findings from the study had been extrapolated to the targets set by the NSF. Although the European guidelines' LDL-C target might be similar to that of the NSF, it was not clear from the claim which cholesterol target was achieved. Instead the claim implied that both the total cholesterol target of ≤ 5mmol/l and the LDL-C ≤ 3mmol/l target were achieved.

Pfizer noted that the claim was written as a second bullet point below the heading 'Survival benefits of early intervention'. Such juxtaposing misled the reader into thinking that the GOALLS study had demonstrated outcome in morbidity and mortality in CHD patients treated with 20mg of Zocor.

Pfizer alleged that the claim was ambiguous, misled by implication, was incapable of substantiation and was all-embracing, in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Merck Sharp & Dohme explained that the design of the GOALLS study was such that all eligible patients were started on Zocor 20mg, the starting dose for the treatment of CHD patients. After six weeks if patients had not achieved the LDL-C target of < 2.6mmol/l they were titrated up to Zocor 40mg daily. LDL-C levels were checked again at week 10 of the study and if at this stage patients had failed to reach the target LDL-C level they were titrated up to Zocor 80mg daily. Because medication was only titrated up and was not titrated down, it was possible to therefore extrapolate that all the patients who were still taking the initial dose of 20mg of Zocor once daily at week 14 of the study must have achieved the target LDL-C level at week 6 of the study. If they had not fallen

into this category their dose of Zocor would have been titrated up. 92.7% of patients had an LDL-C level < 3mmol/l and were taking 20mg of Zocor at week 14, thus substantiating the claim.

With regard to the NSF target of LDL-C of < 3mmol/l or by 30% whichever was the greater, Merck Sharp & Dohme referred to a letter it had written to Pfizer about the same matter in relation to an advertisement. Merck Sharp & Dohme explained that the study was designed to look at the level of LDL-C achieved. This level was clearly focused upon in the advertisement in question. Whilst the focus in this particular advertisement was on the LDL-C level achieved, the company accepted the point that Pfizer had raised and had told Pfizer that it would change the advertisement at its next printing which would be in the next quarter.

Merck Sharp & Dohme noted that in the claim there was an obelus next to 'GOALLS' which referred to a footnote which read 'Getting to Appropriate LDL-C levels with Simvastatin'. This point was then clarified by stating the NSF target for LDL-C of < 3mmol/l. Merck Sharp & Dohme referred to its comments above regarding the NSF targets and that it had already agreed that it would change its advertising.

Merck Sharp & Dohme disagreed that the juxtaposing of the heading on page 2 and the claim in question was misleading. Immediately below the heading was a bullet point referring to interventions in the acute period following an MI. It illustrated that early intervention with a statin had a significant impact on reducing the cumulative probability of death. The GOALLS study reinforced these findings because it demonstrated that early statin intervention was a benefit. If intervention with a proven statin was to get patients to target LDL-C, which the GOALLS study demonstrated, then the benefits of early statin intervention should be reinforced. The GOALLS study did not have any mortality or outcome data and the results of the study had not been promoted in that way.

PANEL RULING

The Panel noted that the claim stated that the GOALLS study had shown that 93% of CHD patients achieved NSF cholesterol targets after 6 weeks' therapy with Zocor 20mg. A footnote below the claim stated that the NSF targets were defined as total cholesterol < 5mmol/l: LDL-C < 3mmol/l. The Panel noted its comments in point A1 above with regard to the differences between the targets set in the GOALLS study, the NSF targets as stated by Merck Sharp & Dohme and the official NSF targets.

The aim of the GOALLS study was to evaluate the effectiveness of Zocor in achieving LDL-C goals as recommended by US and European guidelines. The study design was such that all eligible patients received Zocor 20mg/day for the first 6 weeks. After that time, patients with an LDL-C >2.6mmol/l (the US target level) had their dose doubled to 40mg: patients with an LDL-C ≤ 2.6mmol/l remained on 20mg/day. At week 10 all patients were reassessed, those whose LDL-C remained >2.6mmol/l despite an increase in dose to 40mg had their dose of Zocor further increased to 80mg/day for the final four weeks of treatment. Patients who had originally stayed on the 20mg dose but whose LDL-C had now increased to >2.6mmol/l had their dose increased to 40mg/day. There was no provision for doses of Zocor to be decreased.

The Panel considered, therefore, that those patients who were taking 20mg Zocor at the end of the study (week 14) must have achieved the target of LDL-C ≤ 2.6mmol/l at week 6 and retained that level at week 10. With regard to the European target a table in the published paper showed that 92.7% of patients received 20mg Zocor. The Panel considered that to claim that 93% of patients achieved target lipid levels on the starting dose after 6 weeks was not misleading or exaggerated as alleged. No breaches of Clauses 7.2 and 7.10 were ruled in that regard. The Panel noted, however, that the targets that the 93% of patients were claimed to have achieved were those of the NSF. The NSF targets were to lower total cholesterol to < 5mmol/l (LDL-C below 3mmol/l) or by 30% whichever was greater. These were not the targets set in the GOALLS study; patients in the GOALLS study were titrated to absolute LDL-C targets, not to a percentage change from initial LDL-C levels. The 30% lowering of LDL-C required by the NSF target meant that patients would not be titrated to a single LDL-C level; target LDL-C would be individualised according to LDL-C levels at the start of treatment. The Panel considered that in this regard the claim was misleading and exaggerated and ruled breaches of Clauses 7.2 and 7.10.

The Panel noted the claim stated that the GOALLS study had reinforced the benefit of early statin intervention. The claim appeared on a page headed 'Survival benefits of early intervention' and below a graph showing the benefit, in terms of improved survival, of statin therapy post-MI. The Panel noted that Zocor was indicated in CHD, in patients with a plasma cholesterol level of 5.5mmol/l or greater to reduce the risk of mortality; reduce the risk of coronary death and non-fatal myocardial infarction; reduce the risk for undergoing myocardial revascularisation procedures and to slow the progression of coronary atherosclerosis. The Panel was concerned that the 'benefits' referred to in the claim might be assumed by some readers to be the 'survival benefits' referred to in the heading. The GOALLS study did not have any mortality or outcome data. Nevertheless, on balance it did not consider that readers would be misled into thinking that the GOALLS study had demonstrated outcome in morbidity and mortality in CHD patients. The claim was qualified by reference to cholesterol targets. The Panel considered that the results of the GOALLS study were relevant to the issue of early intervention in that they showed that lipid levels were lowered within a few weeks of therapy. Given the relevance of the data and the licensed indications for Zocor the Panel decided that, on balance, the juxtaposing of the heading and the claim was not misleading as alleged. No breach of Clause 7.2 was ruled.

2 Claim 'Efficacy: Zocor has powerful efficacy across all lipids, with many patients reaching target at starting doses'

This claim appeared on page 3 of the leavepiece below the heading 'Four sound reasons why Zocor

should be your first-line statin'.

COMPLAINT

Pfizer alleged that to indicate that many patients could reach target was all-embracing as it implied that the majority of all different types of patients with dyslipidaemia would reach a 'pre-specified target' (which was also unclear). The GOALLS study showed that the starting dose of 20mg could achieve the LDL-C target ≤ 3mmol/l only in patients with CHD and not at a starting dose of 10mg for hyperlipidaemic patients without established CHD. In addition, 'reaching target' suggested that all different types of targets (eg US, NCEP, JBR and NSF etc) were achievable by prescribing Zocor. The 'starting doses' of Zocor had not been listed anywhere on the same page. Exaggeration in this fashion was clearly intended to mislead the reader. Breaches of Clauses 7.2, 7.4 and 7.8 were alleged.

RESPONSE

Merck Sharp & Dohme submitted that the claim that 'many patients' could reach their target was not all embracing. It did not imply that the majority of all different types of patients reached target. Merck Sharp & Dohme noted that it claimed that Zocor had powerful efficacy across all lipids fractions, it did not suggest across all dyslipidaemia. Zocor had been shown to significantly improve all the lipid parameters, from a reduction in total cholesterol, LDL-C, triglycerides to raising HDL-C. As in the claim, effective 'across all lipids'. Many patients did reach their target at starting doses.

PANEL RULING

The leavepiece was entitled 'Rapid benefits of early statin-based intervention in CHD patients' and so the Panel considered that most readers would assume that all of the claims in the piece related to CHD patients unless otherwise stated. The Panel noted that the claim referred to 'starting doses'. There was only one starting dose for Zocor for CHD and this was 20mg per day. On balance the Panel considered that the claim in question would be taken to be a general claim about the efficacy of Zocor in CHD, ie that many such patients would achieve clinically relevant target lipid levels at the starting dose. In that regard the Panel considered it unnecessary to quantify 'many', specify the targets set or to state the starting dose for CHD patients. The Panel did not consider that the claim was misleading or exaggerated as alleged. No breach of Clauses 7.2 and 7.10 of the Code was ruled.

The Panel noted that Pfizer had alleged a breach of Clause 7.4 of the Code. In the 1998 edition of the Code this required that substantiation be provided without delay at the request of health professionals. Pfizer had cited Clause 7.4 but had not provided any more information about this allegation. Merck Sharp & Dohme had not responded specifically to this allegation. Clause 7.4 in the 1998 edition of the Code was Clause 7.5 in the 2001 edition of the Code. In the circumstances the Panel decided to rule no breach of Clause 7.5 of the 2001 edition of the Code.

3 Claim 'HDL: Zocor increases HDL more than atorvastatin'

This claim appeared on page 3 of the leavepiece and was the third of the 'Four sound reasons why Zocor should be your first-line statin'.

COMPLAINT

Pfizer noted that the claim was substantiated by only two clinical studies (Crouse *et al* 1999 and Jones *et al* 1998) but had omitted consideration of several other comparative studies which demonstrated equivalence or no difference between Zocor and atorvastatin in raising HDL-C. Recto *et al* (2000) demonstrated in a study with 258 patients that atorvastatin 10mg and 20mg increased HDL-C by 8.1% and 8.5%. This was compared with Zocor 20mg and 40mg which increased HDL-C by 8.7% and 9.3% which was not statistically significant (p=0.407). This was a properly conducted study with adequate power to show a difference between the two treatment groups. In another study conducted by Farnier *et al* (1997) atorvastatin 10mg increased HDL-C by 5.7% compared to Zocor 10mg at 2.2% (not statistically significant) and to Zocor 20mg at 3.0% (also not statistically significant). Dart *et al* (1997) looked at the effects of Zocor 10-20mg compared to atorvastatin 10-20mg and found no difference in the increase in HDL-C (of 7%) in both groups.

Finally, a large meta-analysis of 25 clinical studies evaluated the effects of treatment on HDL-C levels across the dose range of atorvastatin 10-80mg, Zocor 10mg and pravastatin 20mg. The results showed that atorvastatin increased HDL-C to a range between 6.7% and 8.6%, where Zocor had a similar increase of 7.6% (Nawrocki *et al* 2000).

Pfizer alleged that the claim disparaged atorvastatin (Pfizer's product Lipitor), was inaccurate, unfair, and did not reflect the evidence appropriately in breach of Clauses 7.2, 7.8 and 8.1 of the Code.

RESPONSE

Merck Sharp & Dohme submitted that the references that it had cited demonstrated that Zocor was better at raising HDL significantly more than atorvastatin. In the CURVES study (Jones *et al*) Zocor 40mg daily increased HDL by 9.6% compared to atorvastatin 40mg daily that only raised it by 4.8% (p≤0.05). Indeed at the higher dose of atorvastatin 80mg daily the HDL level actually fell. Whilst Recto *et al* did not show a significant difference between the rise in HDL levels in the two treatment groups, this study used only a small number of patients. Merck Sharp & Dohme questioned whether the results reported by Farnier *et al* were typical of those seen with Zocor. For example the mean percent change from baseline of 3% for the Zocor 20mg group was very different from the mean percent change reported for Zocor 20mg by Recto *et al* (8.7%) and Jones *et al* (5.2%).

Merck Sharp & Dohme considered that the claim was accurate and based on an up-to-date evaluation of all the evidence. A recent presentation at the Annual Scientific Session of the American College of Cardiology in March 2000 reported that after 18

weeks of treatment with Zocor 80mg compared to Lipitor 80mg the average HDL increases were almost double (7.6% v 3.1% respectively).

Merck Sharp & Dohme also referred to a study by Branchi *et al* (2001) which compared simvastatin 20mg (n=118) with atorvastatin 10mg (n=118). The study concluded that the difference between the two groups in the percentage increase in HDL-C was statistically significant (9.0% versus 4.3% respectively; P<0.05). The data from the study confirmed the results of previous comparative studies of high doses. The data in the study was said to extend the findings to lower but more commonly used doses of atorvastatin and simvastatin, an effect that had not been consistently observed.

Illingworth *et al* (2001) concluded that at the doses used in the study (simvastatin 40mg/day for 6 weeks, 80mg/day for the next 6 weeks and remaining at 80mg/day for the final 24 weeks and atorvastatin 20mg/day for 6 weeks, 40mg/day for the next 6 weeks and 80mg/day for the remaining 24 weeks), simvastatin (n=405) led to greater increases in HDL cholesterol than atorvastatin (n=408). The differences were statistically significant at week 12 and at weeks 18-36.

PANEL RULING

The Panel considered that readers would assume that the claim 'Zocor increases HDL more than atorvastatin' meant that such an effect was generally observed across the dose range. Jones *et al*, however, reported a statistically significant difference only when comparing the 40mg doses of each medicine. There was a mean percent change from baseline of 9.6 for simvastatin 40mg and 4.8 for atorvastatin (p≤0.05). Using 20mg doses of each, however, the mean percent change was 5.2 for simvastatin and 5.1 for atorvastatin 20mg. Crouse *et al* (n=846) reported an advantage for Zocor in terms of increasing HDL-C levels which was particularly evident at the higher doses in patients with low HDL-C at baseline. The study stated that there was a statistically significant difference between simvastatin and the corresponding dose of atorvastatin. Results were given for simvastatin 40mg and 80mg and atorvastatin 20mg and 40mg. Recto *et al* (n=258) and Farnier *et al* (n=272) showed no advantages for Zocor compared with atorvastatin in terms of raising HDL-C. An abstract from Otvos *et al* (2000) showed that in terms of raising HDL-C levels there was no significant difference between doses of atorvastatin 20mg and Zocor 40mg. Zocor 80mg, however, raised HDL-C significantly more than atorvastatin 40mg (p= <0.0001). Branchi *et al* showed differences between 20mg simvastatin and 10mg atorvastatin. Illingworth showed differences at higher doses. The Panel queried whether these data were available when the leavepiece was issued and used.

The Panel considered that the claim was a strong one and while some studies had shown at high doses that Zocor increased HDL-C more than atorvastatin the data at lower doses was not as clear cut. On balance the Panel considered that claim was misleading and exaggerated and ruled breaches of Clauses 7.2 and 7.10 of the Code. The Panel did not consider that the claim disparaged atorvastatin as alleged. No breach of Clause 8.1 was ruled.

C Leavepiece (ref 05-01.ZCR.00.GB.70210.LP.30m.CW.0500)

The front cover of this four page leavepiece featured a photograph of a couple dancing in front of a large neon sun ray with 80mg in its centre. The Zocor product logo with the strapline '20, 40, 80mg Increase the power, not the price' was at the bottom of the front cover and also at the bottom of pages 1, 3 and 4; the prescribing information was printed on page 2. On page 3 were '6 powerful reasons to choose Zocor as your first-line statin'. The back page of the leavepiece asked 'How much are you paying for your statin?' and featured a table showing the costs of 10, 20, 40 and 80mg each of Zocor and atorvastatin.

The leavepiece was no longer in use; it had been withdrawn in the first quarter 2001. This part of the complaint was therefore considered under the requirements of the 1998 Code but under the procedures of the 2001 Code.

1 Claim 'In comparative studies Zocor raises HDL significantly more than atorvastatin'

This was given on page 3 as one of the 6 reasons to choose Zocor as a first-line statin.

COMPLAINT

Pfizer referred to its comments in point B3 above and again alleged breaches of Clauses 7.2, 7.8 and 8.1 of the Code.

RESPONSE

Merck Sharp & Dohme referred to its response in point B3 above.

PANEL RULING

The Panel considered that its rulings in point B3 above applied here. The allegation was considered under the 1998 Code, the Panel thus ruled a breach of Clauses 7.2 and 7.8 and no breach of Clause 8.1.

2 Claim 'Many CHD patients will reach NSF targets (LDL-C < 3mmol/l) using starting doses of Zocor'

This was given on page 3 as one of the six reasons to choose Zocor as a first-line statin.

COMPLAINT

Pfizer stated that it was unclear from the claim what the 'starting doses' were for Zocor in order for CHD patients to achieve their NSF targets defined as LDL-C < 3mmol/l. The NSF targets had not been fully defined – it should be a total cholesterol target of < 5mmol/l or LDL-C < 3mmol/l or by 30% whichever was the greater.

Pfizer stated that in order to claim that 93% of CHD patients in the GOALLS study achieved NSF cholesterol targets after 20mg, one had to demonstrate that LDL-C was lowered to ≤ 3mmol/l or by 30% whichever was the greater (according to the NSF

guidelines). This was not demonstrated in the study. The mean baseline LDL-C level for patients entered in the study was 3.7mmol/l. Although 93% of the patients achieved an LDL-C reduction to ≤ 3mmol/l, this constituted an LDL-C reduction of around 23% only. Furthermore, the study showed that only 72.4% of patients achieved an LDL-C reduction to ≤ 2.6mmol/l, which constituted a reduction of around 30%. According to the NSF, the greater reduction of 30% was acceptable here and not just a reduction to an LDL-C level of 3mmol/l. Therefore, the claim for 93% of patients achieving the NSF cholesterol target was exaggerated.

Pfizer noted that, according to the SPC, there were two different starting doses for Zocor; 20mg/day for CHD patients and 10mg/day for those with hyperlipidaemia. This might lead the reader into assuming that CHD patients could reach their NSF targets on a starting dose of only 10mg, whereas the benefit was only seen in those taking 20 to 80mg of Zocor.

Pfizer alleged that the claim was in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Merck Sharp & Dohme noted that in the claim the NSF target was clarified in brackets (LDL-C < 3mmol/l) and it quite clearly stated in capital letters that CHD patients were the patients being referred to and, as noted by Pfizer, the Zocor SPC clearly stated that the starting dose for CHD patients was 20mg daily. To ensure further clarity, at the bottom of the same page was a strap line '20, 40, 80mg Increase the power not the price'. No mention was made of the 10mg dose as this was the starting dose for patients with hypercholesterolemia and not CHD.

PANEL RULING

The Panel noted that the claim in question did not quantify 'many' and nor did it refer to the GOALLS study specifically. The claim in question was referenced to the National Service Framework for Coronary Heart Disease, March 2000, Data on file and a paper by Smith *et al* (1999). The data on file was preliminary data from the GOALLS study. The Panel noted its comments in point B1 above that it was not misleading or exaggerated to claim that 93% of patients in that study achieved target lipid levels (LDL-C ≤ 3mmol/l) on the starting dose of Zocor after 6 weeks' therapy. The study by Smith *et al* showed that 35% of patients receiving Zocor 10mg daily achieved the LDL-C target (≤ 2.6mmol/l). In the Panel's view a starting dose of 20mg would be expected to result in a larger percentage of patients achieving target lipid levels. The Panel considered that there was data to show that many CHD patients on a starting dose of Zocor would achieve an LDL-C < 3mmol/l as claimed. In that respect the Panel did not consider that the claim was misleading or exaggerated as alleged. No breach of Clauses 7.2 and 7.8 was ruled.

The claim defined the NSF targets as LDL-C < 3mmol/l. The Panel noted that the NSF targets were to lower cholesterol by achieving a total cholesterol ≤ 5mmol/l or LDL-C ≤ 3mmol/l, or by 30% whichever was the greater. The claim had, therefore, wrongly defined the NSF targets and was thus misleading in that respect. A breach of Clause 7.2 was ruled.

With regard to the issue of starting doses the Panel noted that although the claim in question referred specifically to CHD patients there was nothing else in the leavepiece to suggest that it related solely to that patient group. Although the strapline throughout the leavepiece referred only to 20, 40 and 80mg of Zocor, the cost comparison included the 10mg dose. In the absence of any indication to the contrary the Panel considered that some readers might assume that the lowest dose, 10mg, was a suitable starting dose for CHD patients. The Panel considered that within the context of which it appeared, the claim was misleading as alleged. A breach of Clause 7.2 of the Code was ruled.

3 Cost comparison

The cost comparison table on the back page of the leavepiece gave the cost of 10, 20, 40 and 80mg each of Zocor and atorvastatin; the 20, 40 and 80mg strengths of Zocor all cost the same. Increasing strengths of atorvastatin were increasingly expensive.

COMPLAINT

Pfizer noted that the table compared the 28 days' treatment costs between atorvastatin and Zocor (dose ranges from 10-80mg). Such a comparison was meaningless as like had not been compared with like. For example, the efficacy of Zocor 10mg was not the same as that of atorvastatin 10mg in terms of lowering LDL-C or total cholesterol. Atorvastatin on a mg for mg basis had been shown in numerous studies to reduce LDL-C and/or total cholesterol more than Zocor (Jones *et al*, Farnier *et al*).

Pfizer also noted that the cost for a 28 day pack of 80mg atorvastatin was £47.04 and not £94.08. This change in price had been published since December 2000.

Pfizer alleged that the table was misleading directly and by implication. It also contained the wrong price for 80mg atorvastatin, and therefore breached Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the table was used to demonstrate that increasing the dose of atorvastatin increased the 28 day cost of treatment compared to Zocor which had the same 28 day cost across the dose range 20, 40 and 80mg. There was no comparison for efficacy between the doses, indeed, directly below the table was a clear statement which read 'Table: Cost of 28 days' treatment for Zocor and atorvastatin. This table does not imply that equal mg doses of these drugs possess equal life saving, HDL-raising or cholesterol-lowering properties'. This table was meant to purely demonstrate the price differentiation with increasing dosage between the two products. At the time the leavepiece was published there was no

atorvastatin 80mg tablet so the price for atorvastatin 80mg was calculated as 2 x 40mg (2 x £47.04 = £94.08). The launch of atorvastatin 80mg tablet was responsible for the withdrawal of this leavepiece.

Merck Sharp & Dohme stated that following the launch of atorvastatin 80mg tablet earlier this year, some of its literature, including this leavepiece, contained cost comparisons which had become inaccurate. The company contacted Pfizer directly to inform it of this and to reassure it that the inaccurate material would be changed. It was agreed in an e-mail on 30 January that by 6 February Merck Sharp & Dohme would inform all of its representatives of the existence of the new atorvastatin 80mg tablet and the subsequent price change, that the company would have updated versions briefed in by the end of February and all existing materials would be out of circulation by the end of March. Communication was made to all the representatives via voicemail and letter explaining this. Merck Sharp & Dohme had received no response from Pfizer and so assumed this to be in order.

The leavepiece was first published in May 2000 and was removed from circulation in February 2001. It was distributed to GPs and hospital doctors.

Merck Sharp & Dohme did not consider that the leavepiece was in breach of the Code and following the launch of the atorvastatin 80mg tablet prompt action was taken to both inform Pfizer of the company's strategy and to hastily remove any inaccurate literature, within a time scale with which Pfizer did not seem to disagree.

PANEL RULING

The Panel noted that the page in question was headed 'How much are you paying for your statin?'. Below this was a cost comparison table showing the cost of 28 days' treatment with Zocor and atorvastatin. Zocor 10mg cost £18.03; the cost of all the other strengths (20, 40 and 80mg) was constant at £29.69. The cost of treatment with atorvastatin 10, 20, 40 and 80mg was £18.88, £30.60, £47.04 and £94.08 respectively. The strapline '20, 40, 80mg Increase the power, not the price' appeared at the bottom of the page. The Panel accepted that the table was designed to show the price structure of Zocor and atorvastatin but noted the supplementary information to Clause 7.2 of the Code stated that valid comparisons could only be made where like was compared with like. It followed therefore that a price comparison should be made on the basis of the equivalent dosage requirement for the same indication. The Panel noted that it was stated that 'This table does not imply that equal mg doses of these drugs possess equal life saving, HDL-raising or cholesterol-lowering properties'. Nonetheless the Panel considered that some readers would assume that the milliequivalent doses of Zocor and atorvastatin were also clinically equivalent and that to achieve a particular clinical effect it was always less expensive to prescribe Zocor. The Panel considered that on balance the cost comparison would be read as implying a comparison of efficacy. Like was not compared with like and a breach of Clause 7.2 of the Code was ruled.

The Panel noted that, on the launch of atorvastatin 80mg, the cost comparison had become outdated; it had been based on the cost of 2 x 40mg tablets which was £94.08. Atorvastatin 80mg tablets, however, were introduced at the same price as the 40mg tablets ie £47.04. The Panel noted Pfizer's submission that the price of atorvastatin 80mg had been published since December 2000, although the company gave no indication as to where this had been. The first mention of the product in MIMS had been in February 2001. Merck Sharp & Dohme had been in communication with Pfizer about the matter in January 2001 and on 30 January agreed to have new material briefed in by the end of February and all existing material withdrawn by the end of March. The Panel noted that the leavepiece in question had been withdrawn in February 2001.

The Panel was concerned that Merck Sharp & Dohme was prepared to leave material in circulation despite being aware that, following the launch of atorvastatin 80mg, certain price comparisons were misleading. Once a company knew that material was inaccurate, for whatever reason, the material should be withdrawn forthwith; companies should not wait until new material had been made available. Merck Sharp & Dohme had proposed in January that all existing material would be out of circulation by the end of March. In the Panel's view such a proposal was unacceptable. With regard to the leavepiece in question the Panel noted that it had been withdrawn in February. On balance, however, the Panel considered that given Merck Sharp & Dohme's comments about withdrawing material the balance of probability was that it had not been withdrawn forthwith ie as soon as the company knew that the cost comparison was inaccurate. A breach of Clause 7.2 of the Code was ruled.

Complaint received **26 July 2001**

Case completed **11 October 2001**

CASE AUTH/1212/7/01

HOSPITAL PHARMACIST v MERCK SHARP & DOHME

Promotion of Cozaar

A hospital pharmacist complained about a Cozaar (losartan) presentation made at a lunchtime meeting of the pharmacy department by a Merck Sharp & Dohme representative. The representative showed a slide taken from a meta-analysis and stated that the other angiotensin II (AII) antagonists were no more effective than Cozaar. This was clearly misleading, untrue and unrepresentative of the data. There were several published studies which demonstrated that rival AII antagonists were more effective in controlling hypertension. It was well documented that losartan had a flat dose response curve and that there was no increased effect above 50mg daily, whereas this was not the case for the others. The complainant stated that irbesartan was used at his hospital on the basis of its superior efficacy in resistant hypertension.

A further complaint concerned a slide headed 'Licensed indications'. Listed under this slide of indications was 'heart failure'. The representative indicated that Cozaar was licensed for heart failure in a number of countries but not currently in the UK. However the slide should stand correct without qualification. The complainant felt that the way it was presented virtually promoted Cozaar for an unlicensed indication.

The Panel noted that the parties provided differing accounts of the method of presentation. The complainant's recollection, and that of others in his department, was that a PowerPoint presentation had been used and he had referred to two slides. Merck Sharp & Dohme stated that the representative denied using an electronic, 35mm or acetate based presentation at the meeting and that she was not in possession of any of these from the company as they were being updated at the time of the presentation. The representative had used a flip chart and pen to illustrate her talk.

The Panel considered that given the parties' differing accounts it was not possible to determine which mode of presentation had been used. The Panel was concerned about the use of a flip chart and pen by a representative; such a practice meant that, in effect, the representative was creating her own promotional material. The Panel was concerned that the company did not appear to have issued representative briefing instructions to provide guidance on how to present complex data whilst presentations were being updated.

The Panel noted that the paper from which the representative had stated that the other AII antagonists were no more effective than Cozaar, Conlin *et al*, was a meta-analysis of 43 published randomised controlled trials to evaluate the antihypertensive efficacy of losartan, valsartan irbesartan and candesartan. The authors concluded that the four AII antagonists exhibited comparable efficacy, a near flat dose response curve when titrating from starting to maximum recommended dose and substantial potentiation of the antihypertensive effect with addition of hydrochlorothiazide. The authors noted that there had been four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan, some of which had suggested differences in efficacy or responder rates between the medicines. The authors submitted that because these studies contributed less than 20% of all the available evidence on efficacy, a meta-analysis of the sort provided for in their paper might be regarded as a stronger basis for understanding the comparative efficacy of medicines in this class. The Panel noted that two of the criteria used for choosing studies to include in the meta-analysis were a patient population with mild to moderate hypertension and patients representative of the overall hypertensive population. The meta-analysis had not included eprosartan and telmisartan. The complainant was concerned about the comparative efficacy of Cozaar in resistant hypertension. It did not appear to the Panel that the representative had claimed comparable efficacy in relation to such a subgroup, but in relation to the overall patient population. The Panel had no way of knowing precisely what the representative had said at the meeting. It appeared that there was no dispute between the parties with regard to whether the representative had stated that the other AII antagonists were no more effective than Cozaar.

The Panel considered that the claim would be taken as referring to patients with hypertension generally and not a resistant population. The Panel considered that on the evidence before it, in relation to the patient population as a whole, the claim was not misleading as alleged. No breach of the Code was ruled.

With regard to the presentation of data on Cozaar and heart failure, the Panel noted that Merck Sharp & Dohme stated that the representative had listed (on a flip chart) after the licensed indications, and separated by a clear gap, the other disease areas in which research was emerging or ongoing. This was not inconsistent with the complainant's description of the presentation of the data. The complainant stated that the representative had stated that Cozaar did not have a licence for use in heart failure in the UK but did have a licence in 44 other countries. The Panel noted that the parties' evidence was consistent on this point. The representative stated that she was asked two questions by members of the audience. Cozaar was indicated for the treatment of hypertension only.

The Panel considered that it was unacceptable to refer to unlicensed indications at a promotional meeting unless in response to an unsolicited request for such information. The unsolicited provision of such information within a promotional environment amounted to promotion of an unlicensed indication. The representative's statement that Cozaar was not licensed for heart failure in the UK was insufficient to negate the impression that it was being promoted outside its marketing authorization. The Panel ruled a breach of the Code.

A hospital pharmacist complained about a Cozaar (losartan) presentation made at a lunchtime meeting of the pharmacy department by a representative from

Merck Sharp & Dohme Limited. The complainant thought that there were two breaches of the Code at this meeting and wished to emphasise that, for both of these complaints, he did not blame the representative but rather Merck Sharp & Dohme which prepared the presentation.

COMPLAINT

The complainant stated that the representative had a PowerPoint presentation on Cozaar. One slide was taken from a meta-analysis. The representative stated that the other angiotensin II (AII) antagonists were no more effective than Cozaar. This was clearly misleading, untrue and unrepresentative of the data. It was well known that one could get a meta-analysis to demonstrate anything. There were several published studies which demonstrated that rival AII antagonists were more effective in controlling hypertension (Kassler Taub *et al* 1998; Oparil *et al* 1998; Hedner *et al* 1999; Andersson *et al* 1998; Mallion *et al* 1999). It was well documented that losartan had a flat dose response curve and that there was no increased effect above 50mg daily, whereas this was not the case for the others. The complainant stated that irbesartan was used at his hospital on the basis of its superior efficacy in resistant hypertension.

The other complaint with this presentation concerned a slide headed 'Licensed indications'. Listed under this slide of indications was 'heart failure'. The representative indicated that Cozaar was licensed for heart failure in a number of countries but not currently in the UK. However the slide should stand correct without qualification. The complainant felt that the way it was presented virtually promoted Cozaar for an unlicensed indication.

RESPONSE

Merck Sharp & Dohme stated that the meta-analysis used was Conlin *et al* (2000). The relative merits of meta-analysis *vis-à-vis* individual randomised trials was a complex matter and had been debated widely. In presenting data from an overview of published studies of sufficient quality, Merck Sharp & Dohme's intention was to give a reliable estimate of the blood pressure (BP) reductions that could be expected from Cozaar based on a variety of patient types. Similar data were presented for some of the other AII antagonists, where the volume of data were large enough to justify inclusion. One effect of meta-analysis was to minimise the effect of extreme results. For example, with the Cozaar 50mg data, diastolic BP reductions ranged from as little as 4mmHg in one study to as much as 11.9mmHg in another. With such a volume of data, cherry-picking the data that supported one argument was easy, but it would be as wrong for a competitor company to focus on the 4mmHg value as it would be for Merck Sharp & Dohme to focus solely on the 11.9mmHg value. Instead, an integrated meta-analysis was a perfectly valid methodology of providing an overview.

The complainant indicated that his hospital favoured irbesartan because of its superior efficacy in resistant hypertension, yet the papers quoted were not in patients with resistant hypertension. The meta-analysis contained six papers assessing irbesartan, including the two quoted showing diastolic BP reductions of between 7.7mmHg and 11.7mmHg, overlapped by the data for losartan completely. It was of note that both the papers cited demonstrated reductions in excess of the weighted average of 8.7mmHg, including the most extreme value. Similar arguments existed for systolic blood pressure and for dose increases.

In support of the use of meta-analyses providing a fair and balanced view, it was of importance to note the hierarchy of strength of data used when bodies such as NICE assessed evidence based medicine. Data were graded as follows:

Ia evidence from meta-analysis of randomised controlled trials
Ib evidence from at least one randomised trial
IIa evidence from at least one controlled study without randomisation
IIb evidence from at least one quasi-experimental study
III evidence from non-experimental descriptive studies such as comparative studies correlation studies and case-controlled studies
IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Meta-analyses of multiple trials were therefore regarded as carrying more weight than individual randomised studies, providing a more precise estimate of the overall treatment effect. Merck Sharp & Dohme therefore rejected the view that its use of a meta-analysis was misleading, untrue and unrepresentative of the data simply because within the totality of the data some individual studies could be found to have reached statistical significance. The totality of the data indicated that these agents were all effective antihypertensives, lowering BP by about 8-11mmHg in starting doses, 10-13mmHg with upward titration and 12-17mmHg when used in combination with a diuretic. The use of the meta-analysis minimised bias by including all available data, not cherry-picking the individual study that suited a particular argument best.

With regard to the allegation concerning representative behaviour and promotion of an unauthorised indication, Merck Sharp & Dohme stated that it had identified and interviewed the representative concerned, who remembered the meeting very clearly, since the complaint was made almost immediately. The meeting was one of a number of regular updates at which representatives were invited to provide brief presentations on their products. The representative concerned had presented at many such meetings at this hospital before. There were a number of discrepancies between the representative's recollections and those of the complainant which were unlikely to be resolved.

The complainant referred to a PowerPoint presentation. This representative denied using either an electronic, 35mm or acetate based presentation at the meeting. Indeed, she was not in possession of any of these from the company, since they were being updated at the time. She said that she used a flip-

chart and pen to illustrate her talk. Whilst the company took great care producing accurate graphs and concise but complete text for representatives to use in formal sales presentations, the use of paper and pen to draw graphs and make bullet-point lists would always be for illustrative purposes only, as an aide-memoire of the points to be covered during a presentation. Some meetings lent themselves to a less formal style than others depending on the subject matter, the familiarity with those present, the time and facilities available, etc. In this case, with only five minutes per product, an audience with whom she was familiar and no formal presentation materials, use of a pen and flip chart seemed entirely reasonable. The representative had reprints available to back up her presentation.

The representative denied stating that Cozaar was approved for use in heart failure. This was an experienced representative who had passed the ABPI examination, who knew very well the licensed indications for her product and would in no way deliberately misrepresent them. She did however admit to listing on the flip chart, after the licensed indication (and separated by a clear gap) the other disease areas in which research was emerging or ongoing. The complainant himself used the phrase 'I feel the way it was presented virtually promoted it for an unlicensed indication', acknowledging that there was scope for interpretation of her intentions.

The representative stated that the audience asked her 'Why do you not have a licence for heart failure?' and 'Why have you not applied for a licence for heart failure based on the ELITE I and II studies?'. The fact that these two questions were asked seemed to undermine the accusation that the representative led the audience to believe that Cozaar had a product licence for use in heart failure. Furthermore, the complainant stated in his letter that the representative made clear that Cozaar 'was not currently licensed for heart failure in the UK'.

Pharmacists, especially drug information pharmacists, often requested and required information on how Cozaar was used in their hospital. Cozaar was licensed for heart failure in many countries, and cardiologists returning from international conferences often sought clarification from their drug information pharmacists of the situation in the UK. Use of Cozaar in heart failure, in patients who could not take an ACE inhibitor was widespread amongst cardiologists. In answering these questions the representative was providing information on a relevant subject to a relevant audience, not encouraging the use of Cozaar in that indication.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that Merck Sharp & Dohme denied using a PowerPoint presentation. The complainant's recollection and others in his department, was that it was a PowerPoint presentation. He provided a copy of the departmental booking diary which included the comment 'will require a projector for PowerPoint presentation', which was supplied.

The American College of Chest Physicians now put meta-analysis below results from a single randomised controlled trial in its grading of levels of evidence. There was a growing recognition that meta-analysis could be used to demonstrate a variety of results, depending upon how they were carried out and so leading to controversial results. An example of this was albumin in fluid resuscitation. The complainant stated that Merck Sharp & Dohme's comment that the trials that he provided were not in resistant hypertension were not relevant. His point was that losartan was not effective in resistant cases and his hospital believed the available data which demonstrated that alternative AII antagonists were more effective.

The complainant stated that Merck Sharp & Dohme seemed to miss the point about the second complaint which was that heart failure was on a slide headed 'licensed indications'. The representative qualified this by saying that it was not licensed in the UK for this indication but she said it was licensed in 44 other countries. The complainant's view was that a slide should be accurate and stand alone without qualification. During the presentation he thought this was misleading and therefore asked several questions to clarify the situation. However these slides were used widely in various scenarios and were inaccurate and open to confusion. Simply leaving a blank line under a list did not adequately suggest that the product was in fact not licensed in the UK. By bringing up the fact that losartan was widely licensed for heart failure, he believed the representative was promoting the use as this was not in response to a question initially.

The complainant stated that he did not allege that the representative stated that losartan was approved for heart failure.

FURTHER COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme enclosed the slide kit that was issued to the representative concerned for use at general sales meetings, and would ordinarily have been used by her had it not been unavailable at the time, along with some briefing documents; slide 4 detailed the results of the Conlin meta-analysis. Briefing memoranda were issued to representatives when the meta-analysis was published. Copies were provided. Guidance on use of the promotional material was briefed to representatives face-to-face at regular meetings and memoranda were only used for materials issued in between such meetings. However, by way of illustration of how these data would have been briefed-in Merck Sharp & Dohme provided a copy of a similar slide with supporting notes from another kit that was available as a resource for speakers.

In relation to heart failure there was no reference to use of Cozaar in heart failure, or to the ELITE heart failure studies in the 35mm slide kit provided to this representative for use in this type of meeting. The kit clearly identified groups for whom Cozaar was recommended (slides 10-13) all of whom were within the current licence.

Written briefing materials on how to handle questions regarding heart failure were provided. These had already been reviewed by the Panel as part of Case AUTH/1181/5/01, in which no breach was ruled. However, the Panel's comments at the time were noted, and representatives were promptly reminded by way of voicemail that promotion in heart failure was prohibited.

Merck Sharp & Dohme hoped that the Panel accepted that its handling of the Conlin meta-analysis had been appropriate, fair and balanced. It also hoped that the Panel accepted that it had done its best to direct its representatives to promote for hypertension alone. There was substantial use of Cozaar off licence, particularly in hospitals, and representatives often faced questions on this. Whilst Merck Sharp & Dohme provided its representative with background information to enable them to understand and respond to physicians' and pharmacists' questions, it did not encourage them to actively promote outside the current licence.

In response to a subsequent request for information Merck Sharp & Dohme stated that the representative in question had never been provided with a PowerPoint presentation. She had, however, been provided with a 35mm slide presentation. On 5 April the company had requested that such presentations be returned to the company by 12 April.

PANEL RULING

The Panel noted that the allegations concerned claims made at a lunchtime promotional meeting. The parties provided differing accounts of the method of presentation. The complainant stated that his recollection and that of others in his department was that a PowerPoint presentation had been used. The complainant referred to two slides. The complainant had provided a copy of his departmental booking diary which mentioned the meeting and stated 'confirmed on 16/7/01 *will require a projector for PowerPoint presentation!'. The Panel noted that the complainant had written the letter of complaint on the day of the presentation when he would have had a clear recollection of what had occurred. Merck Sharp & Dohme stated that the representative denied using an electronic, 35mm or acetate based presentation at the meeting and that she was not in possession of any of these from the company as they were being updated at the time of the presentation. It was stated that the representative used a flip chart and pen to illustrate her talk.

The Panel considered that given the parties' differing accounts it was not possible to determine which mode of presentation had been used. The Panel was concerned about the use of a flip chart and pen by a representative; such a practice meant that, in effect, the representative was creating her own promotional material. The Panel requested that Merck Sharp & Dohme's attention be drawn to Point 4 of the Guidelines on Company Procedures Relating to the Code of Practice which stated that it should be made clear to representatives as to whether, and in what circumstances they could write letters, or prepare other written materials, which mentioned particular products and were thus almost certain to be considered promotional material. Such items must be certified, either in advance by way of proforma letters or by certifying each individual letter or other item, and must bear prescribing information in accordance with Clause 4.1. The Panel queried whether use of a flip chart and pen would meet these requirements and was concerned that the company did not appear to have issued representative briefing instructions to provide guidance on how to present complex data whilst the presentations were being updated. The Panel noted however that it did not have an allegation before it on this point.

The Panel firstly considered the allegation that the representative had stated that the other AII antagonists were no more effective than Cozaar whilst presenting data from Conlin *et al*. The Panel noted that Conlin *et al* was a meta-analysis of 43 published randomised controlled trials to evaluate the antihypertensive efficacy of losartan, valsartan irbesartan and candesartan. The authors concluded that the four AII antagonists exhibited comparable efficacy, a near flat dose response curve when titrating from starting to maximum recommended dose and substantial potentiation of the antihypertensive effect with addition of hydrochlorothiazide. The authors noted that there had been four published studies in which losartan had been compared directly with valsartan, irbesartan and candesartan, some of which had suggested differences in efficacy or responder rates between the medicines. The authors submitted that because these studies contributed less than 20% of all the available evidence on efficacy a meta-analysis of the sort provided for in their paper might be regarded as a stronger basis for understanding the comparative efficacy of medicines in this class. The Panel noted that two of the criteria used for choosing studies to include in the meta-analysis were a patient population with mild to moderate hypertension and patients representative of the overall hypertensive population. The Panel noted that the meta-analysis had not included eprosartan (Teveten) and telmisartan (Micardis). The meta-analysis stated that it examined the four currently available AII antagonists, losartan, valsartan, irbesartan and candesartan and referred to using Medline and Current Contents through October 1998 as sources of data. Two of the studies referred to by the complainant post-dated 1998 (Hedner *et al* and Mallion *et al*). The three other studies were included in the meta-analysis. The complainant was concerned about the comparative efficacy of Cozaar in resistant hypertension. It did not appear to the Panel that the representative had claimed comparable efficacy in relation to such a subgroup, but in relation to the overall patient population. The Panel had no way of knowing precisely what the representative had said at the meeting. It appeared that there was no dispute between the parties with regard to whether the representative had stated that the other AII antagonists were no more effective than Cozaar.

The Panel did not object to the use of meta-analyses *per se*. It was for companies to support their claims with data and the claims would be judged on the available data.

The Panel considered that the claim would be taken

as referring to patients with hypertension generally and not a resistant population. The Panel considered that on the evidence before it, in relation to the patient population as a whole the claim was not misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel then considered the presentation of data on Cozaar and heart failure. The Panel noted that Merck Sharp & Dohme stated that the representative had listed (on a flip chart) after the licensed indications and separated by a clear gap the other disease areas in which research was emerging or ongoing. This was not inconsistent with the complainant's description of the presentation of the data. The complainant stated that the representative had stated that Cozaar did not have a licence for use in heart failure in the UK but did have a licence in 44 other countries. The Panel noted that the parties' evidence was consistent on this point. The representative stated that she was asked two questions by members of the audience. The Panel noted that according to its summary of product characteristics (SPC) Cozaar was indicated for the treatment of hypertension only.

The Panel noted that Merck Sharp & Dohme had referred to a previous case, Case AUTH/1181/5/01, which concerned an allegation that a representative from Merck Sharp & Dohme had advised GPs that Cozaar had been licensed for heart failure. The Panel had considered that without the identity of the representative it was not possible to ascertain precisely what had occurred. The Panel expressed concern about the reference to the Elite II – Heart failure survival study in the detail aid but considered that in the circumstances it was obliged to rule no breach of Clauses 3.2, 7.2 and 15.2 of the Code.

Turning to the present case the Panel noted that it had not made a ruling in the previous case, Case AUTH/1181/5/01, on the acceptability or otherwise of the briefing materials or detail aid as inferred by Merck Sharp & Dohme. The complaint had been about the conduct of a representative and the Panel had had insufficient evidence before it to determine precisely what had occurred. The circumstances in the present case were different. The Panel considered that it was unacceptable to refer to unlicensed indications at a promotional meeting unless in response to an unsolicited request for such information. The unsolicited provision of such information within a promotional environment amounted to promotion of an unlicensed indication. The representative's statement that Cozaar was not licensed for heart failure in the UK was insufficient to negate the impression that it was being promoted outside its marketing authorization. The Panel ruled a breach of Clause 3.2 of the Code.

Complaint received **26 July 2001**

Case completed **15 October 2001**

PRESCRIBING ADVICE UNIT MANAGER v KNOLL

Reductil information and promotion

The prescribing advice unit manager at an NHS Trust complained about information from Knoll about Reductil (sibutramine) and also about the promotion of the product.

The complainant alleged that when she telephoned Knoll to ask whether sibutramine was related to amphetamine she was given a very evasive reply. At first Knoll said it did not know what was meant by that and then, when the complainant challenged this, said it depended on its pharmacology and could not give a specific answer. Martindale clearly stated that sibutramine was structurally related to amphetamine and certainly many of its side effects were those one might expect to see with an amphetamine related product. The complainant considered that she was given less than an accurate answer.

The Panel noted that Knoll's enquiry form showed that the question had arisen from a GP's concern about the abuse potential of Reductil. Knoll had sent a letter to the complainant dated the same day as the telephone conversation. The letter gave details of two studies investigating the abuse potential of Reductil compared with dexamphetamine and placebo. Copies of the studies were provided. The Panel did not think it unreasonable for the company to explore the reasons behind the enquiry in order that it could give a full answer. A request for information was a two way process. Material had been sent in response to the enquiry. The Panel considered that Knoll had provided accurate and relevant information about Reductil. No breach of the Code was ruled.

The complainant also alleged that the advertising for Reductil suggested that it was a 'new' aid to weight loss when in reality it was a product related to amphetamine and not a completely novel compound.

The Panel noted that Reductil had become available in the UK in May 2001. In accordance with the Code, Reductil was a product which had not been generally available for more than twelve months in the UK and thus it could be described as new. No breach of the Code was ruled.

The prescribing advice unit manager at an NHS Trust complained to Knoll in relation to its product Reductil (sibutramine). The complainant's letter to Knoll Limited had been copied to The Association of the British Pharmaceutical Industry which forwarded it to the Authority whereupon it was taken up as a complaint under the Code.

When writing to Knoll the Authority asked it to consider the requirements of Clauses 7.1 and 7.11 of the Code.

1 Medical information enquiry

COMPLAINT

The complainant alleged that when she telephoned Knoll with a simple enquiry regarding sibutramine she was given a very evasive reply. She wanted to know if the sibutramine molecule was related to amphetamine. At first the information officer said they did not know what was meant by that and then, when the complainant challenged this, said it depended on its pharmacology and could not give a specific answer. Martindale clearly stated that sibutramine was structurally related to amphetamine and certainly many of its side effects were those one might expect to see with an amphetamine related product.

The complainant was disappointed that the company did not give a straight answer to the query. If medicines were to be prescribed safely and effectively then prescribers needed to have accurate information available to them and the complainant considered that she was given less than an accurate answer.

RESPONSE

Knoll stated that the relevant enquiry form showed clearly that on clarification the underlying question was about the abuse potential of sibutramine. Copies of the form and the reply sent to the complainant the same day were provided. These showed that Knoll proposed, and the complainant agreed, that information on sibutramine's abuse potential be sent to her. Unfortunately it would appear that the complainant decided neither to wait and see the information before complaining, nor indeed to raise the complaint during her telephone conversation.

Knoll's policy was to try and elucidate questions before answering them. It believed that this constituted good practice and that it was ultimately helpful to the enquirer. That the company's attempt to clarify the enquiry, and therefore answer it in the most helpful and appropriate manner, had been misinterpreted as being 'evasive' was unfortunate, but made the approach no less valid.

Knoll had two principal rules in answering enquiries from health professionals, first to clarify the question and second to give information, not advice (ie provide information to assist the health professional. It did not manage patients over the phone).

Clearly both in this instance and generally, Knoll sought to provide, upon reasonable request from health professionals, accurate and relevant information about its medicines. It did not accept any breach of Clause 7.1 of the Code.

PANEL RULING

The Panel noted that the complainant had requested information about Reductil and whether it was related to amphetamine. The complainant did not consider that she had been given a straight answer to her enquiry. Knoll's enquiry form showed that the question had arisen from a GP's concern about the abuse potential of Reductil. Knoll had sent a letter to

the complainant dated the same day as the telephone conversation. The letter gave details of two studies investigating the abuse potential of Reductil compared with dexamphetamine and placebo in human volunteers. Copies of the studies were provided.

The Panel noted that Martindale stated that sibutramine was structurally related to amphetamine.

The Panel did not think it unreasonable for the company to explore the reasons behind the enquiry in order that it could give a full answer. A request for information was a two way process. Material had been sent in response to the enquiry. The Panel considered that Knoll had provided accurate and relevant information about Reductil. No breach of Clause 7.1 of the Code was ruled.

2 Use of the word 'new'

COMPLAINT

The complainant stated that the advertising suggested that sibutramine was a 'new' aid to weight loss ie a new type of product, when in reality it was a product related to amphetamine and not a completely novel compound.

RESPONSE

Knoll submitted that it was fully justified in using the word 'new' for sibutramine as this was a new chemical entity licensed in the UK in May 2001. It did not accept any breach of Clause 7.11 of the Code.

PANEL RULING

The Panel noted that Reductil had become available in the UK in May 2001. In accordance with Clause 7.11 of the Code, Reductil was a product which had not been generally available for more than twelve months in the UK and thus it could be described as 'new'.

The Panel therefore ruled no breach of Clause 7.11 of the Code.

Complaint received **30 July 2001**

Case completed **24 September 2001**

CASE AUTH/1214/7/01 *NO BREACH OF THE CODE*

HOSPITAL DIABETES NURSE SPECIALIST v NOVO NORDISK

Human Insulatard package leaflet

A hospital diabetes nurse specialist complained about a Human Insulatard package information leaflet issued by Novo Nordisk. The statement 'Research has shown that it is easier to control diabetes if you use injection pens instead of syringes' appeared in a highlighted box headed 'New Information for Patients using Syringes for Insulin Delivery'. The complainant alleged that the statement was not supported by research as injection pens were merely a device to administer insulin and the device itself did not give the patient 'easier to control diabetes'. The pens offered convenience, portability and ease of use but the statement was misleading and had led patients to believe that the pen itself gave better control.

The Panel noted that when the Director had considered whether a *prima facie* case had been established, the Director's view had been that whether the Code applied at all depended upon whether the patient information leaflet at issue promoted the medicine involved, insulin, as the Code exempted from the definition of promotion the labelling on medicines and accompanying package leaflets insofar as they were not promotional for the medicines concerned. The contents of labels and leaflets were covered by regulations. This was a matter which merited consideration by the Panel and the Director had accordingly allowed the complaint to proceed.

In the Panel's view the statement could have been better worded. It considered that the statement was promotional for the pen device. The Code referred to patient information leaflets not being covered by the Code insofar as they were not promotional for the medicine concerned. In the Panel's view the statement was not promotional for the medicine, insulin. Patients reading the leaflet would already have been prescribed Novo Nordisk's insulin. The statement was not promoting insulin itself. The Panel considered that the Code did not apply and accordingly ruled that there had been no breach.

A hospital diabetes nurse specialist complained about a statement on the Human Insulatard package information leaflet issued by Novo Nordisk Limited.

The leaflet included at the end a highlighted box headed 'New Information for Patients using Syringes for Insulin Delivery' followed by the statement 'Research has shown that it is easier to control diabetes if you use injection pens instead of syringes'. The box then stated that pens and needles were free to everyone with diabetes. Patients were encouraged to discuss the matter with their doctor or nurse.

COMPLAINT

The complainant alleged that the statement 'Research has shown that it is easier to control diabetes if you use injection pens instead of syringes' was not supported by research as injection pens were merely a device to administer insulin and the device itself did not give the patient 'easier to control diabetes'. The pens offered convenience, portability and ease of use but the statement was misleading and had led patients to believe that the pen itself gave better control.

RESPONSE

Novo Nordisk submitted that the statement was included in the patient information leaflets (PILs) for the 10ml vial presentations of Novo Nordisk's human insulin preparations (including Human Insulatard ge). The statement was included as extra-statutory information and read the same in all presentations.

The statement was printed on a pink background. In addition there was a strip running down the leaflet: 'New information for patients using syringes for insulin delivery – see below' and a carton flash 'New information inside'. These were intended to draw the patient's attention to the additional statement. Copy proofs of the carton and the PIL for Human Insulatard ge including the additional text were provided.

Novo Nordisk stated that in agreement with the Medicines Control Agency (MCA) the additional text was included for only a six month period, March to September 2000.

The aim of the additional text was to draw to the attention of patients using human insulin in vials the fact that pen insulin injection devices and the corresponding needles were now available on prescription. This was formally announced by the government in February 2000. The wording was intended to suggest to the patient that pen injection devices could be easier and more convenient to use than conventional syringes. The patient was advised to discuss this with their doctor or nurse if they were interested. There was no intention to give the impression that pen injection devices *per se* could improve diabetic control. Novo Nordisk entirely agreed with the complainant that pen injection devices were another means of injection which offered convenience, portability and ease of use but did not in themselves give improved diabetic control.

As for any change to the PIL/labelling text, the additional text was discussed with the MCA. The final text was approved by the MCA. The MCA restricted the duration of issue of the PILs with the additional text to the 6 months following publication of the availability of pen injection devices/needles on prescription in the Drug Tariff and MIMS. A copy of the correspondence between Novo Nordisk and the MCA was provided.

Reports of six studies which investigated the use of pen injection devices compared to syringes and vials, particularly with regard to acceptability and ease of use, were provided. All of the studies concluded that a majority of patients found pen injection devices easier and more convenient to use than syringes and vials. A majority of patients expressed a desire to continue to use pen injection devices.

In one study (Rosak *et al* 1993) a reduced acceptance of pen injection devices was found in patients over 50 years of age. However, other studies (Cosceli *et al* 1995 and Corsi *et al* 1997) had concluded that use of pen injection devices improved patient compliance.

Novo Nordisk believed that the ease of use of insulin pen injection devices had been convincingly demonstrated and reported in the literature. This was the intended message in the PIL leaflet statement. There was no intention of implying that glycaemic control could be improved by the use of pens *per se*.

PANEL RULING

The Panel noted that when the Director had considered whether a *prima facie* case had been established, as required by Paragraph 6.1 of the Constitution and Procedure for the Authority, the Director's view had been that whether the Code applied at all depended upon whether the patient information leaflet at issue promoted the medicine involved, insulin, as Clause 1.2 of the Code exempted from the definition of promotion the labelling on medicines and accompanying package leaflets insofar as they were not promotional for the medicines concerned. The contents of labels and leaflets were covered by regulations. This was a matter which merited consideration by the Panel and the Director had accordingly allowed the complaint to proceed.

The statement had been used in the patient information leaflet from March 2000 until September 2000. The matter would be considered in relation to the requirements of the 1998 edition of the Code.

In the Panel's view the statement could have been better worded. It considered that the statement was promotional for the pen device. Clause 1.2 of the Code referred to patient information leaflets not being covered by the Code insofar as they were not promotional for the medicine concerned. In the Panel's view the statement was not promotional for the medicine, insulin. Patients reading the leaflet would already have been prescribed Novo Nordisk's insulin. The statement was not promoting insulin itself. The Panel considered that the Code did not apply and accordingly ruled that there had been no breach.

Complaint received **30 July 2001**

Case completed **26 September 2001**

CASE AUTH/1219/8/01

GENERAL PRACTITIONER v UCB PHARMA

Conduct of representative

A general practitioner complained that a UCB Pharma representative who had come to deliver a model shoulder which he had requested had refused to leave it when she found she could not speak to him.

The Panel noted that the reply paid request card for the model shoulder clearly stated 'This offer carries no obligation to see a representative'. The representative in question arrived at the surgery to be told that the GP did not wish to see her. When requested to leave the items she had come to deliver she asked the receptionist if she could return at a later date with the model shoulder. The receptionist agreed and the representative took the model shoulder away with her. The Panel considered that the representative had thus used the promotional aid as an inducement to gain an interview and a breach of the Code was ruled.

A general practitioner complained to UCB Pharma Limited about the conduct of one of its medical representatives. The complainant's letter was copied to the Authority to be dealt with as a complaint under the Code.

COMPLAINT

The complainant stated that the representative called at the surgery to deliver a model shoulder he had requested. The complainant noted that the reply paid request card which he had filled in stated that there was no obligation to see a representative but the representative refused to leave the model unless she spoke to a doctor.

When writing to UCB the Authority asked it to consider the provisions of Clause 15.3 of the Code.

RESPONSE

UCB Pharma accepted that the representative's conduct, although not intentional, was in breach of Clause 15.3 of the Code. The company explained that the GP had requested a joint injection book and shoulder joint model on a reply paid card that accompanied a Preservex mailing sent to GPs in April. The representative called at the practice, handed the card to the receptionist and asked if she could see the GP. The GP declined to see the representative and told the receptionist to ask her to leave the items. The representative left the joint injection book with the receptionist and asked if she could return at a later date with the joint model. The receptionist agreed to this.

UCB had asked the representative to comply fully with the Code in the future.

PANEL RULING

The Panel noted that the reply paid request card for the model shoulder and the joint injection technique book clearly stated 'This offer carries no obligation to see a representative'. The representative in question arrived at the surgery with both items to be told that the GP did not wish to see her. When requested to leave the items she had come to deliver she asked the receptionist if she could return at a later date with the model shoulder. The receptionist agreed to this request and the representative took the model shoulder away with her. The Panel considered that the representative had thus used the promotional aid as an inducement to gain an interview. A breach of Clause 15.3 was ruled.

Complaint received	**10 August 2001**
Case completed	**13 September 2001**

CASE AUTH/1220/8/01

MEDIA/DIRECTOR v AMGEN

Neupogen press conference

In an article in Scrip a professor of medicines policy and consultant in clinical pharmacology was reported to have attacked what he claimed was media manipulation by pharmaceutical companies in order to advertise their products to the public. It was stated that the pattern was fairly standard; typically a campaign worked to raise awareness of a clinical problem, undermined current provision or created the concept of need, and ultimately offered a specific product as a solution. Working at arm's length the company would provide the media with data which was often preliminary or partisan, together with people for interview such as groomed opinion leaders and affected patients. In particular, the professor was reported to have taken exception to a press conference funded by Amgen to highlight the results of two cancer treatment audits it had sponsored.

The article in Scrip stated that the audits had involved 422 breast cancer and 177 advanced lymphoma patients. Results showed that neutropenic events in cancer patients had a significant impact on the ability to administer the planned dose intensity of chemotherapy. It was found that 30% of patients with breast cancer and 47% with lymphoma had had their chemotherapy dose modified. 36% of breast cancer patients received less than 85% of their planned chemotherapy dose intensity, a threshold, Amgen had stated, widely accepted to reflect inferior survival. Amgen had also stated that the main reason for dropping chemotherapy dose intensity was neutropenia.

The professor considered that the real aim of the press conference was to advertise Neupogen (filgrastim, a form of granulocyte-colony stimulating factor (G-CSF)), Amgen's product for the treatment of neutropenia. The results of the audits were published as abstracts only, without statistically valid outcomes, and presented to the press as showing that UK patients were being deprived of a chance of survival because they were not receiving Neupogen to elevate their white blood cell counts. Following the press conference, some UK newspapers ran stories stating that if Neupogen was used as an adjuvant therapy it could improve survival rates in cancer patients, as dose intensity for chemotherapy could be maintained. The professor had stated that while Neupogen might improve survival, there were no outcomes data to prove this and so at present it was no more than a hypothesis. To play with emotions in this way and by this means was unacceptable.

In accordance with established practice whereby public criticisms of the activities of pharmaceutical companies were treated as complaints under the Code of Practice, the matter was taken up with Amgen.

The Panel noted that the press release, entitled 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients', had been widely distributed to the lay and medical media. The aim of the press conference was to publicise the results of the two cancer treatment audits which had been sponsored by Amgen. The press release stated that strong evidence suggested a positive relationship between maintaining chemotherapy dose levels and patient survival and cited in support of this two breast cancer references. It then gave the results of the audits which showed that almost a third of breast cancer and a half of lymphoma patients had their chemotherapy dose modified mainly because of neutropenia. Neupogen was then described as a supportive care medicine which countered the effect of neutropenia making it possible to maintain critical chemotherapy. The press release ended with the statement 'Maintaining chemotherapy dose intensity in curable cancers is very important and evidence suggests it does improve a patient's chance of survival'.

Both audits, published in abstract form only, had been carried out because data indicating the number of patients affected by neutropenia and the impact of neutropenia on overall chemotherapeutic dose intensity received were limited. The objectives of the audits were to record the incidence of neutropenic events, to evaluate their impact on overall dose intensity received, and to review the use of G-CSF and its impact on dose intensity. The results appeared not to have been subject to statistical analysis. The preliminary results of the lymphoma audit stated that neutropenic events had a significant impact on the ability to deliver planned dose intensity in those who experienced a neutropenic event. A trend towards improved relative dose intensity was seen in those neutropenic patients treated with G-CSF. The results of the breast cancer audit referred to a trend towards improved dose intensity in those neutropenic patients treated with G-CSF. The summary of key data booklet with regard to the breast cancer audit stated that whilst conclusions could not be definitive due to the potential bias involved in a semi-prospective multi-site audit, it had been possible to show that neutropenic events did occur and that these might have an impact on the ability to deliver planned dose intensity.

In the Panel's view the press release gave insufficient information regarding the limitations of the audit data. It did not state that the statistical significance of the results was not known. The Panel also considered that the press release was not sufficiently clear about the role of Neupogen. It referred to evidence which suggested that maintaining chemotherapeutic dose levels over a planned treatment duration resulted in a better chance of survival, gave the results of the audits and then referred to Neupogen. Some readers would assume that the audit results meant that if more patients were treated with Neupogen survival rates would improve. In that regard the title of the press release 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients' linked the audits to survival. The audits had not evaluated the impact of

Neupogen on survival. The final statement in the press release referred to 'a patient's chance of survival'. Although it did not specifically state that use of Neupogen would save lives, lack of any statement to the contrary meant that some readers might assume that to be the case.

On balance the Panel considered that the lack of detail regarding the audit results in the press release, particularly in relation to the statistical significance and qualification of the results, meant that it had not been presented in a balanced way. The flow of information and lack of clarity regarding the role of Neupogen meant that the press release raised unfounded hopes about the impact of the product on survival. The Panel ruled a breach of the Code. The Panel did not consider that the press release or press conference constituted disguised promotion of Neupogen and ruled no breach of the Code in that regard.

In a one page article in Scrip, 3 August, Professor Joe Collier, Professor of Medicines Policy and Consultant in Clinical Pharmacology at St George's Hospital, London, was reported to have attacked what he claimed was media manipulation by pharmaceutical companies in order to advertise their products to the public. Professor Collier stated that the pattern was fairly standard; typically a campaign worked to raise awareness of a clinical problem (such as baldness, impotence and migraine), undermined current provision or created the concept of need, and ultimately offered a specific product as a solution. Working at arm's length the company would provide the media with data which was often preliminary or partisan, together with people for interview such as groomed opinion leaders and affected patients. In particular, Professor Collier was reported to have taken exception to a press conference funded by Amgen to highlight the results of two cancer treatment audits it had sponsored.

The article in Scrip stated that the audits had involved 422 breast cancer and 177 advanced lymphoma patients. Results showed that neutropenic events in cancer patients had a significant impact on the ability to administer the planned dose intensity of chemotherapy. They found that 30% of patients with breast cancer and 47% with lymphoma had had their chemotherapy dose modified. 36% of breast cancer patients received less than 85% of their planned chemotherapy dose intensity, a threshold, stated Amgen, widely accepted to reflect inferior survival. Amgen also stated that the main reason for dropping chemotherapy dose intensity was neutropenia.

COMPLAINT

Professor Collier considered that the real aim of the press conference was to advertise Neupogen (filgrastim, a form of granulocyte-colony stimulating factor (G-CSF)), Amgen's product licensed for the treatment of neutropenia.

Professor Collier stated that the results of the audits were published as abstracts only, without statistically valid outcomes, and presented to the press as showing that UK patients undergoing treatment for various cancers were being deprived of a chance of survival because they were not receiving Neupogen to elevate their white blood cell counts.

Following the press conference, some UK newspapers ran stories stating that if Neupogen was used as an adjuvant therapy it could improve survival rates in cancer patients, as dose intensity for chemotherapy could be maintained. Some reported that the reason for its non-use was lack of funding. Amgen's press invitation was entitled: 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients'.

Professor Collier stated that while Neupogen might improve survival, there were no outcomes data to prove this and so at present it was no more than a hypothesis. To play with emotions in this way and by this means was unacceptable. In Professor Collier's opinion, it was difficult to understand why Amgen was allowed to get away with such manipulative behaviour.

In accordance with established practice whereby criticisms of the activities of pharmaceutical companies were treated as complaints under the Code of Practice, the matter was taken up with Amgen, drawing attention to Clauses 7.2, 10.1 and 20.2.

RESPONSE

Amgen stated that the press briefing was held to highlight the results of two neutropenia audits that had been conducted throughout the UK, supported by the company. The two speakers at the briefing were both keenly involved in the audits and, as such, were entirely appropriate to present the data.

The press briefing was entitled 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients' and the key messages were:

- to highlight the importance of received chemotherapy dose intensity on survival outcome in patients with primary breast cancer and lymphoma
- to demonstrate that patients in the UK might not be receiving the intended dose intensity of chemotherapy and currently appeared to receive a lower dose intensity than patients treated in other countries
- to highlight that neutropenia was a key reason why chemotherapy dose intensity was reduced
- to demonstrate that by using [Neupogen] which boosted white cell counts in patients who experienced neutropenia , chemotherapy dose modifications and possible infectious complications (which could prove life threatening) could be avoided
- to point out that there was currently a lack of funding for supportive care medicines in cancer management in the UK.

Amgen noted that Professor Collier commented about the pharmaceutical industry's use of press conferences and also some specific points about Amgen. He had stated that the industry used groomed opinion leaders and affected patients. This statement was unfounded

in the case of Amgen. Both of the speakers at the briefing were strongly independent individuals who would not present anything but their own opinion. Amgen's involvement was to help prepare the data slides that were used by the doctors, not to brief them on what to say.

Amgen noted that Professor Collier had also stated that the industry typically worked to raise awareness of a clinical problem (such as baldness, impotence, migraine), undermined current provision, or created the concept of need, and ultimately offered a specific product as a solution. Amgen considered that patients had the right to knowledge and to understand all issues that related to their disease and its treatment. The UK currently lagged behind many countries in terms of the provision of cancer services, and the rates of survival were lower than many countries. The briefing set out to highlight this and to raise awareness of the data from the neutropenia audits.

Amgen noted that Professor Collier also stated that, in his opinion, the real aim of the press conference was to advertise Neupogen. Amgen refuted this allegation. The aims of the press briefing were clear. It was not the company's intention to link Neupogen to survival outcome, although this appeared to have been done by some journalists. Amgen agreed that this was an unfortunate outcome, but not an intended one.

In summary, Amgen refuted the allegation that it used groomed physicians to manipulate press coverage so as to promote Neupogen directly to the public. The materials presented related to the findings from two neutropenia audits. The speakers were highly respected independent physicians who expressed their own opinions throughout the press briefing, and had not been groomed in any way.

PANEL RULING

The Panel recognised that press conferences were a normal business activity and would often be in disease areas in which the company involved had a commercial interest. It was not necessarily unacceptable for press releases to include details of the company's relevant product(s). Materials given to the press must be in accordance with the Code.

The Panel noted that the press release, entitled 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients', had been widely distributed to the lay and medical media. The aim of the press conference was to publicise the results of the two cancer treatment audits which had been sponsored by Amgen. The press release stated that strong evidence suggested a positive relationship between maintaining chemotherapy dose levels and patient survival and cited in support of this two breast cancer references. The press release then gave the results of the audits which showed that almost one third of breast cancer and almost a half of lymphoma patients had their chemotherapy dose modified. The main reason for dropping the chemotherapy dose intensity was neutropenia. The press release went on to describe Neupogen as a supportive care medicine which countered the effect of neutropenia making it possible to maintain critical chemotherapy. The press release referred to a recent report which showed that there was a widening gap between the UK and similar European countries in the use of new anti-cancer medicines together with supportive care medicines and ended with the following statement from one of the speakers at the briefing: 'Maintaining chemotherapy dose intensity in curable cancers is very important and evidence suggests it does improve a patient's chance of survival'.

The results of the two cancer treatment audits had been published in abstract form only. Both audits had been carried out because data indicating the number of patients affected by neutropenia in clinical practice and the impact of neutropenia on overall chemotherapeutic dose intensity received were limited. The objectives of the audits were to record the incidence of neutropenic events, to evaluate the impact of such events on overall dose intensity received and to review the use of G-CSF and its impact on dose intensity. The results of the audits were given but they appeared not to have been subject to statistical analysis. The preliminary results of the lymphoma audit stated that neutropenic events had a significant impact on the ability to deliver planned dose intensity in those who experienced a neutropenic event. A trend towards improved relative dose intensity was seen in those neutropenic patients treated with G-CSF. The results of the breast cancer audit referred to a trend towards improved dose intensity in those neutropenic patients treated with G-CSF. The summary of key data booklet with regard to the breast cancer audit stated that whilst conclusions could not be definitive due to the potential bias involved in a semi-prospective multi-site audit it had been possible to show that neutropenic events did occur and that these might have an impact on the ability to deliver planned dose intensity.

In the Panel's view the press release gave insufficient information regarding the limitations of the audit data. The press release did not state that the statistical significance of the results was not known. The Panel also considered that the press release was not sufficiently clear about the role of Neupogen. The press release referred to evidence which suggested that maintaining chemotherapeutic dose levels over a planned treatment duration resulted in a better chance of survival, gave the results of the audits and then referred to Neupogen. The Panel considered that some readers would assume that the audit results meant that if more patients were treated with Neupogen survival rates would improve. In that regard the Panel noted that the title of the press release 'UK audit reveals missed treatment opportunities that could compromise survival rates for British cancer patients' linked the audits to survival. The audits had not evaluated the impact of Neupogen on survival. The final statement in the press release referred to 'a patient's chance of survival'. The Panel considered that although the press release did not specifically state that use of Neupogen would save lives, lack of any statement to the contrary meant that some readers might assume that to be the case.

On balance the Panel considered that the lack of detail regarding the audit results in the press release, particularly in relation to the statistical significance and qualification of the results, meant that it had not been presented in a balanced way. The flow of information and lack of clarity regarding the role of Neupogen meant that the press release raised unfounded hopes about the impact of the product on survival. The Panel ruled a breach of Clause 20.2 of the Code. The Panel considered that this ruling included consideration of Clause 7.2 and made no additional ruling with regard to that clause. The Panel did not consider that the press release or press conference constituted disguised promotion of Neupogen and ruled no breach of Clause 10.1.

Complaint received **13 August 2001**

Case completed **26 September 2001**

CASE AUTH/1221/8/01

MERCK SHARP & DOHME v NOVARTIS

Lescol 'Dear Health Professional' letter

Merck Sharp & Dohme complained about a 'Dear Health Professional' letter headed 'Lescol (fluvastatin): Treatment continuity following cerivastatin world-wide withdrawal' produced by Novartis. Merck Sharp & Dohme marketed Zocor (simvastatin).

The letter referred to the withdrawal of cerivastatin, which had occurred as a result of a high reported incidence of rhabdomyolysis, and discussed Lescol's pharmacological profile and efficacy, converting cerivastatin patients and the Novartis patient continuity support programme.

Merck Sharp & Dohme stated that the clear inference in the claim 'Lescol is hydrophilic, whereas cerivastatin, simvastatin and atorvastatin are lipophilic. This means it is difficult for Lescol to cross cell membranes, such as muscle cell membrane, which are composed mainly of lipid' was that the risk of rhabdomyolysis was as great with simvastatin as it was with cerivastatin. The summaries of product characteristics (SPCs) for all the statins licensed in the UK referred to the potential risk of rhabdomyolysis. The claim was alleged to be misleading and also disparaging of Zocor.

The Panel considered that the letter created the impression that simvastatin and atorvastatin had similar features to cerivastatin and differentiated Lescol. A statement that Lescol was mainly metabolised by liver enzyme pathways other than CYP 3A4 was followed by a statement that this meant there was a low potential for an interaction between Lescol and gemfibrozil. The letter inferred that the risk of rhabdomyolysis was as great with simvastatin and atorvastatin as it was with cerivastatin and thus created doubts about the safety of simvastatin and atorvastatin. The first paragraph referred to rhabdomyolysis as an uncommon but potentially fatal adverse event linked to cerivastatin usage with or without concomitant use of gemfibrozil. The SPCs for all statins licensed in the UK referred to the potential risk of rhabdomyolysis. The Panel considered the claim at issue was misleading and a breach of the Code was ruled.

In relation to the claim 'All statin SmPCs caution doctors to be vigilant towards signs of rhabdomyolysis. However, in the 30,000 patients treated with Lescol in clinical trials, there have been no reports of drug related rhabdomyolysis. Unlike all other statins fluvastatin is the only statin to date to have had no reports of rhabdomyolysis in the UK and a very low incidence globally', Merck Sharp & Dohme noted that the Lescol SPC stated that '… with Lescol such cases (rhabdomyolysis) have been reported very rarely'. It was therefore misleading to include a statement that there had been no reports to date of this phenomenon in the UK, as it suggested that rhabdomyolysis was not a concern for UK patients. This was a wholly disingenuous argument and clearly misleading.

The Panel noted that the Lescol SPCs each stated that 'Myopathy including myositis and rhabdomyolysis has been reported in patients receiving other HMG-CoA reductase inhibitors. With Lescol cases of myopathy, myalgia, muscle tenderness, muscle weakness and/or raised creatinine phosphokinase (CPK) have been reported rarely'. The SPC for Lescol XL 80mg listed rhabdomyolysis as a very rare adverse event. The Panel considered that the claim that there had been no reports of rhabdomyolysis in the UK gave the impression that rhabdomyolysis was not associated with Lescol therapy which was not so. In the Panel's view it was not acceptable to highlight the absence of reports from one country when clearly, according to the Lescol XL 80mg SPC, there had been reports of rhabdomyolysis in others, albeit very rarely. The Panel considered that the claim was misleading and ruled a breach of the Code.

The letter referred to the Lescol 'Novartis Patient Continuity Support Programme' and stated that 'Novartis has developed a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol. This programme consists of IT guidance notes on patient identification and change, surgery letters to local pharmacies, a draft set of patient information letters, and reception support …'. Merck Sharp & Dohme alleged that Novartis had clearly linked the provision of these additional services to switching patients from cerivastatin to Lescol which was in breach of the Code.

The Panel noted that the introduction to the patient continuity support programme referred to it having been developed to support the smooth transfer of cerivastatin patients to alternative therapies. The IT guidance notes provided technical instructions for eight different software systems to enable the user to identify patients receiving cerivastatin and effect a switch. The technical instructions merely referred to a switch to alternative therapy. Lescol was not mentioned. Sample letters to patients who were having their medication changed were provided together with sample notices to practice staff to keep them informed of the initiative and letters to pharmacists. Each sample stated that it was an example which could be modified as appropriate. Each was provided in both a draft format with the name of the new medication to be inserted by the doctor and a completed format whereby fluvastatin 40mg was inserted as the new medication. The statement 'After careful review fluvastatin has been chosen as one of a small selection of drugs which the practice believe to be in line with current best thinking. Fluvastatin works to produce the same benefits as your existing medication' also appeared in the completed format letters.

As a result of the withdrawal of cerivastatin GPs would have to identify and transfer patients to suitable alternative medication. Technical instructions enabling practices to identify and switch patients using their existing software would be helpful to practices. It could be argued that such a service would enhance patient care and benefit the NHS. However, the supply of such goods and services must not be done in such a way as to amount to an inducement to prescribe, supply, administer, recommend or buy any medicine. Such goods and services must not bear the name of any medicine but might bear a corporate name. The Panel noted that in contrast to the introduction to the patient continuity support programme which stated that the programme would 'support the smooth transfer of cerivastatin patients to alternative therapies', the letter at issue stated that it would 'support the smooth transfer of cerivastatin patients to Lescol'. In the Panel's view it could be argued that the support programme was being offered to doctors who had decided to transfer patients from cerivastatin to Lescol. Doctors who were considering changing patients from cerivastatin to Lescol could also obtain details, although this was not mentioned in the letter in question. The Panel noted Novartis' submission that the materials were sent to health professionals regardless of their prescribing intention and their ultimate prescribing decision.

The Panel was unsure whether the arrangements amounted to an inducement to prescribe. The benefit to the doctor was a document akin to a computer manual which gave instructions about how to search computers for patients on cerivastatin and how to change these patients to other medication. In addition to the 'computer manual' example letters to send to patients were provided. It appeared that practices would have to carry out the changes. The Panel considered that the position was somewhat unusual in that changes would have to be carried out regardless of whether the practice used the support programme or not, although patients on cerivastatin would not necessarily have to be changed to Lescol. The inducement might be the simplification of changing patients, although in that regard the Panel noted that it was a practice run support programme. Novartis was not providing IT staff to change the practice's computer records etc. There was no inherent value in the documents provided. It was perfectly possible for the support programme to be used in changing patients to a treatment other than Lescol. This would not be apparent from the 'Dear Health Professional' letter which clearly linked the support programme to Lescol. It could be argued that the support programme was part of the promotion of Lescol and was not a medical and educational good or service.

On balance the Panel decided that the support programme was part of the promotion of Lescol. It was not described as anything else in the letter in question. The Panel considered, however, that neither the benefits nor the description of the support programme amounted to a gift, benefit in kind or pecuniary advantage given as an inducement to prescribe Lescol. The Panel therefore ruled no breach of the Code.

Merck Sharp & Dohme Limited complained about a 'Dear Health Professional' letter dated 9 August and headed 'Lescol (fluvastatin): Treatment continuity following cerivastatin world-wide withdrawal' produced by Novartis Pharmaceuticals UK Limited.

The letter referred to the withdrawal of cerivastatin, which had occurred as a result of a high reported incidence of rhabdomyolysis, and subsequently discussed Lescol's pharmacological profile and efficacy, converting cerivastatin patients and the Novartis patient continuity support programme. Novartis stated that the letter was sent out electronically to its representatives on 9 August. Representatives were advised to suspend use of the mailing on the evening of 10 August and were subsequently provided with an amended version of the letter. Novartis confirmed that the text of 9 August was not mailed directly to health professionals.

Merck Sharp & Dohme marketed Zocor (simvastatin).

1 Claim 'Lescol is hydrophilic, whereas cerivastatin, simvastatin and atorvastatin are lipophilic. This means it is difficult for Lescol to cross cell membranes, such as muscle cell membrane, which are composed mainly of lipid'

COMPLAINT

Merck Sharp & Dohme stated that the clear inference in this statement was to suggest that the risk of rhabdomyolysis was as great with simvastatin as it was with cerivastatin. The summaries of product characteristics (SPCs) for all the statins licensed in the UK referred to the potential risk of rhabdomyolysis. The claim was alleged to be misleading in breach of Clause 7.2 and was also disparaging of Zocor in breach of Clause 8.1.

RESPONSE

Novartis stated that the letter was produced to address an increasing number of Lescol enquiries which it had received following the withdrawal of cerivastatin. Its purpose was to identify the potential differences between Lescol and cerivastatin in terms of pharmacology and incidence of rhabdomyolysis.

In order to avoid any potential misinterpretation the letter was revised on 10 August, amending: 'Cerivastatin simvastatin, atorvastatin and gemfibrozil are mainly metabolised by the cytochrome P450 3A4 (CYP 3A4)' to 'Cerivastatin and gemfibrozil are mainly metabolised by cytochrome P450 3A4 (CYP 3A4)' and 'Lescol is hydrophilic, whereas cerivastatin, simvastatin and atorvastatin are lipophilic' to 'Lescol is hydrophilic, whereas cerivastatin is lipophilic'.

Novartis stated that this was sent out to the representatives with clear instructions to destroy the original and it was this revised text which was mailed to health professionals after 10 August.

PANEL RULING

The Panel considered that the letter created the impression that simvastatin and atorvastatin had similar features to cerivastatin and differentiated Lescol. The statement that Lescol was mainly metabolised by liver enzyme pathways other than CYP 3A4 was followed by a statement that this meant there was a low potential for an interaction between Lescol and gemfibrozil. Within the letter, which discussed the withdrawal of cerivastatin, such an impression gave rise to the inference that the risk of rhabdomyolysis was as great with simvastatin and atorvastatin as it was with cerivastatin and thus created doubts about the safety of simvastatin and atorvastatin. The first paragraph referred to rhabdomyolysis as an uncommon but potentially fatal adverse event linked to cerivastatin usage with or without concomitant use of gemfibrozil. The Panel noted the submission that the SPCs for all statins licensed in the UK referred to the potential risk of rhabdomyolysis. The Panel considered the claim at issue was misleading as alleged; a breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 8.1 was covered by this ruling.

2 Claim 'All statin SmPCs caution doctors to be vigilant towards signs of rhabdomyolysis. However, in the 30,000 patients treated with Lescol in clinical trials, there have been no reports of drug related rhabdomyolysis. Unlike all other statins fluvastatin is the only statin to date to have had no reports of rhabdomyolysis in the UK and a very low incidence globally'

COMPLAINT

Merck Sharp & Dohme noted that section 4.4 of the Lescol SPC 'Special Warnings and Special Precautions' stated that '… with Lescol such cases (rhabdomyolysis) have been reported very rarely'. It was therefore misleading to include a statement that there had been no reports to date of this phenomenon in the UK, as it suggested that rhabdomyolysis was not a concern for UK patients. This was a wholly disingenuous argument and clearly misleading in breach of Clause 7.2.

RESPONSE

Novartis did not believe that the letter in any way misled prescribers about the incidence of rhabdomyolysis with Lescol. Novartis noted that Merck Sharp & Dohme had inaccurately quoted from section 4.4. of the Lescol SPC ie '… with Lescol such cases (rhabdomyolysis) have been reported very rarely'. This was not correct, the section contained a warning that rhabdomyolysis had been reported with other HMG-CoA reductase inhibitors and went on to state that cases of myopathy, myalgia, muscle tenderness, muscle weakness and or raised creatinine phosphokinase (CPK) had been reported rarely for Lescol.

The Lescol XL 80mg SPC made reference to the incidence of rhabdomyolysis in section 4.8 'Undesirable Effects' where its incidence was given as very rare. This incidence related to reports received by Novartis' parent company globally and not to reports received from clinical trials or from the UK clinical setting. This fact was, therefore, accurately reflected in the mailing.

PANEL RULING

The Panel noted that Section 4.4 of the SPCs for Lescol 20, 40 and 80mg each stated that 'Myopathy including myositis and rhabdomyolysis has been reported in patients receiving other HMG-CoA reductase inhibitors. With Lescol cases of myopathy, myalgia, muscle tenderness, muscle weakness and/or raised creatinine phosphokinase (CPK) have been reported rarely'. Section 4.8 of the SPC for Lescol XL 80mg headed 'Undesirable Effects' listed rhabdomyolysis as a very rare adverse event. Rare was estimated as 0.001-1% and isolated cases as <0.001%. The Panel considered that the claim that there had been no reports of rhabdomyolysis in the UK gave the impression that rhabdomyolysis was not associated with Lescol therapy which was not so. In the Panel's view it was not acceptable to highlight the absence of reports from one country when clearly, according to the Lescol XL 80mg SPC, there had been reports of rhabdomyolysis in others, albeit very rarely. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

3 Lescol: Novartis Patient Continuity Support Programme

'Novartis has developed a practice run management solution to support the smooth transfer of cerivastatin patients to Lescol. This programme consists of IT guidance notes on patient identification and change, surgery letters to local pharmacies, a draft set of patient information letters, and reception support …'

COMPLAINT

Merck Sharp & Dohme alleged that Novartis had

clearly linked the provision of these additional services to switching patients from cerivastatin to Lescol. This was in breach of Clause 18.1 as explained in the supplementary information accompanying this clause.

RESPONSE

Novartis stated that the Lescol: Novartis Patient Continuity Support Programme consisted of a set of IT guidance notes relating to a number of GP prescribing systems. It provided health professionals with a step-by-step guide by which they were able to select from their systems patients currently receiving cerivastatin who required review. It also provided draft templates for surgery letters to local pharmacies and a set of draft template letters for patients and reception support.

The guidance notes were devised originally to assist health professionals requesting specific assistance from the company in transferring patients from other statins to Lescol, and had been available for some time. However, in the light of recent events, it was quickly realised that such support had a broader value and the decision was taken to make them more widely available. To support this broader usage a number of additional generic template patient letters were included. These guidance notes were available directly from the company via the medical information department as referred to in the mailing. The materials were provided both as hard copy and also on disk so that they could be adjusted to specific needs. The materials were sent to the health professionals regardless of their prescribing intention and their ultimate prescribing decision. Novartis would not therefore accept that these materials were in breach of Clause 18.1 of the Code. Novartis added that health professionals had found these materials to be of considerable value during the patient review process.

PANEL RULING

The Panel noted that, in the introduction to the patient continuity support programme, the penultimate paragraph referred to the programme having been developed to support the smooth transfer of cerivastatin patients to alternative therapies. The patient continuity support programme gave a medical information number for further details. The IT guidance notes provided technical instructions for eight different software systems to enable the user to identify patients receiving cerivastatin and effect a switch. The technical instructions merely referred to a switch to alternative therapy, Lescol was not mentioned. Sample letters to patients who were having their medication changed were provided together with sample notices to practice staff to keep them informed of the initiative and letters to pharmacists. Each sample letter and notice stated that it was an example which could be modified as appropriate. Each was provided in both a draft format with the name of the new medication to be inserted by the doctor and a completed format whereby fluvastatin 40mg was inserted as the new medication. The statement 'After careful review fluvastatin has been chosen as one of a small selection of drugs which the practice believe to be in line with current best thinking. Fluvastatin works to produce the same benefits as your existing medication' also appeared in the completed format letters.

The Panel noted that as a result of the withdrawal of cerivastatin GPs would have to identify and transfer patients to suitable alternative medication. The Panel considered that technical instructions enabling practices to identify and switch patients using their existing software would be helpful to practices. It could be argued that such a service would enhance patient care and benefit the NHS as required by the supplementary information to Clause 18.1 of the Code. However, the supply of such goods and services must not be done in such a way as to amount to an inducement to prescribe, supply, administer, recommend or buy any medicine contrary to the requirements of Clause 18.1 of the Code and its supplementary information. The supplementary information also stated that goods and services must not bear the name of any medicine but may bear a corporate name.

The Panel noted that, in contrast to the introduction to the patient continuity support programme which stated that the programme would 'support the smooth transfer of cerivastatin patients to alternative therapies', the 'Dear Health Professional' letter at issue stated that it would 'support the smooth transfer of cerivastatin patients to Lescol'. The reader was referred to the Novartis medical information department for further details. In the Panel's view it could be argued that the support programme was being offered to doctors who had decided to transfer patients from cerivastatin to Lescol. Doctors who were considering changing patients from cerivastatin to Lescol could also obtain details although this was not mentioned in the letter in question. The Panel noted Novartis' submission that the materials were sent to health professionals regardless of their prescribing intention and their ultimate prescribing decision.

The Panel was unsure whether the arrangements amounted to an inducement to prescribe. The benefit to the doctor was a document, akin to a computer manual, which gave instructions about how to search their computers for patients on cerivastatin and how to change these patients to other medication. In addition to the 'computer manual' example letters to send to patients were provided. It appeared that practices would have to carry out the changes. The Panel considered that the position was somewhat unusual in that changes would have to be carried out regardless of whether the practice used the support programme or not, although patients on cerivastatin would not necessarily have to be changed to Lescol.

The inducement might be the simplification of changing patients although in that regard the Panel noted that it was a practice run support programme; Novartis was not providing IT staff to change the practice's computer records etc. There was no inherent value in the documents provided. It was perfectly possible for the support programme to be used in changing patients to a treatment other than Lescol. This would not be apparent from the 'Dear Health Professional' letter which clearly linked the

support programme to Lescol.

It could be argued that the support programme was part of the promotion of Lescol and was not a medical and educational good or service as described in the supplementary information to Clause 18.1 of the Code.

On balance the Panel decided that the support programme was part of the promotion of Lescol. It was not described as anything else in the letter in question. The Panel considered, however, that neither the benefits nor the description of the support programme amounted to a gift, benefit in kind or pecuniary advantage given as an inducement to prescribe Lescol. The Panel therefore ruled no breach of Clause 18.1 of the Code as alleged.

Complaint received **14 August 2001**

Case completed **16 October 2001**

CASE AUTH/1223/8/01

GENERAL PRACTITIONER v JANSSEN-CILAG

Daktacort mailing

A general practitioner complained about a Daktacort (miconazole/hydrocortisone) mailing sent to him by Janssen-Cilag. The front page featured the statement 'Take the heat out of intertrigo this summer with Daktacort' against a blue background of sea and sky; the word 'Daktacort' appeared in red. The complainant stated that this was the most prominent display of the brand name but noted that the non-proprietary names of the ingredients were missing. The non-proprietary names did appear on the back page but only in a small typeface. The mailing had been prepared in July 2001.

The Panel noted that the requirement to put the non-proprietary name/list of active ingredients immediately adjacent to the most prominent display of the brand name was the same in the 2001 Code as it had been in the 1998 Code. The mailing contained several references to Daktacort and the issue to be decided was which was the most prominent display. The Panel decided that it was the Daktacort brand name on the front cover of the mailing. This was the first mention of the brand name that readers would see and although part of a sentence it was conspicuous and it did catch attention. Failure to include the non-proprietary name/list of ingredients immediately adjacent to this display of the brand name meant that Janssen-Cilag had failed to meet the requirements of the Code and a breach was ruled.

The size in which the names of the active ingredients had to appear had changed from 10 point bold in the 1998 Code to bold type of a size such that a lower case 'x' was no smaller than 2mm in height in the 2001 Code. The latter had come into operation on 1 July but, during the period 1 July to 30 September inclusive, promotional material would not be regarded as being in breach if it failed to comply with the Code only because of newly introduced requirements. In this regard, the Panel noted that on the back page of the mailing the names of the active ingredients did appear immediately beneath the brand name. However, even if that were to be considered the most prominent display of the brand name, as argued by Janssen-Cilag, the mailing would still be in breach because the size in which the active ingredients appeared met neither the requirements of the 1998 Code nor those of the 2001 Code.

A general practitioner complained about a Daktacort (miconazole/hydrocortisone) mailing (ref 01704B) which he had received from Janssen-Cilag Ltd. The front page of the mailing featured the statement 'Take the heat out of intertrigo this summer with Daktacort' against a blue background of sea and sky; the word 'Daktacort' appeared in red. The mailing had been prepared in July 2001.

COMPLAINT

The complainant stated that the most prominent display of the brand name occurred on the front page of the mailing but noted that the non-proprietary names of the ingredients were missing. The non-proprietary names did appear on the back page but only in a small typeface. A breach of Clause 4.3 was alleged.

RESPONSE

Janssen-Cilag noted that Clause 4.3 of the Code stated that the non-proprietary name of a medicine must appear immediately adjacent to the most prominent display of the brand name. The company noted that the word 'prominence' was not defined in the Code. The Collins Concise Dictionary (4th edition 1999) defined 'prominent' as 'standing out from its surroundings; noticeable'. Janssen-Cilag argued that the non-proprietary name/list of active ingredients of Daktacort was indeed adjacent to the most prominent display of the brand name since this was located on the final page of the mailer in the form of a large Daktacort logo. Immediately adjacent to this display of the brand name were the words: 'Miconazole nitrate BP 2% w/w and hydrocortisone Ph Eur 1% w/w'.

Janssen-Cilag noted that the supplementary information to Clause 4.3 stated that (in respect of a letter) 'the most prominent display of the brand name will *usually* be that in the letter itself, rather than in

prescribing information provided on the reverse of the letter' (emphasis added). Thus it was not invariably the case that the most prominent display of the brand name was held to be within the body of the copy; the matter was one for decision on a case-by-case basis.

Janssen-Cilag further argued that the Daktacort logo, while on the final page of the mailing, was nevertheless still within the confines or boundary of the advertising copy of the mailing. The large Daktacort logo followed the prescribing information – but it was not a part of the prescribing information.

Janssen-Cilag contended that, just as the supplementary information to Clause 4.1 stated that legibility was not simply a question of type size, so too was it the case that prominence was not simply a question of type size. The supplementary information to Clause 4.1 noted recommendations to help to achieve clarity: a clear style of type; adequate contrast between the colour of the text and the background; preferably a dark print on a light background and emboldened headings and starting each section on a new line.

In the mailing in question, the first occurrence of the brand name was not the brand logo. It was merely the mention of the brand name in a sentence; it was in the same typeface as the words 'heat' and 'intertrigo' the only difference was that the initial letter was in upper case. The name had not been emboldened and it was in red against a dark blue background. Janssen-Cilag stated that none of the indicia which it proposed applied to a determination of prominence had been met by the first occurrence of the brand name.

Conversely, the final mention of the brand name was in a bold typeface (and was in a larger font than the bold typeface used for the non-proprietary name/list of ingredients); it started on a line separate from other sections of the piece; it was not part of a sentence and constituted the start of a new section to the mailer which promoted 'triple action-satisfaction'. The brand name was again in red, but this time against a yellow background. Clearly the final display of the brand name was at least as prominent as the initial display, if not more so. Janssen-Cilag argued that because it was in a large typeface, emboldened, red on yellow and in a separate section, the brand name/logo stood out from its surroundings and was the most noticeable or conspicuous of any other mention of the brand name in the piece.

Janssen-Cilag stated that no breach of Clause 4.3 should therefore be ruled as the most prominent display of the brand name had the required non-proprietary name/list of ingredients adjacent to it.

With regard to the type size of the non-proprietary name, Janssen-Cilag stated that its advertising agency had informed the art studio/printer that the requirements had changed in the 2001 edition of the Code. The advertising agency had written to Janssen-Cilag about the matter and a copy of the letter was provided. The agency stated that 'it must be acknowledged that there seems to have been an error here … [in that] our instructions to the artwork studio have on this occasion not been interpreted correctly'.

Janssen-Cilag noted that Clause 4.3 in the 2001 Code stated that the non-proprietary name of the medicine or a list of the active ingredients using approved names must appear in bold type of a size such that a lower case 'x' was no less than 2mm in height. In the Daktacort mailing in question, the bold lower case letters used for the generic name/list of ingredients measured only 1.75mm.

Janssen-Cilag requested that, despite the wrong type size being used, no breach be ruled as the 2001 edition of the Code came into operation on 1 July 2001, the same month as the Daktacort mailing was prepared. The 2001 edition of the Code thus applied to this piece. Janssen-Cilag noted that the title page of this edition of the Code, however, stated that 'During the period 1 July 2001 to 30 September 2001, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements which this edition of the Code newly introduces'.

Janssen-Cilag noted that Clause 4.3 of the 2001 Code was based upon the second paragraph of Clause 4.2 of the 1998 Code. However, the new clause substituted type size in millimetres of height for the older standard of printers' measure (size being measured in numerical 'point'). The change in the requirements was not clearly understood by the art studio/printer and the fact that the type size was not correct was then not noticed by Janssen-Cilag.

Janssen-Cilag argued that the change in the requirements constituted a new standard and it would take several months for it to become familiar to all of the different players required to produce promotional materials. The Authority had provided for an equitable solution to complaints made during the three month period which immediately followed the July introduction of the 2001 of the Code, where – as in this case – the complaint related to newly introduced standards.

Janssen-Cilag noted that the actual type size used was a good-faith attempt on the part of all concerned to produce an eminently readable non-proprietary name/list of ingredients; the print was in bold type as required and the words were quite clear and legible. The black print stood out easily against the yellow background.

Janssen-Cilag requested that no breach of Clause 4.3 be ruled with regard to the size of the bold typeface used for the generic name/list of ingredients – as the mistake related to a new standard and was made during the 'forgiveness' period [no[t] regarded as being in breach of the Code] as part of the 'learning curve'.

In response to a request for further information, Janssen-Cilag stated that the printer's type size for the non-proprietary name/list of ingredients was set by the printer in 10 point bold but that in trying to change it over to the new standard [millimetres/height setting], the resultant type was somewhat smaller.

Janssen-Cilag stated that it understood that the non-proprietary name/list of ingredients was initially set in 10 point. The whole section (brand name/logo and

generic name/ingredients) was then turned into an 'illustration' (with the various font styles being converted into 'shapes'). Such shapes allowed the greater artistic creativity than set font styles.

It then became known that instead of a minimum of 10 point bold the 2001 Code required a type size such that a lower case 'x' be not less than 2mm in height – and also be in bold. A decision was made that all the lower case letters of the generic name/ingredients list should therefore be changed to be 2mm in height.

Rather than starting again at the beginning of the process and turning the type of the line containing the generic name/ingredients into a new set of illustrator shapes of correct height size, the project continued as planned, with the entire final section of the piece (brand name/logo and generic name/ingredients list) being imported into a desktop publishing programme ('Quark Xpress') in order to obtain planned-for effects in the actual mailer. It was thought that the computer programme could then correct for the height of the type to be used for the non-proprietary name/list of ingredients.

The computerised printing programme was 'instructed' to downsize the entire section to 76% of the original, thought at the time to be a step which would allow the size of the non-proprietary name/list of ingredients line to be in accordance with the Code. Unfortunately, the calculation was incorrect and the resultant size of the non-proprietary name/list of ingredients line was too small (approximately 1.75mm).

Janssen-Cilag stated that it was happy for the Panel to consider the matter under the requirements of the 2001 Code. The company would, indeed, ask that it be acknowledged that the matter fell within the 'grace period'. The question for the Panel was then to decide whether the 'failure to comply' with the provisions of the new Code as to type height was as to 'provisions … which this [2001] edition of the Code newly introduces', such that the 'grace period' for 'no breach' should apply.

Janssen-Cilag stated that if it had read the Authority's letter requesting further information correctly it would appear that the Panel might have been contemplating a ruling of no breach if it could be shown that, although the company were in breach of the newly introduced height provisions of the 2001 Code, it had adhered to the previous size provisions. Janssen-Cilag submitted the two standards were in reality so different that the height requirement should be regarded as being one which the 2001 Code newly introduced.

Janssen-Cilag stated that, having had publishing methods explained to it, it was convinced that, due to the large number of computer printing programmes being used and the differences between them, the change in requirement from printers' measures (in 'point') to a height in millimetres constituted a newly introduced requirement. Such publishing methods also needed to be taken into account by the Authority. Of course, long gone were the days when printers placed typefaces of a certain point onto a row of a wooden block. However, even linotype and similar methods (used to set type of a certain point) were not used in isolation today. Print already composed or set in one manner was often then run through printing packages for a variety of reasons, resulting in a variety of effects. Some degree of trial and error was needed as to what happened when certain sized print within typed lines, logos, illustrations, photographs etc, were further manipulated by computerised printing programmes.

In the mailing in question it was not the case that Janssen-Cilag did not even attempt to comply with the newly introduced requirement. The company failed to comply because of problems encountered in its good-faith attempt to convert from the old standard to the new one. The company was now working with its advertising agencies and printers to ensure that calculations from printers' measures to height (in mm) would be correct in the future and to ensure that equipment was recalibrated to handle the new height requirements.

Janssen-Cilag reiterated that the new Clause 4.3 (although stemming from old Clause 4.2) imposed a newly introduced height requirement in millimetres, rather than the continued use of 'point'. There was always going to be some period of confusion when technical standards change. The purpose of the three-month 'grace' or 'forgiveness' period from 1 July 2001 [no breach for failure to comply with a newly introduced requirement] was no doubt adopted as an equity measure. It allowed for errors in procedures to be discovered and solutions found during a 'run-in' period.

Under previous editions of the Code, the print industry had – over time – developed standardised operating procedures whereby there could be a good deal of certainty that type of a given point, when introduced into a computerised publishing package and manipulated in various ways (as to enlargement/reduction, etc), would result in a type point which was Code compliant. Art studios/printers now required some small amount of time to try out different type (based now on a standard of millimetres in height) so as to be assured that such type (in mm/height) when combined with various settings on the computerised packages would result in print which complied with the 2001 Code. The three-month 'grace period' was intended to allow for this 'learning curve'.

Janssen-Cilag urged the Panel to decide that the changes made in the new Clause 4.3 as to type in 'mm height' were sufficiently different from the 'point' standard used in the old Clause 4.2 [ie constitutes a 'requirement which this [2001] edition of the Code newly introduces'] such that the 'grace period' or 'forgiveness' provision should be invoked – thus leading to a ruling of 'no breach ' of new Clause 4.3.

PANEL RULING

The Panel noted that the requirement regarding the positioning of the non-proprietary name/list of active ingredients was the same in the 2001 Code as it had been in the 1998 Code. In the 1998 Code the need to put the non-proprietary name/list of active ingredients immediately adjacent to the most prominent display of the brand name was a

requirement of Clause 4.1; in the 2001 Code it was a requirement of Clause 4.3. As there was no change in the requirement itself the matter was considered under the 2001 Code.

The Panel noted that the mailing contained several references to Daktacort; the issue to be decided was which was the most prominent display. The definition of 'prominent' given in the New Shorter Oxford Dictionary was 'Jutting out or protruding from a surface. Standing out so as to catch attention; conspicuous …'. The Panel decided that the most prominent display of the Daktacort brand name was on the front cover of the mailing. This was the first mention of the brand name that readers would see and although part of a sentence it was conspicuous and it did catch attention. Failure to include the non-proprietary name/list of ingredients immediately adjacent to this display of the brand name meant that Janssen-Cilag had failed to meet the requirements of Clause 4.3 and a breach of that clause was ruled.

The Panel then went on to consider whether, if the most prominent display of the brand name was on the rear of the mailing as argued by Janssen-Cilag, the type size of the active ingredients met the requirements of the Code.

The Panel noted that the 2001 edition of the Code had changed the requirement regarding the size of the non-proprietary name/list of active ingredients. The 1998 edition of the Code had required such information to appear in not less than 10 point bold or a type size which occupied a total area no less than that taken by the brand name. The 2001 edition of the Code stated that the non-proprietary name/list of active ingredients must appear in bold type of a size such that a lower case 'x' was no less than 2mm in height or in a type of such a size that it occupied a total area of no less than that taken up by the brand name.

The 2001 edition of the Code came into operation on 1 July 2001. The Code stated that during the period 1 July 2001 to 30 September 2001, no promotional material or activity would be regarded as being in breach of the Code if it failed to comply with its provisions only because of requirements which the 2001 edition of the Code newly introduced.

The mailing was prepared in July 2001 and so could potentially take the benefit of the transitional arrangements set out in the 2001 Code. The Panel considered, however, that companies could only take the benefit of such arrangements if their promotional material met the requirements of the 1998 Code. If this were not the case then it would effectively mean that, where changes in the Code had been introduced, for three months promotional material need not comply with either the old or the new Code. Such a situation would be unacceptable. The Panel noted that the type size of the non-proprietary name/list of active ingredients in the mailing was such that the height of a lower case 'x' was less than the 2mm specified in the 2001 Code; it was also such that it was less than 10 point. The requirements of the 1998 Code had not been met. The transitional arrangements thus did not apply and a breach of Clause 4.3 was ruled.

During the consideration of this case the Panel noted that the mailing included an offer of a cool bag for keeping medicines chilled for house calls. The Panel queried whether this met the requirements of Clause 18.2 of the Code with regard to the relevance of a cool bag to the practice of medicine. The Panel requested that its concerns be drawn to Janssen-Cilag's attention.

Complaint received **24 August 2001**

Case completed **4 October 2001**

CASE AUTH/1225/8/01

GENERAL PRACTITIONER v SHIRE

Promotion of Lodine

A general practitioner complained about a Lodine SR (etodolac) journal advertisement and loose insert issued by Shire. Lodine was a non-steroidal anti-inflammatory drug (NSAID). The summary of product characteristics (SPC) referred to *in vitro* and human cell models which found that Lodine was selective for the inhibition of cyclo-oxygenase 2 (COX-2).

The advertisement featured a photograph of a man smiling at a baby with the headline 'Look who's talking!'. Text below the photograph, headed 'Lodine is the first word of Marketing Director's new baby', gave a spoof report on events in the Pinkerton household when Violet, the baby, spoke for the first time. The report also referred to recent NICE Guidance on COX-2 selective inhibitors which indicated 'Lodine SR's 15-year pragmatic GI tolerability profile, its indications, simple dose and its positive cost differential to coxibs'. The product logo appeared with the strapline 'Purple and Proud'.

The front page of the two page A3 loose insert was a parody of the front page of Pulse. In this case the 'journal' was entitled 'Purple' and there were a number of spoof articles. Readers' attention was drawn to page '28' where 'New NICE Guidance highlights Lodine SR's 15-year pragmatic GI tolerability profile' and to page '92' where they could win a 5-star trip to the Shire offices at Basingstoke. The NICE Guidance was also referred to in two of the articles. The back of the insert was headed 'NICE One Lodine' and gave a number of quotations from the NICE Guidance on the use of COX-2 selective inhibitors. The 'Purple and Proud' product logo appeared on both the back and front of the insert.

The complainant considered that the Lodine SR campaign was facile and confusing. Further, it had been somewhat selective in the NICE Guidelines it had referred to. The complainant stated that it seemed a shame that the industry's image should be tainted in this way.

The Panel noted that the NICE Guidance had been selectively quoted in the loose insert; only the favourable post-marketing gastrointestinal (GI) data had been referred to and not the inconclusive clinical trial data. This made the GI side-effect data for Lodine seem more favourable and robust than it was. In the Panel's view this was compounded by a previous statement regarding clinical trial data for the other COX-2 selective inhibitors and the omission of comments about published evidence indicating that the therapeutic window was much wider for rofecoxib and celecoxib than for meloxicam and etodolac. It appeared that there was unequivocal data to show that Lodine had a more favourable GI side-effect profile than either standard NSAIDs or the other COX-2 selective inhibitors which was not so. The Panel considered that the way in which the NICE Guidance had been presented was misleading. A breach of the Code was ruled.

The advertisement stated that the NICE Guidance indicated Lodine SR's '15-year pragmatic GI tolerability profile'. There was no claim about the nature of the GI tolerability profile. The advertisement did not state or imply that Lodine SR had a favourable GI tolerability profile compared with standard NSAIDs. No breach of the Code was ruled.

The Panel noted the requirement of the Code that materials must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained at all times. The Panel accepted that issues of humour and taste were subjective. The humour in the advertisements was directed either at Shire personnel or the company's offices in Basingstoke. The Panel did not consider that the majority of readers would be offended by the advertisements and no breach of the Code was ruled in that regard.

A general practitioner complained about a promotional campaign for Lodine SR (etodolac) by Shire Pharmaceuticals Ltd. Lodine was a non-steroidal anti-inflammatory drug (NSAID) indicated for acute or long-term use in rheumatoid arthritis and osteoarthritis. The summary of product characteristics (SPC) referred to *in vitro* and human cell models which found that Lodine was selective for the inhibition of cyclo-oxygenase 2 (COX-2).

There were two items at issue, an advertisement (ref 029/102) and an A3 loose insert (ref 029/101). The advertisement featured a photograph of a man smiling at a baby; the headline was 'Look who's talking!'. Text below the photograph, headed 'Lodine is the first word of Marketing Director's new baby', gave a spoof report on events in the Pinkerton household when Violet, the baby, spoke for the first time. The report also referred to recent NICE Guidance on COX-2 selective inhibitors which indicated 'Lodine SR's 15-year pragmatic GI tolerability profile, its indications, simple dose and its positive cost differential to coxibs'. The product logo appeared with the strapline 'Purple and Proud'.

The front page of the two page A3 loose insert was a parody of the front page of the journal Pulse. In this case the 'journal' was entitled 'Purple' and there were a number of spoof articles; readers' attention was drawn to page '28' where 'New NICE Guidance highlights Lodine SR's 15-year pragmatic GI tolerability profile' and to page '92' where they could win a 5-star trip to the Shire offices at Basingstoke. The NICE Guidance was also referred to in two of the articles. The back of the insert was headed 'NICE One Lodine' and gave a number of quotations from the NICE Guidance on the use of COX-2 selective inhibitors. The product logo with the strapline 'Purple and Proud' appeared on both the back and front of the insert.

COMPLAINT

The complainant stated that while she enjoyed and admired many advertisements that provide information in a humorous way, she considered that the Lodine SR campaign was facile and confusing. Further, it had been somewhat selective in the NICE

Guidelines it had referred to. The complainant stated that it seemed a shame that the industry's image should be tainted in this way.

When writing to Shire the Authority asked it to consider the requirements of Clauses 2, 7.2 and 9.1 of the Code.

RESPONSE

Shire stated that it was very strongly of the view that the Lodine SR campaign did not bring discredit upon, or reduce confidence in, the pharmaceutical industry. The humorous parodies were designed to draw attention, in an assertive but inoffensive manner, to Lodine SR and the NICE Guidance on the use of this class of medicine. The humour was intended to reflect how pleased Shire was with the outcome of the NICE Guidance and thus was focussed on Shire itself and not on the medical profession, nor on the pharmaceutical industry as a whole.

In both advertisements, particularly in the A3 loose insert, there was serious reference to the important NICE Guidance. Shire stated that it had sought to make a very serious point to a wide audience in an eye-catching and humorous way.

Shire stated that in its view, the intended audience would have understood both the serious nature of the campaign and appreciated its humorous delivery. The company had had a number of congratulatory letters on its campaign and it believed that the audience overall had not been offended by it.

Shire noted that the complainant was of the view that the company had been somewhat selective in quoting the NICE Guidance. The quotations referred to all COX-2 selective inhibitors as a therapeutic class as a whole, as well as Lodine SR, and dealt with the circumstances in which NICE recommended that they should be used. Shire considered that the quotations were balanced, fair and not misleading and were therefore not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the complaint about the selective referral to the NICE Guidelines was very general.

The back page of the loose insert gave a number of quotations from the NICE Guidance on the use of COX-2 selective inhibitors. The Panel noted that Sections 4.5 and 4.6 of the Guidance were quoted as follows:

> (4.5) 'Indirect comparison of the effects of meloxicam, rofecoxib and celecoxib relative to other NSAIDs based on available (randomised controlled trial) evidence, does not demonstrate a difference in either efficacy or adverse events between them'
>
> (4.6) 'There is post-marketing data for etodolac, collected over 15 years, that provides pragmatic evidence of a reduced incidence of serious gastrointestinal events compared to standard NSAIDs'

The Panel noted that Section 4.6 of the NICE Guidance had not been quoted in full. The actual statement in the Guidance was as follows:

> 'The RCT [randomised controlled trial] evidence for the incidence of gastrointestinal adverse events associated with etodolac compared to other NSAIDs cannot be considered conclusive as many of the studies were insufficiently powered to detect differences in serious gastrointestinal adverse events. There is however post-marketing data for etodolac, collected over 15 years, that provides pragmatic evidence of a reduced incidence of serious gastrointestinal events compared to standard NSAIDs. All of the COX II selective agents exhibit some degree of dose dependency of the incidence of upper gastrointestinal adverse effects but published evidence indicates that the therapeutic window is much wider for rofecoxib and celecoxib than for meloxicam and etodolac.'

The Panel noted that Section 4.6 of the NICE Guidance had been selectively quoted; only the favourable post-marketing GI data had been referred to and not the inconclusive clinical trial data. This had the effect of making the GI side-effect data for Lodine seem more favourable and robust than it was. In the Panel's view this effect was compounded by the previous statement (Section 4.5) regarding clinical trial data for the other COX-2 selective inhibitors and the omission of comments about published evidence indicating that the therapeutic window was much wider for rofecoxib and celecoxib than for meloxicam and etodolac. It appeared that there was unequivocal data to show that Lodine had a more favourable GI side-effect profile than either standard NSAIDs or the other COX-2 selective inhibitors which was not so. The Panel considered that the way in which the NICE Guidance had been presented in the loose insert was misleading. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the advertisement stated that the NICE Guidance indicated Lodine SR's '15-year pragmatic GI tolerability profile'. There was no claim about the nature of the GI tolerability profile. The advertisement did not state or imply that Lodine SR had a favourable GI tolerability profile compared with standard NSAIDs. No breach of Clause 7.2 was ruled in that regard.

The Panel noted the requirements of Clause 9.1 that all material and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained at all times.

The Panel accepted that issues of humour and taste were subjective. The humour in the advertisements was directed either at Shire personnel or the company's offices in Basingstoke. The Panel did not consider that the majority of readers would be offended by the advertisements. No breach of Clause 9.1 was ruled.

The Panel did not consider that the material brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **30 August 2001**

Case completed **8 October 2001**

ANONYMOUS v ORGANON LABORATORIES and WYETH

Conduct of representatives

An anonymous telephone caller claiming to be a general practitioner complained about the conduct of a representative and a regional manager from Organon. The representative was previously employed by Wyeth and allegations were also made about the representative's conduct at Wyeth. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

The Panel considered that there was no evidence before it of any wrongdoing on the part of the representative, the regional manager or the companies. No breach of the Code was ruled.

An anonymous caller, claiming to be a general practitioner, telephoned to complain about the activities of a representative and a regional manager from Organon Laboratories Ltd. The representative had previously been employed by Wyeth.

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

COMPLAINT

The complainant stated that he had two concerns about the conduct of a representative from Organon.

The representative had recently called at his practice to promote Zispin and Livial. Whilst at reception the representative tried to sell what the complainant alleged to be stolen property to the receptionist. The complainant was not present but another partner within the practice was. The representative offered to sell items for cash. No paperwork would be involved.

The complainant had been told by a representative from another company that the representative concerned had been dismissed by Wyeth for 'taking home patients' records and altering them' during the course of an audit. A GP in the practice at issue had informed Wyeth which had subsequently investigated and dismissed the representative.

The complainant would not disclose his identity nor that of the practice.

The complainant subsequently telephoned again. He stated that with regard to his first point the representative was accompanied by his regional manager. The complainant and his partner had been advised by 'an Organon employee' that the regional manager had been sacked from a company for falsifying calls as a representative. He subsequently obtained a position at another pharmaceutical company as a product manager where he was 'sacked for allegedly embezzling money'. The complainant further stated that with regard to the first allegation his partner had gained the strong impression that the goods were stolen.

When writing to Organon and to Wyeth the Authority drew attention to Clauses 2, 9.1, 15.2 and 15.10 of the Code.

CASE AUTH/1226/9/01

RESPONSE

Organon had interviewed both employees and both stated categorically that they had no knowledge of the allegations. Furthermore, the last time that the regional manager accompanied the representative on field visits was some 25 days prior to the anonymous telephone calls of complaint.

Organon confirmed that one of the representatives left his previous employer on the grounds of redundancy with no disciplinary action against him. Both referees spoke positively and stated that they would re-employ the representative.

Unfortunately, as this allegation was anonymous the company did not believe it could further investigate the allegation.

Organon objected strongly to the second concern, which might be libellous, being raised anonymously.

In this particular case the allegation seemed, at the same time, to be both very serious and totally implausible, and as such it would require detailed investigation to establish the true facts.

There was an allegation made against the other representative which was investigated by the then employer and was not proven. No disciplinary action was taken. The representative voluntarily resigned his previous position to join Organon.

Organon of course took all such complaints very seriously, but at the same time was conscious of the need to protect the reputations of its employees from groundless allegations.

In the circumstances, and in the absence of any evidence of wrongdoing, Organon denied any breach of the Code.

PANEL RULING

The Panel noted that very serious allegations had been made by the complainant who was not prepared to identify himself to the Authority or to the company concerned.

The Panel noted Organon's comment about anonymous complaints. The Authority was obliged to deal with such complaints although of course the complainant could not be informed of the outcome. It was extremely difficult for companies to investigate such complaints without knowing the complainant's identity.

The Panel noted that the representatives stated categorically that they had no knowledge of the matters raised by the complainant.

Organon had checked its personnel records and had advised that one of the representatives had been

investigated by a previous employer. The allegation was not proven and the representative had resigned voluntarily. The other representative left their previous employer on grounds of redundancy. There was no disciplinary action.

It was not possible for Organon to investigate the matter further without additional information from the complainant. The Panel considered that there was no evidence before it of any wrongdoing on the part of the representatives or the company. No breach of the Code was ruled.

CASE AUTH/1227/9/01

RESPONSE

Wyeth gave details of when it had employed the representative; the representative's departure from the company was not related to 'taking home patients' records and altering them'. Indeed, the present complaint was the first time this allegation had been brought to Wyeth's attention. At the time of the representative's employment with Wyeth, so far as it was aware given the time that had elapsed, audit was not a promotional activity undertaken by the company.

As the complaint was anonymous and unsubstantiated Wyeth suggested that there was no case to answer.

PANEL RULING

The Panel noted that a very serious allegation had been made by the complainant who was not prepared to identify himself to the Authority or to the company concerned.

The Panel noted that the representative had left Wyeth many years ago. This was the first time that the allegation concerning the representative taking home patient records and altering them had been brought to Wyeth's attention.

The Panel considered that there was no evidence before it of any wrongdoing on the part of the representative or the company. No breach of the Code was ruled.

Complaint received **4 September 2001**

Case completed **20 September 2001**

CASE AUTH/1231/9/01

MEMBER OF THE PUBLIC v PFIZER

Supply of sample by a representative to a member of the public

A member of the public complained that in 1998 a Pfizer representative had given his former wife a sample of Diflucan (fluconazole) Suspension.

The Panel noted that it was accepted by Pfizer that a sample of a prescription-only medicine had been supplied inappropriately. A breach of the Code was ruled as samples could only be provided to health professionals. The representative had failed to maintain a high standard of ethical conduct and comply with all relevant requirements of the Code and a breach of the Code was also ruled in that regard.

The Code required companies to have an adequate system of control and accountability for samples but the Panel considered that it was unable to make a ruling on this point as the incident was over three years ago and records had been destroyed. The Panel noted that the 2001 Code had been expanded in relation to the control and accountability of medicines held by representatives.

A member of the public complained about the conduct of a representative from Pfizer Limited.

COMPLAINT

The complainant stated that in the summer of 1998 his wife was given a bottle of Pfizer's Diflucan (fluconazole) Suspension, a prescription-only medicine, to take for a fungal infection. This was given to her by a neighbour, who the complainant understood to be a medical representative and not a doctor. The complainant's wife had informed the complainant that she had been told by the representative that his company allowed him to give medicines to friends and family.

The complainant knew that it had taken a long time for him to bring this to the Authority's attention but he had only recently discovered that this was entirely inappropriate and that medications should not be given as samples by medical representatives to members of the public.

In a subsequent letter, the complainant explained that at the time of the incident he had been married for four years. His then wife became friendly with the representative who was one of their neighbours. The complainant went away for a weekend and when he returned he found this medication. On questioning his wife, she said that the representative had given it to her as she had thrush. The complainant thought this rather strange and asked if he was allowed to give out medicines to members of the public. His then wife was a computer trainer and not a member of the medical profession. She had spoken to the representative later in the day and he informed her

that his company allowed him to give medicines to friends and family. The complainant had thought this must be correct and thought no more about it.

A few months later the complainant's marriage broke up and they were now divorced. The complainant had recently remarried, his wife was a registered nurse and her father a retired general practitioner. They had found the empty bottle of medicine whilst spring cleaning. When he had told his new wife about the incident she had said that the representative ought not to have given it to his former wife. Even though they were close friends it was still inappropriate. His wife had suggested that he ask her father about it as he was a doctor and might know about the rules. Her father said that it was completely wrong and that the complainant should report it.

When writing to Pfizer the Authority drew attention to Clauses 15.2, 17.1 and 17.9 of the Code.

RESPONSE

Pfizer stated that it was very concerned about the issues raised in the complaint and had immediately launched an investigation into the matter. As a result of its investigation it had found that the allegations made in the complaint appeared to be substantially true.

Pfizer issued the last samples of Diflucan Suspension to its sales force in February 1997.

The representative admitted giving a sample of Diflucan to the complainant's wife, although he maintained that this was an isolated incident in somewhat unusual circumstances. Pfizer understood that the lady specifically asked him for the sample, having told him that she had previously been prescribed the product by her general practitioner. The request had been made on a Sunday, when access to a doctor and/or pharmacy was difficult.

Pfizer understood that, although the lady was a close family friend at the time, neither the lady nor the representative recalled him telling her that he was allowed to give medicines to friends and family.

The representative realised that the supply of a sample in this manner was wholly inappropriate, and in breach of both the Code and company guidelines. In view of the circumstances, Pfizer was satisfied that this was an isolated incident. He had been a Pfizer sales representative for many years and no previous complaints had been received against him.

As a consequence of this complaint, the representative had been issued with a severe reprimand and had also been required to attend retraining in the requirements of the Code.

Pfizer responded to the particular issues raised by the Authority.

1 Pfizer confirmed that the representative had passed the ABPI medical representatives examination.

2 More than four years had elapsed since the last distribution of Diflucan suspension to Pfizer representatives. Pfizer had no record of the procedures in place in 1997 to correlate the number of samples provided to representatives with the number of signed and dated sample request forms. Any records that were directly relevant to the distribution of the particular samples in question were not retained beyond 1998 (Clause 17.3 of the Code required sample requests to be retained for one year).

3 Pfizer had no copies of any materials used in 1997/1998 to brief sales representatives about sampling. As with other promotional materials, these would have been retained for three years (as required by Clause 14.4 of the Code) but destroyed thereafter.

PANEL RULING

The Panel noted that it was accepted by Pfizer that a sample of Diflucan Suspension, a prescription-only medicine, had been supplied inappropriately.

A breach of Clause 17.1 of the Code was ruled as samples could only be provided to health professionals. The representative had failed to maintain a high standard of ethical conduct and comply with all relevant requirements of the Code and a breach of Clause 15.2 was also ruled.

The Panel noted that Clause 17.9 required companies to have an adequate system of control and accountability for samples but considered that it was unable to make a ruling on this point as the incident was over three years ago and records had been destroyed. The Panel noted that the 2001 Code had been expanded in relation to the control and accountability of medicines held by representatives.

Complaint received **18 September 2001**

Case completed **18 October 2001**

CODE OF PRACTICE REVIEW – NOVEMBER 2001

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).