PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 39 FEBRUARY 2003

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.

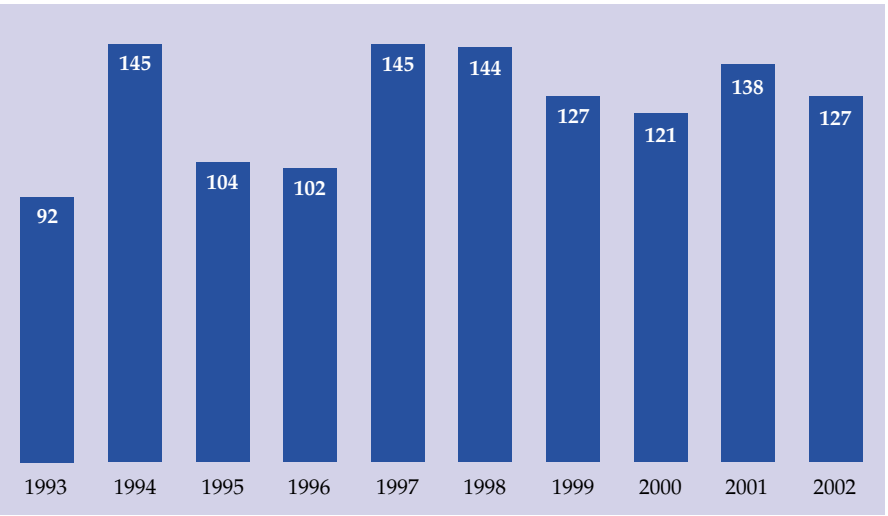
The first ten years

Established on 1 January 1993 the Prescription Medicines Code of Practice Authority has now been operating for ten years.

The ABPI Code of Practice for the Pharmaceutical Industry was first introduced in 1958 and until the end of 1992 it was administered by the ABPI itself. There was some perception, both within and outwith the industry, that a greater degree of independence was needed if there was to be seen to be an effective self-regulatory system and this was a major factor in the decision to establish the Authority.

The Authority has been able to carry out its functions successfully, independently of the ABPI, and without interference from it, whilst nonetheless remaining related to it.

Over the ten years since the establishment of the Authority the number of complaints received each year has ranged widely, as shown below, without any perceptible reason for the variations seen.



Fewer complaints in 2002 than in 2001

In 2002, there were 127 complaints under the Code of Practice as compared with 138 in 2001. The number of complaints in 2002 was on a par with the 121 in 2000 and the 127 in 1999.

There were 122 cases to be considered in 2002 as compared with 147 in 2001. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

Once again the number of complaints from pharmaceutical companies has exceeded the number from health professionals, there having been 59 from pharmaceutical companies and 46 from health professionals as compared with 60 from pharmaceutical companies and 57 from health professionals in 2001. Historically it has generally been the case that the number of complaints from health professionals has exceeded the number from pharmaceutical companies but that was not the case in 1999, 2001 and now again in 2002. Complaints from pharmaceutical companies are usually more complex than complaints from outside the industry.

One complaint was made by the Scottish Medicines Consortium, one by Social Audit and one by a medical writer. Eight complaints were anonymous. The remaining eleven complaints were nominally made by the Director, five resulting from voluntary admissions by companies, two from media criticism of promotion and four from alleged breaches of undertakings.

Changes afoot

Possible changes to the Code of Practice for the Pharmaceutical Industry and the Constitution and Procedure for the Prescription Medicines Code of Practice Authority are at present under consideration. ABPI member companies have been consulted as have those companies which though not member companies have agreed to comply with the Code and accept the Authority's jurisdiction. The Medicines Control Agency, the Office of Fair Trading, the British Medical Association and the Royal Pharmaceutical Society of Great Britain have also been consulted.

It is anticipated that the proposals will go before ABPI member companies at their Annual General Meeting in April. If agreed the revised Code of Practice would come into operation on 1 July but with the usual three month transitional period.

CODE OF PRACTICE TRAINING

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

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

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

Friday, 23 May

Tuesday, 17 June

Tuesday, 1 July

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

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

How to contact the Authority

Our address is:

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London SW1A 2DY

Telephone: 020 7930 9677
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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
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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/1299/4/02

TKT-5S v GENZYME

Promotion of Fabrazyme

TKT Europe-5S AB (TKT-5S) complained about the promotion of Fabrazyme (agalsidase beta) by Genzyme. TKT-5S supplied Replagal (agalsidase alfa). Both products were indicated for the treatment of the rare genetic disorder, Fabry's disease.

The material at issue was a press release made by or on behalf of the Genzyme group in December 2001, commenting on the proceedings of a Genzyme sponsored symposium held in Barcelona in November 2001 and entitled 'The Second European Roundtable on Fabry Disease'. The press release discussed Fabrazyme and was published widely via the Internet and TKT-5S had found it on an Italian and a French website and through a London based newswire service.

The press release presented two year data from Genzyme's open label clinical trial of Fabrazyme together with the results of the first reported comparative study of Fabrazyme and Replagal which showed that the products were 'structurally very similar and functionally equivalent'.

TKT-5S alleged that the claim that Fabrazyme and Replagal were 'structurally very similar and functionally equivalent' was misleading and not substantiated. There were significant differences between the two products. The chemical structure was different; Replagal was an agalsidase alfa product whereas Fabrazyme was agalsidase beta. Replagal was produced by genetic engineering technology in a human cell line whereas Fabrazyme was produced by recombinant Chinese hamster ovary cells. As a result of the differences in production and glycosylation there were a number of differences in the summaries of product characteristics (SPCs) of the two products concerning efficacy and safety.

TKT-5S noted the study which Genzyme used to support this claim of functional equivalence was an *in vitro* study. The Code required that 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. There was no such data presented. The study did, however, endorse the real and meaningful differences in the carbohydrate structure between Replagal and Fabrazyme.

TKT-5S noted the evidence was clear that in respect of efficacy and tolerability the performance of Replagal was materially superior to that of Fabrazyme and, accordingly, the statement breached the Code.

The Panel noted that the press release was created by the Genzyme Corporation and circulated via a European UK based news agency which had placed it on its website on a UK server in December 2001. Given all the circumstances the Panel decided that the press release was subject to the UK Code.

In relation to the claim that Fabrazyme and Replagal were structurally similar the Panel noted that they were both human α-galactosidase A glycoproteins, produced by recombinant Chinese hamster ovary cells and human cell lines respectively. They were not structurally identical. The Panel noted the submission that the amino-acid sequence in the backbone was the same. *In vivo* testing indicated that the peptide map was similar. The Panel noted the list of ten structural similarities provided by Genzyme. The differences resulted from differing glycosylation patterns. The Panel considered that the nature and extent of the similarities were such that 'structurally very similar' was not an unreasonable description; the claim was not misleading or unsubstantiable on this point or inconsistent with the SPC as alleged. No breach of the Code was ruled. The Panel did not agree with TKT-5S's statement that the evidence was clear that in respect of efficacy and tolerability Replagal was materially superior to Fabrazyme. There was no data directly comparing the medicines.

The Panel noted that the press release mentioned 'functionally equivalent' in relation to the results of an *in vitro* comparative study of Fabrazyme and Replagal, the results for which appeared in the Barcelona Roundtable Report. The report stated that a comparison of enzyme kinetics in substrate assays showed no significant difference between the two products in terms of rate of substrate hydrolysis, the concentration of substrate at which the reaction rate was half its maximal value and the products' specific activities. There were numerical between group differences in relation to each component of the monosaccharide analysis, however the statistical significance of these differences was not stated. The introduction section stated that biochemically and structurally, the two enzymes were 'highly similar'. The author concluded that the two products 'appear to be… functionally equivalent'.

The Panel noted that the press release mentioned the proteins' equivalent enzymatic activity and that the uptake of the products in fibroblasts was virtually indistinguishable. It was further stated that '*In vitro* data suggests that the two products are functionally equivalent'. The Panel noted Genzyme's submission that 'functional equivalence was not and should not be construed as a claim of clinical equivalence'. In the Panel's view the press release did not make this sufficiently clear. The Panel considered that the claim 'functionally equivalent' gave the impression that the *in vitro* data was of direct relevance and significance to the clinical situation and that was not necessarily so. Further, the impression was given that the products were clinically equivalent and this had not been shown. A breach of the Code was ruled. The Panel did not consider the claim to be inconsistent with the SPC as alleged. No breach of the Code was ruled.

Upon appeal by Genzyme, the Appeal Board noted that the claim at issue '[Fabrazyme and Replagal] are … functionally equivalent' was attributed to an *in vitro* comparison of the two products; however, the

author was more circumspect about their comparative functioning and stated that 'Based on the comparisons made to date, Fabrazyme and Replagal *appear* [emphasis added] to be structurally very similar and functionally equivalent'. The statement in the press release was thus more definite than the statement in the original paper. The Appeal Board considered that some readers would interpret the claim 'functionally equivalent' as meaning 'clinically equivalent'. The claim in question was not an accurate reflection of the data. Furthermore, the positioning of the claim in amongst clinical data and the linking of 'functionally equivalent' with issues of dosing in a later paragraph meant that it was likely to be interpreted by some as 'clinical equivalence'. Overall the Appeal Board considered that the claim was not a fair reflection of the data, it was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

TKT-5S noted that the licensed dose of active substance for Fabrazyme was 1mg/kg body weight (infused at a rate of 15mg/hour) five times that for Replagal which was to be given at 0.2mg/kg body weight (infused over 40 minutes). The claim 'the *in vitro* comparison of Fabrazyme with Replagal provides no biochemical evidence to support the lower dosing currently recommended for Replagal' was alleged to be misleading and effectively claimed that the dose of Replagal should be the same as that for Fabrazyme. Such a claim was untrue, clinically unsound and disparaged Replagal.

The Panel noted Genzyme's submission that both the EPARs and SPCs had different recommended doses at this early stage in clinical experience with enzyme replacement therapy in Fabry's disease; both EPARs indicated that the optimal dose had not yet been established. Nonetheless the Code required that material was not inconsistent with the SPC. The Panel noted the submission about the specialist clinical audience to whom the press release was directed. The Panel noted that the press release was placed upon the Internet and was thus widely accessible by the general public; it had not been directed towards a specialist audience. The Panel considered that the claim at issue implied that the licensed dosage regime for Replagal was incorrect and considered this was misleading and not capable of substantiation. A breach of the Code was ruled.

TKT-5S alleged that the claim in the press release that 'the reduction in pain observed at 6 months was maintained during the 18 months of additional treatment with Fabrazyme' was misleading and inconsistent with the particulars listed in the SPC for Fabrazyme. The Fabrazyme SPC stated that in a placebo controlled clinical trial and its extension 'Some improvement in the pain score was seen in the first six months, both in the placebo and active treated groups. In the active treated group the improved pain score stabilised during the 6 months of treatment thereafter'. The EPAR for Fabrazyme noted that the measurement of pain in the particular study referred to was a secondary end point and that an assessment of change of pain showed that in many of the pain score categories statistically significant improvements from baseline were observed but that this occurred in both the treatment group and in the placebo group.

TKT-5S considered that, given the statements in the SPC and the EPAR, the claim was exaggerated and misleading because it clearly implied that the pain reduction in the first six months was significant and material whereas according to a review of the data it clearly was not.

The Panel noted that the claim at issue referred to an open label phase 3 extension trial involving 58 patients. The reduction in pain was a secondary efficacy parameter. In many of the pain score categories statistically significant improvements from baseline were observed in both treatment groups. Pain was not a selection criterion and many of the older patients were at a stage of their disease where pain was minimal and almost 75% of patients assessed their pain at baseline as none or mild. Pain medication was allowed but no treatment algorithm had been predefined. However in the active treated group the improved pain score, although not statistically significant, stabilized during the first six months of the open extension study, thus suggesting an effect. The section 'discussion on clinical efficacy' stated that 12 month data available through the interim report from the uncontrolled extension study showed that 'some improvement in the pain score was maintained through one year of treatment… However none of these clinical parameters reached a statistical significant improvement. The lack of clear clinical benefit may be due to the fact that the patients were not selected on the basis of a particular symptom'. Longer follow up was needed. The Panel noted the statement in the Fabrazyme SPC that in relation to the placebo controlled trial 'some improvement in the pain score was seen in the first six months, both in the placebo and active treated groups. In the active treated group the improved pain score stabilised during the six months of treatment thereafter'.

The Panel considered that the claim at issue implied that a statistically significant reduction in pain was achieved at six months and this reduction was maintained over the following 18 month period and that was not so. The claim was misleading and inconsistent with the SPC. A breach of the Code was ruled.

TKT Europe-5S AB (TKT-5S) complained about the promotion of Fabrazyme (agalsidase beta) by Genzyme Inc and/or its group companies. TKT-5S supplied Replagal (agalsidase alfa). Both products were indicated for the treatment of the rare genetic disorder, Fabry's disease. The complaint was taken up with Genzyme Limited in the UK.

TKT-5S stated that the material at issue was a press release made by or on behalf of the Genzyme group on 3 December 2001, commenting on the proceedings of a symposium sponsored by the Genzyme group held in Barcelona on 29 November 2001 and entitled 'The Second European Roundtable on Fabry Disease'. TKT-5S stated that the press release was published

widely via the Internet and TKT-5S had obtained versions in English, French, German and Spanish and it had found the press release in identical terms on an Italian website, a French website and through a London based newswire service. The press release discussed Genzyme's product Fabrazyme, which was also a recently introduced enzyme replacement product for the treatment of Fabry's disease and a direct competitor to TKT-5S's product Replagal. The relevant part of the symposium proceedings and remarks made in a subsequent Genzyme teleconference were also the subject of complaint.

TKT-5S stated that the press release, the symposium proceedings and the teleconference, fell within the broad definitions of promotion in the Code. None of the materials published included any prescribing information.

Genzyme accepted that it had inadvertently breached the requirements of the Code by the omission of prescribing information. It apologised for this breach and had taken steps to ensure that it did not recur.

By way of introduction, Genzyme stated that Fabry's disease was a rare x-linked recessive glycosphingolipid storage disorder caused by a deficiency of the lysosomal enzyme α-galactosidase A (α-gal A). Sufferers lacked the ability to break down a glycosphingolipid substrate called Gb3. It was the accumulation of Gb3 in the body tissues which led to the symptoms of the disease.

Accumulation of Gb3 resulted in progressive impairment of tissue and organ function affecting many body systems including: neurological; dermatological; ocular; gastrointestinal; cardiac and renal systems. Onset was at birth. Organ system damage became apparent in adulthood, between 20 and 30 years. Patients experienced recurring episodes of neuropathic pain in the extremities and could expect to die in their 40s and 50s due to renal, cardiac, or cerebrovascular complications.

1 Claim (referring to Fabrazyme and Replagal) that 'the products are structurally very similar and functionally equivalent'

The press release referred to the two year data from the company's open label clinical trial extension study of Fabrazyme which were presented as were the results of the first reported comparative study of Fabrazyme and Replagal, the results of which showed that the products were 'structurally very similar and functionally equivalent'. Reference was made to the products' similar carbohydrate structures.

COMPLAINT

TKT-5S alleged that this claim was misleading and not substantiated and was thus in breach of Clauses 3.2, 7.2, 7.3 and 7.4 of the Code. There were significant differences between the two products. The chemical structure was different in that Replagal was an agalsidase alfa product whereas Fabrazyme was agalsidase beta. Replagal was a human α-galactosidase A produced by genetic engineering technology in a human cell line whereas the active substance of Fabrazyme was a human α-galactosidase A produced by recombinant Chinese hamster ovary cells. As a result of these differences of production system and glycosylation there were a number of express and deliberate differences in the summaries of product characteristics (SPCs) of the two products concerning efficacy and safety. An analysis of the specific differences in the Committee for Proprietary Medicinal Products (CPMP) opinions was provided.

The study which Genzyme used to support this claim of functional equivalence was an *in vitro* study and, as was well accepted, it could be seriously misleading to seek to draw clinical inferences from a limited *in vitro* study. In this respect, it should be noted that,

(i) there was CPMP guidance on the comparability of medicinal products containing biotechnology-derived proteins which stated that where a manufacturer sought to make a comparison with a product of another manufacturer, comparison based on testing and characterisation of drug substance and drug product was not sufficient to establish all aspects pertinent to the evaluation of quality, safety and efficacy for a biotechnology-derived product. An extensive comparability exercise was required depending on the nature of the drug substance and formulation and the complexity of its molecular structure. For each comparison the comparability strategy might require bridging studies to address the underlying issues relating to pre-clinical pharmacology/toxicology and clinical safety/efficacy and it should be recognised that where satisfactory comparability might not be demonstrable, a full pre-clinical and clinical data package would be required; and

(ii) the supplementary information relating to Clause 7.2 of the Code particularly stated that the use of data derived from *in vitro* studies required special care so as not to mislead as to its significance and that 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. There was no such data presented at the Barcelona symposium reporting the *in vitro* study. The study did, however, endorse the real and meaningful differences in the carbohydrate structure between Replagal and Fabrazyme.

The Code required that comparisons between products must be accurate, balanced, fair and objective and based on an up-to-date evaluation of all of the evidence. The evidence was clear that in respect of efficacy and tolerability the performance of Replagal was materially superior to that of Fabrazyme and, accordingly, the statement breached Clauses 3.2, 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Genzyme stated that in context this claim was part of the statement:

'The study, conducted by Genzyme, was designed to evaluate the bio-chemical properties of the two proteins *in vitro*. The results presented by the senior director of structural protein chemistry at Genzyme, showed that the products are structurally very similar and functionally equivalent.

[The director] reported that Fabrazyme and Replagal have identical amino acid sequences, and similar carbohydrate structures. He also stated that the proteins have equivalent enzymatic activity, and that uptake of Fabrazyme and Replagal in fibroblasts is virtually indistinguishable.'

Structural similarity

Short of identity, 'similarity' was a matter of degree. In the present case, Replagal and Fabrazyme were not identical; but it was the firmly held opinion of Genzyme that they were 'structurally similar' and 'functionally equivalent'; and that the complaint made in respect of this statement was misconceived.

Article 3(2)(2.1) of Commission Regulation 847/2000 contained the definition for the purpose of the EU orphan drug legislation of similarity. The relevant part read 'a similar medicine or product' or 'similar active substance' included the same macromolecule or one that differed from the original macromolecule only with respect to changes in the molecular structures such as proteinatious substances where the difference in structure between them was due to post translational events (such as different glycosylation patterns).

This echoed the FDA definition 'the same drug means ..... (ii) if it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to two different kinds of macromolecules: (A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior'.

Further analysis of those definitions as they applied to Replagal and Fabrazyme was provided; however, it was Genzyme's primary contention that consequent to the statutory definitions there could be no issue on structural similarity, and the following discussion was made without prejudice to that contention.

Enzymes were complex chemical entities. Different forms of an enzyme might have similar, or even identical activity. In Fabry disease, the key measure was the level of enzyme in the lysosomes. This was difficult – if not impossible – to measure in humans.

The two products in question were agalsidase alfa and agalsidase beta. The United States Adopted Names Council (USAN) approved similar names for these glycoproteins because they both contained the same amino acid sequence in the backbone, but the names differed because the USAN received different descriptions for the glycoform and noted that there was a different source for the glycoprotein. Genzyme had requested that USAN make available to it details of the specific differences in the glycoform: to date, the information had not been released by USAN.

By way of background to the question of the similarity between agalsidase alfa and agalsidase beta, Genzyme considered that it might be helpful to consider briefly an analogous situation, that of erythropoietin. Two products, erythropoetin alfa and erythropoetin beta, were available. Both were produced in Chinese hamster ovary (CHO) cells and had the same peptide sequence. The beta form had less sialylation (measured as a greater proportion of more basic isoforms in IEF, and greater binding to certain lectins specific for the non-sialylated form) and isoforms with higher *in vivo*:*in vitro* bioactivity ratios (the *in vitro* bioactivity levels were known to be related to the level of sialylation in these molecules). 'However, in spite of these noted differences, there have been no reports that epoetin alfa differs from epoetin beta in its clinical efficacy' (Storring *et al* 1993).

The amino acid sequence determined the chemical reaction catalysed by the enzyme: in the case of Fabrazyme and Replagal, the amino acid sequence was the same, and the fundamental chemical reaction catalysed by both was the same. In addition to amino acids both Fabrazyme and Replagal contained carbohydrate groups which were added post-translationally. Differences in the carbohydrate groups added gave rise to heterogeneity resulting in each product containing many different (although related) forms of the proteins. The proportions of these different glycoforms varied from batch to batch even for the same product, as well as between Fabrazyme and Replagal.

As a result of this heterogeneity, the products were not identical, for reasons which included: random variation, their differing sources (human fibroblasts in the case of Replagal, and CHO cells in the case of Fabrazyme) and the different purification procedures which might enrich different subpopulations of the glycoforms. Two questions were central to the statements made by Genzyme. What differences existed and of what clinical significance were these differences, if any?

Both agalsidase alfa and agalsidase beta were glycoproteins: glycoproteins were a group of proteins containing covalently linked carbohydrates. A protein was a macromolecule consisting of long sequences of α-amino acids (H_2N-CHR-COOH) in peptide (amide) linkage (elimination of water between the α-NH_2 and α-COOH of successive residues). The amino acids involved were generally the 20 α-amino acids recognised by the genetic code. The action of a protein was known to depend on its 3-dimensional structure as well as its amino-acid sequence. This 3-dimensional structure was determined by complex cross-linkages between parts of the protein molecule. Some differences in 3-dimensional structure affected the way in which a protein behaved; other differences, which might appear to be of a similar nature *in vitro*, had no effect on the way in which a protein behaved.

Both agalsidase alfa and agalsidase beta were enzymes, ie proteins that acted as a catalyst to induce

chemical changes in other substances, themselves remaining apparently unchanged by the process.

Glycoproteins (eg Fabrazyme and Replagal) were not single molecular entities, but comprised a heterogeneous population of different molecular glycoforms. In these isoforms, the covalently linked carbohydrates differed between molecules which were otherwise very similar chemically (and often functionally). While the type and extent of glycosylation was largely determined by the protein sequence when expressed in cells, depending on the source of the glycoprotein (eg yeast, bacteria, hamster, mouse or man), the proportions of various isoforms might differ, to a greater or lesser extent. However, the glycosylation machinery was more highly conserved among mammalian species (such as human and hamster) than between mammalian and non-mammalian species. In addition to this species difference, there might also be differences between individuals of the same species and, at least in relation to genetically engineered and recombinant technology, the conditions of culture.

Glycosylation affected biodistribution, uptake and clearance. In respect of agalsidase alfa and beta, there were three significant features of glycosylation in a dose: the degree to which mannose-6-phosphate was present, the ratio of sialic acid to galactose and the proportion of mannose-containing chains.

A final feature of note was that sialic acid might occur in two forms: N-acetyl neuraminic acid (NANA), the major form, found in human proteins, and N-glycolyl neuraminic acid (NGNA), which was not present on proteins isolated from human tissues. Although this form of sialic acid had been reported to be potentially immunogenic, this arose mainly from reports of serum sickness caused by a NGNA containing glycolypid and not a glycoprotein. Genzyme Transgenics Corporation had carried out clinical trials with transgenic antithrombin containing over 30% of its sialic acid in the N-glycolyl form without any indication of immunogenicity to the NGNA. Additional published evidence of a lack of an effect from NGNA came from examination of patient sera from 90 patients who had received multiple injections of erythropoietin (ESPO or EPOGIN) produced in CHO cells. Although these EPOs contained about 1% NGNA in total sialic acid content, they demonstrated little to no antibody response to this carbohydrate (Noguchi *et al*, 1996).

An earlier paper (Noguchi *et al*, 1995) was cited in an anonymous monograph apparently distributed by TKT-5S entitled 'Enzyme replacement therapies for Fabry disease. Two different products illustrating the importance of glycosylation'. The 1995 paper raised the potential of immunogenicity, though their initial tests with immunogenising chickens (also sensitive to the NGNA) had not found a high level of antibody response to EPO, though they did find an antibody response to fetuin containing 7% NGNA. The monograph did not cite the 1996 article from this research group which demonstrated that the same lack of response was also found in humans, as noted above. In fact, NGNA was not measurable in either Fabrazyme and Replagal.

The following similarities between Fabrazyme and Replagal were found in biochemical and *in vivo* testing:

- N-terminal sequence;
- enzymatic activity (including specific activity, K_m and V_{max}), measured with two different substrates;
- peptide map – an indication of similarity of the total amino acid sequence, with the exception of the glycopeptides (ie peptides with the carbohydrate sidechains attached, due to variations in the glycosylation, see below);
- IEF (Isoelectric focusing) – same range of bands seen;
- purity and appearance on SDS-PAGE gels (polyacrylamide gel electrophoresis) – one major band and one faint band at slightly lower molecular weight;
- little or no aggregation;
- lack of measurable N-glycolylneuraminic acid;
- general shape of serum clearance curves in Fabry KO (knock-out) mice and cynomologous monkeys;
- uptake into liver in Fabry KO mice (% of injected dose at a dose of 3 mg/kg);
- uptake into kidney and heart in Fabry KO mice when given the same dose of 3 mg/kg, based on label concentration (similar ranges mcg/g wet weight of tissue; data from only two animals at each of four timepoints).

The differences between Fabrazyme and Replagal centred on glycosylation and were in any event minor. In summary, the following differences between Fabrazyme and Replagal were seen in biochemical and *in vivo* testing:

Monosaccharides (the individual sugars in the chains). The same levels of sialic acid were seen, but the ratio of sialic acid to galactose was lower in Replagal than in Fabrazyme. This meant that there was a potential for a higher recognition of the Replagal by the asialoglycoprotein receptor in hepatocytes, although the evidence was that this had no effect. Similar liver uptake of Fabrazyme and Replagal was seen in *in vivo* biodistribution studies in Fabry KO mice.

Mannose-6-phosphate (M6P) levels seen in one lot tested were approximately 3-fold higher in Fabrazyme than in Replagal. The evidence was that this had no effect. There was lot-to-lot variability in the levels of M6P tested (for Fabrazyme this ranged from 3-5.7 moles/mole of dimer), with no apparent effect on clinical efficacy. With multiple receptors in the body (M6P, mannose, asialoglycoprotein) and different distribution of these receptors over cell types and organs, M6P levels were not the sole determinant for uptake into organs.

Oligosaccharides (chains of sugars). Replagal had higher level of complex chains; Fabrazyme had higher level of high mannose chains. The evidence was that this had no effect: there was no apparent difference in enzymatic activity or in uptake into various organs.

The differences between Fabrazyme and Replagal were very limited. Where they occurred, the molecular structure of Fabrazyme had characteristics that were generally more desirable on theoretical grounds and provided no basis for a claim that Replagal was structurally dissimilar in relevant respects and functionally to be preferred to Fabrazyme. The differences lay in the glycosylation patterns of these two products. The degree of glycosylation variability that existed between Fabrazyme and Replagal was comparable to that observed with other, single glycoproteins produced by the same cell line under different conditions of culture. For example, Storring *et al* gave examples of the types of variability seen from batch to batch of erythropoietins.

Genzyme referred to extracts from the European Public Assessment Reports (EPARs) for Fabrazyme and Replagal which provided further background information on issues relevant to the structural similarity between Fabrazyme and Replagal.

Summary on similarity

Genzyme stated that the Orphan Drug Regulations quoted above applied in the following ways:

- 'active substance' meant a substance with physiological or pharmacology activity, which applied to both Replagal and Fabrazyme;
- 'similar medicinal product' meant a medicinal product containing a similar active substance or substances as contained in a current authorized orphan medicinal product, and which was intended for the same therapeutic indication – Fabrazyme and Replagal both contained the active substance agalsidase, an enzyme intended to split Gb3 and were intended for the same therapeutic indication, namely Fabry's disease;
- 'similar active substance' meant an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acted via the same mechanism: the active ingredient of Replagal and Fabrazyme was agalsidase, and both acted via the same mechanism, although they were not identical;
- …the same macromolecule or one that differed from the original macromolecule only with respect to changes in the molecular structure such as: pertinacious substances where…the difference in structure between them was due to post-translation events (such as different glycosylation patterns)……These would normally be considered similar;
- Genzyme submitted that on the basis of the above, the relevant regulations defined Fabrazyme and Replagal as similar;
- Genzyme further submitted that irrespective of the regulations the two drugs were indisputably similar and there was no complaint to answer.

This was emphasised by the FDA definitions:

- same drug meant… large molecules (macromolecules), which applied to both Fabrazyme and Replagal;
- a drug that contained the same principal molecular structural features, which applied to Fabrazyme and Replagal since both were enzymes, with an identical amino acid backbone;
- but not necessarily all the same structural features, which applied to Fabrazyme and Replagal since they were not identical;
- and was intended for the same use, both Fabrazyme and Replagal were indicated for the treatment of Fabry's disease;
- …two protein drugs – Fabrazyme and Replagal were both protein drugs;
- …would be considered the same if the only differences in structures between them were due to…other potentially important differences, such as different glycosylation patterns…, the only (relevant) difference between Fabrazyme and Replagal being glycosylation and no other relevant differences applying;
- would not cause the drugs to be considered different unless the differences were shown to be clinical superior. As to clinical superiority, Genzyme submitted that granting both Fabrazyme and Replagal orphan drug status was evidence of the EMEA's inability to identify that one drug was clinically superior to the other.

Therefore, Genzyme submitted, these two orphan drugs were, according to the relevant regulations in the US, statutorily the 'same' and that a claim for similarity was a conservative claim.

Alleged breach of Clause 3.2

When comparing Fabrazyme and Replagal, Genzyme had focused on the structure of the enzymes (amino acid sequence, MW from SDS-PAGE, peptide map, carbohydrate structures) as well as measures of activity and cellular/tissue uptake (see section on functional equivalence below). These tests were taken from the list of biochemical tests which Genzyme had developed, in conjunction with the regulatory reviewers from both the US and the EU, to demonstrate the comparability of its own product after any change. The purpose of these tests was to allow Genzyme to demonstrate equivalence of a product to products previously tested in clinical trials in order to avoid having to repeat clinical trials after a manufacturing change. Although the rationale of collecting the data presented in this document was not to compare different pharmaceuticals, Genzyme submitted that in the circumstances it was entirely reasonable to use them for this purpose.

Manufacturing pharmaceuticals using CHO cells was well-established. For example, Genzyme had 10 years experience with Cerezyme, a treatment for Gaucher's disease which was closely analogous to Fabrazyme. CHO cells lines were also used to produce other medicines; for example, recombinant erythropoietin which was used to treat renal disease-induced anaemia and tissue plasminogen activator which was used to rapidly break down life-threatening blood clots in myocardial infarction and strokes. These CHO-cell derived products were clinically satisfactory

and used to treat thousands of patients world-wide. In fact, although TKT-5S had implied that Fabrazyme was inferior to Replagal because the former was produced in CHO cells and the latter in human cells, the use of genetically altered human cells was not an established technique and, indeed, carried some specific theoretical risks (eg viral transmission). Basing an argument for structural difference on the difference in cells used to produce the two pharmaceuticals was potentially misleading:

- CHO cell-derived medicines were widely used and did not cause the problems explicitly and implicitly alleged;
- the use of human fibroblasts was new and not well-established and might have consequences which were not yet known;
- the use of human cells to produce pharmaceuticals carried some theoretical risks which did not apply to non-human cells;
- the measured differences were small;
- there was no evidence that the measured differences had any clinically significant consequences.

In respect of the alleged breach of Clause 3.2, Genzyme therefore submitted that the claim of 'structural similarity' was in accordance with the regulations governing orphan drugs (both Fabrazyme and Replagal had orphan drug status), in terms of the marketing authorizations of both Fabrazyme and Replagal and was not inconsistent with the particulars listed in the products' SPCs. Genzyme did not accept that there had been any breach of Clause 3.2 in respect of the claim of 'structural similarity'.

Alleged breach of Clause 7.2
On the basis of the material presented above, Genzyme maintained that its statement that Fabrazyme and Replagal were 'structurally very similar' was accurate, balanced, fair, objective, unambiguous, and based on an up-to-date evaluation of all the evidence, and reflected that evidence clearly. The statement was not misleading directly or by implication. Genzyme did not accept that there had been any breach of Clause 7.2 of the Code in respect of the claim of 'structural similarity'.

Alleged breach of Clause 7.3
The material was not misleading, and – see also the discussion on functional equivalence below – compared material, relevant, substantiable and representative features of the two products. No confusion was created between Fabrazyme and Replagal, since Genzyme had consistently made clear the basis on which the statements were made. Genzyme did not accept that there had been any breach of Clause 7.3 of the Code in respect of the claim of 'structural similarity'.

Alleged breach of Clause 7.4
The claim was capable of substantiation, and Genzyme had made available publicly the relevant information. Genzyme did not accept that there had been any breach of Clause 7.4 of the Code in respect of the claim of 'structural similarity'.

In respect of TKT-5S's grounds for complaint, Genzyme submitted that the SPCs for Fabrazyme and Replagal were not relevant to the claim of 'structural similarity'. The possible relevance of the SPCs and EPARs for Fabrazyme and Replagal to the claim of functional equivalence were considered below.

Functionally equivalent

Significance of orphan drug status
Genzyme stated that Fabrazyme and Replagal had joint orphan drug status. That status was designed to provide exclusivity for 10 years to manufacturers developing medicines which had a limited market because of the rarity of a disease (such as Fabry's disease). Because of this intention, orphan drug status was – self-evidently – normally granted to one product. The fact that both the products were registered as orphan medicinal products by the European Medicines Evaluation Agency (EMEA) was unique.

This ten-year exclusivity could only be disregarded if it was scientifically demonstrated that another product was safer and more effective than the existing orphan medicinal product. The registration dossiers for Fabrazyme and Replagal were submitted on the same day. The EMEA was apparently unable to decide on the basis of the available results as to which of the two products was better, safer or more effective. If it had decided that Replagal was safer and more effective, the EMEA could easily have assigned Replagal the status of orphan medicinal product and granted it market exclusivity for a period of ten years. Precisely because the trials on which the registration dossiers were based were so different, the EMEA was unable to determine which of the two products was more effective.

It was Genzyme's first contention that the direct conclusion to be drawn from orphan drug status was that Fabrazyme and Replagal were functionally equivalent.

The demonstration of structural similarity was not, in itself, sufficient to assume functional equivalence. The claim of 'functional equivalence' was based on further data, which was outlined below.

Functional equivalence was based on two factors
Was the fundamental mode of action of Fabrazyme equivalent to that of Replagal? As both were enzymes, this question reduced to whether the amino acid backbone of the two products was the same. Independent evidence, including that of the EPARs for the two products, confirmed the identity of the two products in respect of their amino acid backbone.

Whether the pharmacokinetics of the two products differed to the extent that they would not (in equivalent doses delivered over the same timescale in the same way) be available to – and taken up by – the target tissues to an equivalent degree.

Introduction to argument for functional equivalence
A claim of 'functional equivalence' was not, and should not be construed as, a claim of 'clinical equivalence'. The statement that Fabrazyme was structurally similar and functionally equivalent to

Replagal was clearly based on *in vitro* and non-human *in vivo* data. Genzyme recognised that extrapolating from such data to the clinical situation was not straightforward. However, although Genzyme was not making a claim of clinical equivalence, it submitted that in the context of Fabry's disease and the available treatments, *in vitro* and non-human *in vivo* data were highly relevant to the decisions which needed to be taken, today, by patients and their doctors. The applicability of *in vitro* and non-human *in vivo* data to these decisions was considered below.

Summary of points of functional equivalence
Both medicines were granted orphan drug status for treatment of Fabry's disease. As stated above, the EMEA was apparently unable to decide on the basis of the available results which one of the two products was better, safer or more effective and it took the unique step of assigning orphan drug status to both Fabrazyme and Replagal – reflecting its inability to reach a conclusion on these criteria.

Both Fabrazyme and Replagal reached the relevant organs (heart, kidney) and similar uptake was seen in the liver (% administered dose).

Mannose was also of potential importance in determining functional equivalence, because mannose receptors, present mainly on tissue macrophages, rapidly cleared glycoproteins containing oligomannose chains from the circulation. This aspect of glycosylation was not significantly different between Fabrazyme and Replagal.

General shape of serum clearance curves in Fabry KO (knock-out) mice and cynomologous monkeys indicated similar pharmacokinetics.

Uptake into liver in Fabry KO mice (% of injected dose at a dose of 3mg/kg). In respect of % injected dose found in the liver at various timepoints, there were differences which reached statistical significance at 4 hours and 8 hours, but not at 1 hour or 24 hours. The biological significance of these (small) differences was minimal.

Uptake into kidney and heart in Fabry KO mice when given the same dose of 3mg/kg, based on label concentration (similar ranges mcg/g wet weight of tissue; data from only 2 animals at each of four timepoints).

Reduction of Gb3 in a dose-dependent manner in liver, heart, spleen, plasma, skin and kidney for Fabrazyme and in liver, heart and kidney for Replagal in Fabry knock-out mouse model.

Summary of points of functional non-equivalence
The ratio of sialic acid:galactose (which measured the tendency for enzyme to be bound to hepatocytes in the liver and the amount of enzyme available for target organs and cell types – the higher the ratio, the less bound the enzyme) was 0.88 for Fabrazyme and 0.56 for Replagal. That was, in terms of sialylation, Replagal was not to be preferred to Fabrazyme on *a priori* grounds.

The level of M6P on Fabrazyme was approximately 3 times higher than that present on Replagal (5.7moles/mole vs. 1.9 moles/mole respectively). The higher the level of M6P, the greater the extent to which the enzyme was taken up by cells with the mannose-6-phosphate receptor, and where the replacement enzyme could act to reduce these levels. Again, in terms of M6P, Replagal was not to be functionally preferred to Fabrazyme on *a priori* grounds.

Summary – functional equivalence
In summary, the data showed that Replagal's pharmacokinetics were no more favourable than, and possibly less favourable than, those of Fabrazyme. In this respect, Genzyme's claim that Fabrazyme and Replagal were 'functionally equivalent' was in fact a conservative claim. This reflected Genzyme's wish to promote a responsible scientific debate concerning issues which were vital to the decisions which Fabry's patients and their doctors made. The earlier discussion of structural similarities confirmed that agalsidase alfa and agalsidase beta had identical modes of action, and the pharmacokinetic data confirmed that the dynamic interaction between these two products and non-human *in vivo* models favoured Fabrazyme rather than Replagal. On this basis it could fairly be said of Fabrazyme that it was 'structurally similar and functionally equivalent' to Replagal.

Clause 3.2
In respect of the alleged breach of Clause 3.2, Genzyme submitted that the claim of 'functional equivalence' was in accordance with the terms of the marketing authorizations of both Fabrazyme and Replagal and was not inconsistent with the particulars listed in the SPCs for Fabrazyme and Replagal. Genzyme did not accept that there had been any breach of Clause 3.2 in respect of the claim of 'functional equivalence'.

Clause 7.2
On the basis of the material presented above, Genzyme maintained that its statement that Fabrazyme and Replagal were 'functionally equivalent' was accurate, balanced, fair, objective, unambiguous, and based on an up-to-date evaluation of all the evidence, and reflected that evidence clearly. The statement was not misleading directly or by implication. Genzyme did not accept that there had been any breach of Clause 7.2 in respect of the claim of 'functional equivalence'.

Clause 7.3
The material was not misleading, and – see also the discussion earlier on structural similarity – compared material, relevant, substantiable and representative features of the two products. No confusion was created between Fabrazyme and Replagal, since Genzyme had consistently made clear the basis on which the statements were made. Genzyme did not accept that there had been any breach of Clause 7.3 in respect of the claim of 'functional equivalence'.

Clause 7.4
The claim was capable of substantiation, and Genzyme had made available publicly the relevant information in its possession: other information were matters of public record. Genzyme had at all times

been clear as to the information on which its statements were based. Genzyme did not accept that there had been any breach of Clause 7.4 in respect of the claim of 'functional equivalence'.

Extrapolation from in vitro and non-human in vivo data

Genzyme noted Clause 7.2 of the Code and its supplementary information with regard to the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals. In specifying the need for care it was implicit that there were circumstances in which *in vitro* comparison was appropriate. Genzyme's submission was that the circumstances in which its claims were made were such that the *in vitro* data used were entirely appropriate, reasonable, and consistent with the both the spirit and the letter of the Code.

In the circumstances relevant to the complaint, the use of *in vitro* and non-human *in vivo* data was legitimate and necessary, and in promoting discussion of the significance of such data, Genzyme had acted wholly appropriately and responsibly. The relevant issues were:

- until 3 August 2001, the only licensed pharmaceuticals available for Fabry's disease patients were symptomatic and palliative treatments;
- on 3 August 2001, two treatments (Fabrazyme and Replagal) received marketing authorizations from the EMEA, with identical indications – the long-term treatment of Fabry's disease;
- both products were intended to mimic the action of the enzyme missing in Fabry's disease patients;
- the trials for Fabrazyme and Replagal, on which their respective marketing authorizations were granted, had different designs. For example, the primary endpoint of the pivotal trial for Fabrazyme was reduction in the level of the abnormal metabolite (Gb3) in the microvasculature of the kidney, reflecting the importance of renal failure in the increased morbidity and reduced life expectancy experienced hitherto by Fabry's disease patients; the primary endpoint of the pivotal trial for Replagal was reduction in neuropathic pain. Patients were selected for the two trials on different criteria (for example, in the Fabrazyme trial pain was not a selection criterion, whereas in the Replagal trial patients were excluded if they did not have neuropathic pain). The protocols of the two trials differed: for example, in respect of pain, patients (including the placebo group) in the Replagal trial were required to stop all neuropathic pain medications at baseline, and at weeks 8, 16 and 23; by contrast, in the Fabrazyme study, both groups of patients were allowed to continue pain medication as they and their doctors wished;
- with respect to pain, which was the primary endpoint in the Replagal trial, but only one of a number of secondary endpoints in the Fabrazyme trial, the placebo group in the Replagal trial showed no reduction in pain, whereas the placebo group in the Fabrazyme trial showed a substantial reduction in pain. Because of this, the difference between the Fabrazyme-treated group and the placebo group was not statistically significant, whereas the difference between the Replagal-treated group and the placebo group was statistically significant;
- while accepting fully the standard methodology for assessing the results of clinical trials, Genzyme submitted that an important issue arose if any doctor, seeking to identify the best treatment for a Fabry's disease patient, compared – as (s)he had to do – the information available on the only two enzyme replacement therapies available. A key therapeutic question was the extent to which any difference in the trial results reflected differences in trial design, random variables and possible systematic bias rather than intrinsic differences between Fabrazyme and Replagal;
- the design of the two pivotal trials did not permit direct comparison between Fabrazyme and Replagal. Investigators, not associated with Genzyme, were currently conducting a head-to-head trial of Fabrazyme and Replagal. It would be recognised that, meanwhile, such choices had to be made by doctors and patients on the basis of the present state of knowledge, which was not as complete as Genzyme would wish and involved indirect comparisons;
- untreated, Fabry's disease caused significant morbidity and a substantial reduction in life expectancy. Now that two enzyme replacement therapies were available, there was a powerful incentive not to leave patients without treatment until more definitive clinical trial results were available, and a pressing reason to choose between the two therapies;
- marketing authorizations for both products were granted on an exceptional basis, recognising the therapeutic breakthrough which enzyme replacement therapy offered these patients. Both marketing authorizations therefore noted that further work needed to be done on safety and efficacy, and on optimal dosage, reflecting the (incomplete) state of current knowledge despite which the EMEA felt that marketing authorizations should be granted. It was a condition, equally, of both marketing authorizations, that the holders should conduct further studies.

In this context, therefore, Genzyme submitted that it was important to use all available data to make informed medical decisions in the best interests of the patient. In an orphan disease where trials were relatively small the ability to answer the question as to how the enzymes compared with a large randomised clinical trial was limited. In this setting patients and physicians made decisions by piecing together evidence. How these enzymes compared *in vitro* and in animal studies represented important pieces of evidence. These experiments alone did not prove clinical comparability. However, in this case, the results were clear and supported the position that

the *in vitro* and *in vivo* animal experiments suggested these enzymes were structurally similar and functionally equivalent. While care was still required in extrapolating *in vitro* and non-human *in vivo* data to the clinical situation, using such data was necessary if vital clinical decisions were to be taken on the basis of current, incomplete, knowledge. The quality of those decisions would continue to improve as more data became available.

The context therefore required doctors and patients to use data that was not derived from clinical trials as well as data that was derived from the two trials conducted to date. Fortunately, however, the extrapolation of *in vitro* and non-human *in vivo* data for enzymes was well understood, and standard proxy measures for enzymic activity were available.

The International Conference on Harmonisation Guidance on specifications referred to test procedures and acceptance criteria for biotechnological and biological products:

'An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect. A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include: Animal-based biological assays, which measure an organism's biological response to the product; Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level; and Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.'

The FDA also issued guidance for bioassays used to demonstrate the comparability of human biological products:

'Bioassays are functional tests which sponsors should use to assess the activity/potency of the product. These tests may also serve as measurements of the biological integrity (e.g., correct conformation) of the product and thus complement other analytical measurements. Sponsors should validate these assays and have a specific range of acceptable values for defining product activity. They may include appropriate *in vitro* tests (e.g. cell growth, enzymatic activity, anti-viral assays, infectivity assays) or *in vivo* tests in relevant animal models. If the *in vivo* mechanism of action of the product is known, the bioassay (when possible) should reflect this activity.'

The *in vitro* tests of enzymatic activity used to support Genzyme's arguments were generally accepted as being reasonable proxy measures for *in vivo* activity – which was not, of course, the situation for most pharmaceuticals.

In the case of Fabry's disease, the (single) metabolic defect was well understood. Fabry's disease was a single enzymatic defect, which led to accumulation of Gb3 or ceramidetrihexoside, an intermediate in the catabolism of globoside (2-acetamide-2-deoxygalactosylgalatosyl-galactosyl-glucosyl-ceramide), the major glycosphingolipid in the red-cell membrane and kidney. It was generally agreed that the steady accumulation of Gb3, particularly in the vasculature, resulted in cardiovascular disease, ocular abnormalities, attacks of fever and burning pain in the extremities, and dysfunction of the central nervous system and gastrointestinal and GI tract.

The following extracts from the EPARs of Fabrazyme and Replagal confirmed that the cause of Fabry's disease, and therefore the therapeutic objective, were understood and agreed:

> Because the accumulation of sphingolipids is regarded as the cause for the disease and its clinical presentation, the pharmacodynamic results indicate that a clinical improvement or stabilisation among patients is to be expected. However, a concluding positive assessment of efficacy is not possible based on the pharmacodynamic results alone. (EPAR for Fabrazyme).
>
> The characteristic histopathological finding in Fabry disease is the accumulation of sphingolipids, ultimately leading to the morbidity associated with this disorder. The demonstrated reduction of these tissue deposits may be indicative for a clinical improvement or a stabilisation of the clinical condition. (EPAR for Fabrazyme).
>
> Fabry Disease is a rare X-linked recessive glycosphingolipid storage disorder that is caused by deficient activity – subnormal or absent – of the lysosomal enzyme, α-galactosidase A. This leads to progressive accumulation of neutral GB3, predominantly Gb3 in most tissues and cell types. Due to lack of functioning α-galactosidase A, there is an abnormal accumulation and tissue deposition of the Gb3 especially in the kidney, heart and nervous system. At present, there is no treatment available for the disease, other than palliative care. (EPAR for Replagal).
>
> These data indicate that agalsidase alfa is capable of decreasing the sphingolipid accumulation in the tissue. Because the accumulation of sphingolipids is regarded as the cause for the disease and its clinical presentation, the pharmacodynamic results indicate that a possible clinical improvement or stabilisation among patients is to be expected. However, a concluding positive assessment of efficacy is not possible based on the pharmacodynamic results alone. (EPAR for Replagal).

Fabry's disease, therefore, resulted from the complete or relative lack of a single natural enzyme, which Fabrazyme and Replagal were intended to replace. It was generally agreed that the replacement of this enzyme would break down the abnormal metabolite that had accumulated, and that this would lead to clinical improvement. Still to be determined, as the marketing authorizations for Fabrazyme and Replagal recognised, were the optimal dose, the optimal time at which to commence treatment, and the degree to which the deleterious effects of accumulated Gb3 could be reversed. Nevertheless, in this context, the structural and functional data on enzymatic activity had a well understood proxy relationship with predictable clinical effects. In all the circumstances,

and until more data became available from clinical trials, Genzyme submitted that the use of *in vitro* and non-human *in vivo* data was appropriate for patients and their doctors; and the promotion of debate on this basis as to the relative merits of Fabrazyme and Replagal was entirely appropriate and proper for the manufacturer of either of these products.

As described earlier, Genzyme's experience over a decade with Gaucher's disease (which offered a useful analogy to enzyme replacement therapy (ERT) in Fabry's disease) had indicated that although the mechanism of action of ERT was clear, the optimum dose for an individual patient could not be established unequivocally according to standard dosages, and remained in part a subjective judgement by the treating physician.

Summary as to use of in vitro data

In all these circumstances – the clear causal chain underlying morbidity in Fabry's disease, the single mode of action of Fabrazyme and Replagal, established methods of measuring enzyme activity *in vitro*, the limited clinical experience to date, and more long-standing experience in an analogous situation (Gaucher's disease) – Genzyme submitted that its use of *in vitro* data had been entirely appropriate and legitimate.

In response to requests for further information Genzyme stated that the press release was created by Genzyme Corporation, the US parent. It was circulated by PR Newswire on its website and was directed to the medical press. It was not directed to members of the UK health professions neither was there any encouragement for them to visit the website for the purpose of seeing the press release. It was not circulated in hard copy.

The phase 3 clinical trial extension data was in a draft paper submitted for publication, this included additional data, a copy was provided.

PANEL RULING

The first issue to be determined was whether the press release was subject to the Code.

The Panel noted that the press release was created by the American parent company, the Genzyme Corporation. It was an established principle under the Code that UK based companies were responsible for activities in the UK of their overseas parent. The Genzyme Corporation had circulated the press release via a European UK based news agency which had placed it on its website on a UK server on 3 December 2001 in English, German, French and Spanish. It was not circulated as a hard copy. TKT-5S had provided further copies which did not appear to come from the news agency website. The press release was not directed towards members of the UK health professions. Given all the circumstances the Panel decided that the press release was subject to the UK Code.

In relation to the claim in the press release that the products were structurally similar the Panel noted that Fabrazyme and Replagal were both human α-galactosidase A glycoproteins, produced by recombinant Chinese Hamster Ovary cells and human cell lines respectively. They were not structurally identical. The Panel noted the submission that the amino-acid sequence in the backbone was the same. *In vivo* testing indicated that the peptide map was similar ie the total amino acid sequence with the exception of the glycopeptides. The Panel noted the list of 10 structural similarities provided by Genzyme. The differences resulted from differing glycosylation patterns. The Fabrazyme SPC stated that the amino acid sequence of the recombinant form, as well as the nucleotide sequence which encoded it were identical to the natural form of α-galactosidase.

The Panel also noted the references to the Orphan Drug Regulations and relevant FDA definitions.

The Panel did not agree with TKT-5S's statement that the evidence was clear that in respect of efficacy and tolerability Replagal was materially superior to Fabrazyme. There was no data directly comparing the medicines.

The Panel considered that the nature and extent of the similarities were such that 'structurally very similar' was not an unreasonable description; the claim was not misleading or unsubstantiable on this point or inconsistent with the SPC as alleged. No breach of Clauses 3.2 7.2, 7.3 and 7.4 was ruled.

The Panel noted that the press release mentioned 'functionally equivalent' in relation to the results of an *in vitro* comparative study of Fabrazyme and Replagal the results for which appeared in the Barcelona Roundtable Report. The report stated that in relation to a comparison of enzyme kinetics in substrate assays there was no significant difference between the two products for the rate of substrate hydrolysis, the concentration of substrate at which the reaction rate was half its maximal value and the products' specific activities. There were numerical between group differences in relation to each component of the monosaccharide analysis, however the statistical significance of these differences were not stated. The introduction section stated that biochemically and structurally, the two enzymes were 'highly similar'. The author concluded that the two products 'appear to be… functionally equivalent'.

The Panel noted the supplementary information to Clause 7.2 of the Code regarding the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals which 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 Panel noted the submission of TKT-5S on the CPMP guidance on the comparability of medicinal products containing biotechnology-derived proteins and Genzyme's submission about the products' orphan drug status and summary of points of functional non-equivalence.

The Panel noted that the press release mentioned the proteins' equivalent enzymatic activity and that the uptake of the products in fibroblasts was virtually indistinguishable. It was further stated that '*in vitro*

data suggests that the two products are functionally equivalent'.

The Panel noted Genzyme's submission that 'functional equivalence was not and should not be construed as a claim of clinical equivalence'. In the Panel's view the press release did not make this sufficiently clear. The Panel considered that the claim 'functionally equivalent' gave the impression that the *in vitro* data was of direct relevance and significance to the clinical situation and that was not necessarily so. Further, the impression was given that the products were clinically equivalent and this had not been shown. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled. The Panel did not consider the claim to be inconsistent with the SPC as alleged. No breach of Clause 3.2 was ruled.

APPEAL BY GENZYME

Genzyme noted that the Panel had ruled that the statement that Fabrazyme and Replagal were 'structurally very similar' was not misleading or unsubstantiable or inconsistent with the Fabrazyme SPC. Consequently, the structural similarity statement did not breach the Code. However, the Panel upheld the complaint that the statement (contained in the same sentence as the structural similarity statement) that the products were 'functionally equivalent' breached Clauses 7.2, 7.3 and 7.4 of the Code. The functional equivalence statement was, however, ruled not to be in breach of Clause 3.2 of the Code. The Panel had therefore acknowledged that Fabrazyme and Replagal were structurally very similar, were authorised for use in relation to the same medical condition and that the functional equivalence statement was not inconsistent with the SPC for Fabrazyme. It was Genzyme's contention that the functional equivalence statement was entirely compatible with these observations. In particular the functional equivalence statement was clearly related to considerations of structure and function of Fabrazyme and Replagal at the molecular level. Genzyme therefore appealed the Panel's rulings of breaches of the Code in respect of the functional equivalence statement.

It was Genzyme's case that the functional equivalence statement, properly construed in its full context, did not support an interpretation which implied that Fabrazyme and Replagal were clinically equivalent or must be administered according to an identical dosing regime. Genzyme acknowledged that care should be taken with the presentation of *in vitro* data in support of any statement in respect of a pharmaceutical product. It was for that reason that the statement was presented in the following context:

'The study, conducted by Genzyme, was designed to evaluate the biochemical properties of the two proteins *in vitro*. The results, presented by Timothy Edmunds PhD, Senior Director of Structural Protein Chemistry at Genzyme, showed that the products are structurally very similar and functionally equivalent.'

Genzyme submitted that by fully stating the *in vitro* experimental context of the statement, in particular the design of the study and the specialisation of the presenter, it had eliminated any likelihood that lay readers might interpret the statement as being based on an *in vivo* study or clinical trial.

The claim of functional equivalence was not, and should not be construed as a claim of clinical equivalence. However, Genzyme submitted that in the context of Fabry's disease and the available treatments, *in vitro* and non-human *in vivo* data were highly relevant, given the rarity of the condition, to the decisions which needed to be taken by patients and their doctors.

At the date of the complaint, the dosing regimes for Fabrazyme and Replagal were not finalised. Genzyme made the functional equivalence statement in the context of ongoing experimental research into the structure and behaviour of Fabrazyme and Replagal. The research on which the functional equivalence statement was based represented a valuable contribution to the scientific debate which might ultimately decide the appropriate dosing for both products.

Genzyme acknowledged that the Panel must rule that there had been breaches of the Code where *in vitro* data were wrongly relied upon to back up clinical claims. However, it submitted that, for the reasons given above, the functional equivalence statement did not fall into that category and therefore the appropriate finding was that there had been no breach of the Code.

In the event that the Panel's ruling on the functional equivalence statement reflected a view that Fabrazyme and Replagal were not functionally equivalent or that Genzyme was not justified in claiming that they were on the basis of *in vitro* data, then Genzyme relied on the following submissions and evidence.

Genzyme submitted that, as a matter of fundamental protein chemistry, Fabrazyme and Replagal were demonstrably functionally equivalent. Both products were enzymes ie proteins that acted as a catalyst to induce chemical changes in other substances, themselves remaining apparently unchanged by the process. The amino acid sequence in an enzyme determined the chemical reaction catalysed by it. In the case of Fabrazyme and Replagal, the amino acid sequence and the fundamental chemical reaction catalysed by both was the same. The Panel had already acknowledged the products' identical amino acid sequences in its ruling on the issue of structural similarity. Furthermore, Fabrazyme and Replagal had, uniquely, been granted simultaneous orphan medicinal product status by the EMEA. Orphan drug status normally provided exclusivity for 10 years to manufacturers developing medicines for rare diseases and was granted to only one product. The 10 year exclusivity could only be disregarded if it was demonstrated scientifically that another product was safer and more effective than an existing orphan drug. The registration dossiers for Fabrazyme and Replagal were submitted on the same day. If the EMEA had been able to decide on the basis of the available results which of the two products was better, safer or more effective, orphan status would have been granted to one product and not the other. Genzyme submitted that the conclusion to be drawn from the

simultaneous grant of orphan drug status by the EMEA was that Fabrazyme and Replagal were functionally equivalent.

Genzyme stated that it further relied on the *in vitro* and non-human *in vivo* experimental observations set out in detail in its original response to TKT-5S' complaint, the key points of which were:

- both Fabrazyme and Replagal reached the relevant organs (heart and kidney) and similar uptake was observed in the liver;
- the general shape of serum clearance curves in Fabry KO (knock-out) mice and cynomologous monkeys indicated similar pharmacokinetics;
- uptake of Fabrazyme and Replagal into the kidney and heart of Fabry KO mice exhibited similar ranges of mg/g wet weight of tissue;
- reduction of Gb3 in a dose-dependent manner in liver, heart, spleen, plasma, skin and kidney for Fabrazyme and in liver, heart and kidney for Replagal in Fabry KO mice;
- the pattern of mannose glycosylation was not significantly different between Fabrazyme and Replagal which was of potential importance in determining functional equivalence since mannose receptors, presented mainly on tissue macrophages, rapidly clearing glycoproteins containing oligomannose chains from the circulation.
- For these reasons it could properly and fairly be said of Fabrazyme that it was structurally very similar and functionally equivalent to Replagal.

Genzyme stated that on the basis of the above it maintained that its claim that Fabrazyme and Replagal were functionally equivalent was accurate, balanced, fair, objective, unambiguous and based on an up-to-date evaluation of all the evidence, and reflected that evidence clearly. The statement was not misleading directly or by implication. In addition the claim was not misleading and compared material relevant, substantiable and representative features of the two products. No confusion was created between Fabrazyme and Replagal since Genzyme had consistently made clear the basis on which the statements were made. The claim was capable of substantiation and Genzyme had made available publicly the relevant information in its possession. Other relevant information was in the public record. Genzyme had at all times been clear as to the information on which its statements were based. In conclusion Genzyme denied that the claim was in breach of Clauses 7.2, 7.3 or 7.4 of the Code.

COMMENTS FROM TKT-5S

TKT-5S stated that its complaint was about the claim 'structurally very similar and functionally equivalent' as a single statement which it considered to be misleading in its entirety. In its response Genzyme had devised a lengthy argument for each leg of the statement separately and the Panel responded to the implicit invitation by making two separate and different findings. It had always been TKT-5S's contention that the functionally equivalent claim had a clear meaning and was intended to have the meaning that when 'functioning' in the patient Fabrazyme was the same as Replagal. A comparison of the respective SPCs for Replagal and Fabrazyme showed that the documented clinical effects were materially different one from the other.

Differences in clinical efficacy

Although the respective efficacy of Replagal and Fabrazyme had been investigated for similar lengths of time in placebo controlled clinical trials, Replagal was the only enzyme replacement product that had documented clinically significant benefits compared with placebo, as described below. For Fabrazyme, the EPAR stated that: 'The demonstrated reduction of sphingolipids (Gb3) in the target organs is encouraging and may be indicative for a clinical improvement or a stablisation of the clinical condition. However, although positive trends were observed for the clinical parameters investigated as secondary endpoints, none of these parameters reached a statistically significant improvement'.

Replagal, by contrast, in six month, double-blind, placebo controlled studies followed by open label extension studies of up to 18 months of treatment had been shown to have the following important beneficial effects on the major manifestations of Fabry disease, as documented in the SPC and EPAR.

Differences in clinical safety

Replagal was associated with infusion reactions in approximately 10% of patients. Most of those reactions had been mild. This compared with 50% of patients who experienced adverse reactions on the day of infusion with Fabrazyme. There was a boxed warning in the SPC for Fabrazyme giving guidance for management of patients experiencing mild, moderate or severe hypersensitivity reactions.

In addition, immune responses (IgG antibodies) occurred in over 80% of patients given Fabrazyme compared with 55% of patients given Replagal. After twelve to eighteen months of therapy with Replagal, over 80% of the patients who were antibody positive showed evidence of the development of immunological tolerance.

Importantly, since publication of the SPC and EPAR for Fabrazyme, Professor R J Desnick (New York, USA) had reported two patients who had stopped treatment because of confirmed IgE antibodies to Fabrazyme, a clinically significant risk factor (38th Conference on Genetics, New Perspectives in Glycosomal and Peroxisomal Disorders, 17th-19th January 2002, Porto, Portugal). This report had subsequently been confirmed by Genzyme.

Dosing differences and home treatment

The significant clinical effects of Replagal were achieved with an intravenous infusion of 0.2mg/kg every two weeks over an infusion time of 40 minutes.

By contrast, the recommended dose of Fabrazyme was 1mg/kg every two weeks with an initial infusion rate of 15mg/hour. This meant a total infusion time approaching 4.7 hours for an individual weighing 70kg. In patients with infusion reactions, even a single mild to moderate event, the infusion rate

should be decreased to 10mg/hour, that was, a 7 hour infusion for a 70kg patient. The infusion rate might be increased gradually in patients on Fabrazyme who did not experience infusion reactions. However, even in these patients, the total infusion time could not be less than 2 hours in order to minimise the potential occurrence of hypersensitivity reactions.

The safety profile of Replagal and the short time needed for infusion had led to home treatment being the norm in several countries.

TKT-5S noted that there was no reference anywhere in the press release to 'molecular level'; if Genzyme had intended at the time to limit the functional equivalence claim to the molecular level, as it now argued for the purposes of this appeal, it surely would have included such a reference explicitly.

TKT-5S noted that Genzyme, in its appeal, unlike in its original response, relied on the words which it stated qualified the explicit or implicit meaning of the expression 'functionally equivalent' so that it referred only to the biochemical/molecular properties of the two products. The plain meaning of the words must, in TKT-5S's view, only refer to the clinical characteristics of the products for why else had the distinction been made between structural similarity and functional equivalence? Description of the biochemical functioning of the substance, at the molecular level, only served to illustrate molecular structure and not what the substance did. Although there were no controlled comparative trials, and therefore no equivalence data, the clinical efficacy and safety data, as described above, did not give any justification whatsoever for functional equivalence.

TKT-5S stated that it chose not to appeal the Panel's ruling that the claim of functional equivalence was not inconsistent with the Fabrazyme SPC under Clause 3.2 because it was satisfied with the overall outcome of the complaint.

It was TKT-5S's contention that if 'structural similarity' embraced concepts of molecular structure and activity, 'functional equivalence' made the clear inference that two products had the same clinical effect. The statement in the same press release 'The *in vitro* comparison of Fabrazyme with Replagal provides no biochemical evidence to support the lower dosing currently recommended for Replagal' was a clear indication that Genzyme was inviting the reader to extrapolate from the biochemical to the clinical because dosing was an obvious clinical not 'molecular level' effect. This view of Genzyme's intentions behind the claim was supported by (i) the argument contained in a paper written by Genzyme Europe comparing Fabrazyme with Replagal which expressly related the functional equivalence of the two products to the approved dosages for each and (ii) statements made by Genzyme in introducing Genzyme's quarterly financial results in a webcast teleconference on 17 April 2002: 'We had a great meeting recently in Copenhagen with 130 physicians to talk about Fabrazyme and to talk about particularly dose, because our evaluation of this product and a competing product is that the right clinical dose is very, very critically important for efficacy, long term efficacy in these patients and we feel further confirmed during the quarter, during the discussions that have taken place in recent weeks'. TKT-5S noted that the Genzyme paper had not yet been published because of court orders granted in the Netherlands in proceedings brought against Genzyme by TKT-5S on the same issues which were the subject of the complaint to the Authority.

TKT-5S also had an affidavit sworn by one of its senior executives evidencing a discussion with Genzyme (which affidavit was accepted as evidence in the Dutch proceedings) which, it was submitted, revealed Genzyme's true intentions in making all of the claims in the press release, and the functional equivalence claim in particular, Genzyme having stated 'we have to consider the products to be equal – otherwise we would be out'.

TKT-5S noted that the claim at issue had appeared in a press release which was available indiscriminately to anyone who found it on the internet/wire service whether or not the reader was a specialist, medically qualified or a lay person. The clear inference of functionality was that it concerned how the medicine operated from which it was fair to assume, notwithstanding the attempt at qualifying the full effect of that meaning, that it was referring to the clinical context. That was particularly illustrated by reading on from the quoted extract from the press release the statement linking the biochemical evidence and the Replagal dosage which was quoted above.

TKT-5S stated that it did not understand the importance given by Genzyme in this paragraph to *in vitro* data for products for Fabry's disease because there was now quite extensive clinical data on Replagal and a number of clinical trials had demonstrated its favourable clinical benefits. There were no clinical benefits which had been seen for Fabrazyme when compared with placebo and that was why Genzyme had sought to claim functional equivalence with Fabrazyme relying on *in vitro* data to give it a cross reference to Replagal's good clinical results.

It was incorrect to say that the dosages for Fabrazyme and Replagal 'were not finalised'. The SPC for each product gave the authorised dose while acknowledging that further studies could result in a revised dose for each. Those authorised doses remained in effect today and were not anticipated to be changed in the near term. Further, this statement was entirely inconsistent with the references in the relevant product monograph that the Fabrazyme dosage was optimal. Genzyme's claim that the products were functionally equivalent was instrumental to its view that there was no justification for the relative dosages which differed by a factor of 5. In a promotional piece put out by Genzyme's Spanish affiliate in April 2002, it made the extraordinary assertion that (i) doctors were free to use the lower (Replagal) dose for Fabrazyme and (ii) to do so made Fabrazyme five times cheaper than Replagal. It led subsequently to a statement made on the website of the Spanish Agencia Espanola del Medicamento warning that any variation or modification of the posologies of Replagal or Fabrazyme described in the SPCs did not have the necessary health authorization.

TKT-5S stated that as a matter of fundamental protein chemistry, Fabrazyme and Replagal had considerable structural similarity but operated in the patient with marked differences largely due to the differing glycosylation patterns. Even though the amino acid sequences were identical there were great differences between the products in their protein-linked carbohydrate structures. Since the patterns of glycosylation were different, functional equivalence was not even to be expected and had not been demonstrated.

TKT-5S noted that Genzyme's references to the simultaneous granting of orphan drug status was simply a repetition of the argument used in its response. In any event, the suggestion that the EMEA (presumably a reference to the COMP and the Commission) was unable to determine which of the two products was safer or the more effective and, for that reason, granted simultaneous orphan designation was merely surmised on the part of Genzyme. It was not the case that the Commission decided to grant orphan designation to both products because they had passed some sort of similarity test (which would, in any event, have been a wholly incorrect basis for decision). At a recent international hospital pharmacists meeting sponsored by TKT-5S, the Chairman of COMP gave a presentation at which he explained that the Commission was forced to grant both products orphan designation without any kind of head-to-head comparison because the applications had been submitted at the same time (Prague 21 September 2002).

TKT-5S stated that the clinical benefits of Replagal reflected a sufficient biodistribution and cellular internalisation and an adequate enzymatic effect of the product. If the Fabrazyme clinical trials had demonstrated similar clinical benefits a claim of functional equivalence might have been substantiable but the trials referred to in the Fabrazyme SPC showed no better effects than placebo which was why such reliance was made on the clinically irrelevant *in vitro* study.

TKT-5S believed that the Panel's view that (i) the press release did not make it sufficiently clear that functional equivalence should not be construed as a claim of clinical equivalence, (ii) the claim gave the impression that the *in vitro* data was of direct relevance and significance to the clinical situation and that was not necessarily so and (iii) the impression was given that the products were clinically equivalent and that had not been shown, was the correct one and that nothing in the grounds submitted by Genzyme overcame the fundamentally and obviously misleading nature of the claim.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue '[Fabrazyme and Replagal] are … functionally equivalent' was attributed to the work of Edmunds. In the *in vitro* comparison of the two products, however, Edmunds was more circumspect about their comparative functioning and stated that 'Based on the comparisons made to date, Fabrazyme and Replagal *appear* [emphasis added] to be structurally very similar and functionally equivalent'. The statement in the press release was thus more definite than the statement in the original Edmunds paper.

The Appeal Board further noted that the claim in question appeared in the middle of the press release. Paragraphs before and after the paragraph in which the claim appeared clearly related to clinical issues. In a paragraph after that in which the claim appeared it was stated, with regard to Edmunds' findings, that 'The *in vitro* data suggests that the two products are functionally equivalent, thereby shifting the focus of discussion to questions about appropriate dosing'. The Appeal Board noted that this statement clearly linked the term 'functionally equivalent' to a clinical issue ie dosing. There were differences between the products' licensed doses.

The Appeal Board considered it was not unreasonable to assume that some readers would interpret the claim 'functionally equivalent' as meaning the products were 'clinically equivalent'. The claim in question was not an accurate reflection of the data. Furthermore, the positioning of the claim in amongst clinical data and the linking of 'functionally equivalent' with issues of dosing in a later paragraph meant that it was likely to be interpreted by some as 'clinical equivalence'. Overall the Appeal Board considered that the claim was not a fair reflection of the data, it was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

2 Claim in the press release that 'the *in vitro* comparison of Fabrazyme with Replagal provides no biochemical evidence to support the lower dosing currently recommended for Replagal'

COMPLAINT

TKT-5S noted that the SPC of each product made it clear that the dose for Replagal was 0.2mg/kg body weight and that for Fabrazyme was 1mg/kg body weight, which amounted to a dosage of active substance for Fabrazyme of five times the amount for Replagal. The clinical effects for Replagal were achieved with an intravenous infusion every two weeks over an infusion time of 40 minutes. In contrast, the administration of Fabrazyme was every two weeks with an initial infusion rate of 15mg/hour; ie 4.6 hours for a patient of 70kg. Infusion reactions were a common problem for patients and in the clinic Replagal had shown significantly fewer infusion reactions than those arising in the case of Fabrazyme. The statement in the press release (and the conclusion presented at the Barcelona symposium) that there was no chemical evidence to support the lower dosing recommended for Replagal was completely misleading in that it effectively claimed that the correct dose for Replagal should be the same as that for Fabrazyme, that was 1mg/kg. Not only did that ignore the authorised dose within the SPC but also, being scientifically unsound and clinically untrue, represented a disparagement of Replagal by Genzyme. As such, it did not comply with Clauses 7.3 and 7.4 of the Code which stipulated that comparisons were permitted only if they were not

misleading; that only material, relevant, substantiable and representative features of the products were compared; that the products of a competitor should not be discredited or denigrated and that the comparison must be capable of substantiation.

RESPONSE

Genzyme stated that the context was a statement by the company's senior vice president of therapeutics in Europe:

'This research clarifies some of the misconceptions about Fabrazyme and Replagal that had the potential to distract from important clinical discussions. The *in vitro* data suggests that the two products are functionally equivalent, thereby shifting the focus of discussion to questions about appropriate dosing. Our phase I/II dose ranging clinical trial supports a dose of 1 mg/kg of Fabrazyme. The *in vitro* comparison of Fabrazyme with Replagal provides no biochemical evidence to support the lower dosing currently recommended by Replagal.'

The meaning which TKT-5S sought to attribute was that Genzyme claimed that the Replagal dosage regime was sub-optimal. That was not what Genzyme's statement said. The statement was clear on its face that the *in vitro* comparison (and *in vitro* had been referred to twice) did not provide biochemical evidence to support the lower dosing of Replagal. To suggest that this was a claim that Replagal's dosage regime was sub-optimal was mischievous. To continue as the complaint did to suggest that 'It effectively claims that the correct dose for Replagal should be the same as that for Fabrazyme, that is 1mg/kg. Not only does that ignore the authorized dose within the SPC, but also being scientifically unsound and clinically untrue represents a disparagement of Replagal by Genzyme' was a contention for which there was no possible basis in the statement made.

It was Genzyme's first ground of response that the words quoted could not have the meaning ascribed to them by TKT-5S, and there was no complaint to answer. Without prejudice to that contention Genzyme commented as follows.

As indicated above, clinical experience with both Fabrazyme and Replagal was still limited. Both medicines were authorized exceptionally, for (identical) reasons described in the respective EPARs, on the basis of more limited clinical trial and other data than would normally be required for marketing authorization. In addition, experience with Gaucher's disease suggested that uncertainty about dosing might remain for the foreseeable future, even as more data became available. Meanwhile, doctors and patients needed to make choices between enzyme replacement therapy and the (palliative) alternative treatments, and within enzyme replacement therapy between Fabrazyme and Replagal. These choices were of great potential significance to patients: a suboptimal choice might lead to irreversible but potentially preventable morbidity, or allow the disease to progress more rapidly than it would with effective treatment.

The SPCs and EPARs for both Fabrazyme and Replagal explicitly indicated that the recommendations were provisional, and would be reviewed in the light of further studies which were a requirement on both manufacturers. The pivotal trials did not permit a direct comparison of Fabrazyme and Replagal, and no trial had yet been completed comparing these two medicines head-to-head. Different doses had been recommended for Fabrazyme and Replagal, and, as described elsewhere in this document, probably reflected differences in the therapeutic objectives underpinning the design of the pivotal trials for the two products. There were many reasons to believe that clinical benefits would – within limits yet to be established – be dose-dependent.

The choice of dose (as between Fabrazyme and Replagal, or even between different doses of the same product) was not yet decided, and was not likely to be unequivocally settled for the foreseeable future. In general, the situation appeared to require the treating physician and patient to decide, on the basis of incomplete information, what the benefits and side-effects of various doses were, with a view to making an optimal choice for each individual patient. The data published by Genzyme, which were the subject of the present complaints, were intended to inform these difficult decisions as much as current data permitted, with a view to helping patients and physicians to prescribe treatment which would offer the patient the best outcome.

As discussed above, the structures of agalsidase alfa and agalsidase beta were similar. Using widely accepted measures of enzymatic activity, the two products appeared on the basis of *in vitro* and non-human *in vivo* studies to be functionally equivalent. Unfortunately, the trials on which the marketing authorizations of Fabrazyme and Replagal were based yielded data which did not permit direct comparison of the two. Both products were granted marketing authorizations on exceptional grounds, since they offered – for the first time – the prospect of effective treatment for a serious disease. In both cases, the EPARs recognised the need for on-going studies to establish the optimal dosage of these medicines and other important parameters of treatment, such as when treatment should commence.

Genzyme's therapeutic goal, reflected in the design of the pivotal clinical trial submitted to the EMEA in support of the application for marketing authorization for Fabrazyme, was to reduce radically, if not eliminate, the abnormal metabolite (Gb3) the accumulation of which was the accepted cause of the clinical manifestations of Fabry's disease. In contrast, the pivotal trial submitted to the EMEA in support of the application for marketing authorization for Replagal was aimed primarily at neuropathic pain in Fabry's disease patients.

Although the regulatory authorities (in this case, the EMEA) undertook an independent assessment of the evidence submitted to them, they were not in a position to initiate research themselves, and must rely on the data submitted to them – usually by the applicant. In general, therefore, the EMEA would have to consider the submitted data as it related to doses which the trial sponsor had chosen to

investigate; and, in general, the EMEA would approve a suggested dose (or not) rather than give approval to a medicine at a dose which had not been trialled.

In Genzyme's case, following a phase I/II dose ranging study of 0.3mg/kg, 1.0mg/kg and 3.0mg/kg, a dose of 1.0mg/kg was chosen for Fabrazyme, within the range of doses tested, representing accommodation between clearance of Gb3 and frequency of adverse events.

In Replagal's case, the phase I dose escalation safety study examined single doses of 0.007 mg/kg to 0.11mg/kg. TKT-5S chose a dose of 0.2mg/kg for the pivotal studies, which lay outside the range of doses selected for the dose-ranging study. Its choice seemed to be the consequence of extrapolation from the phase I study, rather than based on observed data.

The difference in dosing between Fabrazyme and Replagal reflected TKT-5S's data which, in turn, reflected the (differing) trial design of the pivotal trials. In both cases, the EPAR explained the EMEA's decision to grant both products marketing authorizations on exceptional grounds because of:

- the anticipated effectiveness of ERT in Fabry's disease
- the lack of effective alternative treatment for a serious condition
- generalising from experience with other enzyme replacement therapies, such as Genzyme's 10 year experience with a similar approach in Gaucher's disease (another lipid storage disease).

In the light of the need to make a decision without access to as much data as might normally be required, both manufacturers were required by the EMEA to conduct post-authorization studies to confirm optimal dosage (as well as safety).

The following extracts from the EPARs for Fabrazyme and Replagal indicated that marketing authorizations for both included an explicit requirement that further work was required to establish the optimum dose. TKT-5S's suggestion that the EPARs/SPCs had settled this matter was a serious misrepresentation of the EMEA's position.

> The dose finding phase I/II study, FB9702-01, addressed mainly pharmacokinetics and initial safety and efficacy. Patients were enrolled to receive agalsidase beta in one of five treatment regimens (3 patients per group): either 0.3mg/kg, 1.0 mg/kg or 3.0mg/kg administered once every 14 days, or 1.0mg/kg or 3.0mg/kg administered once every 48 hours, for a total of five infusions. Plasma samples were taken at every infusion, and tissue (skin and liver) biopsy samples were taken at baseline and following the fifth infusion. Heart and kidney biopsies were considered as optional. Patients were exclusively male and aged 16 and older with a confirmed diagnosis of Fabry disease and with largely unaffected kidneys, as determined by clinical and laboratory kidney function parameters. The study showed that enzyme replacement with agalsidase beta could be administered safely and that it cleared GB3 accumulated in the vascular endothelium in all organs studied. Dose finding was based on plasma GB3 levels. Plasma GB3 levels decreased in a dose-dependent manner for all three dose levels when the 14 day dosing schedule was used. This was compatible with studies in the knock-out mice. With regard to the effect on the tissue deposit, however, the dose dependency was less clear due to the short duration of the study. The selection of the dose 1 mg/kg for the phase III study was based on the most favourable benefit-risk ratio for patients as assessed in the Phase I/II trial. The optimal dose in the long term, especially maintenance dosing – after clearance of the accumulated sphingolipids – will be further explored, as appropriate. (EPAR for Fabrazyme).
>
> TKT001 was an unblinded, single dose, dose escalation, safety study of 10 patients. A single infusion ranging from 0.007 to 0.11mg/kg was shown to be safe and well tolerated in this study. The two major factors that determine the delivery of the enzyme to target tissues are hepatic clearance and plasma concentration. Data suggest that hepatic uptake of the enzyme can be saturated as proportionally less enzyme was taken up by the liver with increasing dose. A dose of 0.2mg/kg was chosen for the pivotal studies so that, according to the applicant, a larger fraction of the dose would potentially be available to other target organs. An alternate week schedule was chosen for patients' convenience. Although the clinical data from the two pivotal clinical studies (TKT003 and TKT005) had shown that the recommended dose is efficacious and safe, efficacy of other doses over a longer time of treatment should be explored. The applicant had committed to performing a Phase IV clinical study post-authorization to evaluate alternative initial and maintenance dosing schedules of agalsidase alfa – after clearance of the accumulation of sphingolipids – and to identify the optimal dose and dosing interval. (EPAR for Replagal).

Both EPARs therefore agreed that optimal dosing had not yet been established. The terms of the CPMP's recommendation in both cases was based on reasonable data being available for new medicines which for the first time offered effective treatment to patients with Fabry's disease. In both cases, the marketing authorization had been granted 'under exceptional circumstances'. The dose of the two medicines had not yet been established beyond doubt, and might be changed in the light of new data.

The EPARs and SPCs for Fabrazyme and Replagal had different recommended doses at this early stage in clinical experience with enzyme replacement therapy in Fabry's disease. Neither the EPARs nor the SPCs for Fabrazyme and Replagal constituted an independent conclusion on the dose of either medicine: it was clear from the EMEA documentation that the EMEA considered the position to be provisional and 'work in progress' in respect of both products. Nor had the EMEA undertaken any comparative work on the two products. The EMEA's remit did not include making comparative judgements between medicines. In any case, the trial results for Fabrazyme and Replagal were not directly comparable, as described above.

Given the terms in which the marketing authorizations were expressed, Genzyme submitted that it was appropriate to raise issues about optimal dosing of its product, Fabrazyme, and the only – closely related – therapeutic competitor, Replagal. Genzyme was gathering further data, by *in vitro* and non-human *in vivo* studies, as well as clinical trials in man, honouring its commitment to the requirements of the marketing authorization.

Genzyme had the most experience of enzyme replacement therapy in lysosomal storage disorders of any pharmaceutical company, having pioneered this approach to these serious diseases and having 10 years' experience of Ceredase and Cerezyme in Gaucher's disease. From this basis, Genzyme considered the clinical trial data for Replagal when it became available, as part of its on-going assessment of the optimum clinical use of Fabrazyme. Recognising that the clinical trials were of different design, which did not permit direct comparison between the two products and pending the results of further clinical trials, Genzyme embarked on *in vitro* and non-human *in vivo* studies to establish what biological basis, if any, might underpin the five-fold difference in recommended dosage between Fabrazyme and Replagal.

Dosage differences of this magnitude might arise for one or more of a number of reasons: Fabrazyme and Replagal might have different modes of action; the bioavailability of Fabrazyme and Replagal might not be the same; it might simply reflect the difference in the Fabrazyme and Replagal trial designs; it might reflect differences in therapeutic objective; or it might be an artefact.

As described above, in considering these possibilities Genzyme concluded that the only proper conclusion to be drawn from the evidence was that Fabrazyme and Replagal had the same mode of action and that there was no evidence that the bioavailability of Replagal was greater than that of Fabrazyme. For the reasons set out above, Genzyme submitted that a concern for questions of structural similarity and functional equivalence was of considerable importance to both patients and doctors, and they were entirely proper subjects for investigation, discussion and debate.

If the explanation of the difference in recommended dosage was not explained by differing modes of action or different bioavailability of Fabrazyme and Replagal, consideration needed to be given to which one or more of the alternative explanations might have given rise to the difference. Helping to resolve this issue was part of the requirements laid upon both Genzyme and TKT-5S as part of post-marketing authorization studies.

The issue was also of direct relevance to patients and doctors. For example, if the difference were to reflect differences in therapeutic objective, it might be concluded that this was not sufficiently reflected in the EPARs and SPCs for the two products, and that these documents might be altered to reflect a growing understanding of these medicines. Doctors would then be able to explain to patients what the choices were, more clearly: for example, one patient might prefer a shorter infusion time, accepting that the treatment regime might be directed more at treating symptoms while being less thorough in clearing Gb3; another patient might prefer a longer infusion in order to pursue a more radical therapeutic objective. In respect of infusion reactions, there was some evidence that these might be dose dependent and patients might also need to make trade-offs between the effectiveness and side effects of treatment.

In order to respond fully to the complaint, Genzyme considered below issues relating to the design of the pivotal trials for Fabrazyme and Replagal.

In the Fabrazyme trial, pain was not a selection criterion, and three quarters of the patients assessed their pain at baseline as none or mild. In addition, pain medication was allowed, but no treatment algorithm had been pre-defined. It was important to note that the treated patients nevertheless had an improved pain score which, although non-significant statistically, stabilised during the first six months of the open extension study, suggesting an effect. In relation to tertiary endpoints, no statistically significant differences between the treatment groups were observed but patients showed little baseline pathology and the study duration might have been too short to detect significant changes.

As described earlier, there was evidence of a relationship between dose of agalsidase and the degree to which the abnormal metabolite Gb3 was reduced. On general grounds, such dose-dependency was not surprising. The relationship appeared not to be linear but more remained to be understood. This was one reason why the optimal dose had not yet been identified, as the marketing authorizations for Fabrazyme and Replagal both explicitly stated. Other reasons for present uncertainty as to the optimal dose included: lack of long term data on the effect of a given level of reduction of Gb3 on the morbidity and mortality of Fabry patients; lack of data on the best time to commence treatment (eg in childhood, before accumulation of Gb3 had occurred significantly, or early adulthood, or later on in the disease process); lack of data on the degree to which the harmful effects of accumulated Gb3 were reversible; and different responses in individuals.

The long-term therapeutic goal for enzyme replacement therapy in Fabry's disease remained to be identified more clearly in Fabry patients generally and possibly in subgroups of such patients. Even in the light of more complete knowledge, patients and doctors might still need to make choices about dosage levels on grounds of side-effects, costs, the clinical manifestations of the disease in the individual, and other factors which tailored clinical decisions to individual circumstances. In this sense, there might not be a single 'optimal' dose.

Experience of enzyme replacement therapy in Gaucher's disease, of which Genzyme had more experience than any other company in the world and which was closely analogous to the situation in Fabry's disease, suggested that defining the optimal dose in general, or even for an individual patient, was likely to remain problematic for the foreseeable future. Ceredase, a placental form of the missing enzyme in

Gaucher's disease was approved after a 12 patient trial. The recommended dose was the dose studied in the 12 patient trial.

Over time physicians had adopted the appropriate strategy of individualised dosing of Ceredase and Cerezyme. Some patients with less severe disease had done well on doses that were considerably less (1/4 of the dose studied) while other patients with more severe disease had been treated with doses that were 4 times higher than the original recommended dosing. In each case the goal was to tailor the replacement enzyme dose to the severity of the disease which was itself related to the total accumulated substrate burden – in this case glucosylceramide. The desired outcome was to administer enough enzyme to remove the accumulated substrate thereby preventing the long-term morbidity and mortality associated with that disease.

Fabry's disease was no different. Symptomatic improvement was important for the Fabry patient. But long-term improvement in morbidity and mortality would depend on the extent to which the accumulated substrate had been cleared.

The following extracts from the EPARs for Fabrazyme and Replagal supported Genzyme's position that there were important and legitimate questions about appropriate dosing:

> From the dose-finding study, it can be extrapolated that plasma concentrations of GL-3 were cleared rapidly and in a dose dependent way…. (EPAR for Fabrazyme).
>
> In one phase I clinical trial in patients with Fabry's Disease (TKT001), following a single intravenous infusion no correlation was observed between the dose administered (0.007-0.11 mg/kg) and pharmacodynamic effects on the liver (decrease in Gb3 accumulation), plasma or 24 hr urine sediment Gb3 levels. (EPAR for Replagal).

The choice of dose for the pivotal studies of Fabrazyme and Replagal was made on a different basis:

> Dose finding was based on plasma GL-3 levels. Plasma GL-3 levels decreased in a dose dependent manner for all three dose levels….. The selection of 1 mg/kg for the phase III study was based on the most favourable risk-benefit ratio for patients as assessed in the phase I/II trial. (EPAR for Fabrazyme).
>
> A dose of 0.2mg/kg was chosen for the pivotal studies so that, according to the applicant, a larger fraction of the dose would be available to the other target organs. (EPAR for Replagal). Note that as the dose-finding study did not include the 0.2mg/kg dose, and the 0.2mg/kg dose was the only one used in the pivotal trial, TKT-5S could not have had any evidence which would be relevant to the question of the optimal dose.

Both Fabrazyme-like molecules (made in Chinese hamster ovary cells) and Replagal were studied in the Fabry KO mouse model. In this model, the animals were missing the enzyme alpha galactosidase A and accumulated Gb3 in the affected organs: liver, kidney, and heart. The model was extremely useful in testing the ability of replacement enzyme therapy to clear the accumulated substrate.

The Fabrazyme-like enzymes were tested in the mouse at doses that ranged from 0.3mg/kg up to 10 mg/kg. After single or multiple doses the individual organs of the mice were examined for total Gb3 content. The liver was easily cleared at all doses. The other organs were cleared in a dose dependent manner: the more enzyme administered, the more GB3 was cleared from the affected organ.

Brady *et al* summarised the Replagal KO mice experiment in a review article. The mice were treated with doses ranging from 0.2mg/kg up to 1.0mg/kg. The liver was easily cleared and the kidney showed clearance of Gb3 in a dose dependent fashion. Brady stated: 'The removal of lipids in these organs (heart, kidney, and lung) was considerably slower than that observed in the spleen and liver, suggesting the benefit of higher dose, long-term therapy for patients with Fabry disease'.

Relevant to the assessment of the complaint by TKT-5S regarding dose was the behaviour of the placebo groups in the pivotal trials on which the marketing authorizations of Fabrazyme and Replagal were based. In the case of the pivotal trial of Fabrazyme reported by Eng *et al* there were statistically significant (and biologically coherent) findings regarding the efficacy of agalsidase beta on the abnormal metabolite, Gb3, which was key to the morbidity and shortened life expectancy experienced by Fabry patients. As expected, levels of Gb3 in the placebo group did not fall and generally continued to rise. However, in respect of pain, the placebo group showed marked improvements. This phenomenon was common in trials in respect of subjective endpoints. As a result of the reduction in pain scores in the placebo group, which matched those in the treatment group, there was no statistically significant difference between the Fabrazyme and placebo groups at six months in respect of pain.

In the case of the Replagal trial, reported by Schiffmann *et al*, in which pain was the primary endpoint, the behaviour of the Replagal group was strikingly different. Treatment with Replagal was associated with a fall in pain scores: although the mechanism was not yet fully understood, this was consistent with current thinking on Fabry disease, in which the accumulation of Gb3 in tissues caused damage. Pain in the placebo group did not fall at all. This was an unusual finding, which Genzyme was seeking to understand more clearly. It might be due to the fact that placebo group patients were required by the trial protocol to stop taking treatment for neuropathic pain for four periods of one week (at baseline, and weeks 8, 16 and 23), which might have exaggerated the general therapeutic effect of reduction of Gb3 on pain symptoms. Note that in the Fabrazyme trial, in which pain was not a primary endpoint, both the Fabrazyme and placebo groups were allowed to continue with pain medication as if they were not in a clinical trial: this, together with the placebo effect consequent on participating in a clinical trial, would be expected to blunt any difference that might otherwise be found between the group treated

with active substance and the group treated with placebo.

It was not possible directly to compare results in respect of pain between the Fabrazyme and Replagal trials, because: the way in which pain was measured differed; inclusion and exclusion criteria were different, in particular in relation to the symptom of pain (which was a positive inclusion criterion in the Replagal trial); and differences in study design (eg the difference referred to above in respect of pain medication during the trial).

Key to the results of the two trials was the behaviour of the placebo groups, rather than the behaviour of the actively treated groups.

Despite the difficulties in making direct comparisons, Genzyme submitted that it was reasonable to raise questions about conclusions drawn from studies of different designs carried out on small numbers of patients, particularly when there was a choice between two theoretically effective treatments, for a disease with serious morbidity and mortality.

In granting the marketing authorization for Fabrazyme, the EMEA explicitly requested that Genzyme should investigate the correct maintenance dosage for Fabrazyme. 'The optimal dose in the long term, especially maintenance dosing – after clearance of the accumulated sphingolipids – will be further explored, as appropriate.' (EPAR for Fabrazyme).

TKT-5S, on the other hand, was requested to investigate the proper initial and maintenance dosage for Replagal. 'Although the clinical data from the two pivotal clinical studies (TKT003 and TKT005) had shown that the recommended dose was efficacious and safe, efficacy of other doses over a longer time of treatment should be explored. The applicant has committed to performing a phase IV clinical study post-authorization to evaluate alternative initial and maintenance dosing schedules of agalsidase alfa – after clearance of the accumulation of sphingolipids – and to identify the optimal dose and dosing interval.' (Replagal EPAR).

On the question of establishing optimum dosage, it should be noted that the Dutch government, in consultation with the Health Insurance Board *(College van Zorgverzekeringen)*, had decided that for the moment Replagal and Fabrazyme should not be included in the system for financing medicinal products. One reason for this was that the optimum dosage was still not clear enough and therefore the data was insufficient to decide which product, at what dosage, should be paid for. Rather than include the product in the system for financing medicinal products, the Dutch government made special subsidies available, with direct comparison studies being done. Amsterdam University Medical Center (AMC) had been commissioned by the Minister of Public Health and the Medical Insurance Board to carry out clinical trials during which one group of patients would receive Replagal and another Fabrazyme, at dosages different to that determined by the EMEA. This was because the Minister and the Medical Insurance Board believed that it was essential for further studies to be carried out to determine the optimum dosage for treatment before deciding which medicinal product should be paid for, and on the basis of what dosage.

As demonstrated in this response, the issue which Genzyme sought to raise was as follows:

- both agalsidase alfa and agalsidase beta appeared to be structurally similar and functionally equivalent;
- in particular, they had the same fundamental mode of action and pharmacokinetics suggesting that, if anything, Replagal could be expected on *a priori* grounds to be no more effective, milligram for milligram, than Fabrazyme;
- Fabry's disease was caused by the lack of a single enzyme which both Fabrazyme and Replagal sought to replace for therapeutic purposes;
- there was a dose-dependent relationship between the amount of enzyme infused and reduction of the abnormal metabolite which was the root cause of the clinical symptoms and signs of Fabry's disease;
- no other mechanism of action had been proposed for either Fabrazyme or Replagal than the effect of enzyme replacement therapy on reduction of accumulated Gb3;
- the present state of knowledge was incomplete, but real choices had to be made by patients and doctors as to which medicine to prescribe and whether to use the doses recommended in the SPCs for both products;
- these choices had potentially significant consequences for patients with a serious disease; and
- that differences in trial results, in both cases involving small numbers of patients over a limited period of time, between these two medicines required – for the sake of patients – further consideration, provisional explanation and – as per the marketing authorizations for both products, investigation and might be artefactual and/or non-comparable therapeutic objectives in the two pivotal trials.

The EMEA could only base its judgements on evidence presented to it by an applicant. Therefore, in effect, the EPAR and SPC could only reflect acceptance or rejection of a proposal made by the applicant at any given point in time. Differences in dosage suggested by an applicant might, in a case like that of Fabrazyme and Replagal, be due to:

- measuring different endpoints;
- studying different patient populations;
- variability due to small numbers in either or both of the placebo group and the group treated with active substance;
- a subjective choice of different doses in a clinical trial protocol.

In all the circumstances, Genzyme submitted that it was wholly appropriate and reasonable for Genzyme to raise questions in a professional forum about how a five-fold difference in recommended dosage between these two medicines should best be understood.

In raising the question of the fivefold difference in currently recommended dosage of agalsidase alfa and agalsidase beta, Genzyme sought – and continued to seek – a debate on what such a difference meant for Fabry patients. Genzyme was currently conducting further investigations as part of its obligations under the terms of marketing authorization for Fabrazyme and as a responsible pharmaceutical company wished to base the use of Fabrazyme on clinical trial data. However, as the marketing authorizations for both Fabrazyme and Replagal explicitly stated, the optimal dose/dosage schedule was not yet established, and for some patients choices with potentially significant clinical consequences could not wait for trials to be considered, trial results to be reported, and the results to be assessed and understood.

Genzyme's provisional view, based on its work with Fabrazyme and generally in the field of enzyme replacement therapy in lipid storage diseases, in which it had more experience than any other company in the world, was that a conservative judgement of the *in vitro* and animal studies comparing Fabrazyme and Replagal suggested that at a minimum Fabrazyme was equivalent to Replagal. Until further data became available, it was reasonable to base clinical decisions on the likelihood that at the same dose Fabrazyme and Replagal could be expected to have identical effects.

Summary
Raising the question of the appropriate dose (of both Fabrazyme and Replagal) was legitimate and appropriate for Genzyme as a responsible pharmaceutical company and consistent with the questions raised by the EMEA as part of the marketing authorizations for both Fabrazyme and Replagal.

An elucidation of the appropriate dosing would have financial consequences for UK funding bodies, given that the manufacturer's recommended price for 0.2mg Replagal was marginally higher than that for 1 mg Fabrazyme.

Raising the question did not, and could not be construed to be, a denial of the recommended dose set out in the SPC for Replagal with which the sophisticated specialist clinical audience addressed by Genzyme would be fully aware.

Suggesting that physicians might expect that Fabrazyme at a dose of 0.2mg/kg would have the same, or very similar, effects to Replagal at that dose, was reasonable. The recommended dose in an SPC was recommended and not the only legitimate dose as TKT-5S's use of the word 'authorized' in its complaint sought to suggest. It was not uncommon for medicines to be prescribed at doses different from those recommended in the SPC. In general, Genzyme as a responsible pharmaceutical company would not seek actively to promote debate about optimal dosage prior to the availability of clinical trial data but in the circumstances (considered at length in this response), particularly the explicit recognition by the marketing authorizations of both Fabrazyme and Replagal that the optimal dose had yet to be established, Genzyme submitted that the comments made by Genzyme and complained of by TKT-5S were reasonable, legitimate, appropriate, and substantiated.

Genzyme wholly rejected the implication in the complaint that the issue of optimal dosage was settled, and that the final determination of appropriate dosing enshrined a five-fold difference between Fabrazyme and Replagal. This was a perverse suggestion, not supported by the marketing authorizations for the two products

A statement that there was an absence of evidence to support a five-fold difference in dosing was not – and was never intended as – a statement that there was evidence for the absence of a difference. The sophisticated professional audience to which Genzyme's claims were addressed would fully recognise this.

Accordingly, Genzyme did not accept that it had breached Clauses 7.3 and 7.4.

PANEL RULING

In relation to the press release the Panel noted that the Fabrazyme SPC stated that the recommended dose was 1mg/kg body weight administered once every two weeks as an intravenous infusion. The stated dose for Replagal was 0.2mg/kg body weight every other week by intravenous infusion over 40 minutes. Each SPC gave further instructions on preparation and administration.

The Panel noted Genzyme's submission that both the EPARs and SPCs had different recommended doses at this early stage in clinical experience with enzyme replacement therapy in Fabry's disease; both EPARs indicated that the optimal dose had not yet been established. Nonetheless the Code required that material was not inconsistent with the SPC. The Panel noted the submission about the specialist clinical audience to whom the press release was directed. The Panel noted that the press release was placed upon the Internet and was thus widely accessible by the general public; it had not been directed towards a specialist audience. The Panel considered that the claim at issue implied that the licensed dosage regime for Replagal was incorrect and considered this was misleading and not capable of substantiation as alleged. Breaches of Clauses 7.3 and 7.4 were ruled.

3 Claim (referring to Fabrazyme) 'the reduction in pain observed at 6 months was maintained during the 18 months of additional treatment with Fabrazyme'

This claim appeared in the press release.

COMPLAINT

TKT-5S alleged that this constituted a breach of Clauses 3.2 and 7.2 of the Code in that it did not comply or was inconsistent with the particulars listed in the SPC for Fabrazyme and was misleading.

The Fabrazyme SPC stated in Paragraph 5.1 (pharmacodynamic properties) 'clinical and laboratory efficacy analyses in the placebo controlled clinical trial and its extension included pain assessment (Short Form McGill), quality of life

questionnaire (SF-36), kidney function and plasma GL-3. Some improvement in the pain score was seen in the first six months, both in the placebo and active treated groups. In the active treated group the improved pain score stabilised during the 6 months of treatment thereafter'.

The CPMP scientific discussion published in the EPAR for Fabrazyme pointed out that the measurement of pain in the particular study referred to was a secondary end point and the analysis included an assessment of change of pain which showed that in many of the pain score categories statistically significant improvements from baseline were observed but that this occurred in both the treated patient group and in the placebo patient group. 'Pain was not a selection criterion and many of the older patients were at a stage of the disease where pain was minimal, and almost three quarters of patients assessed their pain at baseline as none or mild. In addition, pain medication was allowed, but no treatment algorithm had been pre-defined. However, in the active treated group the improved pain score, although still non-significant, stabilised during the first six months of the open extension study, thus suggesting an effect'. The scientific discussion concluded on this aspect 'however, although positive trends were observed for the clinical parameters investigated as secondary end points, none of these parameters reached a statistically significant improvement'.

It was the view of TKT-5S that, given the statement in the SPC and having regard to the conclusion of the CPMP in its opinion so far as it concerned pain as a parameter, the claim made in the press release did not comply with the SPC and amounted to an exaggerated and misleading claim because it clearly implied that the pain reduction in the first six months was significant and material whereas according to the CPMP's review of the data it clearly was not.

RESPONSE

Genzyme stated that the statement was correct. The context of the claim was:

'The meeting also included a presentation by Genzyme's senior vice president of therapeutics in Europe of two year data from the company's open-label phase 3 clinical trial extension study of Fabrazyme. Notably, [he] reported that renal function remains stable for Fabry patients who have received Fabrazyme for 24 months, while the natural history of the disease suggests that renal function should decline over that period. For these same patients, the reduction in pain observed at 6 months was maintained during the 18 months of additional treatment with Fabrazyme.'

The EPAR for Fabrazyme stated:

'However, in the active treated group the improved pain score, although still non–significant (statistically), stabilised during the first six months of the open extension study, thus suggesting an effect.'

Genzyme's first response was that the complaint was without foundation.

The discussion of the relevant material to this issue had already been undertaken above. Rather than repeat the material, Genzyme summarised it as follows.

In the pivotal trial reported on by Eng *et al* pain was markedly reduced in the Fabrazyme group. The absence of a statistical significance between the Fabrazyme group and the placebo group in that trial was logically as much a comment on the behaviour of the placebo group as it was on the study group. The placebo group exhibited a marked reduction in pain. The absence of a statistically significant difference between the Fabrazyme and placebo group was not evidence of the absence of a clinical effect in the Fabrazyme group. Results of the use of Fabrazyme suggested that in fact it had a substantial impact on pain. This finding was confirmed by reports from treating physicians. The statement that 'the reduction in pain observed at six months was maintained during the 18 months of additional treatment with Fabrazyme' was true. Moreover, the fact that the pain reduction in the placebo group at six months was maintained in the following 18 months of the open-label study supported the conclusion that Fabrazyme had a real effect on pain. At the end of 24 months both those who had been on Fabrazyme throughout, and those who had been on placebo for six months and Fabrazyme for the balance of 18 months, had a real reduction in pain.

Genzyme did not accept the implication of TKT-5S's complaint that Genzyme should not make statements about pain in relation to Fabrazyme on the grounds that there was no statistically significant difference in pain between the Fabrazyme group and the placebo group in the Fabrazyme trial and/or that pain was not a primary end point of the Fabrazyme trial.

Neither of these were reasonable grounds for criticising the claim at issue. It was an epidemiological truism that statistical significance and clinical significance were not identical. A phenomenon might be statistically significant but clinically insignificant; pari passu a phenomenon might be statistically non-significant but clinically significant. As a responsible pharmaceutical company Genzyme recognised that standard trial methodology, including statistical analysis, helped doctors and patients to make the best possible decisions. Nevertheless, this did not mean that raising any issue or making any statement about a phenomenon which was not statistically significant was of itself illegitimate, irresponsible, or a breach of the Code.

The Code, and supplementary information relating to Clause 7.2, stated that 'Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. Such a statement made sense if the Code permitted responsible presentation and debate about matters on which results did not reach conventional statistical significance.

In all the circumstances Genzyme submitted that the claim was factually correct, and that it was not presented in a misleading way, that it should be taken

in context, that it was aimed at a sophisticated audience who would know thoroughly the existing literature on Fabry's disease and on Fabrazyme and Replagal; and that it was entirely legitimate, responsible, and appropriate for Genzyme to raise these questions.

Clause 7.2
Genzyme did not accept that the claim breached Clause 7.2.

Clause 3.2
Further, there was nothing in the claim which (explicitly or implicitly) was not in accordance with, or consistent with, the marketing authorization and the SPC for Fabrazyme, and accordingly Genzyme did not accept that the claim breached Clause 3.2.

PANEL RULING

The Panel noted that the claim at issue referred to an open label phase 3 extension trial involving 58 patients. The reduction in pain was a secondary efficacy parameter. In many of the pain score categories statistically significant improvements from baseline were observed, but this occurred in both treatment groups. Pain was not a selection criterion and many of the older patients were at a stage of their disease where pain was minimal and almost 75% of patients assessed their pain at baseline as none or mild. Pain medication was allowed but no treatment algorithm had been predefined. However in the active treated group the improved pain score, although not statistically significant, stabilized during the first six months of the open extension study, thus suggesting an effect. The section 'discussion on clinical efficacy' stated that 12 month data available through the interim report from the uncontrolled extension study showed that 'some improvement in the pain score was maintained through one year of treatment… However none of these clinical parameters reached a statistical significant improvement. The lack of clear clinical benefit may be due to the fact that the patients were not selected on the basis of a particular symptom'. Longer follow up was needed.

The Panel noted that Section 5.1 of the Fabrazyme SPC stated that in relation to the placebo controlled trial 'some improvement in the pain score was seen in the first six months, both in the placebo and active treated groups. In the active treated group the improved pain score stabilised during the six months of treatment thereafter'.

The Panel considered that the claim at issue implied that a statistically significant reduction in pain was achieved at six months and this reduction was maintained over the following 18 month period and that was not so. The claim was misleading and inconsistent with the SPC as alleged. Breaches of Clauses 3.2 and 7.2 were ruled.

Complaint received	**10 April 2002**
Case completed	**11 November 2002**

CASE AUTH/1318/5/02

SOCIAL AUDIT v GLAXOSMITHKLINE

Promotion of Seroxat

Social Audit complained about statements made about Seroxat (paroxetine) which appeared in articles in The Independent and Mental Health Today attributed to the UK Director of Corporate Media for GlaxoSmithKline.

In The Independent, 1 October 2001, the Director of Corporate Media was reported as saying (of paroxetine and other selective serotonin reuptake inhibitors (SSRIs)) 'There's no reliable scientific evidence to show they cause withdrawal symptoms or dependency'. When asked to confirm that he had been correctly quoted the Director stated that he had; when he was asked to substantiate the statement he simultaneously stated that he was not referring to withdrawal symptoms but had been accurately quoted. He claimed he had been quoted out of context. Social Audit noted reported comments of the same general kind, attributed to the Director, in an article in Mental Health Today, April 2002: 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation, which is why our data sheets [doctor and patient information leaflets] reflect new advice to taper off the medication. The data sheet is a living document and as usage of the product increases the labelling reflects the current usage experience'.

Social Audit considered that the statement 'there is no reliable scientific evidence that Seroxat leads to addiction and dependency' was not inconsistent with the summary of product characteristics (SPC) but alleged it to be unfair, ambiguous and misleading due to the lack of evidence to which the EMEA and CPMP referred and a narrow and inappropriate interpretation of the definition of dependence in the International Classification of Diseases.

With regard to the statement that 'There have been one or two reports of discontinuation symptoms with abrupt cessation' – especially in the context of a reference to tens of millions of satisfied users, Social Audit's view was that although the SPC did not put a figure on the incidence, all available evidence indicated that this was a misleading underestimate. The European Medicines Evaluation Agency (EMEA)/The Committee for Proprietary Medicinal Products (CPMP) position paper, published in April 2000, acknowledged that withdrawal reactions were 'well-recognised'. It also stated that the term 'withdrawal reactions' should be used, not 'discontinuation reactions' as had been proposed by some marketing authorization holders. The incidence of withdrawal reactions reported in the US label since modification by the FDA in late 2001 was greater than 1:100 and should therefore be described as 'common'. The implication that withdrawal symptoms occurred only with 'abrupt cessation' was unwarranted.

Social Audit accepted the point made in the EMEA/CPMP review (1999) that 'strong evidence which would allow definitive statements about the frequency of withdrawal reactions with the different SSRIs, is not available'. However, investigators had consistently reported an incidence of withdrawal problems far greater than the incidence proposed by GlaxoSmithKline.

Social Audit objected to the statement that 'there have been one or two reports of discontinuation symptoms with abrupt cessation' on the ground that GlaxoSmithKline had known for many years that the frequency of withdrawal symptoms was likely to be substantial, following studies on healthy volunteers, carried out in the 1980s: 'On average about half the volunteers taking part in a group of studies specifically designed to detect withdrawal problems suffered symptoms which suggest they had become physically dependent on the drug' (Boseley, 2001).

The further implication of the statement was that withdrawal symptoms existed only when there was abrupt cessation of treatment. Social Audit accepted that gradual reduction of dosage might attenuate withdrawal problems, but clearly it did not abolish them. Gradual tapering of dosages had been employed in some instances. Social Audit also referred to the 1000-odd spontaneous reports from SSRI users on the Social Audit website, the large majority of which related to withdrawal and dependence problems with paroxetine (Paxil, Seroxat, Aropax) rather than other SSRIs.

A breach of Clause 2 of the Code was also alleged.

The Panel was concerned that there were two quotations from an employee of GlaxoSmithKline that Seroxat did not cause withdrawal symptoms. These being 'There's no reliable scientific evidence to show they cause withdrawal symptoms or dependency' in The Independent, 1 October 2001, and 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation …' in Mental Health Today, April 2002.

The Seroxat SPC (Section 4.8) stated: 'In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of Seroxat. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering be carried out'.

Given the circumstances GlaxoSmithKline needed to be extremely careful about references to withdrawal symptoms/discontinuation symptoms. The company itself referred to the position as complex.

The Panel noted that there was no contemporaneous evidence or record of the conversations between the journalists and the Director of Corporate Media UK. The Panel queried whether it was likely that two journalists would misquote with similar effect. If the Director had been quoted accurately, the statements were inconsistent with the Seroxat SPC and GlaxoSmithKline's briefing documents. On the evidence before the Panel it was not possible to determine precisely what had been said; in such circumstances it had had no option other than to rule no breach of the Code.

Upon appeal by Social Audit, the Appeal Board noted the two quotations at issue and the statement in Section 4.8 of the Seroxat SPC. The Appeal Board also noted the 'Reactive and Key Messages and Issues Document' (September 2001) stated 'Abrupt stopping of any antidepressant can result in a small number of patients experiencing discontinuation symptoms'; this was updated in December 2001 to read 'Stopping any antidepressant can result in some patients experiencing discontinuation symptoms'.

The Appeal Board noted GlaxoSmithKline's submission that the Director of Corporate Media UK was one of only three employees working in a very busy environment. He was an experienced senior member of staff fully aware of the Seroxat briefing documents. There could be no absolute certainty as to precisely what was said. At the appeal hearing GlaxoSmithKline's representatives stated that if the Director had been reported accurately then there was a breach of the Code. In its original response GlaxoSmithKline had accepted that if the Director had made the statement 'There have been one or two reports of discontinuation symptoms with abrupt cessation' then a breach of the Code would have occurred.

The Appeal Board noted the parties' submissions regarding the various definitions of 'dependence', 'withdrawal symptoms/reactions', 'discontinuation symptoms/reactions' and 'addiction'. People's understanding of these terms differed depending on their background. The Appeal Board noted that at the appeal the GlaxoSmithKline representatives stated that the Seroxat patient information leaflet (PIL) stated that Seroxat was not addictive.

It was not the Appeal Board's role to assess the safety of a medicine or to approve the contents of its SPC or PIL; these were roles for the regulatory authorities. In the case now before it the Appeal Board had to decide firstly whether the Director of Corporate Media UK had been quoted accurately and, if so, whether what was said met the requirements of the Code.

The Appeal Board was concerned that the quotations were not consistent with the briefing documents. The Appeal Board considered that given the importance and sensitivity of the matter, the company must be very clear about the issues to avoid confusion. This was particularly important when providing information directly or indirectly to the public about side effects. In the Appeal Board's view the briefing documents did not sufficiently address the need for caution. The Appeal Board considered that although there was no written/recorded evidence of the interviews available it was very unlikely that one person would be misquoted twice on the same issue, especially considering the sensitivity of the matter. The Appeal Board considered that on the balance of probability the Director of Corporate Media UK had been quoted accurately. It was misleading to state that 'There's no reliable scientific evidence to show that they [Seroxat or other SSRIs] cause withdrawal symptoms …' or that 'There have been one or two reports of discontinuation symptoms with abrupt cessation' when the SPC clearly stated that 'withdrawal symptoms have been reported on stopping treatment'. The information supplied by the GlaxoSmithKline spokesperson to the press was misleading with respect to withdrawal symptoms. The Appeal Board ruled a breach of the Code. The Appeal Board noted that the Code required that the promotion of a medicine must not be inconsistent with the particulars listed in the SPC. The statements were issued to the media and as such did not constitute the promotion of Seroxat; Seroxat was a prescription only medicine and should not be promoted to the public. On this narrow point the Appeal Board upheld the Panel's ruling of no breach of the Code.

The Appeal Board noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such circumstances. The Appeal Board considered that, given the nature of the evidence, on balance the circumstances did not warrant a ruling of such a serious breach of the Code. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 2.

Social Audit Ltd complained about information supplied about Seroxat (paroxetine) by GlaxoSmithKline UK Limited. The complaint related to comments attributed to the Director of Corporate Media UK, in articles which appeared in The Independent, 1 October 2001, and Mental Health Today, April 2002. Social Audit referred to a previous case considered under the International Federation of Pharmaceutical Manufacturers Association (IFPMA) Code of Pharmaceutical Marketing Practices, Case AUTH/IFPMA/5/7/01, and asked the Authority to take that case into account.

COMPLAINT

In an article in The Independent, 1 October 2001, the Director of Corporate Media UK was reported as saying (of paroxetine and other selective serotonin reuptake inhibitors (SSRIs)) 'There's no reliable scientific evidence to show they cause withdrawal symptoms or dependency'. The complainant telephoned him in October to ask if he had been accurately quoted. He confirmed he had: 'Absolutely, [the reporter] reported exactly what I said'. The complainant then wrote to the Director of Corporate Media UK asking him to substantiate his statement. The Director of Corporate Media UK replied in October 2001 simultaneously stating that he was not referring to withdrawal symptoms but had been accurately quoted. He claimed he had been quoted

out of context, but that this 'is not the fault of the journalist as she was covering a complex situation'. This contradicted his earlier statement that he had been accurately quoted, but the complainant did not pursue this issue, as Social Audit was then engaged in another complaint (Case AUTH/IFPMA/5/7/01) against GlaxoSmithKline in relation to a statement that withdrawal reactions from paroxetine were 'very rare'.

The complainant would have left it at that, had he not seen reported comments of the same general kind, attributed to the Director, Corporate Media UK, in an article in Mental Health Today April 2002: 'You have a product that's been available for over ten years and has benefited tens of millions of patients. As more patients use the product globally you are bound to get these reports of bizarre side effects', says the Director of Corporate Media UK. 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation, which is why our data sheets [doctor and patient information leaflets] reflect new advice to taper off the medication. The data sheet is a living document and as usage of the product increases the labelling reflects the current usage experience'.

The complainant wrote to the Director of Corporate Media UK again asking him to confirm he had been accurately quoted. The Director of Corporate Media UK replied and declined either to confirm or deny the remarks attributed to him. The complainant considered that the statement 'there have been one or two reports of discontinuation symptoms with abrupt cessation' was misleading and unacceptable. As the Director of Corporate Media UK knew, or ought to have known, withdrawal reactions indicative of dependence had been reported with paroxetine (eg to the World Health Organisation (WHO) Centre at Uppsala and to the Medicines Control Agency (MCA)) more than any other medicine.

The statements at issue were alleged to violate Article 7 of the WHO Ethical Criteria and Sections I.2 and I.3 of the IFPMA Code.

The complainant stated that Social Audit had previously supplied both the Authority and the company with evidence of its concerns relating to the nature, extent and severity of withdrawal symptoms and dependence with paroxetine – in particular, the monograph (Medawar, 1997) published in the International Journal of Risk and Safety of Medicine and the further evidence reported (1997-2001) on the Social Audit website, The Antidepressent Web. However, the complainant outlined below the facts that persuaded Social Audit that GlaxoSmithKline was in breach of several provisions of the Code.

Clause 3.2 The statement 'There have been one or two reports of discontinuation symptoms with abrupt cessation' – especially in the context of a reference to tens of millions of satisfied users – was tantamount to claiming that withdrawal reactions were very rare (traditionally, <1:10,000). Though the summary of product characteristics (SPC) did not put a figure on the incidence, all available evidence indicated that this was a grotesquely misleading underestimate. The European Medicines Evaluation Agency (EMEA)/The Committee for Proprietary Medicinal Products (CPMP) position paper published in April 2000 acknowledged that withdrawal reactions were 'well-recognised'. It also stated that the term 'withdrawal reactions' should be used, not 'discontinuation reactions' as had been proposed by some marketing authorization holders. The incidence of withdrawal reactions reported in the US label since modification by the FDA in late 2001 was greater than 1:100 and should therefore be described as 'common'. The implication that withdrawal symptoms occurred only with 'abrupt cessation' was unwarranted.

Clause 7.2 The Director of Corporate Media's statement that 'there is no scientific evidence that Seroxat leads to addiction and dependency' was not inconsistent with the SPC but was alleged to be unfair, ambiguous and misleading, all the more so as a statement directed to a lay readership. The assertion that paroxetine was not a medicine of dependence relied on (a) the lack of evidence to which EMEA/CPMP referred; and (b) a studiedly narrow and inappropriate interpretation of the definition in the 10th edition of the International Classification of Diseases (ICD).

Since publication of the ICD-10 guidelines, the WHO (1998) had published a statement on 'Selective serotonin reuptake inhibitors and withdrawal reactions', which made it clear (a) that dependence should be regarded as not an 'on or off' phenomenon, but as a condition that should be measured by degree; (b) that on existing definitions, sensibly interpreted, SSRIs could and did cause 'dependence'; and (c) that in the last analysis, the patient's experience with the medicine was the test of whether or not a medicine caused dependence:

> 'There is obviously some confusion about the concept of dependence … The simplest definition of drug dependence given by WHO is 'a need for repeated doses of the drug to feel good or to avoid feeling bad' (WHO, Lexicon of alcohol and drug terms, 1994). When the patient needs to take repeated doses of the drug to avoid bad feelings caused by withdrawal reactions, the person is dependent on the drug. Those who have difficulty coming off the drug even with the help of tapered discontinuation should be regarded as dependent, unless a relapse into depression is the reason for their inability to stop the antidepressant medication.
>
> In general all unpleasant withdrawal reactions have a certain potential to induce dependence and this risk may vary from person to person. Dependence will not occur if the withdrawal symptoms are so mild that all patients can easily tolerate them. With increasing severity, the likelihood of withdrawal reactions leading to dependence also increases …' (WHO Drug Information 1998).

Referring specifically to the Director of Corporate Media's comment that 'there have been one or two reports of discontinuation symptoms with abrupt cessation', Social Audit referred to the published evidence cited in its previous complaint. It accepted the point made in the EMEA/CPMP review (1999)

that 'strong evidence which would allow definitive statements about the frequency of withdrawal reactions with the different SSRIs, is not available'. However, investigators had consistently reported an incidence of withdrawal problems far greater than the incidence proposed by GlaxoSmithKline. Typical figures were 3/6 cases – 50% (Barr *et al* 1994); 5/13 – 38.5% (Keuthen *et al*, 1994); 10/50 – 20% (Coupland *et al*, 1996); and 5/12 – 41.6% (Bhuamik and Wildgust, 1996). One recent review concluded:

> 'In summary, with several 'newer' antidepressants, including sertraline, paroxetine and venlafaxine, abrupt discontinuation after a moderate length of treatment leads to at least 1 out of 3 patients spontaneously reporting one or more discontinuation symptoms. Higher rates are reported when information on symptoms is solicited and in one study (Rosenbaum *et al* 1998) approximately 2 out of 3 paroxetine and sertraline recipients fulfilled criteria for a discontinuation syndrome.' (Haddad, 2001)

In addition to the aforementioned study by Rosenbaum *et al*, the complainant referred to the study reported by Oehrberg *et al* (1995); the correspondent in the published report was identified as a doctor from SmithKline Beecham Pharmaceuticals. The investigators reported: '… only 19 patients out of 55 (34.5%) who had received paroxetine reported any adverse event on discontinuation, as compared with seven out of 52 (13.5%) on placebo. This trial was especially significant because GlaxoSmithKline indicated in response to the IFPMA complaint (letter of August 2001) that its estimate of the incidence of withdrawal reactions was substantially based on the finding that only 7 patients out of the 8,143 on its clinical trials database were reported to have experienced a withdrawal syndrome. Apart from the fact that the design of many trials on the SmithKline Beecham's database (number unknown, but believed to be the large majority) would positively obscure evidence of the nature, incidence and severity of withdrawal – the number of patients experiencing withdrawal reactions in this one trial reported by Oehrberg *et al* was over twice the number on the SmithKline Beecham clinical trials database. Not only was this trial excluded from the company's database, but it also signalled an incidence of withdrawal reactions far in excess of the low levels the company implicitly claimed.

Nor could the assertion that withdrawal symptoms were very rare (<1:10,000) be reconciled with evidence from spontaneous reporting. However troublesome the interpretation of these data might be, the major confounding factor was under-reporting. Yet by September 2001, the Committee on Safety of Medicines (CSM) had received 1,242 reports of withdrawal reactions to paroxetine – a far higher number than for any other medicine on the ADROIT database. The prominence of paroxetine in the ADROIT tabulation was underlined by the analysis by Price *et al* in the MCA/CSM: 'withdrawal reactions with paroxetine constitute a greater proportion of reports (5.1%) than with the other SSRIs (0.06-0.9%)'.

The same picture emerged from the data generated by the Uppsala Monitoring Centre (January 2001) which had operational responsibility for the WHO's Programme for International Drug Monitoring. A table was provided which identified medicines on the Centre's database that had attracted most reports of withdrawal problems indicative of dependence. By a wide margin, paroxetine with 2003 reports was at the top of this list.

The complainant objected to the statement that 'there have been one or two reports of discontinuation symptoms with abrupt cessation' on the ground that GlaxoSmithKline had known for many years that the frequency of withdrawal symptoms was likely to be substantial, following studies on healthy volunteers, carried out in the 1980s: 'On average about half the volunteers taking part in a group of studies specifically designed to detect withdrawal problems suffered symptoms which suggest they had become physically dependent on the drug' (Boseley, 2001). The source of this information was Dr David Healy, who had personally examined this documentation in discovery relating to a US court case. Healy (2001) reported his concerns to the MCA, indicating that the results of these studies showed 'withdrawal syndromes occurred at a much higher rate than occur on benzodiazepines'.

The further implication of the statement at issue was that withdrawal symptoms existed only when there was abrupt cessation of treatment. In Case AUTH/IFPMA/5/7/01, the complainant requested the company to produce such relevant evidence as it had to support this assertion, but it did not respond. The complainant had no problem accepting that gradual reduction of dosage might attenuate withdrawal problems, but clearly it did not abolish them. Gradual tapering of dosages had been employed in the three cases reported by Barr *et al*; in four of the five cases reported by Keuthen *et al*; and 'the majority of cases occurred despite slowly tapered withdrawal' in the series reported by Coupland *et al*. Reference was also made to CADRMP, 1998; and DTB, 1999. Referring to the practice of dose tapering on cessation of treatment, one recent review concluded; 'as yet there is no controlled data to recommend its effectiveness, the length of time over which it should occur or the minimum dose that one should taper to' (Haddad, 2001).

Clause 7.9 Social Audit relied on the arguments and evidence set out above and invited GlaxoSmithKline to inspect the 1000-odd spontaneous reports from SSRI users on the Social Audit website, the large majority of which related to (a) withdrawal and dependence problems with paroxetine (Paxil, Seroxat, Aropax) rather than other SSRIs; and (b) reactions that were unexpectedly severe, disabling and often intensely disturbing. The website was only one of several where users so complained. Such a volume of reports, describing severe problems of a kind that manufacturers routinely denied and of which many prescribers appeared unaware, could and should be considered 'available evidence' within the meaning of the Code.

Clause 20.2 The complainant relied on the arguments and evidence set out above, drawing attention also to the following supplementary information in the Code; 'Particular care must be taken in responding to

approaches from the media to ensure that the provisions of this clause are upheld'.

Clause 2 The complainant recognised that the Authority regarded a ruling of a breach under Clause 2 as a sign of particular censure, to be used sparingly but nevertheless requested that a breach under this provision be ruled, taking into account:

1 The outcome of the previous IFPMA complaint and GlaxoSmithKline's acceptance of that decision and 'assurance that it would take all possible steps to avoid similar breaches of the IFPMA Code occurring in the future' (The remarks attributed to the Director of Corporate Media UK did not suggest that steps had been taken, but the complainant kept an open mind on this. If GlaxoSmithKline had taken any steps, it was invited to explain what had been done.)

2 The evidence provided of an established pattern of unacceptable behaviour.

3 That misleading statements were made to a lay rather than professional audience.

4 The Director of Corporate Media's seniority in the company.

5 The damaging consequences of such statements for patients and prescribers alike.

In relation to this last point, the users' comments provided were representative of recurrent themes: many prescribers were not aware of the significance of withdrawal and dependence problems (Young and Currie, 1997); users were not often warned about the possibility of withdrawal effects and dependence; prescribers were often unaware of the risks of mistaking withdrawal symptoms for 'relapse' and sometimes reluctant to accept patients' accounts of withdrawal symptoms, causing considerable distress; patients unable to discontinue medicines were obliged to resume taking them, much against their free will; withdrawal effects might be extremely distressing and disabling; and withdrawal and post-withdrawal effects were reported to be worse than the condition for which the medicine was prescribed.

RESPONSE

GlaxoSmithKline stated that the comment attributed to the Director of Corporate Media UK in the Independent (October 2001) stated (referring to paroxetine and other SSRIs) 'There's no reliable scientific evidence to show they cause withdrawal symptoms or dependency'. The Director of Corporate Media UK corrected this in his letter of 17 October 2001 where he stated that he was not referring to withdrawal symptoms. Contrary to what was stated in the complaint he did not say in that letter that he had been correctly quoted. In response to the reporter, the Director of Corporate Media UK intended to convey that SSRIs were not reliably shown to cause addiction/dependency.

Discontinuation symptoms, also referred to as withdrawal symptoms, comprised a diverse range of symptoms, but did not in themselves indicate dependence (Haddad, 1998 and Haddad, 2001). Dependence was a syndrome and diagnosis required several other features such as tolerance, inability to control medicine use, primacy of medicine taking behaviour, and continued use despite harmful consequences (Haddad *et al* 1998). Dependence was often used synonymously with the term addiction. In 2000, following a comprehensive review, the EMEA/CPMP released a position paper on 'Selective Serotonin Uptake Inhibitors (SSRIs) and Dependency/Withdrawal reaction'. A copy was provided. It endorsed the conclusions of the April 1998 CSM review that had not identified evidence that SSRIs were medicines of dependence, but that the product information for all SSRIs should contain appropriate warnings about well-recognised withdrawal reactions. They noted that following the request of the European Commission that the CPMP considered this issue, further evaluation of the clinical evidence relating to dependence associated with SSRIs was carried out by France and Germany, and that no evidence that SSRIs were medicines of dependence was found. Based on this and other evidence, the CPMP concluded that the available clinical evidence did not suggest that the SSRIs caused dependence. With respect to discontinuation or withdrawal, it recommended that the key elements of withdrawal reaction statements in the SPCs should be harmonised throughout the European Union and recommended the following, among other things:

- A statement that although withdrawal reactions might occur on stopping therapy, the available preclinical and clinical evidence did not suggest that SSRIs caused dependence.
- A list of symptoms reported in association with withdrawal reactions for that product.
- A statement that the majority of withdrawal reactions were mild and self-limiting.
- Advice that prescribers should consider gradual dose reduction when stopping treatment.

In accordance with the recommendations of the CPMP, the Seroxat SPC stated under Section 4.8 (undesirable effects) 'In common with other SSRIs, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg parasthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt discontinuation of Seroxat. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose tapering be carried out.' In accordance with these principles, the relevant sections of the briefing document approved for use in October 2001 were as follows:

'Addiction

- Seroxat unlike, for example, smoking or alcohol is not addictive. There are well-defined international criteria for drug dependency and addiction and Seroxat is clearly shown as being neither addictive nor causing dependence.

Discontinuation

- Abrupt stopping of any antidepressant can result in a small number of patients experiencing discontinuation symptoms.
- These symptoms – such as dizziness – are generally mild, short-lasting and self-limiting.
- As recommended by The British National Formulary (BNF) and the EMEA, the likelihood of these symptoms is minimised by gradually tapering the daily dose.
- Seroxat's high volume of usage compared to other SSRIs means that clinicians might perceive these symptoms occur more frequently with Seroxat. It is important to remember that this is a class effect and can occur with all SSRIs.
- The Seroxat SPC states 'In common with other SSRIs, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt discontinuation of Seroxat. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose tapering be carried out'.

GlaxoSmithKline stated that the comments reported in Mental Health Today (April 2002) were 'You have a product that's been available for over 10 years and has benefited tens of millions patients. As more patients use the product globally you are bound to get these reports of bizarre side effects', says the Director of Corporate Media UK. 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation, which is why our data sheets [doctor and patient information leaflets] reflect new advice to taper off the medication. The data sheet is a living document and as usage of the product increases the labelling reflects the current usage experience'.

There were two specific parts of this statement that the complainant discussed. Firstly, 'there is no scientific evidence that Seroxat leads to addiction and dependency'. Secondly, 'there have been one or two reports of discontinuation symptoms with abrupt cessation'.

With regard to the first part, GlaxoSmithKline concurred with the complainant that this comment was consistent with the Seroxat SPC, and clearly also with the briefing document enclosed. The relevant sections of this briefing document approved for use in December 2001 and used since then stated:

'Discontinuation

- Stopping any antidepressant can result in some patients experiencing discontinuation symptoms. The most common of these symptoms may include dizziness, sensory disturbances, agitation, anxiety, nausea and sweating. In most cases these symptoms are mild to moderate in nature and self-limiting.
- As recommended by the BNF and the EMEA the likelihood of discontinuation symptoms is minimised by gradually tapering the daily dose.
- Discontinuation symptoms are completely different to addiction or dependence. Haddad and Young, BMJ 1998, stated 'Discontinuation symptoms do not in themselves indicate drug dependence. Dependence is a syndrome, and diagnosis requires several other features, such as tolerance, inability to control drug use, primacy of drug taking behaviour, and continued use despite harmful consequences. Antidepressants are not associated with these features and are not drugs of dependence'.
- The Seroxat summary of product characteristics (SPC) states that 'In common with other SSRIs, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt discontinuation of Seroxat. They are usually mild, self-limiting and symptomatic treatment was seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose tapering be carried out'.

Addiction/Dependence

- Seroxat is not addictive. There are well-defined international criteria for drug dependency and addiction and Seroxat is clearly shown as being neither addictive nor causing dependence.
- The European Regulatory Body, the CPMP, have recently completed (April 2000) a thorough review of safety data collected following the discontinuation of all SSRIs and other newer serotonergic antidepressant medications. The Medicines Control Agency (MCA) and CPMP had concluded that SSRIs did not cause dependency/addiction.
- There has been no reliable scientific evidence from either preclinical studies, long term clinical trials or clinical experience, to suggest that Seroxat is addictive, shows dependence or is a drug of abuse.'

All these statements were supported by published data and the Seroxat SPC. As stated above, GlaxoSmithKline submitted that the EMEA/CPMP position paper on SSRIs and Dependency/ Withdrawal Reactions (2000) provided comprehensive and clear recommendations that were incorporated within the Seroxat SPC and hence into its briefing document.

GlaxoSmithKline stated that the anecdotal reports of adverse events by users of paroxetine from the Social Audit website supplied by the complainant had been

reported to the company's clinical safety department as part of its standard adverse event reporting procedure. However, it believed that Social Audit's website was not a source of valid and reliable data, presenting many potential biases and containing unverified data. GlaxoSmithKline did not believe it should be considered 'available evidence' within the meaning of the Code. GlaxoSmithKline hoped that Social Audit advised any patients reporting adverse events that their treating physicians should be notified in order that they could complete appropriate Yellow Card reporting of their symptoms to the CSM.

With regard to the specific comment attributed to the Director of Corporate Media UK that 'There have been one or two reports of discontinuation symptoms with abrupt cessation', the position of GlaxoSmithKline with respect to discontinuation of Seroxat was clearly enunciated in the relevant briefing document (December 2001) given above. GlaxoSmithKline acknowledged that the statement attributed to the Director of Corporate Media UK by Mental Health Today was not consistent with this briefing document. This statement was attributed to the Director of Corporate Media UK as part of a 'long conversation with Mental Health Today initiated by media interest in changes to the product data sheet and patient leaflet for the antidepressant Seroxat'. The Director of Corporate Media UK explained in his letter to the complainant that he could not remember the precise details of the conversation with the journalist, but that if detailed figures had been required, referral to an appropriate medical expert in the company would have been made.

In summary, the statement 'there have been one or two reports of discontinuation symptoms with abrupt cessation' attributed to the Director of Corporate Media UK was not consistent with the briefing document. However, the information in its briefing document was consistent with the Seroxat SPC and published data, being a factual and balanced document, which underwent the required internal approval process.

As no transcripts were available, there was difficulty in ascertaining exactly what was said in the conversation between the Director of Corporate Media UK and the journalists. Nevertheless, the statement in the Independent (October 2001) referring to paroxetine and other SSRIs, as made by the Director of Corporate Media UK was consistent with the SPC and briefing document and GlaxoSmithKline did not believe this statement had led to a breach of the Code. The comment reported in Mental Health Today (April 2002) of 'There is no scientific evidence that Seroxat leads to addiction and dependency' was consistent with the briefing document and the Seroxat SPC. As such, GlaxoSmithKline did not accept that a breach of Clauses 3.2, 7.2, 7.9 and 20.2 of the Code had occurred, with respect to that specific comment. However, the comment 'There have been one or two reports of discontinuation symptoms with abrupt cessation' was not consistent with either the appropriate briefing document (December 2001) or the Seroxat SPC.

Hence GlaxoSmithKline accepted that, if the statement was made by the Director of Corporate Media UK, a breach of Clauses 3.2, 7.2, 7.9 and 20.2 of the Code had occurred with respect to this specific comment.

Finally, GlaxoSmithKline had fully accepted the previous IFPMA ruling and the Director of Corporate Media UK had been fully compliant with all of the complainant's regular requests, with appropriate written responses within adequate timelines. GlaxoSmithKline took this very seriously and it denied that a breach of Clause 2 of the Code had occurred.

The amendment to the SPC was approved by the MCA in June 2001 and included in packs on the market from July 2001. Following the recommendations of the CPMP the SPC was supplemented to include the following additional statement 'In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence'. This amendment was approved in conjunction with a number of other changes to the Seroxat SPC. These changes were a result of a company review of Seroxat and a review of the SSRIs by the MCA.

The dates on the briefing documents of September and December corresponded to the final approval dates and these documents were therefore available for use from those dates onwards. Consequently the briefing document available in October for use in responding verbally to media enquiries was the version approved in September.

PANEL RULING

The Panel noted the reference to Case AUTH/IFPMA/5/7/01 which concerned Social Audit and GlaxoSmithKline. That case had been considered under the IFPMA Code and related to statements made by a SmithKline Beecham employee. The Authority dealt with the matter under the Constitution and Procedure for the Authority. With reference to discontinuation syndrome, it had been stated that what had been seen in terms of anecdotal reports was that it happened very rarely. The US product information described the frequency of withdrawal syndrome as a rare event. The statement was considered to be misleading in breach of the IFPMA Code. IFPMA agreed with the opinion of the Code of Practice Appeal Board that there was a breach of the IFPMA Code (Sections 1.3 and 1.7). The requisite undertaking had been received and the report for the case was made public by the IFPMA in January 2002.

The Panel was concerned that there were two quotations from an employee of GlaxoSmithKline that Seroxat did not cause withdrawal symptoms. These being 'There's no reliable scientific evidence to show they cause withdrawal symptoms or dependency' in The Independent, 1 October 2001, and 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation …' in Mental Health Today, April 2002.

The Seroxat SPC (Section 4.8) stated:

> 'In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of Seroxat. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering be carried out'.

Given the circumstances GlaxoSmithKline needed to be extremely careful about references to withdrawal symptoms/discontinuation symptoms. The company itself referred to the position as complex.

Complaints about items in the media were judged upon the material and comments provided by the company to the journalist. The Panel noted that there was no contemporaneous evidence or record of the conversations between the journalists and the Director of Corporate Media UK. The company submitted that the Director of Corporate Media UK could not remember the precise details of the conversation with the journalist at Mental Health Today. It might be that the journalists had misquoted the Director of Corporate Media UK. If so it did not appear that this had been followed up by GlaxoSmithKline. The Panel queried whether it was likely that two journalists would misquote with similar effect. If The Director of Corporate Media UK had been quoted accurately, the statements were inconsistent with the Seroxat SPC and GlaxoSmithKline's briefing documents. The company must ensure that material and comments were not inconsistent with the SPC. No written materials had been supplied to the journalists. Such documentation might have avoided the problems. Companies would be well advised to back up oral interviews with written material and to keep good records as to what was said.

On the evidence before the Panel it was not possible to determine precisely what had been said; in such circumstances it had had no option other than to rule no breach of Clauses 2, 3.2, 7.2, 7.9 and 20.2 of the Code.

APPEAL BY SOCIAL AUDIT

Social Audit stated that it was now clear that SSRI and related antidepressants, and paroxetine in particular, had induced withdrawal symptoms of sufficient severity and frequency to cause unprecedented levels of adverse reports from doctors and patients. Social Audit offered as new evidence data from the Medicines Control Agency (MCA), showing the number of Yellow Cards sent in (to July 2002) for the top 20 medicines suspected of causing withdrawal reactions. The absolute numbers were almost meaningless, but the ranking order had clearly indicated a problem; paroxetine was top of the list, in a league of its own, and five of the top six medicines were SSRI/SRNIs.

Social Audit's original complaint included a list of comments from 40-odd paroxetine users. Their meaning should be interpreted in the light of these many Yellow Card reports. Social Audit made it clear that these comments were like many thousands of others, all saying the same kind of thing: many people who wanted to stop taking paroxetine, found they could not – they felt addicted, well and truly hooked. Of course these comments could not compare with good, strong 'scientific' evidence – but Social Audit could not conceive of anyone reading them through and not concluding that some sort of dependence-related problem did exist, and that for some it was severe.

Social Audit contended that reports from users, collectively, were of real value in helping to understand the aetiology and nature of this problem, also in pointing towards solutions. The people who wrote to Social Audit, and many like them, would not be happy to learn that the company proposed to bury its problems in some database, loftily declining to offer any comment on their overall meaning, murmuring about bias, invalidity, lack of reliability and the impossibilities of verification. Social Audit stated that the UK in this brave new world of transparency, 'concordance' and 'The Expert Patient' (ABPI, 2000), was teetering on the brink of trusting companies enough not to fear Direct-To-Consumer Advertising – and there was the biggest pharmaceutical company in Europe, simply stating it did not want to know. Social Audit asked the Appeal Board to rule that users' comments might be counted as admissible evidence under the Code, and requested GlaxoSmithKline gave a proper account of its assessment of their meaning.

Social Audit believed these comments pointed to a deep and dangerous misunderstanding that now existed and thought it reasonable to request that the company took steps to remedy the persisting failures of communication that would only make it worse. The nub of the problem was that the company was relying on a definition of 'dependence' that was profoundly confusing to users and probably many doctors as well. This was not surprising because the word 'dependence' was recently radically redefined. Until the 1990s, health professionals understood that withdrawal symptoms on their own signalled 'dependence' – just as users knew that not being able to stop a medicine, especially after repeated and determined attempts, signalled that the medicine was habit forming and that the user might feel addicted or hooked. Then the definition was radically changed: suddenly 'dependence' meant there had to be other features of medicine abuse, as explained in Social Audit's original complaint. It was clear that there was great scope for confusion and Social Audit contended that the company's response was seriously deficient in not addressing such an obvious and important point. GlaxoSmithKline surely realised that the definition it relied on was widely misunderstood, but it did not acknowledge the possibility at all.

The company had simply not responded to the WHO statement (1998) cited in Social Audit's complaint,

that the SSRIs might indeed be medicines of dependence even within the formal definitions that now applied. Did GlaxoSmithKline accept this; if not why not?

Social Audit asked that the Appeal Board take account of what members of the public might infer, when assured that a medicine was not habit forming, addictive or liable to cause dependence. Social Audit also offered as evidence of the existence of some sort of 'dependence' problem with paroxetine – and confusion over meanings – the definition relied on by Drug Abuse Warning Network (DAWN); a nationwide network operated by the Substance Abuse and Mental Health Services Administration of the US Department of Health & Human Services:

> 'Dependence: A physiological or psychological condition characterized by a compulsion to take the drug on a continuous or periodic basic is order to experience its effects or to avoid the discomfort of its absence (eg had to take, had to have, needed a fix).'

If GlaxoSmithKline completely rejected this interpretation, which appeared to pretty much reflect public understanding, it should explain why. Why did the company see no need to clarify its meaning, and to reduce the high likelihood of misunderstandings, given the relevant requirements of the Code? Why did it rely instead on a narrow interpretation by the two authors of a BMJ article (especially when they failed to disclose that they were echoing the views of a seven strong 'Consensus Panel' convened by Eli Lilly and Company, the manufacturers of Prozac)?

It seemed unacceptable that resolution of this issue through self-regulation should stand or fall on the question of exactly what the Director of Corporate Media UK said. On the balance of probabilities, he clearly conveyed to the journalist in question that what some paroxetine users felt to be a problem was barely a problem at all. Assuming he had followed the brief in GlaxoSmithKline's 'Reactive Key Messages and Issues Document' (December 2001), that was certainly what he would have wanted to convey.

The issue here was not simply whether this brief complied with statutory standards but whether, in the light of the above, it satisfied the requirements to provide clear, reliable and balanced information, as specified below. Social Audit contended that this company brief fell short of Code requirements in failing to recognise and address the widespread and evident controversy and confusion over definitions and meanings, as explained above. Relevant Code provisions included Clauses 7.2 and 20.2 of the ABPI Code and the following: Article 7: WHO, Ethical criteria for medicinal drug promotion, Sections I.2, I.3 and I.7 of the IFPMA Code and Article 3 of the EFPIA Code.

In Social Audit's original complaint (relating to Clause 7.2), it conceded that the Director of Corporate Media UK's statement that, 'there is no scientific evidence that Seroxat leads to addiction and dependency' was not inconsistent with the SPC – though Social Audit thought it unfair, unambiguous and misleading, especially when directed to a lay readership. Social Audit still contended that Clause 3.2 of the Code did not override the above requirements – ie that concordance with the SPC was necessary, but not in itself sufficient for compliance with the Code. This distinction appeared to have been lost on the company: 'the information in our briefing document is consistent with our Seroxat SPC and published data, being a factual and balanced document, which underwent the required internal approval process'. Social Audit invited the Appeal Board to rule that this clause was intended to mean that product information must comply with statutory requirements, not that compliance with this provision satisfied the requirements of Clause 3.2.

Interpreting the Code in this spirit, Social Audit contended that the brief on which the Director of Corporate Media UK would have relied ('Reactive Key Messages and Issues Document' – December 2001) was itself in breach of Code requirements, in several respects and full details were provided. Social Audit was suggesting that whatever the Director of Corporate Media UK said, it would have reflected some of the lack of balance, misleading information and partial interpretation in the company's briefing document, 'Reactive Key Messages and Issues Document'.

Finally, Social Audit contended that the finding in favour of the company, on the grounds that the Panel was unable to determine precisely what had been said was unjustified for the following reasons:

- The Panel gave no evidence that it made contact with Mental Health Today to establish whether or not the journalist stood by the remarks published. Assuming no such checks were made, Social Audit believed it was quite inappropriate to speculate that The Director of Corporate Media UK might have been misquoted (albeit on two different occasions) and to find in the company's favour on the grounds of uncertainty about what the Director of Corporate Media UK actually had said.
- The Director of Corporate Media UK was given every opportunity to deny that he could or would have made the remarks quoted, but he did not do so. As the remarks published in Mental Health Today were evidently inappropriate, one would have expected the Director of Corporate Media UK to make a shocked and categorical denial, rather than some belated and hedged response. The inference would be that the Director of Corporate Media UK did say something very much along the lines of the remarks attributed to him, and/or that he did not appreciate how inappropriate the remarks attributed to him actually were. If he had, he would surely have made some effort to persuade a critical complainant that this certainly was not the impression he intended to give.
- The supplementary information to Clause 20.2, clearly suggested that companies should be in a position to provide copies of information supplied: 'particular care must be taken in responding to approaches from the media to ensure the provisions of this clause are upheld. In

the event of a complaint which relates to the provisions of this clause, companies will be asked to provide copies of any information supplied, including copies of any relevant press releases and the like. This information will be assessed to determine whether it fulfils the requirement of this clause'. Social Audit noted the company had no transcript. But did it not make a tape recording, or keep any record of what was said? This was surely a question the Appeal Board should pursue.

- It would not reflect the spirit of the Code; it might undermine confidence in self-regulation.

Returning to the point Social Audit made at the outset, it emphasised that it would readily drop this appeal if GlaxoSmithKline accepted the need to properly address the problems that now existed and agreed to take prompt and effective steps to deal with them. Failing this, Social Audit wished to pursue its complaint, notably under Clause 2 of the Code, relating to promotional activities that 'bring discredit upon, or reduce confidence in, the pharmaceutical industry'. Now having seen the promotional materials ('Reactive Key Messages and Issues Document', December 2001), which guided the Director of Corporate Media UK, and on which the company generally relied, Social Audit was more than ever convinced of an established pattern of unacceptable behaviour.

COMMENTS FROM GLAXOSMITHKLINE

In its appeal, Social Audit referred to several separate issues, some of which GlaxoSmithKline did not believe were relevant to the original complaint. Several of these issues related to GlaxoSmithKline's December 2001 briefing document, which it enclosed with its original response.

Regarding Social Audit's concerns relating to Clause 3.2 of the Code, this clause clearly stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC. This was wholly the case regarding GlaxoSmithKline's briefing document and Social Audit's comments relating to this briefing document, approved for use in December 2001, were unfounded. A detailed response was provided.

GlaxoSmithKline stated that the briefing document was supported by published data and the Seroxat SPC. Importantly, the EMEA/CPMP position paper on 'Selective Serotonin Reuptake Inhibitors (SSRIs) and Dependency/Withdrawal reactions' (2000) provided comprehensive and clear recommendations that were incorporated within the Seroxat SPC and hence into GlaxoSmithKline's briefing document.

Furthermore, the new evidence that Social Audit presented in its appeal (the top 20 medicines associated with reports of suspected withdrawal reactions), was taken directly from the UK ADROIT database and represented the total number of suspected withdrawal reactions over time. It was important to note that the unadjusted nature of these data might lead to wide misinterpretation of the relative risks of withdrawal reactions to these antidepressants. In fact, advice was given by the MCA in the guidance notes on the ADROIT system, warning against the use of spontaneous reports when making quantitative comparisons between medicines. It stated 'Numerical comparisons should not be made between reactions associated with different drugs on the basis of the data in these prints alone. Comparisons were invalid unless they took account of variations in the level of reporting, the extent of use of the drugs, and a number of other confounding variables'. GlaxoSmithKline therefore believed that not only was this evidence not relevant to the original complaint and out of context, but also was misleading, and the detailed analysis and interpretation of such data should be conducted by the MCA. In fact, correspondence (dated from June 2002) between Social Audit and the MCA published on the Social Audit website regarding paroxetine/SSRIs and reports of withdrawal/dependence, highlighted a potential review of SSRI's by the Committee on Safety of Medicines (CSM), this being the appropriate forum for such a review.

GlaxoSmithKline stated that a similar point was made in its original response to Social Audit's complaint regarding the anecdotal reports of adverse events reported by users of paroxetine from the Social Audit website. The context of the data was of paramount importance and GlaxoSmithKline believed that this website was not a source of valid and reliable data, presenting many potential biases and containing unverified data. GlaxoSmithKline continued to believe that the data on this website should not be considered 'available evidence' within the meaning of the Code.

Regarding the specific topic of dependence, GlaxoSmithKline reiterated its response to this question in Social Audit's original complaint, that discontinuation symptoms, also referred to as withdrawal symptoms, comprised a diverse range of symptoms, but did not in themselves indicate dependence. Dependence was a syndrome, and diagnosis required several other features, such as tolerance, inability to control drug use, primacy of drug taking behaviour, and continued use despite harmful consequences. Dependence as it was commonly understood, meant the same thing as addiction or substance dependence. In 2000, following a comprehensive review, the EMEA/CPMP released a position paper on SSRIs and Dependency/Withdrawal Reactions. They endorsed the conclusions of the April 1998 CSM review that had not identified evidence that SSRIs were medicines of dependence, but that the product information for all SSRIs should contain appropriate warnings about well-recognised withdrawal reactions. They noted that, following the request of the European Commission, the CPMP considered this issue and that no evidence that SSRIs were medicines of dependence was found. Based on this and other evidence, the CPMP concluded that the available clinical evidence did not suggest that the SSRIs caused dependence.

GlaxoSmithKline noted that in accordance with the recommendations of the CPMP, its SPC for Seroxat clearly stated under Section 4.8 (Undesirable Effects) that 'In common with other selective serotonin reuptake inhibitors, withdrawal symptoms have been

reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of 'Seroxat'. They are usually mild self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering be carried out'.

Regarding the issue of the Director of Corporate Media's statements to the journalists, GlaxoSmithKline noted that Social Audit stated that the Panel was unjustified in making its decision because of an inability to determine precisely what had been said. GlaxoSmithKline was not in a position to comment on the actions of the Panel in reaching its decision, but would again refer to its response to the complaint, acknowledging fully the advice that the Panel had given regarding written back up of oral interviews and good record keeping.

FURTHER COMMENTS FROM SOCIAL AUDIT

Social Audit stated that GlaxoSmithKline had failed to address almost all of the issues raised in Social Audit's appeal and submitted that GlaxoSmithKline's refusal to address these issues gave further and substantial grounds for its complaint that the company was bringing discredit on, and reducing confidence in the pharmaceutical industry, in breach of Clause 2 of the Code.

GlaxoSmithKline's submission in relation to Clause 3.2, wholly missed Social Audit's point. GlaxoSmithKline's defence was that its briefings and promotional materials complied with the SPC as that clause required. But it had not addressed Social Audit's point, that compliance with the SPC was necessary, but not in itself sufficient for compliance with the Code. For reasons stated in Social Audit's appeal, GlaxoSmithKline's briefings and promotional materials – particularly because they were directed at lay media and patient audiences – were seriously misleading, notably by giving the impression that both the MCA/CSM and EMEA had made some definitive assessment of the dependence problem and arrived at some binding conclusion. GlaxoSmithKline had no reason to continue to defend its position that this issue was cut and dried, since the company learned that the CSM would be reinvestigating this issue, one month before it wrote to the Authority in response to Social Audit's appeal.

It was really quite chilling to read that GlaxoSmithKline was unable to find any meaning in the sample of reports from users, claiming that such evidence was inadmissible under the Code. The collective significance of these reports was a key factor in persuading the CSM to reinvestigate. For the company to argue, in effect, that there was no problem of the kind that many paroxetine users were reporting reinforced Social Audit's view that patients had little reason to trust it.

Social Audit stated that GlaxoSmithKline was disingenuous in assessing the finding that five of the top six medicines for which suspected withdrawal reactions had been reported were SSRIs, with paroxetine at number 1. This was a key factor that persuaded the MCA/CSM to reinvestigate and the evidence was extrapolated from the ADROIT data specifically at Social Audit's instigation. In the light of what Social Audit stated in its appeal about the significance of the actual numbers, it seemed impertinent for GlaxoSmithKline to suggest its concerns were irrelevant and misleading.

With regard to GlaxoSmithKline's response to the appeal that some of the issues raised by Social Audit were not relevant to the original complaint, Social Audit stated that this seemed ambiguous, but Social Audit rejected both possible meanings. It was unacceptable for GlaxoSmithKline simply to say it believed 'some' of the issues Social Audit raised were not relevant, without specifying which, and why; but it would be absurd for GlaxoSmithKline to suggest that the critical comments Social Audit made about parts of the briefing document were not relevant to the original complaint. The Director of Corporate Media UK would/should clearly have relied on statements in the GlaxoSmithKline 'Reactive Key Messages and Issues Document' (19 December 2001). The central relevance of this document to Social Audit's complaint was underlined by the fact that GlaxoSmithKline sent it to the Authority to defend itself against the allegations Social Audit originally made.

Social Audit submitted that the MCA supported its concern about GlaxoSmithKline's use of the term 'discontinuation reactions' rather than 'withdrawal reactions' in GlaxoSmithKline's Reactive Key Messages and Issues Document (December 2001). The MCA stated that relevant SPCs for SSRIs and related antidepressants refer to 'withdrawal reactions' and not 'discontinuation reactions'.

The company's Reactive Key Messages and Issues Document referred to 'discontinuation symptoms' three times, while the only reference to withdrawal symptoms was in the passage cited directly from the SPC. Social Audit considered that the use of the term, 'discontinuation symptoms' in the Reactive Key Messages and Issues Document was not consistent with the SPC, and in breach of Clause 3.2 as alleged, and also misleading and in breach of Clauses 7.2, 7.9 and 20.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted the two quotations at issue 'There's no reliable scientific evidence to show they [Seroxat or other SSRIs] cause withdrawal symptoms or dependency', The Independent, 1 October 2001, and 'There is no scientific evidence that Seroxat leads to addiction and dependency. There have been one or two reports of discontinuation symptoms with abrupt cessation …', Mental Health Today, April 2002, were attributed to the Director of Corporate Media UK, GlaxoSmithKline.

The Appeal Board noted that Section 4.8 of the Seroxat SPC stated 'In common with other selective

serotonin reuptake inhibitors, withdrawal symptoms have been reported on stopping treatment. The available evidence does not suggest these are due to dependence. Dizziness, sensory disturbance (eg paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of 'Seroxat'. They are usually mild, self-limiting and symptomatic treatment is seldom warranted. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when antidepressive treatment is no longer required, gradual discontinuation by dose-tapering be carried out'. The Appeal Board also noted the 'Reactive and Key Messages and Issues Document' (September 2001) stated 'Abrupt stopping of any antidepressant can result in a small number of patients experiencing discontinuation symptoms'; this was updated in December 2001 to read 'Stopping any antidepressant can result in some patients experiencing discontinuation symptoms'.

The Appeal Board noted GlaxoSmithKline's submission that the Director of Corporate Media UK was one of only three employees working in a very busy environment. He was an experienced senior member of staff fully aware of the Seroxat briefing documents. There could be no absolute certainty as to precisely what was said. At the appeal hearing GlaxoSmithKline's representatives stated that if the Director of Corporate Media UK had been reported accurately then there was a breach of the Code. In its original response GlaxoSmithKline had accepted that if the Director of Corporate Media UK had made the statement 'There have been one or two reports of discontinuation symptoms with abrupt cessation' then a breach of the Code would have occurred.

The Appeal Board noted the parties' submissions regarding the various definitions of 'dependence', 'withdrawal symptoms/reactions', 'discontinuation symptoms/reactions' and 'addiction'. People's understanding of these terms differed depending on their background. The Appeal Board noted that at the appeal the GlaxoSmithKline representatives stated that the Seroxat patient information leaflet (PIL) stated that Seroxat was not addictive.

It was not the Appeal Board's role to assess the safety of a medicine or to approve the contents of its SPC or PIL; these were roles for the regulatory authorities. In the case now before it the Appeal Board had to decide firstly whether the Director of Corporate Media UK had been quoted accurately and, if so, whether what was said met the requirements of the Code.

The Appeal Board was concerned that the quotations were not consistent with the briefing documents. The Appeal Board considered that given the importance and sensitivity of the matter, the company must be very clear about the issues to avoid confusion. This was particularly important when providing information directly or indirectly to the public about side effects. In the Appeal Board's view the briefing documents did not sufficiently address the need for caution. The Appeal Board considered that although there was no written/recorded evidence of the interviews available it was very unlikely that one person would be misquoted twice on the same issue, especially considering the sensitivity of the matter. The Appeal Board considered that on the balance of probability the Director of Corporate Media UK had been quoted accurately. It was misleading to state that 'There's no reliable scientific evidence to show that they [Seroxat or other SSRIs] cause withdrawal symptoms …' or that 'There have been one or two reports of discontinuation symptoms with abrupt cessation' when the SPC clearly stated that 'withdrawal symptoms have been reported on stopping treatment'. The information supplied by the GlaxoSmithKline spokesperson to the press was misleading with respect to withdrawal symptoms. The Appeal Board ruled breaches of Clauses 7.2, 7.9 and 20.2 of the Code. The appeal of these aspects was successful. The Appeal Board noted that Clause 3.2 required that the promotion of a medicine must not be inconsistent with the particulars listed in the SPC. The statements were issued to the media and as such did not constitute the promotion of Seroxat; Seroxat was a prescription only medicine and should not be promoted to the public. On this narrow point the Appeal Board upheld the Panel's ruling of no breach of Clause 3.2. The appeal of this aspect was unsuccessful.

The Appeal Board noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such circumstances. The Appeal Board considered that, given the nature of the evidence, on balance the circumstances did not warrant a ruling of such a serious breach of the Code. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 2. The appeal of this aspect was unsuccessful.

The Appeal Board was extremely concerned about the statements made by the Director of Corporate Media UK. It considered that GlaxoSmithKline had not maintained a high standard as required by Clause 9.1 of the Code. There was however no allegation in this regard.

Complaint received **21 May 2002**

Case completed **5 November 2002**

CASE AUTH/1320/5/02

ANONYMOUS HEALTH PROFESSIONAL v AVENTIS PHARMA

Cardiology Meetings

An anonymous health professional complained about cardiology meetings held by Aventis Pharma. It was established practice that anonymous complaints were to be accepted and considered by the Authority in the usual way.

The complainant alleged that Aventis was running a series of meetings for cardiology trainees and consultants in 'Some pretty exotic locations'. The meeting attended by the complainant was '100% British but happened somewhere a lot nicer'. The complainant stated that the organisers of the meeting were the ramipril team.

The Panel noted that Aventis had provided details of seven meetings which occurred between September 2000 and May 2002. The Panel decided that the meetings held in Rome and Lisbon prior to 30 September 2001 would be considered in relation to the 1998 Code. The meetings held in Cannes, Barcelona and Lake Maggiore would be considered in relation to the requirements of the 2001 edition of the Code.

The Panel noted the invitations for the meetings in Cannes, Barcelona and Lake Maggiore stated that they were sponsored by an educational grant from Aventis Pharma. The Panel noted from the invitation that the meeting at Lake Maggiore, Italy, May 2002, was entitled 'Preventing Cardiovascular Disease, Solutions for Today, Strategies for Tomorrow'. The invitation featured a letter, signed by a 'marketing assistant – cardiovascular' which made reference to an 'exciting international meeting' and to clinicians from across Europe attending to discuss recent advances in the field of cardiovascular event prevention and the management of acute coronary syndromes. Invitees were advised to contact their local Aventis representative. A preliminary programme was provided together with a description of three local tourist attractions. Delegates travelled to the venue on Friday where a buffet dinner was provided. The educational session ran on Saturday morning from 09.00 to 13.00 hours when lunch was served. The period from 14.00 to 19.00 was described as 'Afternoon at Leisure' the day concluding with dinner. Breakfast and lunch were provided on Sunday morning; there was no educational activity. The final costings had not been provided as they were unavailable. The estimated cost of the provision of leisure facilities; based on either a boat trip to an island or mountain bike tour was provided and the estimated total per head cost was £856.48.

The invitation, timings and agenda for both the Barcelona and the Cannes meetings were similar to those for the Lake Maggiore meeting. The estimated cost per person was £1,211.18 for the Barcelona meeting and £1,023.58 for the Cannes meeting.

The Panel noted that Aventis UK had paid for doctors to attend the meetings in Cannes, Barcelona and Lake Maggiore. The Panel noted that all of the speakers at the meetings were from the UK, with co-chairmen from the host country. On the evidence before it, the Panel did not consider that these were a series of truly international meetings. The majority of delegates appeared to be the UK health professionals. The Panel considered that delegates would be attracted by the venue rather than the educational content. The company did not appear to have valid and cogent reasons for holding the meetings outside the UK. The Panel considered that the meetings held at Cannes, Barcelona and Lake Maggiore were unacceptable due to the limited educational content and the excessive hospitality. A breach of the Code was ruled.

The meetings held in Rome and Lisbon (3 meetings) featured a not dissimilar programme and level of hospitality. The Panel considered that the arrangements for the meetings held in Rome and Lisbon were similarly unacceptable to those referred to above. The Panel ruled a breach of the 1998 Code.

The Panel considered that in relation to all seven meetings Aventis had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled. It further considered that the arrangements for all seven meetings were such that they brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

The Panel further considered that the lack of educational content, the level of hospitality provided, the impression created by the arrangements and the number of meetings held was such that the circumstances warranted reporting Aventis to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that Aventis had held a total of seven meetings in various locations throughout Europe, not one meeting had been held in the UK. In all, approximately 700 UK doctors had been invited to the meetings. Aventis had submitted that all of those invited were consultant cardiologists and senior career grade physicians. The Appeal Board noted that a small number of delegates were GPs.

Each meeting followed a similar format. The Appeal Board accepted that the educational part of the meetings was of a high standard but considered that the balance of the meetings was in favour of hospitality and leisure. A two day meeting had been organised around a half day scientific programme. The Appeal Board considered that the arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel's ruling of a breach of Clause 2 was upheld.

The Appeal Board then considered the report made to it by the Panel in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about the arrangements for the meetings and the conduct of Aventis. The certification arrangements for the meetings were inadequate as acknowledged by Aventis at the appeal. The Appeal Board decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Aventis should be required to undergo an audit of its procedures in relation to the Code. This would be carried out by the Authority.

Upon receipt of the audit report the Appeal Board noted that Aventis had also organised meetings for primary care doctors. The Appeal Board considered that its rulings in Case AUTH/1320/5/02 might apply to the primary care meetings. The Appeal Board requested that Aventis be advised of its concerns and that the company should ensure that all meetings complied with the Code.

The Appeal Board noted that Aventis had accepted the report and had started work on incorporating the findings and recommendations into its procedures. The Appeal Board decided that at present, as Aventis had agreed to implement the recommendations and respond to the findings, it would not report the matter to the ABPI Board of Management. The Appeal Board decided that Aventis should undergo another audit in six months' time. On receipt of that audit report the position would be reconsidered.

An anonymous health professional complained about cardiology meetings held by Aventis Pharma Ltd. It was established practice that anonymous complaints were to be accepted and considered by the Authority in the usual way.

COMPLAINT

The complainant alleged that Aventis was running a series of seminars for cardiology trainees and consultants in 'Some pretty exotic locations'. The meeting attended by the complainant was '100% British but happened somewhere a lot nicer'. The complainant claimed to have been told by an Aventis representative that this was against the rules but she was unable to do anything about it, and suggested the complainant write to the Authority. The organisers of the meeting were the ramipril team.

Aventis was asked to respond in relation to the requirements of Clauses 19.1, 9.1 and 2 of the Code.

RESPONSE

Aventis provided details of symposia organised by the ramipril team over the past 3 years, namely; Rome September 2000, Lisbon March 2001, Lisbon April 2001, Lisbon June-July 2001, Cannes February 2002, Barcelona March 2002 and Lake Maggiore May 2002.

Aventis stated that it had adhered to the Code. Aventis personnel certified the meeting venues and content, the principal focus of all the meetings had been educational, costs for the delegates' accommodation and travel were not unrealistic, symposia were CPD (continuing professional development) approved for their educational content, delegates from other European countries attended all of the meetings, hospitality provided was of a reasonable level and no spouses attended any of the meetings.

In response to the request for further information Aventis stated that the reason for holding the meetings in mainland Europe was that the series was conceived as a European initiative with delegates from other European countries attending, including Norway, Finland, Holland, Republic of Ireland, Spain and Sweden. Delegate numbers and details of their nationalities for the 2002 meetings were provided (Cannes, Barcelona and Lake Maggiore).

The objective for each of the meetings was to disseminate current evidence-based medicine within cardiology via presentations and interactive question time to clinicians across Europe. The faculty employed for the series of meetings was of the highest calibre and were world experts in their field. The agenda for each of the meetings held in Cannes, Barcelona and Lake Maggiore were identical, with the same faculty presenting the same data.

Due to the educational content of the series and the eminent faculty, only senior doctors were invited namely at specialist registrar and consultant level.

The company confirmed the delegate numbers in relation to the 2002 meeting; for example, at the Cannes meeting there were 15 doctors from Finland, 120 from Norway and 2 from Holland. An Aventis director based in Paris invited 4 clinicians to the Cannes meeting.

The meeting space was defined as the total required seating for each of the meetings, including Aventis staff.

The meetings were a European initiative and this was reflected in the total number of attendees for the series of meetings. In Cannes, February 2002, 109 UK delegates, 142 international delegates and 25 Aventis staff attended. The figures for Barcelona were 96 UK delegates, 65 international delegates and 26 Aventis staff and the figures for Lake Maggiore were 113 UK delegates, 52 international delegates and 27 Aventis staff.

All venues were chosen based on the quality of their conference facilities: the hotel in Cannes and the hotel in Barcelona were city hotels, whilst the hotel in Baveno was 40 minutes from Milan.

Final cost information was provided which included hospitality costs for the Cannes and Barcelona meetings. The costs for the Italian meeting were yet to be finalised so a detailed estimate was provided, together with an estimate for a UK venue as a comparison. The hospitality provided was of a reasonable level and the total cost for the venues was similar, if not cheaper, than an equivalent UK location.

Details were provided about the meeting held in Rome and the three meetings held in Lisbon.

PANEL RULING

The Panel noted that Aventis had provided details of seven meetings which occurred between September 2000 and May 2002. Three meetings (Cannes,

Barcelona and Lake Maggiore) were held after the 2001 edition of the Code came into operation on 1 July 2001. Four meetings (Rome and three in Lisbon) had occurred prior to this date when the 1998 edition of the Code was in operation. The 2001 edition of the Code introduced a new Clause 14.2 which required that all meetings which involved travel outside the UK be formally certified in advance in accordance with the provisions of Clause 14.1. There had been some changes to the wording of Clause 19.1 in the 2001 Code. In the Panel's view the substantive provisions of Clauses 19.1 pertinent to this complaint had not significantly changed. Nevertheless the Panel decided that the meetings held in Rome and Lisbon prior to 30 September 2001 (to allow for the transitional provisions that during the period 1 July 2001 to 30 September 2001 that no activity would be regarded 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) would be considered in relation to the 1998 Code. The meetings held in Cannes, Barcelona and Lake Maggiore would be considered in relation to the requirements of the 2001 edition of the Code.

The Panel noted that Clause 19.1 of the 2001 Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK but considered that there had to be valid and cogent reasons for so doing. The supplementary information to Clause 19.1 of the 2001 Code stated that the impression created by the arrangements for any meeting must be borne in mind. It should be the programme that attracted delegates, not the associated hospitality or venue.

The Panel noted Aventis' submission that the reason for holding the meetings in mainland Europe was that the series of meetings was conceived as a European initiative with delegates from other European countries attending. The objective was to disseminate evidence-based cardiology medicine via presentations to clinicians across Europe. The invitations for the meetings in Cannes, Barcelona and Lake Maggiore stated that they were sponsored by an educational grant from Aventis Pharma. The address for the UK company was provided. It appeared that Aventis UK was responsible for all seven meetings.

The Panel noted from the invitation that the meeting at Lake Maggiore, Italy, May 2002, was entitled 'Preventing Cardiovascular Disease, Solutions for Today, Strategies for Tomorrow'. The invitation featured a letter, signed by a 'marketing assistant – cardiovascular' which made reference to an 'exciting international meeting' and to clinicians from across Europe attending to discuss recent advances in the field of cardiovascular event prevention and the management of acute coronary syndromes. Invitees were advised to contact their local Aventis representative. A preliminary programme was provided together with a description of three local tourist attractions. Delegates travelled to the venue on Friday where a buffet dinner was provided from 20.00 hours onwards. The educational session ran on Saturday morning from 09.00 until 11.10 when coffee was served and thereafter from 11.45 to 13.00 hours when lunch was served. Delegates received three one hour presentations entitled 'Recent advances in the management of Acute Coronary Syndromes', 'Secondary care prevention of cardiovascular events in patients with a history of CHD or diabetes' and 'The future of secondary prevention – how ACE inhibitors really work'. There was 25 minutes at the end of the morning session for 'Panel Discussion'. The period from 14.00 to 19.00 was described as 'Afternoon at Leisure' (leisure activities were provided by the company from 14.30 hours to 18.00 hours) the day concluding with dinner. Breakfast and lunch were provided on Sunday morning; there was no educational activity. The final costings had not been provided as they were unavailable. The preliminary budget available for the meeting referred, *inter alia*, to 'predinner drinks' for 150 people, thereafter a 3 course dinner on an island including 1/2 a bottle of wine per person were estimated to cost approximately £111 per head. The estimated cost of the provision of leisure facilities; based on either a boat trip to island or mountain bike tour was £4,511.99 (£30.08 per head). The estimated total per head cost was £856.48.

Aventis provided inconsistent information about the number of delegates. According to its initial response 150 UK bedrooms were needed. 15 Finnish delegates, 26 delegates from the Republic of Ireland and 20 Swedish delegates attended the meeting. In its subsequent response it submitted that 113 UK, 52 international delegates and 27 Aventis staff attended. The delegate list indicated that 124 UK delegates attended.

The invitation, timings and agenda for the Barcelona meeting were similar to those for the Lake Maggiore meeting. In addition a letter providing flight tickets and an expense form making reference to further administrative details was provided. Two final reconciliations, one providing greater detail and a preliminary budget were provided for the Barcelona meeting. The final reconciliation made reference to a city tour at a cost of £25 per head (total cost £4,000). Dinner on Saturday evening comprised the hire cost of a castle (£4,656.25) and 3 course dinner and predinner drinks for 200 (£13,125). Reference was made to night-club tickets for 80 at £585.60. The final reconciliation included reference to 'Tuna Band' at £800 and 'Rumberos' at £1,218.75. Reference was made on the final reconciliation to Irish delegates whose attendance did not appear to be mentioned elsewhere. The estimated cost per person was £1,211.18.

It was initially stated that 150 UK bedrooms were needed and that 44 Norwegian delegates attended with 15 Finnish and 24 Spanish delegates attending the meeting but accommodation for the Finnish and Spanish delegates was provided elsewhere. Aventis subsequently submitted that 96 UK and 65 international delegates and 26 staff were in attendance.

The invitation, timings and agenda for the Cannes meeting were similar to those for the Lake Maggoire meeting. A preliminary budget and two final reconciliations were provided for the Cannes meeting. The cost of dinner on Saturday night was listed as £38,301.47 for 279 persons which appeared to include an international contingent. Reference was made to leisure activities; including a Picasso tour, wine tasting, Monaco tour and mountain biking. The total cost £4,132.20 for 131 delegates, approximately £31 per head. The per person total cost on the final reconciliation was £1,023.58.

Again inconsistent information was provided about the number of delegates. According to its initial response 153 UK bedrooms were needed. 120 Norwegian delegates attended, 2 Dutch and 5 French delegates attended with 15 Finnish delegates attending but accommodation for the Finnish and Norwegians appeared to be provided elsewhere. Aventis subsequently submitted that 109 UK delegates, 142 international delegates and 25 Aventis staff attended this meeting.

The Panel noted that Aventis UK had paid for doctors to attend the meetings in Cannes, Barcelona and Lake Maggiore. The Panel noted that all of the speakers at the meetings were from the UK; with co-chairmen from the host country. On the evidence before it, the Panel did not consider that these were a series of truly international meetings. The majority of delegates appeared to be the UK health professionals. The Panel considered that delegates would be attracted by the venue rather than the educational content. The company did not appear to have valid and cogent reasons for holding the meetings outside the UK at the chosen venues. The Panel was very concerned that the educational content amounted to half a day which did not justify the provision of two nights' accommodation. The hospitality was not secondary to the educational content.

The Panel noted that whilst reasonable hospitality could be provided the cost of the meetings should not exceed those which participants might normally pay. Entertainment however could not be provided. The Panel was concerned at the leisure activities which were paid for by Aventis. The impression created by such arrangements should be borne in mind. The Panel considered that the meetings held at Cannes, Barcelona and Lake Maggiore were unacceptable due to the limited educational content and the excessive hospitality. A breach of Clause 19.1 of the 2001 Code was ruled.

The meetings held in Rome and Lisbon (3 meetings) featured a not dissimilar programme and level of hospitality. Tickets for a nightclub were provided. No breakdown of delegates were given for these meetings. It appeared that dinner was paid for 170 people in Rome (2000) with approximately 146 UK delegates listed. It appeared dinner was paid for 200 people in Lisbon (March 2001) with approximately 150 UK delegates. The situation was similar with the other two meetings held in Lisbon (April and June).

The Panel considered that the arrangements for the meetings held in Rome and Lisbon were similarly unacceptable to those referred to above. The Panel ruled a breach of Clause 19.1 of the 1998 Code.

The Panel considered that in relation to all seven meetings Aventis had failed to maintain a high standard of ethical conduct and a breach of Clause 9.1 of the Code was ruled. It further considered that the arrangements for all seven meetings were such that they brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed. These clauses were the same in both the 1998 Code and the 2001 Code.

The Panel considered that the lack of educational content, the level of hospitality provided, the impression created by the arrangements and the number of meetings held was such that the circumstances warranted reporting Aventis to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY AVENTIS

In its written submission Aventis noted that Clause 19.1 of the 2001 Code permitted companies to hold scientific meetings with appropriate hospitality and that these meetings could be held outside the UK provided there existed valid and cogent reasons for doing so. Aventis strongly disagreed with the ruling of the Panel and considered that in determining the acceptability of these international meetings, due consideration was given to the educational programme, overall cost, facilities of the venue, nature of the audience and hospitality provided. These considerations were reiterated below. Aventis remained confident that it had fully complied with the Code and its actions had not represented a breach of Clauses 2 and 19.1 of the Code.

As the Authority was aware, meetings similar to the subject of this case were widespread practice within the industry eg UK only doctors taken to France for a meeting for the dissemination of results from a clinical trial. The ruling against Aventis in this case therefore questioned what could be considered as 'clear educational content' and 'appropriate hospitality', with regard to doctors attending international and indeed local meetings (regardless of industry sponsorship).

Aventis wished to restate its position as follows:

1 Educational content

The primary purpose of the meetings was education. This was made clear in the initial invitations by the prominent display of the meeting title and agenda within the invite. No mention was made of the dinner venue or other activities (other than the brief description of some local attractions within easy reach of the hotel). This therefore precluded potential delegates from seeing this as an attraction. The Panel highlighted the phrase 'exciting international meeting'. The 'excitement' of this meeting was the outstanding internationally recognised panel assembled to deliver the educational programme. It would be difficult to think of a group of speakers to cover these particular topics who had a more distinguished clinical background.

Aventis noted that the Panel also drew attention to the fact that the invitation was signed by a member of the

marketing department. The Code had not prohibited marketing departments from organising educational meetings. Indeed, co-ordination of the meeting by the marketing department was a reflection of the importance with which they treated clinical education. There was of course also extensive input from the medical department in the choice of speakers and the content of the topics covered.

In addition to the eminent faculty, the granting of 4 CPD credits for full attendance further supported the educational quality of the meeting. The number of credits was consistent with that given for attendance at other academic international meetings, eg European Society of Cardiology where a one hour talk was given one credit.

In summary, Aventis was confident that this meeting was primarily educational and that delegates were first and foremost attracted by the high quality of the educational programme, not the venue. Aventis did not believe that venues chosen would have offered any greater attraction to a senior clinician than a central London or country house hotel in the UK. The majority of such doctors regularly attended international meetings and it was unlikely therefore that these venues would have been of any greater interest than a UK venue. Aventis argued that the necessity to travel to a European destination for the meeting rather than remain in the UK was as likely to have discouraged as encouraged attendance. Aventis could not therefore agree with the Panel's conclusion that the education was a secondary purpose of the meeting.

2 International Meetings

Aventis disagreed with the Panel's supposition that the nationality of the faculty at a meeting determined whether or not it could be considered 'international'. Many international congresses had considerable bias towards certain nationalities of both speaker and delegate. To have chosen speakers from other countries on the basis that the meeting appeared more 'international' should not be an overriding consideration.

The faculty was, as noted, primarily from the UK. This was a reflection of the internationally renowned status of the speakers. By making the assumption that delegates would be attracted by the venue rather than the educational content, the Panel was implying that the doctors concerned were willing to compromise their professional integrity to spend a weekend in Europe. This line of reasoning was demeaning to the faculty and also called into question the conduct of the delegates in attending the meeting. As discussed above, Aventis believed it was extremely unlikely that the intended audience found the venue a major attraction.

The meetings were a European initiative, with between 30-50% non-UK delegates. Whilst agreeing with the Panel's assessment that the majority were from the UK, Aventis did not believe this was *prima facie* evidence that the meeting was not international. The attendance of significant numbers of international delegates at every meeting had made these meetings by definition international.

The inconsistencies in the number of delegates attending the meeting noted by the Panel related to numbers of planned vs acceptance, vs actual attendance. In addition, some countries organised their own accommodation and this had not appeared on Aventis' details.

3 Level of hospitality and appropriateness to audience

Aventis disagreed with the Panel that the level of hospitality provided was excessive.

Aventis had provided the Panel with full costings of the venues and flights together with costings for hosting the same meeting within the UK. These clearly indicated that the location of the meeting, in or out of the UK, did not materially affect the cost of the meeting.

The cost of the conference dinner per head in Barcelona and Cannes was £118.34 and £137.28 respectively. As a comparison, the Panel might wish to consider that tickets for the Gala Evening for the 2002 ESC congress were on sale for 183 euros (£117 at current exchange rates). The ESC congress catered for a similar group of clinicians as those attending the Aventis-sponsored meetings, namely consultant cardiologists and senior career grade physicians. Thus given the stature of participants and the cost such doctors were prepared to personally pay to attend similar events hosted by professional associations, the level of hospitality was clearly not excessive.

In review of the case, Aventis would also like the Panel to consider that the doctors that had attended these meetings should be aware of the General Medical Council (GMC) guidance on professional conduct. Indeed the GMC booklet 'Good Medical Practice' quoted in the Code stated, 'You may accept personal travel grants and hospitality from companies for conferences and meetings as long as the main purpose of the event is educational. The amount you receive must not be more than you would normally spend if you were paying for yourself'. It was clear that the GMC placed an onus on doctors to only attend meetings whose main purpose was educational. By attending the meeting, it would appear that the clinicians involved had made the judgement that the purpose of the meeting was educational and that the costs involved were not beyond what they would consider appropriate and be willing to pay for themselves. Should the Panel's judgement differ from that of both Aventis and the delegates, this would have raised a number of issues regarding the professional conduct of the physicians.

At the appeal hearing the representatives confirmed that there was no appeal of the rulings of breaches of Clauses 9.1 and 19.1. Aventis had taken the matter extremely seriously. Aventis acknowledged that there had been errors of judgement and process for which it apologised. The company had looked at its procedures with regard to meetings, sponsorship and support, agreements with opinion leaders, training particularly of sales and marketing, junior and middle management and the certification process with an action plan to eradicate any deficiencies.

The Aventis representatives referred to a recent article in the BMJ referring to guidelines for doctors issued by the Royal College of Physicians.

APPEAL BOARD RULING

The Appeal Board noted that the appeal was limited to the ruling of a breach of Clause 2. The Panel's rulings of a breach of Clauses 9.1 and 19.1 of the Code were not appealed.

The Appeal Board noted that Aventis had held a total of seven meetings in various locations throughout Europe, not one meeting had been held in the UK. In all, approximately 700 UK doctors had been invited to the meetings. Aventis had submitted that all of those invited were consultant cardiologists and senior career grade physicians. The Appeal Board noted, however, from the participant lists provided, that a small number of delegates were GPs.

Each meeting followed a similar format: delegates would arrive on Friday evening and have dinner; there was a 4-4^1/$_2$ hour scientific session on Saturday morning; Saturday afternoon was taken up with leisure activities paid for by Aventis; there was a dinner on Saturday evening and delegates returned home on Sunday. The Appeal Board accepted that the educational part of the meetings was of a high standard but considered that the balance of the meetings was in favour of hospitality and leisure. A two day meeting had been organised around a half day scientific programme. The Appeal Board considered that the arrangements were such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel's ruling of a breach of Clause 2 was upheld. The appeal was unsuccessful.

REPORT FROM THE PANEL TO THE APPEAL BOARD

The Appeal Board then considered the report made to it by the Panel in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about the arrangements for the meetings and the conduct of Aventis. The certification arrangements for the meetings were inadequate as acknowledged by the Aventis representatives. The Appeal Board decided that in accordance with Paragraph 10.4 of the Constitution and Procedure, Aventis should be required to undergo an audit of its procedures in relation to the Code. This would be carried out by the Authority.

Upon receipt of the audit report, the Appeal Board noted that the audit had revealed that Aventis had organised meetings for primary care doctors. Details had not been provided. The complainant had referred to 'seminars for cardiology trainees and consultants'. The Appeal Board considered that its rulings in the current case, Case AUTH/1320/5/02, might apply to the primary care meetings. Aventis had signed an undertaking in that case to avoid similar breaches of the Code in the future. The Appeal Board requested that Aventis be advised of its concerns and that the company should ensure that all meetings complied with the Code.

The Appeal Board noted that Aventis had accepted the report and had started work on incorporating the findings and recommendations into its procedures. The Appeal Board decided that at present as Aventis had agreed to implement the recommendations and respond to the findings, it would not report the matter to the ABPI Board of Management. The Appeal Board decided that Aventis should undergo another audit in six months' time. On receipt of that audit report the position would be reconsidered. In the meantime the case report would be published in the Code of Practice Review.

Complaint received	**16 May 2002**
Case completed	**10 October 2002**
PMCPA proceedings completed	**20 November 2002**

CASE AUTH/1349/8/02

GLAXOSMITHKLINE v TAKEDA

Promotion of Actos

GlaxoSmithKline complained about the promotion of Actos (pioglitazone) by Takeda. GlaxoSmithKline alleged that a one page press release 'New study highlights lipid advantages of Actos for patients with type 2 diabetes' was in breach of the Code as it featured claims which were essentially similar to those made for GlaxoSmithKline's product, Avandia (rosiglitazone), in Case AUTH/1123/1/01 which were ruled in breach of the Code. Statements to the effect that Actos had the potential to reduce cardiovascular risk and improve outcomes, unsupported by the results of any outcome studies, were made.

The Panel noted that Actos was indicated only in oral combination treatment of type 2 diabetes mellitus. The press release discussed the results of the EVIDENT study (Boyle *et al*) which compared the effects of Avandia and Actos on blood lipids and glycaemic control. It was stated that patients who were prescribed Actos achieved a significantly greater improvement across the whole lipid profile compared to patients who received rosiglitazone. It was further stated that 'while each drug achieved similar glycaemic control there were significant differences between the two, which may have important implications for cardiovascular risk among patients with type 2 diabetes' and that the study 'confirmed the potential for pioglitazone to reduce cardiovascular risk in the longer term. However, we all await the outcome studies'. With regard to cardiovascular disease being a frequent cause of death for patients with type 2 diabetes, it was stated that 'any therapy that can reduce that risk is a welcome addition'.

The Panel noted the study authors' caveats regarding the need for outcome studies to determine whether, *inter alia*, cardiovascular benefit was realized and considered that there was no endpoint data to support a claim for a reduction in cardiovascular risk. The press release referred to the need to await outcome studies and that Actos 'may have important implications for cardiovascular risk' and 'the potential to reduce cardiovascular risk'. Nonetheless the Panel considered the overall prominence given to the potential reduction in cardiovascular risk in the absence of outcome studies rendered the press release misleading and inconsistent with the summary of product characteristics (SPC) on this point. Breaches of the Code were ruled.

GlaxoSmithKline noted that although the claim was made that '… patients with type 2 diabetes who were prescribed Actos achieved significantly greater improvement across the whole lipid profile compared to patients treated with rosiglitazone', it was not made clear that these results were achieved with an unlicensed dose of pioglitazone [45mg]. In GlaxoSmithKline's view, the sentence in the last paragraph, 'The EVIDENT study related to use in the US', was wholly inadequate. GlaxoSmithKline alleged breaches of the Code.

The Panel noted that in the UK the licensed daily dose of Actos was 15 or 30mg in combination with metformin or sulphonylurea. The Panel considered that it had not been made sufficiently clear that the results discussed in the press release were achieved in an Actos patient group of whom 30% were receiving a dose higher than that licensed in the UK. The reference to the EVIDENT study relating to US use was insufficient in this regard. The Panel considered that the press release was misleading and inconsistent with the SPC as alleged; breaches of the Code were ruled.

GlaxoSmithKline was concerned about the manner and tone in which EVIDENT, a retrospective case-note analysis, had been presented. Although the word 'retrospective' was mentioned once, the use of a meaningless and impressive-sounding 'acronym' – 'EVIDENT' – for the study, the all-embracing nature of the claims based upon it, and the use of selected third-party endorsements, all served to give the impression that the results obtained had far more significance than the nature and methodology of the study would normally warrant.

The Panel considered that its rulings above were relevant. The press release described the EVIDENT study as a multicentre, retrospective random review of 1,115 selected medical records. The Panel considered that the retrospective nature and methodology of the trial was thus sufficiently clear. The Panel considered that the press release did not sufficiently reflect the authors' caveats about the clinical significance of their results in relation to lipid profile and cardiovascular risk, the four month observational period and the authors' conclusion that longer term studies were needed. The Panel ruled breaches of the Code. The Panel did not consider that the press release was all-embracing as alleged. No breach of the Code was ruled.

A loose insert in a pocket at the back of a detail aid headed 'Are all glitazones the same?' compared Actos and rosiglitazone in relation their effect on cardiovascular risk factors and cost. Beneath the heading '… and has positive effects on cardiovascular risk factors' a table listed aspects of the lipid profile and indicated that the total C:HDL-C ratio for Actos decreased and remained unchanged for rosiglitazone. GlaxoSmithKline noted that the effects of rosiglitazone on the total cholesterol:HDL-cholesterol (TC:HDL-C) ratio was represented as 'unchanged'. This was not consistent with the SPC for Avandia, which stated that 'the ratio of total cholesterol:HDL-C was unchanged or improved in long term studies'.

The Panel noted that the statement in the SPC appeared in Section 4.8 of the SPC headed 'Undesirable effects'. The statement appeared in association with information about adverse experiences of hypercholesterolaemia. The Panel considered that given the statement in the Avandia SPC the depiction of the total C:HDL-C ratio as unchanged in the material now at issue was misleading; it was not a complete picture of Avandia's effect on the TC:HDL-C ratio. Breaches of the Code were ruled.

GlaxoSmithKline noted a table indicated that LDL-C remained unchanged for Actos and increased for rosiglitazone. GlaxoSmithKline referred to its submission on this point in Case AUTH/1337/6/02 that this severely misrepresented the effects of Avandia on this parameter. Administration of Avandia did result in a small, short-term increase in LDL-C levels, which stabilised over the longer term. This effect, however, appeared to be associated with an Avandia-induced shift in LDL-C particle size towards larger less dense (and hence less atherogenic) LDL-C particles. GlaxoSmithKline alleged that it was misleading to mention the small quantitative changes in LDL-C associated with Avandia, while omitting to mention the much more clinically significant qualitative changes.

The Panel considered that this was an emerging area of science upon which there was, as yet, no medical consensus. The Panel did not consider that the failure to refer to rosiglitazone's effects on the qualitative aspects of LDL-C was misleading as alleged. No breach of the Code was ruled.

GlaxoSmithKline did not accept the dose equivalences or cost advantage for Actos implied by a table in a section headed 'Glitazone cost comparison'. The available evidence, the great majority from non-head-to-head studies, suggested that the efficacy and tolerability of the 4mg/day dose of Avandia was comparable to those of the 30mg/day dose of Actos. Furthermore, it noted that only the 30mg dose of Actos was promoted; whereas, for Avandia, both doses were promoted, with a recommended starting dose of 4mg od (as per the licence). All available data suggested that, where dosage was specified, the majority of prescriptions for Avandia were for the 4mg od dose. This would weight the cost comparison more in favour of Avandia than of Actos. GlaxoSmithKline alleged that the dose equivalences and cost 'advantage' implied by this table were inaccurate and misleading.

The Panel noted the cost per 28 days' treatment of Actos and rosiglitazone at their respective licensed doses were set out in separate adjacent tables which were of identical size. The cost data for 30mg od Actos occupied the same amount of space as that for rosiglitazone 4mg bd and 8mg bd. The Panel did not accept that the juxtaposing of the tables nor the space allocation of the 30mg od Actos and 4mg bd and 8mg bd rosiglitazone data implied dose equivalence and thus a cost advantage for Actos as alleged. The Panel thus ruled no breaches of the Code on this narrow point.

GlaxoSmithKline noted that claims were made that Actos was 'The only glitazone which significantly raises HDL-C and lowers triglycerides whilst causing no significant increase in LDL-C compared to placebo', '… Actos is the only glitazone that has a positive effect on the lipid profile by lowering triglycerides and increasing the HDL cholesterol, while causing no significant change to LDL-C compared to placebo' and 'Has positive lipid effects by significantly improving *triglyceride* and *HDL-C* levels with no significant change in LDL-C compared with placebo – unlike other glitazones'. GlaxoSmithKline alleged that the claims sought to make an unjustifiable and unwarranted differentiation between Actos and Avandia, to the detriment of the latter. Avandia had been, *inter alia*, shown to significantly increase levels of HDL cholesterol and its most atheroprotective subfractions. The claims at issue could be interpreted as meaning either that Avandia had no lipid effects, which was patently untrue, or that Actos possessed unique and clinically significant advantages over Avandia. In reality, the effects of the two products on the majority of lipid parameters were similar. GlaxoSmithKline alleged that to 'cherry-pick' a series of claims to which the word 'only' could be applied, implying a clear-cut superiority of one product over another, when the totality of available evidence did not support such an inference, was inherently misleading and disparaging.

The Panel did not accept GlaxoSmithKline's allegation that the claims, individually, or as a whole, could be interpreted as meaning that Avandia had no lipid effects at all. The Panel considered that on the evidence before it in relation to the effect of rosiglitazone the claims '… Actos is the only glitazone that has a positive effect on the lipid profile by lowering triglycerides and increasing the HDL cholesterol, while causing no significant change to LDL-C compared to placebo' and 'Has positive lipid effects by significantly improving *triglyceride* and *HDL-C* levels with no significant change in LDL-C compared with placebo – unlike other glitazones' implied that Actos possessed unique and clinically significant advantages in relation to effects on the lipid profile and that only Actos had positive effects on the lipid profile. This was not necessarily so. The Panel considered that the claims were misleading and not capable of substantiation; breaches of the Code were ruled. The Panel did not consider that the two claims were disparaging and no breach of the Code was ruled. The Panel considered that the claim 'The only glitazone which significantly raises HDL-C and lowers triglycerides whilst causing no significant increase in LDL-C compared to placebo' was not unreasonable as alleged and no breach of the Code was ruled.

GlaxoSmithKline UK Limited complained about the promotion of Actos (pioglitazone) by Takeda UK Ltd. GlaxoSmithKline produced Avandia (rosiglitazone).

A Takeda press release headed 'New study highlights lipid advantages of Actos for patients with type 2 diabetes'

The one page press release discussed the results of a retrospective case record analysis, Boyle *et al* (2002) [EVIDENT] which compared the effects of Avandia and Actos on blood lipids and glycaemic control. It featured quotations from three health professionals.

The press release was distributed to a selection of electronic and print medical publications.

1 Outcome claims

COMPLAINT

GlaxoSmithKline noted that in Case AUTH/1123/1/01, in which Takeda was the

complainant, the Panel's ruling that the claim 'Avandia has the potential to delay disease progression and reduce complications' was in breach of the Code was upheld on appeal. Despite positive effects of Avandia on a range of cardiovascular risk factors, the Panel and the Appeal Board considered that, in the absence of outcome studies, this claim was misleading and inconsistent with the Avandia summary of product characteristics (SPC), in breach of Clauses 3.2 and 7.2.

Notwithstanding that ruling, Takeda made essentially similar claims for pioglitazone in the press release in question. Statements to the effect that Actos had the potential to reduce cardiovascular risk and improve outcomes, unsupported by the results of any outcome studies, were made four times (once 'editorially' and three times through third-party endorsements).

GlaxoSmithKline alleged that, in the light of Case AUTH/1123/1/01, this press release must be, *ipso facto*, in breach of Clauses 3.2 and 7.2 of the Code and the severity of these breaches was aggravated by the particular circumstances referred to.

RESPONSE

Takeda noted that Case AUTH/1123/1/01 dealt with three aspects of GlaxoSmithKline's promotion of Avandia's lipid benefits. Points A2(i) and A2(ii) dealt with inappropriate claims for reduction of triglycerides and TC:HDL-C ratio respectively. Neither included a claim for risk reduction. Point E2 related to a claim for the product's risk reduction potential in relation to all cardiovascular risk factors; 'Avandia has the potential to delay disease progression and reduce complications' which was found in breach. Takeda believed that the claim at issue relating to Avandia was a far broader claim than the references made in the press release now at issue.

Takeda stated that its original complaint was based on a number of issues relating to Avandia's effectiveness in controlling risk factors, quoting the Food and Drugs Administration (FDA) and European Medicines Evaluation Agency (EMEA), the latter stated that Avandia's effects on lipid profile 'cannot be predicted and therefore raise concerns'. The National Institute for Clinical Excellence (NICE) expressed reservations.

Takeda noted that in its press release it referred to the following: '… Lipid Advantages …' (headline), 'differences … which may have important implications for cardiovascular risk …' (paragraph 2), 'The trial … confirmed the potential … to reduce cardiovascular risk …. However, we all await the outcome studies' (paragraph 3), 'Until publication of the outcome studies, EVIDENT gives us the confidence to believe that pioglitazone's effects on the lipid profile should translate into long term benefits' (paragraph 4) and 'This study provides reassuring evidence that … a significant effects was seen across the lipid profile. The improvement in the HDL/LDL ratio is particularly important for UK clinicians' (paragraph 5).

Takeda stated that no outright risk reduction claims were made. The text merely mentioned that the study highlighted the potential to reduce risk. The absence of any outcome studies was mentioned twice and was specifically included so as to ensure that there was no implication that any outcome studies existed or that EVIDENT was such a trial.

Takeda considered that it had made strenuous efforts to ensure that the message delivered was that Actos only had the potential to reduce risk and that these likely benefits were speculative and built on a hypothesis that had yet to benefit from any data from outcome studies with the product.

The three external experts quoted in this press release all gave their opinions freely. They were at the top of their specialities. Details were provided.

The press release fairly and accurately represented the EVIDENT data and that these data were consistent with the broader body of scientific evidence relating to the lipid effects of Actos and Avandia. Indeed there were seven published prospective head-to-head studies of Avandia and Actos in addition to EVIDENT. The lipid effects seen in these seven studies supported the claim for the effects of Actos on lipids. Takeda also noted that the lipid effects seen with Actos in EVIDENT and elsewhere were of a similar order to those proven to have a beneficial effect on cardiovascular risk.

PANEL RULING

The Panel noted that according to its SPC Actos was indicated only in oral combination treatment of type 2 diabetes mellitus. The press release was headed 'New study highlights lipid advantages of Actos for patients with type 2 diabetes'. Results of the EVIDENT study, (Boyle *et al*) were discussed. It was stated that patients who were prescribed Actos achieved a significantly greater improvement across the whole lipid profile compared to patients who receive rosiglitazone. It was further stated that 'while each drug achieved similar glycaemic control there were significant differences between the two, which may have important implications for cardiovascular risk among patients with type 2 diabetes' and that the study 'confirmed the potential for pioglitazone to reduce cardiovascular risk in the longer term. However, we all await the outcome studies'. With regard to cardiovascular disease being a frequent cause of death for patients with type 2 diabetes it was stated that 'any therapy that can reduce that risk is a welcome addition'.

The Panel noted that the EVIDENT study assessed the effects of Actos and rosiglitazone on blood lipid levels and glycaemic control in patients with type 2 diabetes via a retrospective review of randomly selected medical records from 650 primary care practices. Treatment with Actos was associated with greater beneficial effects on blood lipid levels than treatment with rosiglitazone whereas glycaemic control was equivalent. The study authors stated that the clinical implications of these distinctions related to potential reductions in risk for the sequelae of diabetes and concluded that longer-term studies were needed to determine whether, *inter alia*, cardiovascular benefit was realized.

The Panel noted the study authors' caveats regarding the need for outcome studies and considered that there was no endpoint data to support a claim for a reduction in cardiovascular risk. The Panel noted that the press release referred to the need to await outcome studies and that Actos '**may** have important

implications for cardiovascular risk' (emphasis added) and '**the potential** to reduce cardiovascular risk' (emphasis added). Nonetheless the Panel considered the overall prominence given to the potential reduction in cardiovascular risk in the absence of outcome studies rendered the press release misleading and inconsistent with the SPC on this point. Breaches of Clauses 7.2 and 3.2 were ruled.

2 Dosage

COMPLAINT

GlaxoSmithKline noted that the EVIDENT study which formed the basis of the press release included patients treated with pioglitazone 45mg [the maximum licensed UK dose was 30mg]. Whilst GlaxoSmithKline accepted that it might be legitimate under the Code to issue press releases of scientific interest on the results of studies conducted with off-label doses or in unlicensed indications, it believed that it was mandatory in such cases to state explicitly in what respects the study concerned was not in accordance with the product's UK licence.

In the press release in question, although a very broad claim was made ('… patients with type 2 diabetes who were prescribed Actos achieved significantly greater improvement across the whole lipid profile compared to patients treated with rosiglitazone'), it was not made clear that these results were achieved with an unlicensed dose of pioglitazone. In GlaxoSmithKline's view, the sentence in the last paragraph ('The EVIDENT study related to use in the US') was wholly inadequate. GlaxoSmithKline alleged breaches of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Takeda disagreed that its explanation of the differences between the American and European licences was given insufficient prominence. The final paragraph of the press release gave a full explanation of the different situations between the US and Europe and it had gone to some lengths to ensure that readers were aware of the UK licence for Actos. It consciously made no mention of the 45mg daily dose schedule as this might have constituted promotion outside the terms of its marketing authorisation.

Takeda considered that the final paragraph was sufficiently prominent a position for such a clarification statement and noted that of the Actos patients studied in EVIDENT, the majority (70.29%) were on 30mg daily.

PANEL RULING

The Panel noted that in the UK the licensed daily dose of Actos was 15 or 30mg in combination with metformin or sulphonylurea (ref SPC). In the EVIDENT study 70% of patients who were prescribed Actos received 30mg/day and 30% received 45mg/day. The final paragraph of the press release read 'The EVIDENT study relates to use in the US' and then stated the UK indication.

The Panel considered that it had not been made sufficiently clear that the results discussed in the press release were achieved in an Actos patient group of whom 30% were receiving a dose higher than that licensed in the UK. The reference to the EVIDENT study relating to US use was insufficient in this regard. The Panel considered that the press release was misleading and inconsistent with the SPC as alleged; breaches of Clauses 7.2 and 3.2 were ruled.

3 Overall impression of press release

COMPLAINT

GlaxoSmithKline was concerned about the entire manner and tone in which EVIDENT, a retrospective case-note analysis, had been presented. Although the word 'retrospective' was mentioned once in the press release, the use of a meaningless and impressive-sounding 'acronym' – 'EVIDENT' – for the study (a practice normally reserved for large-scale prospective trials), the all-embracing nature of the claims based upon it, and the use of selected third-party endorsements all served to give the impression that the results obtained had far more significance than the nature and methodology of the study would normally warrant. Breaches of Clauses 7.2, 7.3 and 7.10 of the Code were alleged.

RESPONSE

Takeda noted that there was no restriction on the use of acronyms to any particular study types. The allegations were unfounded as the description of the study was included in the first sentence of the second paragraph, a sufficiently prominent position to ensure that the reader would not be misled into believing that the study was anything it was not.

Without wishing to get into an argument that constituted more than a scientific aside in this context, Takeda took issue with GlaxoSmithKline's dismissal of EVIDENT as 'nothing more than a retrospective case-note analysis'. As well as the longer established heritage of retrospective case-control studies as a method of post-marketing surveillance, there was also support for this type of study as a valid method of assessing efficacy. Some had even concluded that they might represent a more accurate picture of the clinical situation than prospective randomised clinical trials in selected groups of patients.

For the reasons given above, Takeda therefore refuted GlaxoSmithKline's allegation of a breach of Clauses 7.2, 7.3 and 7.10 of the Code.

PANEL RULING

The Panel considered that its rulings at points A1 and A2 above were relevant. The press release favourably compared Actos with rosiglitazone in relation to improvement in the lipid profile and the implications for cardiovascular risk. The Panel also noted its comments on the EVIDENT study above. In addition, in relation to the change in LDL-C levels the study authors stated that whether this magnitude of change and intergroup difference was sufficient to produce clinical benefits that distinguished one medicine from another was an open question and 'speculated that cardiac risk reduction would be more likely with

pioglitazone than rosiglitazone treatment…'. The authors acknowledged 'concerns over the validity of retrospective work'. Steps taken during the planning of the study to reduce bias were discussed. The differences in therapeutic response were observed over a 4 month period but 'longer studies were needed to determine whether treatment effects in lipids, glycaemic control and body weight persist over time …'.

The Panel noted that the press release described the EVIDENT study as a multicentre, retrospective random review of 1,115 selected medical records. The Panel considered that the retrospective nature and methodology of the trial was thus sufficiently clear.

The Panel noted that it had already ruled breaches of the Code on specific allegations (points A1 and A2 above). The Panel considered that the press release did not sufficiently reflect the authors' caveats about the clinical significance of their results in relation to lipid profile and cardiovascular risk, the four month observational period and the authors' conclusion that longer term studies were needed. The Panel ruled breaches of Clauses 7.2 and 7.3 of the Code. The Panel did not consider that the press release was all-embracing as alleged. No breach of Clause 7.10 was ruled.

B Actos detail aid

A loose insert (ref AC010701B) in a pocket at the back of a detail aid (ref AC010701) headed 'Are all glitazones the same?' compared Actos and rosiglitazone in relation their effect on cardiovascular risk factors and cost. It was used between September 2001 and May 2002 by primary care sales representatives.

1 Comparison of total C:HDL-C ratio

Beneath the heading '… and has positive effects on cardiovascular risk factors' a table listed aspects of the lipid profile and indicated that the total C:HDL-C ratio for Actos decreased and remained unchanged for rosiglitazone.

COMPLAINT

GlaxoSmithKline noted that the effects of rosiglitazone on the total cholesterol:HDL-cholesterol (TC:HDL-C) ratio was represented as 'unchanged'. This was not consistent with the SPC for Avandia, which stated that 'the ratio of total cholesterol:HDL-C was unchanged or improved in long term studies. In Case AUTH/1123/1/01, referred to above, GlaxoSmithKline undertook to include the 'unchanged' portion of this SPC statement in all materials mentioning the effects of Avandia on the TC:HDL-C ratio. GlaxoSmithKline considered it only proper, therefore, that Takeda should mention the 'improved' portion.

Inasmuch as the graphic concerned misrepresented the effects of Avandia on the parameter in question, and was inconsistent with the Avandia SPC, GlaxoSmithKline alleged breaches of Clauses 7.2, 7.3 and (assuming the provisions of the clause could be extended to competitor products) 3.2 of the Code.

RESPONSE

Takeda stated that the table was not intended as a comparison of SPC statements, but as a summary of the main body of scientific evidence relating to the lipid effects of the two products. The references on which the assessments of the two products' effects on lipid profiles were comprehensive and adequately explained, referring to four scientific reports, two NICE Technology Assessment Reports and two CPMP Assessment Reports from the EMEA.

Takeda noted that part of its complaint in Case AUTH/1123/1/01 was that the scientific data used to support GlaxoSmithKline's claim for a reduction in TC:HDL-C included long-term studies in which statin use was inadequately controlled. In those patients who did not have a statin added there was no evidence of any change in ratio. Takeda considered that this group of patients represented the only source of meaningful data on rosiglitazone's effects on TC:HDL-C. For this reason it considered an unchanged or horizontal arrow was a fair and balanced description of Avandia's effects in this respect.

Takeda was not in a position to comment on the EMEA's reasoning behind its authorising a statement that Avandia's effects on TC:HDL-C ratio were 'unchanged or improved'. It therefore had not complained about GlaxoSmithKline using this summary of Avandia's effects in its promotional material. In Case AUTH/1123/1/01, Takeda's complaint was against the use of an unqualified 'improved'. However Takeda reserved its right to correct, interpret and summarise the only reliable scientific data available and use the phrase 'unchanged' in its material.

Takeda noted the allegation that it might be in breach of Clause 3.2 for failing to promote within the terms of the Avandia SPC. If this was the case, its response was that if the SPC stated that a product's effect on any patient attribute was 'unchanged or improved', to describe it as 'unchanged' would be within the terms of the licence.

PANEL RULING

The Panel noted that in Case AUTH/1123/1/01 a table on a slide which indicated that the TC:HDL-C ratio was elevated in the typical patient with type 2 diabetes and remained unchanged at six months and decreased at 18 months in patients receiving Avandia was alleged to be misleading. The Panel had noted that Section 4.8 of the Avandia SPC headed 'Undesirable effects' stated that the elevated total cholesterol levels were associated with increase in both LDL-C and HDL-C, but the ratio of total cholesterol: HDL-C was unchanged or improved in long-term studies. The table showed that the TC: HDL-C ratio was unchanged at six months and decreased at 18 months. It was unclear whether this was a fair reflection of the studies cited on this point as neither company had provided the references. However the Panel noted Takeda's submission regarding the possible use of statin therapy within the 18 month data and the SmithKline Beecham data on file. The Panel considered the slide was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that Case AUTH/1337/6/02 concerned a claim that 'Avandia has favourable effects on lipid profile'. The Panel had ruled that the claim was misleading in breach of Clause 7.2 of the Code. GlaxoSmithKline had appealed this ruling and as part of its submission it had referred to the qualitative changes in LDL-C. The Appeal Board had upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

Turning to the present case, Case AUTH/1349/8/02, the Panel noted that the heading to the rosiglitazone data referred the reader to an adjacent note in small print which read 'Changes at 26 weeks compared to placebo'. The Panel considered that the issue in the previous case, Case AUTH/1123/1/01, had some relevance here as did the outcome of Case AUTH/1337/6/02. The Panel noted that the statement in the SPC appeared in Section 4.8 of the SPC headed 'Undesirable effects'. The statement appeared in association with information about adverse experiences of hypercholesterolaemia. The Panel considered that given the statement in the Avandia SPC the depiction of the total C:HDL-C ratio as unchanged in the material now at issue was misleading; it was not a complete picture of Avandia's effect on the TC:HDL-C ratio. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted GlaxoSmithKline's alleged breach of Clause 3.2 in relation to references to competitor products in promotional material and whether such material needed to comply with the SPC. Clause 3 of the Code was clear that the promotion of a medicine must be in accordance the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not be promoting the competitor medicine and therefore the Panel considered that Clause 3 would not apply. The Director therefore decided there was no *prima facie* case to answer in this regard.

2 Comparison of LDL-C

The table indicated that LDL-C remained unchanged for Actos and increased for rosiglitazone.

COMPLAINT

GlaxoSmithKline noted that in the similar comparison between the effects of the two products on LDL-C, those of rosiglitazone were represented as an increase in this parameter. However, as noted in GlaxoSmithKline's recent submission concerning Case AUTH/1337/6/02, brought by Takeda, this severely misrepresented the effects of Avandia on this parameter. As explained (and referenced) in the previous submission, administration of Avandia did result in a small, short-term increase in LDL-C levels, which stabilised over the longer term. This effect, however, appeared to be associated with an Avandia-induced shift in LDL-C particle size towards larger less dense (and hence less atherogenic) LDL-C particles. GlaxoSmithKline alleged that to mention the small quantitative changes in LDL-C associated with Avandia, while omitting to mention the much more clinically significant qualitative changes, was a breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Takeda noted that in the two main studies used in GlaxoSmithKline's promotional material, Avandia in combination with metformin or a sulphonylurea increased both LDL-C and HDL-C with no significant change in the TC:HDL-C ratio.

In the EVIDENT study treatment with rosiglitazone was associated with an increase in LDL-C. In addition in 5 out of 6 head-to-head studies where LDL was measured Avandia was associated with an increase in LDL-C. In the one head-to-head study where a decrease was seen in LDL-C, this was not a statistically significant change compared to baseline.

In relation to the submission that the LDL-C particle's size and density were important factors to be taken into account Takeda stated this was based on recent studies on the qualitative aspects of LDL-C and might, in the future, lead to a consensus scientific opinion on the desirable qualitative aspects of LDL-C and changed guidelines on lipid management incorporating recommended ranges for LDL-C particle size and density. In the meantime clinicians continued to use quantitative measures. National and local guidelines included measures such as LDL-C normal range and acceptable or desirable upper limits.

Takeda welcomed research to further clarify the situation in patients with dyslipidaemia. Actos, like Avandia, had data showing differing effects on the various LDL-C fractions. However, while the current level of scientific knowledge of LDL-C fractions persisted, Takeda submitted that it was appropriate to continue using assessments based on quantitative measures to describe the differences between the lipid effects of products.

PANEL RULING

The Panel noted GlaxoSmithKline's comments about the previous case, Case AUTH/1337/6/02.

Turning to the case now before it, Case AUTH/1349/8/02, the Panel noted GlaxoSmithKline's submission about LDL-C particle size but considered that this was an emerging area of science upon which there was, as yet, no medical consensus. The Panel did not consider that the failure to refer to rosiglitazone's effects on the qualitative aspects of LDL-C was misleading as alleged. No breach of Clauses 7.2 and 7.3 of the Code was ruled.

3 Cost comparison

A section headed 'Glitazone cost comparison' compared the 28 day cost of Actos 15mg and 30mg once daily and rosiglitazone 4mg once daily, 4mg twice daily and 8mg once daily in separate tables which were side by side.

COMPLAINT

GlaxoSmithKline noted that the box enclosing the price data for Actos 30mg od was twice as large as the other boxes, thus occupying the same amount of space as the two adjacent boxes for the 4mg bd and 8mg od doses of Avandia. GlaxoSmithKline believed

this to be a subtle, but incontrovertible attempt to assert a spurious equivalence between the 15mg and 30mg doses of Actos and the 4mg/day and 8mg/day doses of Avandia, respectively. This, in turn, would lead the reader to infer an equally spurious cost advantage for Actos.

GlaxoSmithKline did not accept the dose equivalences implied by this table. The available evidence, the great majority from non-head-to-head studies, suggested that the efficacy and tolerability of the 4mg/day dose of Avandia was comparable to those of the 30mg/day dose of Actos. Furthermore, it noted that, as in all Actos materials produced by Takeda, only the 30mg dose was promoted; whereas, for Avandia, both doses were promoted, with a recommended starting dose of 4mg od (as per the licence). All available data suggested that, where dosage was specified, the great majority of prescriptions for Avandia were for the 4mg od dose. This would, if anything, weight the cost comparison more in favour of Avandia than of Actos. However, given the difficulty of comparing doses with the evidence available, it refrained in its own materials from attempting, overtly or otherwise, to make price comparisons between Avandia and Actos.

GlaxoSmithKline alleged that the dose equivalences and cost 'advantage' implied by this table were inaccurate and misleading in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Takeda noted that the cost comparison charts were clearly labelled as such. No claims for comparative efficacy were made.

The charts listed the lower and upper doses for both Actos and rosiglitazone according to their respective marketing authorizations and provided the monthly costs for the various dose schedules included. Using a larger box for the pioglitazone 30mg od schedule was an option it had to use because of the presence of two dose schedules for rosiglitazone at its upper authorised dose (8mg once daily or 4mg twice daily).

Takeda stated that the implication that it promoted Actos 30mg because the 15mg dose had inadequate efficacy was inappropriate. Diabetologists were under increasing pressure to reach treatment targets in type 2 diabetes. The majority of patients were under-treated against HbA1c targets. They frequently needed the highest dose of thiazolidinedione in combination with existing treatment, whether it was pioglitazone 30mg/day or rosiglitazone 8mg/day. This table allowed the prescriber to assess the maximum likely cost of his/her chosen glitazone.

Takeda denied that the cost comparison was in breach of Clauses 3.2, 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted the cost per 28 days' treatment of Actos (15mg and 30mg) and rosiglitazone (4mg od, 4mg bd and 8mg od) at their respective licensed doses were set out in separate adjacent tables which were of identical size. The cost data for 30mg od Actos occupied the same amount of space as that for rosiglitazone 4mg bd and 8mg bd. The Panel did not accept that the juxtaposing of the tables nor the space allocation of the 30mg od Actos and 4mg bd and 8mg bd rosiglitazone data implied dose equivalence and thus a cost advantage for Actos as alleged. The Panel thus ruled no breach of Clauses 7.2 and 7.3 of the Code on this narrow point.

C Actos lipid claims

These claims appeared in various items.

COMPLAINT

GlaxoSmithKline stated that the precise wording of these claims had been the subject of previous dispute between Takeda and (then) SmithKline Beecham. However, the wording at issue at the time ('Actos is the only thiazolidinedione that in combination with a sulphonylurea or metformin significantly reduced triglyceride concentrations and caused no significant increase in LDL cholesterol compared to placebo') had been significantly modified and strengthened in current Takeda materials.

Thus, in leavepiece AC010903, the claim was made that Actos was 'The **only glitazone** which significantly raises HDL-C and lowers triglycerides whilst causing no significant increase in LDL-C compared to placebo' (emphasis as in original).

In mailing AC01708B (a letter from the product manager) the emphasis chosen was even more telling: '… Actos is the only glitazone that has a positive effect on the lipid profile by lowering triglycerides and increasing the HDL cholesterol, while causing no significant change to LDL-C compared to placebo' (underlining as in original).

In advertisement AC011211, the claim made was that Actos 'Has positive lipid effects by significantly improving *triglyceride* and *HDL-C* levels with no significant change in LDL-C compared with placebo – unlike other glitazones' (italics as in original).

Similar statements were made in several other Actos materials.

Notable differences between these claims and the original wording referred to above included:

- the inclusion of HDL-C as a differentiating parameter;
- the change in wording from 'The only thiazolidinedione that …' had the listed effects to 'The only glitazone that has a positive effect on the lipid profile by …';
- the variety of added emphases (emboldening, underlining, italicisation), as noted above.

Taken as a whole, GlaxoSmithKline alleged that the claims sought to make an unjustifiable and unwarranted differentiation between Actos and Avandia, to the detriment of the latter. In reality, as noted and referenced in its submission regarding Case AUTH/1337/6/02 Avandia had been shown to significantly increase levels of HDL cholesterol and its most atheroprotective subfractions. Avandia had also been shown to significantly reduce circulating levels

of non-esterified fatty acids and the SPC stated that the TC:HDL-C ratio was unchanged or improved in long-term studies. While slight increases in LDL-C levels had been seen with Avandia, these were associated with a change in particle density towards a less dense and less atherogenic form of LDL-C. Furthermore, although studies to date had not demonstrated an unequivocal reduction in triglyceride levels with Avandia, these studies were conducted in normo- or near-normotriglyceridaemic patients, whereas those with Actos included frankly hypertriglyceridaemic patients.

The claims at issue could easily be interpreted (and, GlaxoSmithKline believed, were intended to be interpreted) as meaning either that Avandia had no lipid effects at all (which was patently untrue); or that Actos possessed unique and clinically significant advantages over Avandia. In reality, the effects of the two products on the great majority of lipid parameters were broadly similar. The only differential evidence related to effects on triglycerides, the clinical relevance of which was, to say the least, arguable.

In summary, GlaxoSmithKline alleged that to 'cherry-pick' a series of claims to which the word 'only' could then be applied, thus implying a clear-cut superiority of one product over another, when the totality of available evidence did not support such an inference, was inherently misleading and disparaging. This was compounded by the choice of wording and emphasis within the claims themselves. Taken individually and as a whole, therefore, GlaxoSmithKline alleged that the claims referred to above were in breach of Clauses 7.2, 7.3, 7.10 and 8.1 of the Code.

RESPONSE

Takeda noted that in Case AUTH/1121/1/01 SmithKline Beecham had complained about an Actos journal advertisement that included the phrase '… this advanced drug offers additional glycaemic control in combination with metformin or a sulphonylurea, with favourable effects on the lipid profile'. In its ruling in Point 2 of the case the Panel found other aspects of the advertisement to be in breach of Clause 7.2 because it failed to place sufficient emphasis on the requirements of the marketing authorization that Actos should only be added in patients inadequately controlled on metformin or a sulphonylurea. The above text was not directly commented on by the Panel and SmithKline Beecham did not appeal that aspect of the judgement.

Takeda noted that in addition to the three claims at issue, GlaxoSmithKline had specifically objected to the use of changes in HDL-C as a differentiating parameter between pioglitazone and rosiglitazone stating that Takeda implied that Avandia had no beneficial effect on HDL-C.

Takeda stated that each of the three claims now at issue needed to be read in their entirety. In each the phrase 'the only glitazone' had been appropriately qualified by a list of lipid attributes. The statement was that Actos was the only glitazone to do all of these. It was therefore appropriate to include beneficial effects on HDL-C in the list. Rosiglitazone might have similar effects on HDL-C but not on all the lipid parameters listed. For this reason the claim in any of the above forms was appropriate.

In relation to the claims 'positive lipid effects' and 'positive effect on lipid profile' in two of these items Takeda referred to the Authority's findings in Case AUTH/1121/1/01, when 'favourable effects on the lipid profile' was not found in breach.

All of the above items were directed at target doctors in primary care. Although most primary care professionals had an adequate and increasing knowledge of lipid risk factors, the direct and indirect feedback Takeda had received from customers had suggested that many would appreciate clarification of some of the issues in this area. The company therefore considered it appropriate to include a comment to qualify that the lipid parameters being altered were being affected in a positive direction.

GlaxoSmithKline also claimed Takeda had been using a variety of formatting and text changes to enhance the claims to a degree that they considered unacceptable.

These included the following: the use of bold text and underlining for the phrase 'the only glitazone', the use of underlining on the phrases 'the only glitazone' and 'lipid profile' and the use of italic text on the words 'triglyceride' and 'HDL-C'. Takeda did not consider that any of these text format changes had materially altered the meaning of the claim. The Actos style was an informal one: using a typeface and wording that was more everyday than was usual in scientific communication. The use of italics, emboldening and underlining was part of that format and did not materially alter the message.

Takeda disputed GlaxoSmithKline's comment that triglycerides might be irrelevant. A number of studies had concluded that high triglyceride levels, independent of HDL-C, were a significant risk factor for cardiovascular disease.

Several studies (Framingham Heart Study, the Prospective Cardiovascular Munster Study, the Helsinki Heart Study and the Baltimore Coronary Observational Long-term study) suggested that triglyceride levels should be considered in coronary heart disease assessment and that the current goals for triglycerides should be reduced. The majority of opinion leaders in this area agreed that they were an important factor to take into account. So whilst it might be debated that raised triglycerides *per se* might not be independent factors for increased risk of coronary heart disease, a cohort of patients with low HDL-C levels or a high LDL-HDL cholesterol ratio in association with elevated triglyceride levels might be at increased risk. Many patients with type 2 diabetes fitted this pattern.

The results of VAHIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) might be open to interpretation but did show for the first time that raising low levels of HDL-C and decreasing triglycerides in patients with documented CHD and normal LDL-C values improved cardiovascular and cerebrovascular event free survival for long-term follow up. There was a substantial reduction in triglycerides raising the question of whether benefits in risk reduction were attributable to the increase in HDL-C, the decrease in triglycerides or some combination. It was difficult to uncouple the increase in HDL-C from the reduction in triglycerides because

these lipids were physiologically linked in a 2-way exchange pathway mediated by cholesterol ester transfer protein. It had been suggested that design limitations might be implicated in this lack of statistical correlation between triglycerides and outcome in the VAHIT study.

It was also recognised that lower plasma triglyceride levels slowed the lipid exchange thereby reducing the atherogenicity of the LDL subfraction by changing the nature of LDL from small dense particles to larger lighter particles. The subject of particle density was a matter that GlaxoSmithKline itself referred to in support of lipid effects of Avandia.

Takeda noted that although triglyceride targets might not be included in every national and local guideline, they were included in the current Coronary Heart Disease National Service Framework targets and the proposed NSF in diabetes and the draft NICE glycaemic control in Type 2 diabetes guidelines. They had also been the subject of a number of articles on dyslipidaemia published recently in the general medical press. Triglycerides were also included in the American Diabetes Association targets.

Takeda noted that GlaxoSmithKline had commented that the patients in the pioglitazone studies were hypertriglyceridaemic. Hypertriglyceridaemia was, however, an integral part of insulin resistance syndrome and those patients with higher triglycerides were at greater cardiovascular risk and hence reduced triglycerides in these patients was important.

Takeda noted that GlaxoSmithKline had accused it of cherry-picking lipid claims for Actos. Takeda considered that it was beyond dispute that the lipid parameters clinicians used on a regular basis were HDL-C, LDL-C triglycerides and TC:HDL-C ratio. Actos had beneficial or neutral effects on all of these parameters. Making claims for lipid effects with Actos was not cherry-picking.

For the reasons given above, Takeda again denied that these items were in breach of Clauses 7.2, 7.3, 7.10 and 8.1 of the Code.

PANEL RULING

The Panel noted that there were only two glitazones licensed in the UK, Actos and rosiglitazone. The Panel considered that as submitted by Takeda each claim had to be read in its entirety. Each claim described the effect of Actos on a range of lipid parameters and in the opinion of the Panel did not preclude the possibility that another product might have the same effect upon one or more of these; however, no other glitazone would have the same effect on all of the parameters listed. The Panel did not accept GlaxoSmithKline's allegation that the claims, individually, or as a whole, could be interpreted as meaning that Avandia had no lipid effects at all. The Panel considered that the comments made in Cases AUTH/1337/6/01 and AUTH/1123/1/01, as detailed at point B1 above, were relevant here.

The Panel considered that on the evidence before it in relation to the effect of rosiglitazone the claims '… Actos is the only glitazone that has a positive effect on the lipid profile by lowering triglycerides and increasing the HDL cholesterol, while causing no significant change to LDL-C compared to placebo' and 'Has positive lipid effects by significantly improving *triglyceride* and *HDL-C* levels with no significant change in LDL-C compared with placebo – unlike other glitazones' implied that Actos possessed unique and clinically significant advantages in relation to effects on the lipid profile. They implied that only Actos had positive effects on the lipid profile. This was not necessarily so. The Panel considered that the claims were misleading and not capable of substantiation; breaches of Clauses 7.2 and 7.3 were ruled.

The Panel did not consider that the two claims were disparaging and no breach of Clause 8.1 of the Code was ruled.

The Panel considered that the claim 'The **only glitazone** which significantly raises HDL-C and lowers triglycerides whilst causing no significant increase in LDL-C compared to placebo' was not unreasonable as alleged and no breach of Clauses 7.2, 7.3 and 8.1 was ruled.

Complaint received **8 August 2002**

Case completed **6 November 2002**

GENERAL PRACTITIONER v NOVARTIS

Stepwise campaign

A general practitioner complained about the Stepwise campaign run by Novartis. He provided a copy of a booklet 'Feet & Nails stamping out fungal nail infections and athlete's foot' in which a number of claims and statements had been highlighted, including the following: page 4 '… it is worthwhile going back to your doctor for further advice. You cannot buy treatments for fungal nail infection from your pharmacist. If you have tried over-the-counter products that haven't worked, you should talk to your GP who can prescribe effective treatments that do'; 'Once your doctor has decided to treat your fungal nail infection you may be prescribed tablets or capsules which are taken by mouth, or a treatment that needs to be applied regularly to the affected nails. Remember it is important to treat fungal nail infection as it can spread to other parts of your body and to other people'; page 6 '…visit your doctor who can now treat the condition effectively' 'Your doctor can advise on effective treatments for fungal nail infection. Only your doctor can advise on effective treatments for fungal nail infection. If your doctor decides to treat your infection, you may be prescribed either tablets or capsules that you swallow, or a treatment that you need to apply to each of the affected nails'; Athlete's foot; page 8 '… because it is so easy to spread to other people and other parts of the foot and body, it should be treated' page 11 'If you do pick up athlete's foot or a fungal nail infection, get it treated. That way you will minimise the risk of spreading it to other parts of your body, and to other people'.

The complainant queried whether the booklet, in particular the statements listed and accompanying advertising campaign, were in breach of the Code which related to the direct selling of prescription medicines to the public. The complainant also wanted to know the basis of the statement on page 8 about the spread of athlete's foot since he had always understood the condition to be more soil than seed. If the scientific basis for the transfer of infection argument was suspect, then the whole thrust of the campaign related to cosmetic disfigurement and indeed the focus of the booklet was on nail infection, which of course required a much more protracted and therefore more profitable course of treatment. The complainant asked who, apart from Novartis, put money into 'Stepwise'.

The complainant was also concerned that nowhere was there mention of the serious potential side-effects of oral medication.

The Panel noted that the complainant had queried the scientific basis for the statement that athlete's foot should be treated because it was easily spread to other people and other parts of the foot and body. Similarly he had questioned what evidence there was to support the statement 'Remember it is important to treat fungal nail infection as it can spread to other parts of your body and to other people'. The Panel noted that Novartis had supplied a number of papers which supported these statements: Denning *et al* (1995), Williams (1993) and Roberts (1992). The Panel thus considered that the statements in the booklet with regard to the spread of infection were not unreasonable. The Panel considered that the statements were factual; no breach of the Code was ruled.

With regard to fungal nail infection, the complainant had also queried the statement 'Go and see your doctor for advice as it rarely gets better without treatment, and it is likely to get worse'. Again several references had been provided by Novartis to substantiate this: Roberts (1999) and Denning *et al* (1995). The Panel thus considered that the statement in the booklet was not unreasonable. The Panel considered that it was a factual statement; no breach of the Code was ruled.

The Panel noted that the booklet at issue discussed the treatment of fungal nail infections and athlete's foot in general terms. No specific medicine was mentioned and no undue emphasis was given to any particular form of medicine. The Panel did not consider that the booklet was an advertisement for a medicine. No breach of the Code was ruled.

The booklet in question made no mention at all with regard to side-effects; there was nothing in the booklet to suggest to patients that treatment for fungal nail infections or athlete's foot would not be associated with side-effects. Page 5 of the booklet stated 'Your doctor will be able to answer any questions you have about fungal nail infections and about treatment'. In the circumstances the Panel did not consider that failure to discuss side-effects was unreasonable. No breach of the Code was ruled.

The complainant appealed all of the Panel's rulings. In relation to claims about the transmissibility of infections, the Appeal Board noted the supporting studies supplied by Novartis and the complainant's comments upon them but overall considered that the statements in the Stepwise booklet were not unreasonable. The Panel's ruling of no breach of the Code was upheld.

The Appeal Board considered that the statement 'Go and see your doctor for advice as it rarely gets better without treatment, and it is likely to get worse' was not unreasonable. Novartis had provided references to support the statement. The Appeal Board thus upheld the Panel's ruling of no breach of the Code.

The Appeal Board noted that the booklet did not mention a specific medicine and no undue emphasis was given to any particular form of medicine. The Appeal Board did not consider that the booklet was an advertisement for a medicine. The Panel's ruling of no breach of the Code was upheld.

The booklet made no mention of side effects. There was nothing in the Stepwise booklet to suggest that treatment for fungal nail infections or athlete's foot would not be associated with side effects. In the circumstances the Appeal Board did not consider the failure to discuss side effects unreasonable and upheld the Panel's ruling of no breach of the Code.

A general practitioner complained about the Stepwise campaign run by Novartis Pharmaceuticals UK Ltd.

He provided a copy of a booklet 'Feet & Nails stamping out fungal nail infections and athlete's foot' (ref STEP1/2002) in which the following claims and statements had been highlighted:

Front cover: the Stepwise logo which incorporated the phrase 'Your first step towards healthier *looking* nails' (emphasis added by the complainant).

Fungal nail infections

Page 4 '… it is worthwhile going back to your doctor for further advice.

You cannot buy treatments for fungal nail infection from your pharmacist. If you have tried over-the-counter products that haven't worked, you should talk to your GP who can prescribe effective treatments that do.'

'Once your doctor has decided to treat your fungal nail infection you may be prescribed tablets or capsules which are taken by mouth, or a treatment that needs to be applied regularly to the affected nails.

Remember it is important to treat fungal nail infection as it can spread to other parts of your body and to other people' (the complainant had written 'evidence' beside this statement).

Page 6 '…visit your doctor who can <u>now</u> treat the condition effectively' (emphasis added by the complainant).

'Your doctor can advise on effective treatments for fungal nail infection.

Only your doctor can advise on effective treatments for fungal nail infection.

If your doctor decides to treat your infection, you may be prescribed either tablets or capsules that you swallow, or a treatment that you need to apply to each of the affected nails.'

Page 7 'Go and see your doctor for advice as it rarely gets better without treatment, and it is likely to get worse' (an exclamation mark had been written beneath this statement).

Athlete's foot

Page 8 '… because it is so easy to spread to other people and other parts of the foot and body, it should be treated.'

Page 9 'If you are a regular sufferer, you should discuss this with your doctor.'

Foot and nail care

Page 11 'If you do pick up athlete's foot or a fungal nail infection, get it treated. That way you will minimise the risk of spreading it to other parts of your body, and to other people.'

Back cover: The statement that Stepwise was sponsored by Novartis was highlighted. The doctor had drawn a circle around the company name and linked that to his own statement 'Lamisil!! £300 for 6/12'.

COMPLAINT

The complainant queried whether the booklet and accompanying advertising campaign were in breach of Clauses 20.1 and 20.2 of the Code which related to the direct selling of prescription medicines to the public. In particular he noted the statements on pages 4, 6 and 11 as listed above. The complainant also wanted to know the basis of the statement on page 8 about the spread of athlete's foot since he had always understood the condition to be more soil than seed. If the scientific basis for the transfer of infection argument was suspect, then the whole thrust of the campaign related to cosmetic disfigurement and indeed the focus of the booklet was on nail infection, which of course required a much more protracted and therefore more profitable course of treatment. The complainant asked who, apart from Novartis, put money into 'Stepwise'.

The complainant was concerned that nowhere was there mention of the serious potential side-effects of oral medication, it being left to the GP to disabuse and disappoint the patient at an unnecessary appointment.

* * * * *

When writing to Novartis, the Authority noted that this complaint had some similarities with two previous cases. Case AUTH/1058/7/00 concerned an allegation that claims that 'the fungus won't go away without treatment' and 'it is likely to get worse without treatment' might not be entirely true. The Code of Practice Panel ruled no breach of Clause 20.2 of the Code as it considered the claims were not unreasonable. Similarly Case AUTH/1302/4/02 concerned an allegation about the statement 'the infection won't go away without effective treatment from your GP' which was also considered by the Panel not to be unreasonable; again no breach of the Code was ruled. Neither of these cases were taken to appeal by the complainants.

Paragraph 5.1 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication, it might be allowed to proceed at the discretion of the Director if new evidence was produced by the complainant or if the passage of time or a change of circumstances raised doubts as to whether the same decision would be made. The Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel which was not the subject of appeal. As the rulings in Cases AUTH/1058/7/00 and AUTH/1302/4/02 were not appealed and the material at issue was not exactly the same as in the previous cases this complaint was allowed to proceed.

* * * * *

RESPONSE

Novartis noted that the complainant had suggested that the campaign was unacceptable under Clause 20 of the Code since in his opinion it breached the existing guidelines on direct selling of prescription medicines to the public. The complainant had highlighted a number of quotes from the booklet which appeared to fall into three distinct areas as being illustrative of this concern. These areas were:

1 Referral of patients back to their GP for advice and appropriate treatment, particularly where medications purchased over the counter had failed to manage their athlete's foot or fungal nail infections or where they were regular sufferers of athlete's foot.

2 Explanations to the patient that once their doctor had decided to treat their fungal nail infection they might be prescribed tablets or capsules which were taken by mouth, or a treatment that needed to be applied regularly to the affected nails.

3 Reminders to patients that it was important to treat a fungal nail infection or athlete's foot, as it could spread to other parts of their body and to other people.

Novartis submitted that the Stepwise campaign was based on research indicating that there was a large untreated reservoir of patients in the community who did not recognise that they had a fungal infection or who had received ineffective therapy in the past which had led them to consider their condition untreatable. An analysis of such patients had shown that as with athlete's foot, only a small percentage of patients with fungal nail infection sought professional advice, although 80% considered that they would have done so if they had realised that they were suffering from a treatable fungal infection (Roberts 1992).

If untreated, athlete's foot and onychomycosis served as reservoirs of infection which could spread to other parts of the patient's body, their family and into the environment, especially amongst users of communal bathing places. It had been postulated that without an effective public health campaign, this level of ignorance in the community would lead to an increased prevalence of dermatophyte infection (Roberts).

The aim of the Stepwise campaign was thus to provide helpful information to the public about foot and nail care generally, as well as alerting people who suffered from some of the common foot and nail problems that they could be fungal in nature and thus infectious. The Stepwise materials had been devised to encourage people to take more interest in their own healthcare and contained therapeutic area information and advice only and no reference to any prescription medicine. It should be remembered that patients responding to the Stepwise advertisements would have already identified what they believed to be a fungal nail infection and be seeking advice and guidance on how to manage it. They might have noted for themselves a progression of their athlete's foot or a gradual deterioration of their nails as the infection spread and the nail changed colour and crumbled.

On average, patients who had responded to the Stepwise advertisement had had their infection for 3.2 years and had the infection in 3 or 4 of their nails. It was clear that by the time the patient's nail had reached this level of deterioration, successful self-medication had become highly unlikely. Such failure might lead the patient to consider their condition untreatable. Failure to appropriately treat such an infection once an accurate diagnosis had been made could lead to progressive cosmetic and functional disability as well as contributing to the infectious pool for cross infection between individuals. These were exactly the patients for whom the Stepwise materials were designed to avoid such an outcome and ensure that they received appropriate treatment and advice and were wherever possible, removed from the infectious pool.

Novartis did not accept a breach of Clause 20 of the Code as suggested by the complainant. This issue had been the subject of previous complaints including a ruling of no breach of the Code in 1997 (Case AUTH/516/3/97), which had been subject to appeal by the complainant. The Appeal Board had considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake. It had further concluded that the Stepwise materials were of a high standard and were not designed to encourage patients to request a specific medicine. The Panel's ruling of no breach of the Code was upheld. This attitude to appropriate patient education had been reflected in the latest modifications to the Code and the incorporation of a statement into the supplementary information to Clause 20.2 which recognised that 'companies may conduct disease awareness and public health campaigns provided that the purpose of these is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'. Novartis was confident therefore that the concept of the Stepwise campaign was acceptable under the Code and that each of the statements referred to by the complainant was fully consistent with the requirements of Clause 20 of the Code.

Novartis noted that the complainant had questioned the accuracy of the statements contained in the materials regarding the relationship between athlete's foot and fungal nail infections, and had referred to athlete's foot as 'more soil than seed'. It was generally accepted however, that toenail infection was, as referred to in the materials, most often the result of a secondary spread from a persistent athlete's foot infection. It was, therefore, entirely appropriate to advise patients to actively manage their athlete's foot to help control spread of fungal infection to their nails. Similarly, advice on the active management of athlete's foot helped to remove these patients from the infectious pool generally and through the provision of advice on foot hygiene helped them avoid re-infection.

Novartis refuted the complainant's suggestion about the importance of fungal nail infection to the patient. Although fungal nail infections might sometimes be incorrectly disregarded as superficial or cosmetic, it would be wrong to underestimate the implications to the patient or the eventual consequences of onychomycosis, which could become unsightly, embarrassing and occasionally disabling. It was clear that patients did not consider such conditions as cosmetic as the complainant suggested or they would not feel prompted to find out more about the Stepwise campaign.

Novartis stated that it was proud of its association with the Stepwise campaign and had always accepted that anything sponsored by the company or carried out on its behalf was its direct responsibility. The company's sponsorship of the campaign was clearly displayed on all materials associated with the campaign. Stepwise was entirely sponsored by Novartis as indicated in the advertising and materials.

Novartis submitted that since the Stepwise materials contained no information about specific treatments for athlete's foot or fungal nail infections, the association of side-effects with particular medication was not relevant to compliance with Clause 20. However, it was suggested by the complainant that concerns about the side-effects of therapy should preclude active treatment of fungal skin and nail infections. This would not appear to be the conclusion from the literature, where key opinion leaders advocated active management once a fungal infection had been verified. Novartis agreed that the risk/benefit for all prescribed medicines must be taken into account before selecting appropriate interventions. It would not agree however, that any discussion with a patient of the appropriate management of their fungal nail or skin infection needed to end in 'disabuse and disappointment at an unnecessary appointment' as the complainant suggested.

In summary, Novartis recognised a continuing commitment to health education, of which the Stepwise campaign formed a part. The purpose of the Stepwise materials was to encourage patients to take more interest and responsibility for their own healthcare. It was clear from the feedback the company had received from patients that the programme was working in raising patient awareness. Advice received from the Stepwise materials had clearly led to patients successfully managing, with their health professional's support, long-term embarrassing fungal infections using a variety of treatment options.

Novartis remained confident that the Stepwise campaign complied fully with the requirements of the Code.

PANEL RULING

The Panel considered that patient education programmes about a disease area were a legitimate activity for a pharmaceutical company to undertake. Such activity had to comply with the Code. Although disease awareness campaigns might facilitate the market development of the sponsoring company's products this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

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

It appeared to the Panel that the complainant regarded fungal nail infections primarily as a cosmetic disfigurement for which the cost of treatment with Lamisil was not justified. The complainant had queried the scientific basis for the statement that athlete's foot should be treated because it was easily spread to other people and other parts of the foot and body. Similarly he had questioned what evidence there was to support the statement 'Remember it is important to treat fungal nail infection as it can spread to other parts of your body and to other people'. The Panel noted that Novartis had supplied a number of papers which supported these statements. Denning *et al* (1995) reported that of those patients with athlete's foot, 20-30% also had affected nails. Williams (1993) stated that factors which would predispose to an increased incidence of athlete's foot eg wet communal areas such as swimming pools, were important factors in determining the incidence of fungal nail infections. Roberts (1992) stated that fungal nail infection served as a reservoir of infection which could spread to other sites of the body as well as to other nails. Dissemination into the environment, particularly via communal bathing places, would also spread the infection to other users. The Panel thus considered that the statements in the booklet with regard to the spread of infection were not unreasonable. The Panel considered that the statements were factual; no breach of Clause 20.2 was ruled.

The Panel noted that, with regard to fungal nail infection, the complainant had also queried the statement 'Go and see your doctor for advice as it rarely gets better without treatment, and it is likely to get worse'. Again several references had been provided by Novartis to substantiate this, for example '… the well documented lack of spontaneous remission totally invalidates any wait and watch policy' (Roberts 1999); 'Treating onychomycoses is difficult but is important because they do not resolve spontaneously' (Denning *et al* 1995) and 'Involvement of the nail plate leads ultimately to complete destruction of the nail, a process that can take several years from initial infection' (Roberts 1999). The Panel thus considered that the statement in the booklet was not unreasonable. The Panel considered that it was a factual statement; no breach of Clause 20.2 was ruled.

The Panel noted that the booklet at issue discussed the treatment of fungal nail infections and athlete's foot in general terms. No specific medicine was mentioned and no undue emphasis was given to any particular form of medicine. The Panel did not consider that the booklet was an advertisement for a medicine. No breach of Clause 20.1 was ruled.

Clause 20.2 required that information about medicines made available to the general public must not, *inter alia*, be misleading with respect to the safety of a product. The booklet in question made no mention at all with regard to side-effects; there was nothing in the booklet to suggest to patients that treatment for fungal nail infections or athlete's foot would not be associated with side-effects. Page 5 of the booklet stated 'Your doctor will be able to answer any questions you have about fungal nail infections and about treatment'. In the circumstances the Panel did not consider that failure to discuss side-effects was unreasonable. No breach of Clause 20.2 was ruled.

APPEAL BY THE COMPLAINANT

The complainant considered that the following issues warranted further consideration.

1 'Sponsored by Novartis'

The New Oxford English Dictionary (1998) defined a sponsor as 'a person or organisation that provides funds for a project or activity carried out by another in particular: an individual or organisation that pays some or all of the costs involved in staging a sporting or artistic event in return for advertising; a person who pledges to donate a certain amount of money to another person after they have participated in a fund-raising event organised on behalf of a charity'.

Both of these definitions as well as conveying a general air of altruism implied that the beneficiary had a choice about involvement, that the sponsorship had been sought and that there was a prior desire for the event or activity to take place. In contrast the definition of 'pay' taken from the same source, was 'give (someone) money that is due for work done'. It seemed highly improbable that whoever produced the Stepwise material intended to do so irrespective of the availability of Novartis 'sponsorship'. The key to the relationship was contained in Novartis' claim to have 'entirely sponsored' the Stepwise campaign. However, contrary to the company's response to the complaint this was not what was indicated on the booklet, the word 'entirely' being absent. Taking the definitions as above, the complainant suggested the correct endorsement would be 'Entirely Paid For By Novartis' or 'Issued on Behalf of Novartis'. The public at least deserved the chance to differentiate altruism from self-interest. The complainant did not think this issue was adequately resolved by Case AUTH/516/3/97.

2 Transmissibility of fungal infections

There were several expressions of opinion relating to the transmission of athlete's foot but no evidence in the material provided by Novartis. There was a solitary photograph caption 'the feet of an entire family ….. with onychomycosis. In this case there was no doubt that one family member was responsible for infecting the others' (Roberts 1999) which was used to support the proposed infectivity of fungal nail infections, hardly scientific evidence of cause and effect.

Williams (1993) by contrast provided evidence for the importance of host susceptibility and referred to a study which suggested there was in fact little evidence for transmission of onychomycosis between marriage partners. And for what it was worth the 1995 BMJ Good Practice Review made no reference to the risk of onward transmission of infection.

The complainant considered that better evidence was needed before implying that treatment of the individual was a public health issue, and a less questionable basis on which to worry the individual that they owed a duty of care to society; '…..get it treated ' Stepwise page 11.

3 Safety and effectiveness of oral treatment

Although the booklet referred to topical treatments the clear implication was that the 'effective treatment' alluded to was taken by mouth. Why else did the first bullet point in the 'Talking to your Doctor' section indicate that they were taken?

The effectiveness (100% implied) of treatment available from the GP was referred to repeatedly, only in the section 'Talking to your Doctor' was there was a question mark. Surely a booklet designed to inform should include an indication of likely duration of treatment and final success rate on which to base a decision to consult the GP?

Also, as the thrust of the booklet was to promote the concept that effective treatments needed to be taken by mouth and since all oral treatments shared similar class risks (BNF March 2002) a booklet that sought to present a balanced view would make it clear that there were risks associated with the proposed effective treatment.

4 Nature of advertising

Although it was true that there were a range of prescription only medicines (POMs) available for the treatment of fungal nail infections, the British National Formulary (BNF) (March 2002 p 294) was unequivocal: 'Terbinafine is the drug of choice for fungal nail infections…..'. For a GP to prescribe anything else in the face of such authoritative guidance required particular justification.

Clearly to include the statement 'Terbinafine is the drug of choice for fungal nail infections' in the Stepwise material would be construed as direct advertising to the public. However, Novartis being fully aware of the BNF recommendation, knew the net effect of getting the patient to consult their GP was the same as if the statement were on public display.

The New Oxford English Dictionary defined advertise as 'describe or draw attention to (a product, service, or event) in a public medium in order to promote sales or attendance'. The Stepwise material drew attention to a service (the possibility or even necessity of treating fungal nail infections via a GP consultation) with the reasonable expectation for the reasons given that this would result in increased sales of a Novartis product.

The complainant alleged that Novartis was in breach of both Clauses 20.1 and 20.2.

COMMENTS FROM NOVARTIS

Novartis commented as follows:

1 'Sponsored by Novartis'

Novartis was sure that a number of different definitions of the term 'sponsorship' could be found. However the declaration of sponsorship statement included in the Stepwise materials was worded entirely in accord with the requirements of Clause 9.9 of the Code.

2 Transmissibility of fungal infections

Novartis stated that the publications provided in support of this statement, originating as many of them had from eminent UK dermatologists, entirely supported the infectious nature of fungal infections. Novartis noted that a quick review of advice to

patients contained in a sample of international web sites provided exactly the same advice across the world. Novartis had also sought the advice of an eminent UK dermatologist, Dr DT Roberts (Consultant Dermatologist, South Glasgow University Hospitals NHS Trust) on this issue in the light of the complainant's appeal and provided a summary of the advice. This would shortly form the content of a presentation to the European Academy of Dermatology and Venereology regarding the public health issue of fungal transmission. Further confirmation was contained in the Cochrane Review of Topical Treatments for Fungal Infections of the Skin and Nails of the Foot, which stated:

'Fungal infections of the nail are often associated with a skin infection, in which case they can probably act as a source of reinfection if only the skin is treated'

and:

'Fungal infections of the skin and nails of the foot are common, reflecting the contagious nature of the organisms. They are often thought to occur when individuals regularly use communal changing rooms and swimming pools. Some groups of workers e.g. coal miners, have been found to have a prevalence of 80 per cent. However, people living in institutions with shared bathing facilities such as boarding schools and long-term care hospitals show a higher than average prevalence of this condition.'

3 Safety and effectiveness of oral treatment

There was no suggestion in any of the Stepwise materials that the only effective treatments for fungal nail infection were taken by mouth. Each time that treatment options were discussed on pages 4 and 6 the patient was informed that their treatment might be oral or applied topically. The phrase 'how they are taken' had been included to clarify that there might be more than one route, and to avoid the word administered, which was not considered appropriate for materials aimed at patients rather than health professionals. As the Panel acknowledged in its ruling, no specific medicine was mentioned and no undue emphasis was given to any particular form of medicine.

Equally there was no suggestion, direct or implied, that any antifungal therapy was 100 per cent effective, as the complainant had suggested. The section of the booklet on page 5 made it clear that the discussion between the patient and their doctor would include discussion of how effective the treatment selected was likely to be.

As noted in the Panel's ruling, the Stepwise booklet made no mention at all of any specific treatments or side effects of treatments; nor was there anything to suggest to patients that treatment of fungal nail infections or athlete's foot would not be associated with side-effects. The booklet instructed the patient to talk to their doctor about their treatment and ask any questions they might have about therapy. As with other treatment discussions such a dialogue would include discussion of the relative risk benefits of the available treatments.

4 Nature of advertising

Novartis did not believe that the inclusion of one sentence in the BNF could be seen as unequivocal evidence of the treatment that all GPs would select for a particular condition. The BNF clearly stated that it was designed as a 'digest for rapid reference' and that its content should be 'interpreted in the light of professional knowledge'.

The Stepwise materials contained no reference to any specific treatment of fungal nail infection or athlete's foot whether prescribed or available over the counter. The decision to select a particular medicine taken orally as tablet or capsule or applied topically was left entirely to the discretion of the health professional caring for the patient.

Novartis chose not to discuss the semantics of the word 'advertising' any further, but reiterated the supplementary information to Clause 20.2 of the Code that 'Companies may conduct disease awareness and public health campaigns provided that the purpose of these is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'.

Novartis remained confident that the Stepwise programme complied fully with these requirements of the Code.

FURTHER COMMENTS FROM THE COMPLAINANT

1 'Sponsored by Novartis'

The complainant considered the fact that Novartis offered no alternative definitions of the term 'sponsorship' suggested that there were none which differed materially from the ones to which he referred in his appeal. Reference to Clause 9.9 of the Code was however inappropriate since this section dealt explicitly with communication directed at health professionals. This target audience knew perfectly well that 'sponsorship' was shorthand for commercial promotion and that the material needed to be read in the context of the promoter's self interest, hence the requirement for prominent declaration.

This complaint was no mere semantic quibble. On first reading the Stepwise booklet the complainant found himself looking for details of the organisation responsible for the publication and its content. Even the size of the typeface used gave the impression that Novartis' involvement was extremely modest. The public deserved transparency.

2 Transmissibility of fungal infections

The opinion of even the most eminent individuals or organisations was generally regarded as the least robust 'evidence' on which to base medical activity. Novartis had provided no scientific evidence in support of its claim that treating the individual benefited society. Again the complaint was not academic. The complainant's attention was initially drawn to the Stepwise campaign by a patient with a long standing asymptomatic fungal nail infection who consulted him only because she thought she had a duty to undergo treatment.

3 Safety and effectiveness of oral treatment

Treatment was described as 'effective' without qualification on four occasions in the booklet. Perhaps Novartis could clarify how this did not imply 100% effectiveness? The single reference which implied less than 100% effectiveness was in the 'Talking to your Doctor' section. If Novartis wished to claim that this section should carry greater weight the use of the word 'taken' also assumed greater significance and clearly suggested that the prescribing decision of the GP would involve oral medication.

4 Nature of advertising

The complainant was amazed that a UK pharmaceutical company could adopt such a dismissive attitude to the status of the BNF. The extremely selective and incomplete quotations taken from the preface painted a picture most users of the BNF would not recognise.

The truth, of course, was that in different circumstances Novartis would champion the standing and independence of the BNF and be naturally delighted at the inclusion of the one sentence 'Terbinafine is the drug of choice for fungal nail infections….' It was disingenuous to suggest that such a definitive recommendation (striking by its rarity) in the BNF would not influence the prescribing of the vast majority of GPs. Indeed the professional indemnity organisation of the GP whose patient suffered damage as a result of an alternative prescription would need exceptional documentation to defend a negligence claim.

It was true that the BNF was not the only source of prescribing advice. There were also eminent dermatologists such as Dr DT Roberts. 'Systemic treatment is recognised to be the most effective and terbinafine is the most potent antidermatophyte agent'.

There was also a lack of evidence for the effectiveness of topical treatments for fungal nail infections (Cochrane Review referred to in Novartis' comments on the appeal).

In brief, as Novartis was fully aware, the patient requesting treatment of their fungal nail infection as a result of the Stepwise campaign was extremely likely to receive a prescription for oral terbinafine without needing to know which POM to ask for in advance of the consultation.

The complainant considered that Novartis' response to his appeal did not properly deal with the issues raised.

APPEAL BOARD RULING

The Appeal Board noted the comments made by the Panel about patient education programmes. Such programmes would increase the number of people consulting health professionals for advice about conditions and their treatment. This was not necessarily a breach of the Code.

In relation to claims about the transmissibility of infections, the Appeal Board noted that Novartis had supplied a number of supporting studies: Denning *et al* (1995), Williams (1993) and Roberts (1992). The Appeal Board noted the complainant's comments upon these studies but overall considered that the statements in the Stepwise booklet with regard to the spread of infection were not unreasonable and upheld the Panel's ruling of no breach of Clause 20.2 of the Code. The appeal on that point was unsuccessful.

The Appeal Board considered that the statement 'Go and see your doctor for advice as it rarely gets better without treatment, and it is likely to get worse' was not unreasonable. Novartis had provided references to support the statement. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 20.2 of the Code. The appeal on this point was unsuccessful.

The Appeal Board noted that the booklet did not mention a specific medicine and no undue emphasis was given to any particular form of medicine. The Appeal Board did not consider that the booklet was an advertisement for a medicine. It was for the GP to decide whether treatment was appropriate and if so what treatment would be recommended. The Appeal Board noted the statement in the BNF. This had not been included in the Stepwise materials. The Appeal Board upheld the Panel's ruling of no breach of Clause 20.1 of the Code. The appeal on this point was unsuccessful.

The booklet made no mention at all with regard to side effects. There was nothing in the Stepwise booklet to suggest that treatment for fungal nail infections or athlete's foot would not be associated with side effects. The booklet made reference to the doctor answering any questions the patient had about treatment. In the circumstances the Appeal Board did not consider the failure to discuss side effects unreasonable and upheld the Panel's ruling of no breach of Clause 20.2 of the Code. The appeal on that point was unsuccessful.

The Appeal Board noted that, in his appeal, the complainant had raised much more detailed issues about the use of the word 'sponsorship'. In the original complaint, however, he had only referred to sponsorship through the question 'Who, apart from Novartis, put money into 'Stepwise?'. There was no allegation in the complaint that the booklet was misleading with regard to the declaration of sponsorship and the Panel had thus made no ruling upon the use of the word; there could, in turn, therefore be no appeal upon the matter. The Appeal Board noted that Clause 9.9 of the Code required companies to declare sponsorship on any materials relating to medicines and their uses and this had been done in the Stepwise booklet.

Complaint received **9 August 2002**

Case completed **20 November 2002**

CASE AUTH/1351/8/02

ASTRAZENECA v SANOFI-SYNTHELABO

Promotion of Solian

AstraZeneca complained about the promotion of Solian (amisulpride) by Sanofi-Synthelabo. The items at issue were a leavepiece and an advertisement.

The centre pages of the leavepiece featured two cost comparison bar charts. One was headed 'Cost comparison of atypical antipsychotic treatment PER DAY' and the other was headed 'Cost comparison of atypical antipsychotic treatment over 28 DAYS'; both charts compared Solian, risperidone, olanzapine and quetiapine. Both the daily and monthly costs showed that Solian was the least expensive product and that quetiapine was the second most expensive. Beneath the charts a table of data showed the cost of a pack of each medicine; the 'Modal repeat average daily dose in schizophrenia*' from Psychotrak research data for each of the four products was also given (these doses were used as the basis for the comparison). The asterisk referred the reader to a statement below the table which read 'No comparison of efficacy was conducted'.

AstraZeneca alleged this was an unfair and misleading comparison as there was no evidence from head-to-head studies to show that Solian was at least as effective as the comparators at the doses compared in the graph. The overall impression was such that the reader could assume the medicines at the doses used were of equivalent efficacy. There was no evidence in this regard. Stating in a small footnote that no efficacy comparison was conducted did not validate the price comparison.

The Panel noted that the leavepiece compared four atypical antipsychotics with regard to aspects of their cost and that the allegation related to the impression that the doses used were equivalent in efficacy and there was no data to support this. Such a comparison, based on the prescribing habits of consultant psychiatrists, would inform doctors how expensive it was likely to be, in terms of medicine acquisition costs, to treat a typical patient with each of the four atypicals depicted. The Panel considered that on the narrow grounds of the allegation it was not misleading to compare the costs of the modal repeat average daily dose in the absence of evidence from head-to-head studies. There was no implication that the doses were clinically equivalent. The Panel ruled no breach of the Code. This ruling was appealed by AstraZeneca.

The Appeal Board noted that according to its summary of product characteristics and depending on the symptoms Solian had a wide range of available doses, 50mg a day to up to 1200mg a day. The Appeal Board noted the data provided by AstraZeneca that although the modal repeat average daily dose for Solian was 400mg the repeat mean daily dose was 541mg. If the costs were calculated using the mean doses the cost comparison would look quite different. In the Appeal Board's view the use of the modal repeat average daily dose gave an inaccurate reflection of the relative costs of the medicines.

The Appeal Board considered that the layout of the cost comparison was such that it inferred that the doses used were therapeutically equivalent. The Appeal Board noted Sanofi-Synthelabo's submission that the modal repeat average doses were therapeutically equivalent. However the Appeal Board noted that this evidence was based solely upon the clinical experience of a number of prescribers with a small number of patients and not on comparative studies. The Appeal Board considered that the cost comparisons were misleading and ruled a breach of the Code.

The journal advertisement depicted a set of weighing pans. The weighing pan in the background of the advertisement depicted a pile of papers representing clinical evidence with the caption 'After weighing the evidence …'. The weighing pan in the foreground was empty and bore the Solian product logo beneath the claim '… NICE concludes'.

AstraZeneca alleged that the advertisement gave the impression that, after considering the evidence, NICE recommended Solian as the atypical of choice in the treatment of schizophrenia, based on clinical evidence and cost. AstraZeneca noted that NICE did not find one particular atypical to be the most appropriate in terms of cost or efficacy. The implication was also made that Solian was the least expensive atypical antipsychotic. This was both misleading and unsubstantiable since when compared to Zoleptil (zotepine) (an atypical also considered in the NICE review) Solian was clearly more expensive.

The Panel noted that the angle at which the scales had been depicted made it appear that the evidence was weighted in favour of Solian. The impression that the evidence was weighted in favour of Solian was compounded by the use of the product logo on the empty weighing scale together with the use of the brand name next to the scales. The Panel considered that the advertisement implied that NICE had concluded that Solian was the atypical of choice which was not so. The advertisement was misleading and was not capable of substantiation and breaches of the Code were ruled. This ruling was appealed by Sanofi-Synthelabo.

The Appeal Board considered that the design of advertisement was such that the reader's eye was drawn diagonally down the page reading 'After weighing the evidence', '… NICE concludes' 'Solian'. The Appeal Board noted that the NICE guidance had not favoured any one of the five atypicals it had reviewed. The advertisement was misleading and not capable of substantiation. The Appeal Board upheld the Panel's ruling of breaches of the Code.

AstraZeneca UK Limited complained about the promotion of Solian (amisulpride) by Sanofi-Synthelabo Limited. The items at issue were a leavepiece (ref SOL-01/050) and an advertisement (ref SOL 02/031). AstraZeneca marketed Seroquel (quetiapine).

1 Leavepiece

The front page of the four page leavepiece included the headline 'Take the weight off her mind …and your budget'. The centre pages featured two cost comparison bar charts. One was headed 'Cost comparison of atypical antipsychotic treatment PER DAY' and the other was headed 'Cost comparison of atypical antipsychotic treatment over 28 DAYS'.

Both charts compared Solian, risperidone, olanzapine and quetiapine. Solian was the least expensive product shown; quetiapine was the second most expensive. The daily cost of Solian was given as £2.20 compared with £3.77 for quetiapine. The 28 day costs of the medicines similarly showed that Solian was the least expensive medicine; £61.60 compared with £105.56 for quetiapine. Beneath the charts a table of data showed the cost of a pack of each medicine; the 'Modal repeat average daily dose in schizophrenia*' from Psychotrak research data for each of the four products was also given (these doses were used as a basis for the comparison). The asterisk referred the reader to a statement below the table which read 'No comparison of efficacy was conducted'.

The leavepiece was distributed to hospital psychiatrists and hospital pharmacists during the early part of 2002 by the sales representatives.

COMPLAINT

Although the criteria chosen on which to make the comparison were the same, AstraZeneca alleged this was an unfair and misleading comparison as there was no evidence from head-to-head studies to show that Solian was at least as effective as the comparators at the doses compared in the graph. The supplementary information to Clause 7.2 of the Code stated that a price comparison must be made on the basis of the equivalent dosage requirement for the same indications.

The overall impression was such that the reader could assume the medicines at the doses used were of equivalent efficacy. There was no evidence in this regard. Stating in a small footnote that no efficacy comparison was conducted did not validate the price comparison as recent cases had demonstrated.

RESPONSE

Sanofi-Synthelabo stated that the cost comparison was a simple cost relating to acquisition costs and compared cost per day and treatment over 28 days. This comparison was supported by market research data and was clearly referenced. The leavepiece did not present any information pertaining to cost-effectiveness, which would transform the comparison into a cost-effectiveness comparison requiring validation by an appropriately designed comparative clinical trial.

Clause 7.2 of the Code required that 'comparisons must be accurate, balanced, fair, objective and unambiguous'.

Sanofi-Synthelabo submitted that the comparison was accurate because it precisely conveyed the findings of the referenced market research; balanced and fair because it included all four of the widely used first-line atypical antipsychotic agents; objective because it referred to the results of robust, independently conducted and reported market research; unambiguous and clearly and simply presented the results of the referenced market research. Further, a clearly labelled footnote informed the reader that no comparison of efficacy had been conducted, a point acknowledged by AstraZeneca.

The supplementary information to Clause 7.2 highlighted that where usage rates varied between medicines, a mg for mg comparison of costs for atypical antipsychotics would be misleading. The comparison made in the Solian leavepiece was based on typical clinical usage which in this context referred to 'the usual dose' of each atypical required to satisfactorily manage patients with schizophrenia; these data were supported by the market research cited.

The market research examined the use by over 200 UK consultant psychiatrists of atypical antipsychotic agents in the management of schizophrenia. Data were collected on a total of 1864 patients (including 83 treated with Solian and 116 with quetiapine). The market research was conducted by an independent and well-known research agency; its methodology was consistent and robust and its results were respected and widely used within the pharmaceutical industry.

Had a mean dosage been calculated for each agent, the resulting dose would be skewed and have no relevance to clinical practice. Furthermore, no meaningful cost could be attached to such a mean dosage. A median dose could be influenced by outliers (although in this case, median doses provided a similar profile of costs to the analysis presented). Therefore it was decided that modal doses would be the most appropriate parameter to demonstrate a fair comparison that would not be misleading.

The modal doses obtained were all within the recommended dose ranges stated in the respective summaries of product characteristics (SPCs). The modal dose identified for quetiapine in the market research was 400mg. This dose was also consistent with the findings of a retrospective analysis of flexibly-dosed patients in open-label studies which concluded that the 'most common dose of Seroquel was between 400 and 600mg/day' (ref: Seroquel leavepiece 01/8580 issued June 2001). Since the modal dose of quetiapine identified in the Solian leavepiece was at the lower end of the usual dose range identified in the Seroquel leavepiece, the Solian leavepiece would tend to underestimate the cost of treating a patient with Seroquel. It was therefore difficult to understand how the comparison could be described as either unfair or misleading.

Costs could also have been compared across the dosage range specified in the respective SPCs, from lowest usual dose to maximum dose (details were provided). However, such a presentation was less informative to the reader about 'usual clinical practice' compared with presentation of the doses most frequently used by psychiatrists.

Since the market research referred to in the leavepiece was conducted between December 2000 – November

2001, and the individual drug costs were current, Sanofi-Synthelabo believed that the cost comparison represented an up-to-date evaluation of the situation.

PANEL RULING

The Panel noted that the leavepiece compared four atypical antipsychotics with regard to aspects of their cost and that the allegation related to the impression that the doses used were equivalent in efficacy and there was no data to support this.

The Panel noted that no clinical data comparing the products had been submitted. It was not necessarily a breach of the Code to compare products based on the modal repeat daily dose. Such a comparison, based on the prescribing habits of consultant psychiatrists, would inform doctors how expensive it was likely to be, in terms of medicine acquisition costs, to treat a typical patient with each of the four atypicals depicted. The basis of the comparison had to be made clear. The Panel considered that on the narrow grounds of the allegation it was not misleading to compare the costs of the modal repeat average daily dose in the absence of evidence from head-to-head studies. There was no implication that the doses were clinically equivalent. The Panel ruled no breach of Clause 7.2 of the Code.

During its consideration of this case, the Panel was concerned that the basis of the comparison had not been made sufficiently clear. It might have been helpful if information had been given about the licensed range of doses so that the modal repeat average daily dose could have been set in context. The Panel was also concerned that the cost of four atypical antipsychotics had been compared. A fifth atypical medicine, zotepine, had not been included. The Panel noted that Sanofi-Synthelabo had stated that the cost comparison included all four of the widely used first-line atypical antipsychotics. The basis of the selection had not been made clear. The Panel requested that Sanofi-Synthelabo be advised of its concerns.

APPEAL BY ASTRAZENECA

AstraZeneca noted that the underlying principle in the Code, as stated in Case AUTH/1211/7/01, was 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'. AstraZeneca did not accept that market research data were sufficiently robust or accurate to support the comparison in question which was based on modal doses from a relatively small sample of market research rather than head-to-head efficacy studies or like-for-like licensed doses.

Lack of comparative clinical data

As market research clearly could not give accurate efficacy comparisons, AstraZeneca was surprised at the Panel's ruling given the outcomes of previous cases:

Case AUTH/1061/8/00, Case AUTH/1211/7/01 and Case AUTH/1205/7/01.

AstraZeneca provided detailed comment on the previous cases and stated that these appeared to confirm AstraZeneca's belief that cost comparisons should compare like-for-like doses and that these should be based on the equivalent dosage requirement for the same indication with clinical data showing equivalence.

Limitations of data used

AstraZeneca repeated that it did not believe that market research could be used to gauge clinical efficacy and noted that the questions used in market research ultimately determined the results. Sanofi-Synthelabo did not submit the market research methodology and data to the Panel. This had made it impossible to specifically comment on the precise process by which the modal repeat average daily dose was calculated. However, AstraZeneca had sourced the data and believed that it endorsed its argument that the cost comparison was misleading, and that the supporting data was insufficient.

The Psychotrak market research used had the following limitations in the context of its use in the comparison made:

- The number of psychiatrists sampled was small (200 consultant psychiatrists – only 4% of the population of practising psychiatrists).
- The number of patients used for Solian and Seroquel was also small (less than one patient per psychiatrist – 83 for Solian and 116 for Seroquel).
- The treatment of schizophrenia was not an exact science. Many patients received polypharmacy, taking more than one antipsychotic at a time. If data such as these were not excluded from the modal dose calculations, the research would be even less likely to reflect doses of equivalent efficacy.
- In any disease area geographical and demographical variations occurred therefore selection of the centres for the sample was likely to affect the results.
- Formulary decisions could exclude certain medicines in some areas.
- The choice of which dose to prescribe for a medicine could also vary geographically due to local cost pressures. For example, Solian might be prescribed at a lower dose in cost constrained areas than in an area where cost pressures did not exist. This was because Solian was marketed on its cost and psychiatrists were being told that 400mg was less costly and as efficacious as other atypicals therefore higher doses of Solian were less likely to be used.
- Particular medicines were preferred in certain patient groups for example risperidone tended to be favoured in the elderly, a group which required much lower doses.

AstraZeneca stated that modal doses only offered a valid description of prescribing patterns if data were normally distributed, and without prejudice to AstraZeneca's previous argument, were only a valid comparison between products if the distribution of

the data for all products were similar. However, schizophrenia was a complex area and as such the data was skewed differently for each medicine thus rendering the modal dose inaccurate and invalid for cross-comparison. The examples of limitations of the data described above would certainly skew the distribution of these medicines and this was illustrated by the dosage spread for the medicines from the Psychotrak data. AstraZeneca did not accept that using mean doses would make the comparison valid but it did believe that it would be a more accurate descriptor in this case.

The Psychotrak data showed that the modal doses varied considerably to the mean doses, particularly in the case of Solian and olanzapine (see below). The differences between mean dose and modal dose were greater for Solian (mean = 541mg, modal = 400mg) compared with Seroquel (mean = 426mg, modal = 400mg). The mean dose versus modal dose was therefore 35% higher for Solian compared with 7% higher for Seroquel. The modal dose therefore, compared to the mean dose was certainly more favourable to Solian (in terms of resultant cost of prescribing the dose) in the cost comparison compared with Seroquel.

To further compound the issue, it was far from clear to the reader that modal doses (from market research data) had been used as the basis for this cost comparison as this was stated in relatively small typeface near the foot of the page.

In summary AstraZeneca alleged that the leavepiece was in breach of Clause 7.2 of the Code. The cost comparison was based on market research showing what doses consultants most commonly prescribed. The assumption appeared to have been made that the dose doctors most commonly prescribed was therefore the same as the most effective dose and that this could form the basis for comparison with other medicines.

RESPONSE FROM SANOFI-SYNTHELABO

Choice of Cost Comparison

Sanofi-Synthelabo submitted that the cost comparison was valid because: like was compared with like, using modal doses for each medicine; modal doses were appropriate given the data used in the analysis and their asymmetrical distribution; the market research methodology was robust and based on a large sample of psychiatrists.

The leavepiece was a simple comparison of cost. If a comparison of efficacy were presented, invited or implied then equivalent dosage requirements for the same indication would be a necessary requisite. The Solian cost comparison was not a comparison of efficacy or cost effectiveness and this was clearly stated in the footnote.

The supplementary information to Clause 7.2, concerning price comparisons, did not stipulate that data from randomized controlled trials were a requisite for a valid price comparison. Sanofi-Synthelabo believed that the statement 'It follows therefore that a price comparison should be made on the basis of equivalent dosage requirement for the same indications' had been misinterpreted by the complainant.

The modal doses obtained were all within the recommended dose ranges stated in the respective SPCs.

Sanofi-Synthelabo noted the Panel's concerns in its ruling that the doses listed were not placed in context by including the licensed dose ranges.

Previous cases cited by AstraZeneca

Sanofi-Synthelabo did not consider that the previous cases, cited by the complainant, were relevant to this case and gave detailed reasons.

HMSL Psychotrak Market Research Data

Sanofi-Synthelabo stated that the market research data analysed reflected the following facts: data were combined for the period December 2000 to November 2001; the data were balanced across what were the Regional Health Authorities; the data came from 659 physician consultations and 1,318 clinics; 2063 patient prescriptions for schizophrenia were included; a total of 92 patients were prescribed Solian, in contrast to 83 cited by the complainant (77 on monotherapy – 83%); 62 patients were prescribed quetiapine, in contrast to the 116 cited by the complainant (49 on monotherapy – 79%).

More recent evaluations along the same lines were consistent with that used.

Sanofi-Synthelabo noted the Panel's concern in its ruling that the cost comparison in the Solian leavepiece excluded zotepine. This was done for a number of reasons: Firstly the leavepiece predated the publication of guidance on the use of atypical antipsychotics by the National Institute of Clinical Excellence (NICE). Had the cost comparison been produced following the publication of the guidance, zotepine would have been included. Secondly the zotepine market share was very small at that stage and only 5 patients were prescribed zotepine in the market research data (HMSL Psychotrak), reflecting the very low market share.

In summary, this item presented a simple cost comparison based on the most prescribed doses from market research data which reflected current and usual clinical practice. The leavepiece did not invite or imply a comparison of efficacy. Sanofi-Synthelabo therefore agreed with the Panel's ruling of no breach of Clause 7.2 of the Code.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that Sanofi-Synthelabo seemed to be over-simplifying the criteria by which a comparison could be described as like with like. Modal dose meant the dose at which that medicine had the greatest number of prescriptions across the range of licensed doses. It could not be assumed that any statistical measure of a dose was cross-comparable between medicines. Statistical measurements required adequate description of their meaning and validity to be meaningful to non-statisticians. Such descriptions were notably absent in the leavepiece.

As with any statistical measure there would be pros and cons for its use. AstraZeneca was concerned that there was a much greater difference between mean and modal doses for amisulpride than for Seroquel and that the mean dose for amisulpride was significantly greater than the modal dose.

AstraZeneca had already raised concerns regarding the market research. AstraZeneca disagreed that the sample size was large; from the data provided by Sanofi-Synthelabo only 301 physicians actually completed the questionnaire with only 49 patients prescribed Seroquel and 77 prescribed amisulpride (as monotherapy) in the timeframe used.

Sanofi-Synthelabo had argued that the leavepiece was a simple comparison of cost, however, a medicine was not chosen on cost alone. A physician would only select a medicine on the basis of cost if (s)he knew the consequences of using that medicine in terms of efficacy. Therefore the readers of this leavepiece would be likely to assume that the efficacy must be equivalent or the comparison was irrelevant. A simple cost comparison should surely have been placed in the context of the whole dose range as indicated in the Panel's assessment of this piece.

Sanofi-Synthelabo had stated that there were differences between the cases cited by AstraZeneca, which AstraZeneca acknowledged. There would always be differences between individual cases; however, the cases cited had crucial similarities to the case in question. AstraZeneca believed that these cases were relevant and had summarised the key points.

AstraZeneca believed that the underlying principle in the Code as stated in Case AUTH/1211/7/01 was 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'. Further comments were made about the previous cases.

AstraZeneca had a number of concerns over the market research. In particular it did not believe that market research could be used to support a like-for-like cost comparison. The most commonly prescribed doses for a range of medicines did not necessarily equate to any therapeutic equivalence across the range used in the market research. AstraZeneca continued to be concerned about the small sample size and the statistical validity of the comparison. AstraZeneca also highlighted that Sanofi-Synthelabo first cited the number of patients on amisulpride and Seroquel as 83 and 116 respectively, not AstraZeneca as alleged by Sanofi-Synthelabo.

AstraZeneca continued to view the cost comparison as misleading and invalid.

APPEAL BOARD RULING

The Appeal Board noted that the supplementary information to Clause 7.2 stated: 'Price comparisons, as with any comparison, must be accurate, fair and must not mislead. Valid comparisons can only be made where like is compared with like. It follows therefore that a price comparison should be made on the basis of the equivalent dosage…'

The Appeal Board noted that according to its SPC and depending on the symptoms, Solian had a wide range of available doses, 50mg a day to up to 1200mg a day. The Appeal Board noted the data provided by AstraZeneca that although the modal repeat average daily dose for Solian was 400mg the repeat mean daily dose was 541mg. If the costs were calculated using the mean doses the cost comparison would look quite different. In the Appeal Board's view the use of the modal repeat average daily dose gave an inaccurate reflection of the relative costs of the medicines.

The Appeal Board considered that the layout of the cost comparison was such that it inferred that the doses used were therapeutically equivalent. The Appeal Board noted Sanofi-Synthelabo's submission that the modal repeat average doses were therapeutically equivalent, ie, that they provided control and were effective in a clinical setting. However the Appeal Board noted that this evidence was based solely upon the clinical experience of a number of prescribers with a small number of patients and not on comparative studies.

The Appeal Board considered that the cost comparisons were misleading. The Appeal Board ruled a breach of Clause 7.2. The appeal on this point was successful.

2 Advertisement

The advertisement depicted a set of weighing pans. The weighing pan in the background of the advertisement depicted a pile of papers representing clinical evidence with the caption 'After weighing the evidence …'. The weighing pan in the foreground was empty and bore the Solian product logo beneath the claim '… NICE concludes'. The advertisement had appeared in BMJ, 27 July 2002.

In the bottom left-hand corner a statement attributed to recent NICE guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia read:

> 'It is recommended that the oral atypical antipsychotic drugs are considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia. Where more than one atypical antipsychotic drug is considered appropriate, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed'.

COMPLAINT

AstraZeneca submitted that even if the scales were balanced this could still suggest that from the evidence reviewed, NICE recommended Solian in particular as an atypical of choice in schizophrenia.

AstraZeneca considered that the advertisement gave the impression that, after considering the evidence, NICE recommended Solian as the atypical of choice in the treatment of schizophrenia, based on clinical evidence and cost. AstraZeneca noted that in schizophrenia there was a wide variation in the individual patient's response to antipsychotics and

dose requirements as well as differences between the various antipsychotics themselves, especially in terms of tolerability profiles. Individuals' responses and acceptability of the various atypicals would be highly variable. NICE did not find one particular atypical to be considered as the most appropriate in terms of cost or efficacy. The implication was also made that Solian was the least expensive atypical antipsychotic. This was both misleading and unsubstantiable since when compared to Zoleptil (zotepine) (an atypical also considered in the NICE review) Solian was clearly more expensive.

RESPONSE

Sanofi-Synthelabo noted that the NICE guidance advocated the use of the oral atypical antipsychotic drugs amisulpride, olanzapine, quetiapine, risperidone and zotepine in schizophrenia. The key points of the guidance were that:

- the choice of antipsychotic should be made jointly by the individual and clinician responsible,
- the oral antipsychotics listed above be considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia,
- finally the cost of the medicine was an important factor that should be considered when more than one atypical was considered appropriate for an individual.

The purpose of the advertisement was to act as a reminder of the value of the use of oral atypical antipsychotics for patients with newly diagnosed schizophrenia. The imagery reflected the value of Solian as one of the oral atypical antipsychotics recommended by the recent NICE guidance.

Sanofi-Synthelabo did not agree that the advertisement created the impression that Solian alone was the atypical of choice. The advertisement highlighted clearly the following statement taken from the NICE guidance: 'It is recommended that the oral atypical antipsychotic drugs are considered in the choice of first-line treatments for individuals with newly-diagnosed schizophrenia'.

The visual complemented this statement by depicting the Solian logo in one pan equally balanced with the other atypical antipsychotics in the other pan. The impression was therefore that the evidence for Solian was as good as the other atypical antipsychotics depicted in the adjacent pan. The statement from the guidance served to clarify that the atypical antipsychotic class as a whole had been endorsed by the recent NICE guidance on the use of newer drugs in schizophrenia. The benefits of this class were based on two important facets in the management of this group of individuals: clinical efficacy and cost-effectiveness.

AstraZeneca correctly pointed out that there was a wide variation in the individual patient's response to antipsychotics and dose requirements as well as differences between the various antipsychotics themselves, especially in terms of tolerability profiles. But it failed to mention that, increasingly, cost was an important consideration for the prescriber. To place an advertisement with general guidance on the use of the class as a whole without mentioning costs would be misleading and inconsistent with the NICE guidance as this was an important factor in the choice of atypical antipsychotic. This was reflected in the advertisement by a second, clearly positioned quote from the NICE guidance: 'Where more than one atypical antipsychotic drug is considered appropriate, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed'.

Sanofi-Synthelabo could not understand AstraZeneca's concern that the advertisement conveyed the message that Solian was the least expensive atypical antipsychotic. This interpretation was remarkable given that there was no claim relating to the cost of Solian or cost-effectiveness compared with the other atypical antipsychotics in the advertisement.

PANEL RULING

The Panel noted that the angle at which the scales had been depicted made it appear that the evidence was weighted in favour of Solian. From another angle the weighing scales might be level but this was not immediately obvious from the illustration. The impression that the evidence was weighted in favour of Solian was compounded by the use of the product logo on the empty weighing scale together with the use of the brand name next to the scales. The Panel considered that the advertisement implied that NICE had concluded that Solian was the atypical of choice which was not so; the NICE guidance had not favoured any one of the five atypicals it had reviewed. The advertisement was misleading and was not capable of substantiation and breaches of Clauses 7.2 and 7.4 of the Code were ruled.

APPEAL BY SANOFI-SYNTHELABO

Sanofi-Synthelabo stated that the objective of the advertisement was to convey the message that, of the medicines considered by NICE in its guidance on atypical antipsychotics, Solian was one of those reviewed and the evidence for and against Solian was not outweighed by the other atypicals endorsed.

Sanofi-Synthelabo submitted that the Panel's ruling reflected a subjective impression of the imagery. Indeed, the Panel stated in its ruling that the 'weighing scales might be level but this was not immediately obvious from the illustration'. Sanofi-Synthelabo felt compelled to defend the image and point out that the illustration was clear in depicting that the weighing scales were level because the image was in visual perspective. The following supported the initial impression of the image depicting a set of scales in perspective: the two pans of the scales were unequal in size; the nearer pan was clear, whereas the more distant pan was blurred; the links of the chains holding the nearer pan were clear, whereas the links of the chains holding the distant pan was blurred; the chains holding up the nearer pan were larger compared with those of the more distant pan and shadowing on the clinical papers in the far pan highlighted the perspective. Once the image was seen

to be in visual perspective, then it was also clear that the pans were equally balanced and that the Solian pan did not outweigh the pan holding the clinical evidence. On this basis, one could only draw the conclusion that the evidence for Solian was in equilibrium with the pan holding the clinical data and rendered the illustration consistent with the NICE guidance. The advertisement was not, therefore, in breach of Clauses 7.2 and 7.4 of the Code.

The Panel considered that the Solian logo on the empty pan implied that the 'evidence was weighted in favour of Solian'. The Solian logo simply represented the clinical evidence for Solian, which would otherwise have been depicted by more clinical papers. Again, the embossed Solian logo should not detract from the fact that the two pans were in equilibrium.

Notwithstanding the above, the advertisement clearly emphasised the point that the NICE guidance recommended all the oral atypical antipsychotics that were considered and this was evident by the inclusion of the statement from the NICE guidance about the use of atypicals in newly diagnosed patients.

Finally, the Panel's ruling did not make any reference to AstraZeneca's concern that the advertisement conveyed the message that Solian was the least expensive atypical antipsychotic. As there was no claim relating to the cost of Solian or cost-effectiveness compared with the other atypical antipsychotics in the advertisement, Sanofi-Synthelabo wished to question whether the Panel's ruling encompassed this aspect of the original complaint. Indeed, Sanofi-Synthelabo maintained that there was no claim relating to the cost of Solian or cost-effectiveness compared with the other atypical antipsychotics and therefore, believed that the advertisement was not in breach of Clauses 7.2 and 7.4 on this point.

RESPONSE FROM ASTRAZENECA

The NICE guidance did not find one particular atypical to be more appropriate in terms of cost or efficacy with the exception of clozapine, which was reserved for treatment-resistant schizophrenia. However, the impression given by the advertisement was that NICE reviewed the evidence and singled out Solian for particular merit in the treatment of schizophrenia.

AstraZeneca repeated that its reason for this belief was that on first inspection the scales appeared to be balanced in favour of Solian and even if the scales were balanced equally this could still suggest that, from the evidence reviewed, NICE recommended Solian in particular as an atypical of choice in schizophrenia. This impression conveyed was largely due to the juxtaposition of the statement '…NICE CONCLUDES' immediately above the Solian logo embossed on the nearest pan of the scales. It was important to note that the Solian logo on this pan was by far the most striking feature of the advertisement thus placing the '…NICE CONCLUDES' statement above it had obvious connotations as to what NICE had concluded 'AFTER WEIGHING THE EVIDENCE'.

Sanofi-Synthelabo had given five reasons as to why it believed the scales were equally balanced. AstraZeneca believed that the argument was tenuous and irrelevant as the overall impression gained by the reader was critical and this could only be judged by the individual actually looking at the advertisement. On the basis of overall impression the argument put by Sanofi-Synthelabo that the advertisement clearly emphasised that the NICE guidance recommended all the atypical antipsychotics considered was invalid given that this statement appeared in small typeface at the bottom corner of the advertisement and would have minimal impact in the context of the overall impression from the advertisement.

Sanofi-Synthelabo refuted that there was any cost claim within the advertisement. The body of text at the foot of the page contained the following extract from the NICE guidance: 'Where more than one atypical antipsychotic drug is considered appropriate, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed'.

AstraZeneca submitted that by including the NICE recommendation without further qualification it implied that Solian met this criteria. This was both misleading and unsubstantiable since when compared to Zoleptil (an atypical antipsychotic also considered in the NICE review) Solian was clearly more expensive.

APPEAL BOARD RULING

The Appeal Board considered that the design of the advertisement was such that the reader's eye was drawn diagonally down the page reading 'After weighing the evidence', '… NICE concludes' 'Solian'. The Appeal Board noted that the NICE guidance had not favoured any one of the five atypicals it had reviewed. The advertisement was misleading and not capable of substantiation. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4 of the Code. The appeal on this point was unsuccessful.

Complaint received **13 August 2002**

Case completed **18 December 2002**

CASE AUTH/1352/8/02

MEDIA/DIRECTOR v SCHERING HEALTH CARE

Promotion of Yasmin

An article in the Drug and Therapeutics Bulletin, August 2002, entitled 'Is Yasmin a 'truly different' pill?', criticised claims made by Schering Health Care for its combined oral contraceptive (COC) Yasmin (drospirenone and ethinylestradiol). It was established practice that media criticism was taken up and dealt with as a complaint under the Code of Practice.

The article began by noting that advertising for Yasmin claimed that the product was 'truly different', as reliable and safe as other COCs and was 'the pill for well-being', with 'no associated weight gain' and 'a demonstrable positive effect' on pre-menstrual symptoms and skin condition. It was also noted that such claims had appeared in the lay media. Reference was made to an on-line article which had appeared on www.femail.co.uk (a Daily Mail website) entitled 'New Pill that beats weight gain'. The Drug and Therapeutics Bulletin article concluded 'There is no compelling published evidence to suggest Yasmin offers any advantages over other, longer established, COCs with regards to weight gain, skin condition or pre-menstrual symptoms. Furthermore, we believe that the claim that Yasmin 'is the pill for well-being' is unjustified and misleading and should be withdrawn. Yasmin's effects on cardiovascular risk (including venous thromboembolic disease) have not been quantified'.

The Panel noted that Yasmin was the only COC to contain drospirenone. Schering Health Care submitted that it was this component which provided the combination of benefits which set Yasmin apart from other products.

The central element of the promotional campaign was the feeling of well-being reported by women on Yasmin; this was reflected in the headline 'Well. And truly different' and the strapline 'The pill for well-being'. In the advertisement supplied by Schering Health Care the claim 'Women feel well on Yasmin' was referenced to Parsey and Pong (2000) and Boschitsch *et al*. The secondary objective of Parsey and Pong was to evaluate the effects of Yasmin on menstrual cycle control. The results showed that Yasmin had a positive impact on the perception of the severity of some menstrual cycle symptoms compared to baseline. There was no effect on other menstrual cycle symptoms, including feelings of well-being, at any phase of the cycle.

Boschitsch *et al* investigated the feelings of women who had taken either Yasmin or Marvelon in two clinical trials by means of a survey which evaluated how they felt after the trial had finished, compared with when they were taking the trial preparations. Marvelon differed from Yasmin only in respect of its progestogen component which was desogestrel and not drospirenone. The women who had been taking Yasmin felt statistically significantly worse with respect to before and during menses, their body weight and the condition of their skin and hair once the trials had ended ie they felt better while taking Yasmin. With regard to their effect on others and sexual sensitivity the results showed that women felt better when the trials had finished ie they felt worse while taking Yasmin.

The Panel considered that well-being was a very broad term and encompassed many aspects of physical, emotional and psychological health. Yasmin had been shown to have a positive impact on some aspects but not on all aspects. The Panel thus considered that general unqualified claims for well-being on Yasmin were misleading and could not be substantiated. Breaches of the Code were ruled. These rulings were appealed.

The Appeal Board did not consider that there was sufficient evidence to make the general unqualified claims for well-being on Yasmin. There was limited comparative data. The Appeal Board considered that the claims were misleading and could not be substantiated and upheld the Panel's rulings of breaches of the Code.

With regard to body weight, the Panel noted that the Yasmin summary of product characteristics (SPC) listed, *inter alia*, fluid retention and body weight changes as uncommon (<1/100, ≥ 1/1000) adverse reactions. The SPC stated that drospirenone possessed mild antimineralocorticoid properties and that there were indications from clinical studies that these properties resulted in a mild antimineralocorticoid effect. The advertisement supplied by Schering Health Care stated '[Yasmin] has been shown repeatedly to have no associated weight gain', referenced to Foidart *et al*, Huber *et al* and Oelkers *et al*.

The Panel considered that although the statement in the Yasmin SPC was unclear as to whether body weight changes were positive or negative there was clinical data to show that the majority of women taking Yasmin maintained a stable body weight and that the product was not associated with weight gain in the first two years of treatment. Foidart *et al* and Huber *et al* both showed, however, that a small percentage of women did gain more than 2kg body weight while taking Yasmin. The Foidart study also showed that in cycles 25 and 26 the mean body weight of women taking Yasmin was slightly above baseline; the statistical significance of this change was not stated. There was a statistically significant difference in mean body weight from baseline in cycles 1-13 (p=0.0001) and cycles 14-26 (p=0.009). The Panel considered that the claim that Yasmin had been shown repeatedly to have no associated weight gain was a strong, absolute claim which did not reflect all of the evidence and was misleading in that regard and could not be substantiated. A breach of the Code was ruled. This ruling was appealed.

The Appeal Board did not consider there was sufficient evidence to support the strong absolute claim that '[Yasmin] has been shown repeatedly to have no associated weight gain'; data from three clinical studies did not justify use of the term 'repeatedly'. The Appeal Board upheld the Panel's ruling of breaches of the Code.

The advertisement supplied by Schering Health Care stated that Yasmin had a demonstrable positive effect on skin condition which was referenced to Boschitsch *et al*. The results showed that women thought their skin was clearer when they were taking Yasmin compared to when they were not. Schering Health Care also referred to data by Huber *et al* and Van Vloten *et al*. The Panel considered that there was data to show that Yasmin had a positive effect on skin condition. The Panel thus did not consider that the claim was misleading; it could be substantiated. No breach of the Code was ruled.

With regard to pre-menstrual symptoms the advertisement provided by Schering Health Care stated 'Yasmin has a demonstrable positive effect on PM symptoms' referenced to Parsey and Pong and Boschitsch *et al*.

The Panel considered that there was data to show that with regard to some specific pre-menstrual symptoms Yasmin had a positive effect; with other symptoms there was no change. The Panel considered that the use of the term 'PM symptoms' in the advertisement was too broad and was misleading in that regard; a claim for a demonstrable positive effect on PM symptoms could not be substantiated. Breaches of the Code were ruled. These rulings were appealed.

The Appeal Board noted the claim 'Yasmin has a demonstrable effect on [pre-menstrual] symptoms' was referenced to Parsey and Pong and Boschitsch *et al*. The Appeal Board noted that there was some data to show that Yasmin had a positive effect on some specific pre-menstrual symptoms; with other symptoms there was no change. The Appeal Board considered that the claim 'a demonstrable positive effect on PM symptoms' was too broad and could not be substantiated. The Appeal Board upheld the Panel's ruling of breaches of the Code.

The Panel noted its rulings above and considered that a claim that Yasmin was 'truly different', based on a combination of reports of well-being, positive effects on skin condition and no associated weight gain, was misleading and could not be substantiated. Breaches of the Code were ruled. These rulings were appealed.

The Appeal Board considered, in view of its previous rulings, that the claim that Yasmin was 'truly different' was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

The Panel found two articles which referred to Yasmin on the femail.co.uk website cited in the Drug and Therapeutics Bulletin. The first was a general review entitled 'The Pill: All you need to know'. Schering Health Care had not provided any information for this article. The second was specifically about Yasmin and was entitled 'New Pill that beats weight gain'. It was stated that Yasmin counteracted fluid retention as well as reducing mood swings and breast tenderness. A spokeswoman for Schering Health Care was quoted as saying 'The new pill offers a number of physical and mental lifestyle benefits for women. It is a major development in the 40-year history of the Pill and sets a new standard in combined oral contraception for women in the UK, finally liberating them from the less desirable side-effects commonly associated with the Pill'. Schering Health Care had also provided a copy of an article which appeared in the Daily Mail. The text was similar to that which appeared on-line.

The 'Schering Holding Statement – Launch of Yasmin', which had been given to the Daily Mail, stated, *inter alia*, that Yasmin was a major development in contraception because unlike other oral contraceptives it provided a unique package of physical and mental well-being benefits including: no associated weight gain from fluid retention and beneficial effects on skin, hair and pre-menstrual symptoms. The Panel noted its rulings above and considered that the holding statement was not factual. A breach of the Code was ruled. This ruling was appealed.

The Appeal Board noted that the 'Schering Holding Statement – Launch of Yasmin', which had been given to the Daily Mail, stated, *inter alia*, that Yasmin was a major development in contraception because unlike other oral contraceptives it provided a unique package of physical and mental well-being benefits including: no associated weight gain from fluid retention and beneficial effects on skin, hair and pre-menstrual symptoms. The Appeal Board noted its rulings above and considered that the holding statement was not factual. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Panel noted that in the Daily Mail article of 30 March 2000, one of Schering Health Care's medical advisers was quoted as saying that '… the evidence to date was that the risk of blood clots with Yasmin was the same as with other low-dose pills'. The Drug and Therapeutics Bulletin article stated that Yasmin's effects on cardiovascular risk (including venous thromboembolic disease) had not been quantified. The SPC for Yasmin listed thromboembolism as a rare (<1/1000) adverse reaction. It also listed serious adverse events that had been reported in women using COCs. The list included, *inter alia*, venous thromboembolic disorders, arterial thromboembolic disorders and hypertension. It was stated that epidemiological studies had shown the incidence of venous thromboembolism in users of oral contraceptives with low oestrogen content (<50mcg ethinylestradiol) ranged from about 20-40 cases per 100,000 women years, but that that risk estimate varied according to the progestogen. The Panel considered that Yasmin's effects on cardiovascular risk had been quantified. The Panel did not consider, given the statements in the SPC, that the quote about blood clots which had appeared in the Daily Mail article was unreasonable. No breach of the Code was ruled in that regard. The Drug and Therapeutics Bulletin criticised the Panel's ruling of no breach and this was treated as an appeal.

The Appeal Board accepted that Schering Health Care might have evidence to support the statement which appeared in the Daily Mail that '… the

evidence to date was that the risk of blood clots with Yasmin was the same as with other low dose pills'. However the Yasmin SPC stated 'It is not yet known how Yasmin influences the risk of VTE compared with other oral contraceptives'. The Appeal Board considered that the statement in the Daily Mail was not balanced and ruled a breach of the Code.

An article in the Drug and Therapeutics Bulletin, August 2002, entitled 'Is Yasmin a 'truly different' pill?', criticised claims made by Schering Health Care Ltd for its combined oral contraceptive (COC) Yasmin (drospirenone and ethinylestradiol). It was established practice that media criticism was taken up and dealt with as a complaint under the Code of Practice.

COMPLAINT

The article began by noting that advertising for Yasmin claimed that the product was 'truly different', as reliable and safe as other COCs and was 'the pill for well-being', with 'no associated weight gain' and 'a demonstrable positive effect' on pre-menstrual symptoms and skin condition. It was also noted that such claims had appeared in the lay media. Reference was made to an on-line article which had appeared on www.femail.co.uk (a Daily Mail website) entitled 'New Pill that beats weight gain'. The Drug and Therapeutics Bulletin article reviewed Yasmin and its associated clinical evidence. The article concluded 'There is no compelling published evidence to suggest Yasmin offers any advantages over other, longer established, COCs with regards to weight gain, skin condition or pre-menstrual symptoms. Furthermore, we believe that the claim that Yasmin 'is the pill for well-being' is unjustified and misleading and should be withdrawn. Yasmin's effects on cardiovascular risk (including venous thromboembolic disease) have not been quantified'.

When writing to Schering Health Care, the Authority drew its attention to the requirements of Clauses 7.2, 7.3, 7.4, 7.9 and 20.2 of the Code.

RESPONSE

Schering Health Care stated that its promotion of Yasmin to date had rested largely on the differentiation provided by the new progestogen, drospirenone, and its unique clinical effects and pharmacological profile. Both of these properties had been substantiated by a variety of published clinical data.

The central element of the current campaign was that of the increased well-being described by women after using Yasmin, and the favourable skin effects demonstrated from a randomised, blinded, clinical study comparing Yasmin with Dianette. The published work cited in support of claims for 'well-being' was Boschitsch *et al* (2000) and for the skin effects, the same work which referenced 'data on file' had been recently published (van Vloten *et al* 2002). The claim of 'no associated weight gain' was substantiated by both the pharmacological plausibility of the drospirenone anti-mineralocorticoid activity (Oelkers *et al* 1995 and the summary of product characteristics (SPC)) and the various published clinical trial data (Boschitsch *et al*; Huber *et al* 2000; Foidart 2000).

Schering Health Care stated the claims were reviewed by the Medicines Control Agency (MCA) and its subsequent assessment was favourable. The company noted that the Drug and Therapeutics Bulletin provided it with a first draft copy of the proposed article (as routinely occurred whenever a company product was mentioned). Although the format and content of the 'near final' and published version of the article were significantly different to the 'first circulation' and 'final circulation' drafts, no use was made of the information Schering Health Care had provided. Copies of the various drafts and correspondence were provided.

Schering Health Care stated that it refuted the conclusions of the Drug and Therapeutics Bulletin that there was no 'compelling' published evidence of any advantage over other COCs with regard to weight gain. The company was confident that the promotional claim of '… no associated weight gain' was adequately supported by the published references provided and accompanying explanation of the mineralocorticoid effect of drospirenone on water retention. The evidence for a favourable effect on skin was clear and concise, recently published in the literature, and, the company considered, had not been assessed or reviewed by the Drug and Therapeutics Bulletin in an even-handed manner. The favourable effects of Yasmin on both pre-menstrual symptoms and well-being were substantially documented, and had been further established by a recently completed clinical study.

Schering Health Care stated that the Drug and Therapeutics Bulletin concluding statement that Yasmin's effect on cardiovascular risk had not been quantified was untrue, and was published in complete disregard of the information offered by the company.

Schering Health Care had reviewed the website www.femail.co.uk, where the page referenced by the Drug and Therapeutics Bulletin could not be accessed. A search of the site found three pieces containing mention of Yasmin. The first, dated 23 June 2001, contained no information provided by the company, the second was the text of an article in the newspaper dated 30 March 2002, and the third was a piece dated just prior to the launch of Yasmin on 17 April 2002. Schering Health Care had provided the Daily Mail with some information in two telephone conversations with its journalist at the end of March 2002, which the company believed contributed to (and were quoted in) the article published on 30 March 2002. This material did not appear to have been used verbatim in the third 'femail.co.uk' piece of 17 April, and the company assumed that additional information for this was obtained from some other source. The 'Schering Holding Statement' sent to the Daily Mail on 27 March included an offer to provide additional information prior to launch. In the event, further information was not requested by the Daily Mail, and was therefore not supplied.

In its response Schering Health Care provided a copy of a current advertisement for Yasmin (ref L0201077A)

which featured the headline 'Well. And truly different'. Text beneath the headline stated that Yasmin was different in many ways 'It has been shown repeatedly to have no associated weight gain. In addition, Yasmin has a demonstrable positive effect on PM [pre-menstrual] symptoms and on skin condition'. It was stated that this new combination of benefits was a product of drospirenone and that 'Women feel well on Yasmin'. The strapline beneath the product logo was 'The pill for well-being'.

PANEL RULING

The Panel noted Schering Health Care's submission that the MCA had reviewed the claims. The Panel nevertheless had to address the issues raised by the Drug and Therapeutics Bulletin article.

The Panel noted that Yasmin was the only COC to contain drospirenone. Schering Health Care had submitted that it was this component which provided the combination of benefits which set Yasmin apart from other products.

The central element of the promotional campaign was the feeling of well-being reported by women on Yasmin; this was reflected in the headline 'Well. And truly different' and the strapline 'The pill for well-being'. In the advertisement supplied by Schering Health Care the claim 'Women feel well on Yasmin' was referenced to Parsey and Pong (2000) and Boschitsch *et al*. Parsey and Pong was an open-label, multicentre study. The primary objective was to determine the efficacy and safety of Yasmin. The secondary objective was to evaluate the effects of Yasmin on menstrual cycle control. Diary cards were used and the evaluation of the effect of Yasmin on women's self-perception of menstrual health was by means of a questionnaire at baseline and after 6 months. The questionnaire consisted of 23 items to include symptoms of impaired concentration, water retention, negative affect, increased appetite, well being and undesirable hair change. These were compared to baseline at three phases of each menstrual cycle – pre-menstrual, menstrual and post-menstrual. The results showed that Yasmin had a positive impact on the perception of the severity of some menstrual cycle symptoms compared to baseline. Symptoms of water retention and negative affect were less severe in all three phases of the cycle by cycle 6. Symptoms of increased appetite lessened in the pre-menstrual and menstrual phases by cycle 6 although there was no effect post-menstrually. There was no effect on any of the other menstrual cycle symptoms, including feelings of well being, at any phase of the cycle.

Boschitsch *et al* investigated the feelings of women who had taken either Yasmin or Marvelon in two clinical trials by means of a survey which evaluated how they felt after the trial had finished, compared with when they were taking the trial preparations. Marvelon differed from Yasmin only in respect of its progestogen component which was desogestrel and not drospirenone; both products otherwise contained 30µg ethinylestradiol. The women who had been taking Yasmin felt statistically significantly worse with respect to before and during menses, their body weight and the condition of their skin and hair once the trials had ended ie they felt better while taking Yasmin. With regard to their effect on others and sexual sensitivity the results showed that women felt better when the trials had finished ie they felt worse while taking Yasmin.

The Panel considered that well-being was a very broad term and encompassed many aspects of physical, emotional and psychological health. Yasmin had been shown to have a positive impact on some aspects but not on all aspects. The Panel thus considered that general unqualified claims for well-being on Yasmin were misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

With regard to body weight, the Panel noted that section 4.8, Undesirable effects, of the Yasmin SPC listed, *inter alia*, fluid retention and body weight changes as uncommon (<1/100, ≥ 1/1000) adverse reactions. Section 5.1 of the SPC stated that in therapeutic dosages, drospirenone possessed mild antimineralocorticoid properties and that there were indications from clinical studies that these properties resulted in a mild antimineralocorticoid effect. The advertisement supplied by Schering Health Care stated '[Yasmin] has been shown repeatedly to have no associated weight gain', referenced to Foidart *et al*, Huber *et al* and Oelkers *et al*.

Foidart *et al* was an open label, randomized study comparing the efficacy, cycle control and tolerability of Yasmin and Marvelon over 26 cycles, plus a 3 month follow-up period. Women recorded their own body weights at home; the results showed a statistically significant difference between the two groups. In the Yasmin group the mean body weight per cycle remained slightly below baseline throughout the study except in cycles 25 and 26. In contrast the mean body weight of women in the Marvelon group was slightly below baseline only in cycles 1-5 and from cycle 7 it was above. In the follow-up phase mean body weight was above baseline in both groups. The authors reported that although mean body weight decreased in the Yasmin group and increased in the Marvelon group, not all women showed the same pattern of change. In both groups the majority of women maintained a stable body weight within 2kg of baseline. More women in the Yasmin group lost more than 2kg from baseline weight than in the Marvelon group. However, against the general trend some women in the Yasmin group gained more than 2kg from baseline weight and some in the Marvelon group lost more than 2kg.

Huber *et al* similarly compared the efficacy and tolerability of Yasmin and Marvelon over 13 cycles in an open-label study. Women recorded their own body weight on three consecutive days before treatment and weekly thereafter. The two treatments differed in their effect on body weight, the difference being statistically significant. In the Yasmin group there was a distinct decrease over the whole treatment phase, while a subtle and less distinct decrease was documented in the Marvelon group ($p<0.0072$). As in the study by Foidart *et al*, the majority of women in both groups maintained a stable body weight of ±2kg but once again some in the Yasmin group gained

more than 2kg and some in the Marvelon group lost more than 2kg.

Oelkers *et al* compared the effect of variable doses of ethinylestradiol and drospirenone (the components of Yasmin) and one combination of ethinylestradiol and levonogestrel (Microgynon) over 6 treatment cycles. All persons in the trial were unaware of the treatment group to which each woman belonged. Body weight was measured by the women themselves every second day throughout the trial on home scales. Body weight fell in all three groups taking some combination of ethinylestradiol and drospirenone whereas it rose in the Microgynon group. The differences between the drospirenone groups and the Microgynon group were significant.

The Panel considered that although the statement in the Yasmin SPC (Section 4.8 Undesirable effects) was unclear as to whether body weight changes were positive or negative there was clinical data to show that the majority of women taking Yasmin maintained a stable body weight and that the product was not associated with weight gain in the first two years of treatment. Foidart *et al* and Huber *et al* both showed, however, that a small percentage of women did gain more than 2kg body weight while taking Yasmin. The Foidart study also showed that in cycles 25 and 26 the mean body weight of women taking Yasmin was slightly above baseline; the statistical significance of this change was not stated. There was a statistically significant difference in mean body weight from baseline in cycles 1-13 ($p=0.0001$) and cycles 14-26 ($p=0.009$). The Panel considered that the claim that Yasmin had been shown repeatedly to have no associated weight gain was a strong, absolute claim which did not reflect all of the evidence and was misleading in that regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The advertisement supplied by Schering Health Care stated that Yasmin had a demonstrable positive effect on skin condition which was referenced to Boschitsch *et al* – the same paper which was submitted as substantiation for claims of well-being and discussed above. The results showed that women thought their skin was clearer when they were taking Yasmin compared to when they were not. Huber *et al* had also compared the effects of Yasmin and Marvelon on skin condition although subjects were not selected on the basis of their skin condition. In both groups the incidence and severity of acne declined substantially as did the incidence of seborrhoea. However, only about 20% of the study population reported any kind of skin problems and only a minority had severe complaints. Van Vloten *et al*, however, conducted a double-blind, randomized comparative study of the effects of Yasmin and Dianette in women with mild to moderate facial acne with or without seborrhoea and/or hirsutism. After 9 cycles the median total acne lesion count was reduced markedly by 62.5% in the Yasmin group and 58.8% in the Dianette group. Both preparations also reduced sebum production and reduced hair growth. Treatment differences were not seen. Subjective evaluation of the effect of treatment on facial acne by dermatologists, gynaecologists and the women themselves indicated an excellent or good improvement for most subjects in both groups.

The Panel considered that there was data to show that Yasmin had a positive effect on skin condition. The Panel thus did not consider that the claim was misleading; it could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

With regard to pre-menstrual symptoms the advertisement provided by Schering Health Care stated 'Yasmin has a demonstrable positive effect on PM symptoms' referenced to Parsey and Pong and Boschitsch *et al*. These were the papers discussed above with regard to the claims for well-being. Parsey and Pong showed that pre-menstrually there were statistically significant decreases from baseline to cycle 6 for negative affect, water retention and increased appetite. There were no statistically significant changes for impaired concentration, undesirable hair changes or feelings of well-being. Boschitsch *et al* reported that pre-menstrually women felt better when they were taking Yasmin than when they were not.

The Panel considered that there was data to show that with regard to some specific pre-menstrual symptoms Yasmin had a positive effect; with other symptoms there was no change. The Panel considered that the use of the term 'PM symptoms' in the advertisement was too broad and was misleading in that regard; a claim for a demonstrable positive effect on PM symptoms could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the article in the Drug and Therapeutics stated that Yasmin's effects on cardiovascular risk (including venous thromboembolic disease) had not been quantified. No claim regarding the effect of Yasmin on cardiovascular risk had been made in the advertisement and so the Panel made no ruling in this regard.

The Panel noted its rulings above and considered that a claim that Yasmin was 'truly different', based on a combination of reports of well-being, positive effects on skin condition and no associated weight gain, was misleading and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The Panel found two articles which referred to Yasmin on the femail.co.uk website cited in the Drug and Therapeutics Bulletin. The first, dated 23 June 2001, was a general review entitled 'The Pill: All you need to know'. Schering Health Care had not provided any information for this article. The second, dated 17 April 2002, was specifically about Yasmin and was entitled 'New Pill that beats weight gain'. It was stated that Yasmin counteracted fluid retention as well as reducing mood swings and breast tenderness. A spokeswoman for Schering Health Care was quoted as saying 'The new pill offers a number of physical and mental lifestyle benefits for women. It is a major development in the 40-year history of the Pill and sets a new standard in combined oral contraception for women in the UK, finally liberating them from the less desirable side-effects commonly associated with the Pill'. Schering Health Care had also provided a copy of an article which appeared in the Daily Mail, 30 March 2002. The text was similar to that which

appeared on-line on 17 April. Schering Health Care was also quoted as stating that '[Yasmin] is quite an exciting new product because it is quite different'.

The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company or its agent to the journalists. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The 'Schering Holding Statement – Launch of Yasmin', which had been given to the Daily Mail, stated, *inter alia*, that Yasmin was a major development in contraception because unlike other oral contraceptives it provided a unique package of physical and mental well-being benefits including: no associated weight gain from fluid retention and beneficial effects on skin, hair and pre-menstrual symptoms. The Panel noted its rulings above and considered that the holding statement was not factual. A breach of Clause 20.2 was ruled.

The Panel noted that in the Daily Mail article of 30 March 2000, one of Schering Health Care's medical advisers was quoted as saying that '… the evidence to date was that the risk of blood clots with Yasmin was the same as with other low-dose pills'. The Drug and Therapeutics Bulletin article stated that Yasmin's effects on cardiovascular risk (including venous thromboembolic disease) had not been quantified. Section 4.8, Undesirable effects, vascular system, of the SPC for Yasmin listed thromboembolism as a rare (<1/1000) adverse reaction, hypertension and hypotension were uncommon adverse reactions (<1/100, ≥ 1/1000) and migraine was listed as a common (≥ 1/100) adverse reaction. This section also listed serious adverse events that had been reported in women using COCs. The list included, *inter alia*, venous thromboembolic disorders, arterial thromboembolic disorders and hypertension; readers were referred to section 4.4. In section 4.4 of the SPC, Special warnings and special precautions for use, it was stated that epidemiological studies had shown the incidence of venous thromboembolism in users of oral contraceptives with low oestrogen content (<50mcg ethinylestradiol) ranged from about 20-40 cases per 100,000 women years, but that that risk estimate varied according to the progestogen. The Panel considered that Yasmin's effects on cardiovascular risk had been quantified. The Panel did not consider, given the statements in the SPC, that the quote about blood clots which had appeared in the Daily Mail article was unreasonable. No breach of Clause 20.2 was ruled in that regard.

APPEAL BY SCHERING HEALTH CARE

1 Well-being

Schering Health Care noted that Parsey and Pong considered the impact of Yasmin (at cycle 6) on some common menstrually related symptoms such as impaired concentration, negative affect, water retention, increased appetite, hair change and feelings of well-being. These were compared to baseline at 3 phases of the menstrual cycle ie pre-menstrual, menstrual and post-menstrual phases. The authors concluded: 'Statistically significant decreases from baseline to cycle 6 were observed for all subjects and in all menstrual phases for negative affect and water retention. In pre-menstrual and menstrual phases, the severity level of increased appetite was significantly lower at cycle 6 compared to baseline. For all subjects, there were no statistically significant changes for impaired concentration, undesirable hair change, or feelings of well-being for any phase of the menstrual cycle'.

As the Panel ruling acknowledged, well-being was a broad term encompassing many aspects of physical, emotional and psychological health. What could not be disputed from this study was that all the changes concerning menstrually related symptoms which took place whilst the subjects were on Yasmin were in a positive direction and there were no changes in a negative direction. It was acknowledged that there were no statistically significant changes for some menstrually related symptoms. Schering Health Care submitted that if only positive or no changes in symptoms were demonstrated, this should be sufficient to claim an 'overall' improvement in symptoms. The company noted that at no point had it specifically claimed that 'all aspects of well-being' were improved.

Parsey and Pong went on to conclude: 'The low rate of discontinuation in this study resulting from [adverse events] could result, in part, from the positive effect that Yasmin had on perceptions of water retention and negative affect. Both items are often cited as reasons for discontinuing [oral contraceptives] during clinical trials'.

Schering Health Care noted that Boschitsch *et al* found that there was a significant improvement in specific aspects of well-being including skin condition, hair, body weight and well-being before and during menstruation. The authors concluded that '[Yasmin] has a unique clinical profile in that it is associated with stable or slightly reduced body weight and has a positive effect on the skin. This combination of features would be expected to improve feelings of well-being and this in turn, might improve compliance and decrease the incidence of pill discontinuation. The results from the survey of well-being…..appear to support this hypothesis'.

Schering Health Care noted that the Panel considered that well-being was a very broad term and that general unqualified claims for well-being on Yasmin were misleading and could not be substantiated. Schering Health Care contended that an overall claim of well-being was objectively justified based on the clinical data.

Well-being was a general term, but it was of great importance to prescribers and women using the pill, because the extent to which women experienced side effects impacted on patient compliance. Health was defined by the World Health Organization as a state

of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Schering Health Care submitted that well-being encompassed several symptoms which affected women users and were of most concern to them. The nature of promotional material was such that a medicine's strengths in comparison with its competitors were highlighted in an objective and balanced manner. Schering Health Care also submitted that it was unreasonable to expect a company to list in its promotional material all a medicine's many effects.

Schering Health Care considered that the claims for Yasmin in relation to well-being were not in breach of Clauses 7.2 and 7.4; the claims were accurate, balanced, objective and unambiguous and were capable of substantiation by published clinical studies. Company data on file from an unpublished European study further supported these claims.

2 Body weight changes

Schering Health Care noted that the claim relating to weight referred to there being no associated weight gain. At no time had the company claimed that Yasmin caused weight loss to occur. Weight gain was commonly perceived to result from using the Pill, and a Pill that had no weight gain associated with its use was of great significance to prescribers and patients.

The Panel's overall conclusion was that 'there was clinical data to show that the majority of women taking Yasmin maintained a stable body weight and that the product was not associated with weight gain in the first two years of treatment'. However, the Panel appeared to be critical of Schering Health Care for not explaining in detail in the promotional material that a minority of women could gain weight whilst on Yasmin.

Schering Health Care considered the claim that Yasmin had been shown repeatedly to have no associated weight gain was an accurate, balanced and objective evaluation of the available evidence and was, indeed, supported by the Panel's overall assessment of the literature. Contrary to the Panel's assessment Schering Health Care considered the claim was not 'absolute'. The Oxford English Dictionary defined 'repeatedly' as meaning 'several times'. The claim also talked of 'associated weight gain'. It clearly related to the overall evaluation of the evidence on weight gain.

Schering Health Care stated that it was unreasonable to expect it to set out in detail in its promotional material the specific data on body weight changes, and in particular a minority gaining weight, when there was clear clinical data suggesting that there was overall no associated weight gain.

The clinical data referenced by Schering Health Care made clear that body weight changes occurred in both directions but the majority of women (over 80%) maintained a stable body weight (or lost weight) when taking Yasmin. Foidart *et al* concluded that in both groups (Yasmin and Marvelon), the majority of women maintained a stable body weight within 2kg of their baseline weight.

The authors went on to state that more women in the Yasmin group lost more than 2kg compared to the Marvelon group and more women in the Marvelon gained more than 2kg compared to the Yasmin group. Bearing in mind the above, Schering Health Care considered that the Panel's observation that 'some women in the Yasmin group gained more than 2kg from baseline weight' was not a fair reflection of the study results.

Huber *et al* reached the same conclusions as above and provided percentage figures for women in each category. Overall 61.4% of women on Yasmin maintained a stable body weight within 2kg of their baseline weight and 24.8% of the women on Yasmin had a weight loss greater than 2kg. This meant that 86.2% of women had no associated weight gain (taking into account the 24.8% who had a weight loss).

With regard to Oelkers *et al*, the Panel had concluded, correctly, that 'Body weight fell in all three groups taking some combination of ethinylestradiol and drospirenone whereas it rose in the Microgynon group. The differences between the drospirenone groups and the Microgynon group were significant'.

The ruling of the Panel was inconsistent with the study findings set out above and Schering Health Care considered the claim that Yasmin had been shown repeatedly to have no associated weight gain was an accurate, balanced and objective evaluation of the available evidence, which was unambiguous and capable of substantiation by published clinical studies. The findings of the relevant studies were set out above and in the circumstances, Schering Health Care disputed the Panel's ruling that the claim relating to no associated weight gain was in breach of Clauses 7.2 and 7.4.

3 Pre-menstrual symptoms

Schering Health Care noted the conclusions reached by Parsey and Pong and Boschitsch *et al* set out above. The company noted that it did not at any point claim that 'all pre-menstrual symptoms' were improved by Yasmin nor that Yasmin improved pre-menstrual syndrome.

Schering Health Care noted that the Panel ruling acknowledged that 'there was data to show that with regard to some specific pre-menstrual symptoms Yasmin had a positive effect; with other symptoms there was no change'. Schering Health Care reiterated that in the Parsey and Pong study, all the changes in menstrually related symptoms which took place whilst on Yasmin were in a positive direction and there were no negative changes. The observation that no effect was measured post-menstrually was an expected one, as women with such symptoms commonly improved spontaneously in that phase. As the Panel noted, the 'Boschitsch *et al* study reported that pre-menstrually women felt better when they were taking Yasmin than when they were not'.

The assessment of the severity of pre-menstrual symptoms was difficult to evaluate and by their nature, the assessment was highly subjective and dependent on the individual woman concerned.

Schering Health Care contended that the demonstration of positive improvements in some specific aspects of some pre-menstrual symptoms, together with no negative changes, was sufficient to make the claim that Yasmin had a demonstrable positive effect on pre-menstrual symptoms. This was not a situation where the positive and negative effects balanced each other.

Schering Health Care considered that the claims for Yasmin in relation to pre-menstrual symptoms were not in breach of Clauses 7.2 and 7.4; the claims were accurate, balanced, objective and unambiguous and were capable of substantiation by published clinical studies.

4 Claim that Yasmin 'was truly different'

Schering Health Care noted that the Panel's ruling on the claim that Yasmin was 'truly different' was based on a combination of the disputed rulings relating to well-being and no associated weight gain (as well as the ruling supporting Schering Health Care's claim for positive effects on skin condition).

In fact, Schering Health Care's statement in its promotional literature that Yasmin was 'truly different' was explained in the underlying text: 'Yasmin is different in many ways. It has been shown repeatedly to have no associated weight gain. In addition, Yasmin has a demonstrable positive effect on pre-menstrual symptoms and on skin condition'. The claim was based on the disputed rulings relating to weight gain and pre-menstrual symptoms (together with the supportive ruling on skin condition) not the disputed well-being claim.

Schering Health Care contended that if its appeals relating to the claims for pre-menstrual symptoms and no associated weight gain, as set out above, were upheld, then the Appeal Board should rule that there was no breach of Clauses 7.2, 7.3 and 7.4 in relation to the claim that Yasmin was 'truly different'. Furthermore, Schering Health Care contended that even if only one of the claims was upheld, taking into account the Panel's ruling on the claim for positive effects on skin condition, there was sufficient evidence to justify the claim for Yasmin being 'truly different'.

5 Schering Holding Statement

Schering Health Care noted that the Panel's ruling about its holding statement was based on a combination of the disputed rulings relating to well-being, no associated weight gain and pre-menstrual symptoms (as well as the ruling supporting the claim for positive effects on skin condition).

The holding statement was not written in the same terms as Schering Health Care's promotional literature. It stated that Yasmin offered a number of physical and mental well-being benefits over other oral contraceptives, 'including: no associated weight gain from fluid retention and beneficial effects on skin, hair and pre-menstrual symptoms'.

As was appropriate in the case of information provided to journalists, the statements made were factual and were worded more generally than Schering Health Care's promotional literature. Schering Health Care considered that the Panel was wrong to treat the holding statement as a combination of the claims previously reviewed. Each of the statements made in the holding statement should be reviewed in context and based on the actual words of the statement. This referred to 'no associated weight gain *from fluid retention*' (emphasis added) and to 'beneficial' effects on pre-menstrual symptoms rather than 'demonstrable positive' effects.

6 General points of appeal

a) Schering Health Care noted that the claims relating to Yasmin, which were included in the advertisements in Doctor of 11 and 25 April 2002, had been positively reviewed by the MCA which requested a copy of the references made in the promotion in the usual course of events. The MCA was provided with the relevant materials, including the scientific literature referred to by the Panel, in making its rulings. The MCA responded on 13 June 2002 stating that 'based on the information supplied to us and the current state of scientific knowledge, it appears to the MCA that there is no current basis for taking any action in relation to this advertisement'. A copy of the advertisement, which referred to all the claims relating to this appeal, and correspondence with the MCA had already been provided to the Authority.

In its ruling the Panel noted the MCA review but stated that it nevertheless had to address the issues raised by the Drug and Therapeutics Bulletin article. Schering Health Care accepted that review of the material by the MCA did not preclude consideration by the Authority and appreciated that the Panel must consider complaints recognised by it. However, Schering Health Care was concerned that the MCA and Authority had essentially reached different decisions on the same claims, whilst operating under the same general rules and relying on the same scientific literature supporting such claims. The presentation of different and conflicting views by separate authorities might be confusing for the medical profession and made it extremely difficult for the industry to comply with the relevant requirements.

b) The promotional claims relating to Yasmin had been widely presented in the medical literature and journals since April 2002 but to date, no other complaint had been generated as a result of these promotional claims. Schering Health Care would suggest that views held by the Drug and Therapeutics Bulletin and the Panel in relation to the claims in dispute were a minority view in comparison to the views held by the majority of medical professionals.

RESPONSE FROM THE DRUG AND THERAPEUTICS BULLETIN

Before Schering Health Care had submitted its appeal, the Drug and Therapeutics Bulletin wrote to the Authority commenting on all of the Panel's rulings. The Drug and Therapeutics Bulletin was subsequently sent a copy of Schering Health Care's appeal but it offered no comments upon it. On the morning of the appeal the Drug and Therapeutics Bulletin's original

letter of comment was provided to Schering Health Care for information only.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'The Pill for Well-being' which appeared in the advertisement was referenced to Parsey and Pong. The advertisement also included the claim 'Well. And truly different'. The Parsey and Pong study assessed the effect of Yasmin on well-being by means of a questionnaire. The Appeal Board noted that the results indicated that Yasmin had no statistically significant change upon feelings of well-being for any phase of the menstrual cycle. There were no statistically significant changes for impaired concentration and undesirable hair changes. Statistically significant decreases from baseline to cycle 6 were observed for all subjects and in all menstrual phases for negative affect and water retention. Statistically significant decreases from baseline to cycle 6 were observed for increased appetite in the pre-menstrual and menstrual phases. Boschitsch *et al*, cited in support of a claim that women felt well on Yasmin, investigated by means of a survey the feelings of women who had taken Yasmin or Marvelon in two clinical trials. The median time after taking the last trial pill to when the questionnaire was completed was 8 weeks. The Appeal Board noted that the authors reported that some aspects of well-being were worse and some were better on Yasmin. The survey was unable to detect a significant change in overall feeling of well-being.

The Appeal Board did not consider that there was sufficient evidence to make the general unqualified claims for well-being on Yasmin. There was limited comparative data. The Appeal Board considered that the claims were misleading and could not be substantiated and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

With regard to changes in body weight the Appeal Board noted that the Yasmin SPC (Section 4.8) listed 'fluid retention and body weight changes' as uncommon adverse events (<1/100, ≥ 1/1000). The Appeal Board noted that the statement '[Yasmin] has been shown repeatedly to have no associated weight gain' was referenced to Foidart *et al*, Huber *et al* and Oelkers *et al*. The studies showed that the majority of women maintained a stable body weight. However, both Foidart *et al* and Huber *et al* showed that a minority of women gained more than 2kg body weight. The Appeal Board noted that in the Foidart study, although mean body weight per cycle initially fell below baseline with Yasmin, by cycle 12 it began to increase such that by cycles 25 and 26 it was greater than baseline and appeared to still be rising when the study finished. The Appeal Board expressed concern that this rise might have continued but this had not been investigated. The Appeal Board did not consider there was sufficient evidence to support the strong absolute claim that '[Yasmin] has been shown repeatedly to have no associated weight gain'; data from three clinical studies did not justify use of the term 'repeatedly'. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted the claim 'Yasmin has a demonstrable effect on [pre-menstrual] symptoms' was referenced to Parsey and Pong and Boschitsch *et al*. The Appeal Board noted the results in Parsey and Pong referred to above. The Appeal Board noted that there was some data to show that Yasmin had a positive effect on some specific pre-menstrual symptoms; with other symptoms there was no change. The Appeal Board considered that the claim 'a demonstrable positive effect on PM symptoms' was too broad and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board considered that, in view of its previous rulings, the claim that Yasmin was 'truly different' was misleading and could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted that the 'Schering Holding Statement – Launch of Yasmin', which had been given to the Daily Mail, stated, *inter alia*, that Yasmin was a major development in contraception because unlike other oral contraceptives it provided a unique package of physical and mental well-being benefits including: no associated weight gain from fluid retention and beneficial effects on skin, hair and pre-menstrual symptoms. The Appeal Board noted its rulings above and considered that the holding statement was not factual. The Appeal Board upheld the Panel's ruling of a breach of Clause 20.2 of the Code. The appeal on this point was unsuccessful.

APPEAL AS A RESULT OF COMMENTS FROM THE DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin commented on the Panel's rulings. Its critical comment on one of the Panel's rulings of no breach of the Code was treated as an appeal.

The Drug and Therapeutics Bulletin disagreed with the Panel's ruling of no breach with regard to the quotation in the Daily Mail attributed to Schering Health Care's medical advisers on fertility control that '… the evidence to date was that the risk of blood clots with Yasmin was the same as with other low-dose pills'. In the Drug and Therapeutics Bulletin's view such a claim was at odds with the unambiguous statement in the current Yasmin SPC that 'It is not yet known how Yasmin influences the risk of VTE [venous thromboembolism] compared with other oral contraceptives'.

RESPONSE FROM SCHERING HEALTH CARE

Schering Health Care stated that the wording of the SPC with respect to VTE risk was deliberately cautious. By stating that, 'It is not yet known how Yasmin influences the risk of VTE compared with other oral contraceptives', it presented the position agreed earlier this year with the European regulatory authorities.

As with any product, the understanding of the safety profile increased with an increasing patient

population and length of usage. By April 2002, Yasmin had reached a calculated exposure in the combined European and American market, together with clinical trial data, of some 1,000,000 patient-years of use. An ongoing assessment of the spontaneous adverse drug reaction reports received both by regulatory authorities and by Schering Health Care had been routinely and regularly quantified in the formal periodic safety update reports submitted by the company to the appropriate authorities. These data showed an observed reporting rate of VTE cases to be approximately 6 events per 100,000 women-years of use. Even allowing for under-reporting of spontaneous case reports, this figure was unlikely to exceed the estimation made by the Committee on the Safety of Medicines of 15 VTE events per 100,000 years of use associated with second generation combined oral contraceptives.

Furthermore, an independently run, multi-national and extensive post-marketing surveillance study, funded by the company, had been in progress since shortly after Yasmin was launched in Germany in November 2000. An interim analysis of 18,000 women in this study, which became available in March 2002, showed that among those taking Yasmin (30% of the study population) one VTE had been observed, whereas 5 venous thromboses cases had been reported among the women taking other contraceptives (70% of the study population).

These data formed the basis of the statement made by a Schering Health Care medical advisor to the Daily Mail. Schering Health Care regarded this as presenting important, substantial, and relevant additional information, and could not accept that this material should not be shared outside the company simply because the SPC had yet to be updated.

Schering Health Care strongly contested the appeal by the Drug and Therapeutics Bulletin against the Panel's ruling and submitted that the statement in question was unambiguous and clearly reflected, as stated, the understanding of the issue current at the time it was made.

FURTHER COMMENTS FROM THE DRUG AND THERAPEUTICS BULLETIN

The Drug and Therapeutics Bulletin did not provide any further comments.

APPEAL BOARD RULING

The Appeal Board accepted that Schering Health Care might have evidence to support the statement which appeared in the Daily Mail that '… the evidence to date was that the risk of blood clots with Yasmin was the same as with other low dose pills'. However the Yasmin SPC stated 'It is not yet known how Yasmin influences the risk of VTE compared with other oral contraceptives'. The Appeal Board considered that the statement in the Daily Mail was not balanced and ruled a breach of Clause 20.2 of the Code. The appeal on this point was successful.

Proceedings commenced **15 August 2002**

Case completed **17 December 2002**

CASE AUTH/1353/8/02

GENERAL PRACTITIONER v NOVARTIS

Promotion of Starlix

A general practitioner forwarded a copy of a letter which he and his partner had written to the BMJ complaining about the promotion of Starlix (nateglinide) by Novartis. It had been put on the BMJ website. In their letter the authors stated that they had attended a primary care team meeting on the management of diabetes mellitus and coronary heart disease, organised by their local health care committee, which had postgraduate education allowance accreditation and was sponsored by Novartis. It was stated at the meeting that high post-prandial glucose concentrations doubled the risk of death in diabetics. The complainants questioned this statement and asked to see evidence for it; on the following day they were presented with the DECODE study by the Novartis representative.

The DECODE study was a meta-analysis from thirteen prospective European cohort studies looking at the relationship between glucose tolerance and mortality. The study compared the oral glucose tolerance test with the fasting glucose levels as diagnostic tools for diabetes mellitus and glucose intolerance and predictors of mortality. The glucose tolerance test was performed two hours after a glucose load. The study concluded that the oral glucose tolerance test was more sensitive than the fasting glucose level at identifying people with impaired glucose tolerance and diabetes, for which there were effective, evidence-based interventions known to reduce morbidity and mortality.

The meeting used the DECODE study as evidence to change clinical practice, ie manage post-prandial glucose levels in diabetic patients. The DECODE study did not investigate whether reducing post-prandial glucose concentrations reduced mortality. This was a fundamental misinterpretation of the study which the complainants believed was driven by Novartis; the company quoted the study in its literature, implying that it suggested the mortality rate in diabetics could be reduced by reducing post-prandial glucose levels. The speaker, however, emphasised the fasting glucose level as the important screening tool in diabetes, in preference to the oral glucose tolerance test.

The Panel noted that the organisation of the meeting was the responsibility of the local health care committee. Novartis' representatives had attended and there had been a company stand on which were, *inter alia*, copies of a Starlix leavepiece and detail aid. It was unclear who had made the statement in question; Novartis submitted that it was the speaker. Novartis stated that the DECODE study was provided by its representative pursuant to the complainant's request for information about the risk of mortality and post-prandial glucose concentrations. The letter to the BMJ clearly stated that the speaker emphasised the fasting glucose level as the important screening tool in preference to the oral glucose tolerance test.

The Panel noted the complainant's comments about the DECODE study. The study included 25,364 participants, 1275 of whom had been previously diagnosed as having diabetes, and assessed the risk of death according to the different diagnostic glucose categories. The authors stated that fasting blood glucose alone was not sufficient to predict mortality related to hyperglycaemia. The oral glucose tolerance test provided additional prognostic information and enabled detection of individuals with impaired glucose tolerance, who had the greatest attributable risk of death.

Page 5 of the leavepiece referred to post-prandial glucose (PPG) spikes and included a claim that Starlix was specifically designed to manage PPG spikes. The risks associated with PPG spikes were described on page 6; these included cardiovascular risk and mortality. The DECODE study was cited in support of the statement 'cardiovascular risk and mortality'. A short statement referring to the outcome of the DECODE study read 'PPG spikes >11.0mmol/l vs normal (<7.8mmol/l) = double risk of death'. Page 10 of the detail aid was similar to page 5 of the leavepiece. The effective reduction of PPG spikes was listed as a benefit of Starlix treatment on page 13 of the detail aid.

The Panel considered that the leavepiece and detail aid by linking PPG spikes to an increased risk of death and stating that Starlix managed PPG spikes implied that Starlix reduced cardiovascular risk and mortality. There was no evidence to show that this was so. The Panel considered that the leavepiece and detail aid gave a misleading impression of the effect of Starlix on cardiovascular mortality and risk. A breach of the Code was ruled.

A general practitioner forwarded a copy of a letter which he and his partner had written to the BMJ complaining about the promotion of Starlix (nateglinide) by Novartis Pharmaceuticals UK Ltd. The letter had been put on the BMJ website.

COMPLAINT

The letter to the BMJ stated that the authors had attended a meeting on diabetes mellitus and coronary heart disease organised by their local health care committee with postgraduate education allowance accreditation and sponsored by Novartis. The meeting was aimed at the primary care team involved in chronic disease management.

One of the statements made at the meeting was that high post-prandial glucose concentrations doubled the risk of death in diabetics. The complainants questioned this statement and asked to see evidence for this claim, and on the following day were presented with the DECODE study by the Novartis representative.

The DECODE study was a meta-analysis from 13 prospective European cohort studies looking at the relationship between glucose tolerance and mortality. The aim of the study was to compare the oral glucose tolerance test (OGTT) with the fasting glucose levels as diagnostic tools for diabetes mellitus and glucose intolerance and predictors of mortality in the European population. The study found that mortality

was significantly related to high glucose concentrations 2 hours after a glucose load (the glucose tolerance test) independently of fasting glucose levels. This was a particularly important finding in that current guidelines led by the American Diabetic Association were putting more emphasis on fasting glucose levels as a screening tool for diagnosing diabetes mellitus in preference to the oral glucose tolerance test. The study concluded that the oral glucose tolerance test was more sensitive than the fasting glucose level at identifying people with impaired glucose tolerance and diabetes, for which there were effective, evidence-based interventions known to reduce morbidity and mortality.

Summary of results:

31% of diabetics as identified by the oral glucose tolerance test had normal fasting glucose concentrations.

	glucose (mmol/l)	*mortality rates*
fasting blood glucose	>7	16%
normal fasting glucose: 2 hour OGTT	>11.1	15%
normal fasting glucose: 2 hour OGTT	7.8-11.1	12%
normal glycaemic fasting and at 2 hours		6.4%

The meeting used the DECODE study as a major source of evidence in changing clinical practice, ie managing post-prandial glucose levels in diabetic patients. The DECODE study did not investigate whether reducing post-prandial glucose concentrations reduced mortality in diabetics, in fact it did not look into the treatment of diabetes, but was an investigation into the diagnosis of diabetes in an unscreened population. This was a fundamental misinterpretation of the DECODE study and the complainants believed was driven by a deceptive analysis by Novartis, which quoted the study in its literature, implying that it suggested the mortality rate in diabetics could be reduced by reducing the post-prandial glucose levels. The DECODE study was the only study mentioned in the Novartis literature, apart from small print references at the end of the pamphlet.

The irony of this was that the speaker emphasised the fasting glucose level as the important screening tool in diabetes, in preference to the oral glucose tolerance test.

The complainants queried whether pharmaceutical companies should be allowed to indiscriminately use notable papers, which practitioners had often heard of, but not always read, in support of their products, thus gold-stamping them?

Novartis had invented a disease, high post-prandial glucose concentrations in diabetic patients, and come up with a product, Starlix, a short acting ß-cell stimulant to be taken with meals, reducing post-prandial glucose spikes, and by inference, reducing mortality in diabetic patients. Nateglinide cost about four times more than gliclazide.

When writing to Novartis, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Novartis stated that the meeting in question was a local initiative, the complete organisation was the responsibility of the local health care committee. The meeting was not arranged via Novartis head office. The local clinical governance coordinator put the agenda together and selected and briefed the speakers. Novartis had no involvement in the selection or briefing of the nurse speaker referred to by the complainant, and had no contact with the speaker prior to the meeting. Novartis did not supply any of the speaker's slides. Members of the local health care committee consisting of general practitioners, nurses and pharmaceutical advisors attended the meeting. The meeting was attended on behalf of Novartis by the local healthcare manager and by the local representative, and a promotional stand was placed outside the main meeting room. Novartis contributed to the meeting solely by supporting the catering for it in conjunction with another pharmaceutical company which also had a promotional stand at the meeting.

Novartis stated that it was the speaker who made the claim that high post-prandial glucose concentration doubled the risk of death in people with diabetes. Novartis understood that the complainant specifically asked the Novartis representative for information about the risk of mortality and post-prandial glucose concentrations, which was why a copy of the DECODE study was subsequently given to him. The information was not specifically supplied to support any claims made by the speaker but was in response to a request for information from the complainant.

Novartis confirmed that in relation to Starlix, the Novartis stand carried copies of the Starlix Detail Aid, the DECODE study, a Starlix leavepiece (ref STA 02000249) and a monofilament, eye chart and eye occluder.

Novartis addressed each of the issues in turn.

Use of the DECODE study

The main rationale for citing the DECODE study in promotional material had been to emphasise the importance of measuring post-prandial glucose levels rather than simply relying on fasting plasma glucose levels when diagnosing type 2 diabetes. This was in accordance with the complainants' analysis and interpretation of the DECODE study. Fasting plasma glucose levels were, however, also an important indicator in type 2 diabetes and should not be overlooked. A copy of the representatives' briefing material was provided.

In terms of the suggestion that increased post-prandial glucose levels might increase the risk of mortality, as the complainants stated, the DECODE study concluded that 'mortality is significantly related to high glucose concentrations 2 hours after glucose load'. There were also several other published studies that supported this idea. For example:

- Shaw *et al* (1999), showed that people with isolated post-challenge hyperglycaemia (IPH) had an increased risk of all cause mortality and cardiovascular mortality compared to non-diabetics.

- Barrett-Connor *et al* (1998), found that women with IPH had a significantly increased risk (more than double) of fatal cardiovascular disease and heart disease compared to non-diabetic women.
- Balkau *et al* (1999), reported that in the upper levels of the glucose distributions, the risk of death progressively increased with increased fasting and 2 hour post-challenge blood glucose concentrations.

These data clearly supported the suggestion that high post-prandial glucose concentrations increased the risk of mortality and, in some cases, might double that risk.

Starlix leavepiece (ref STA 01/145)

Novartis stated that it had been in direct communication with the Medicines Control Agency (MCA) as a result of the MCA having received similar comments relating to this particular item. It was not Novartis' intention to mislead the reader or suggest that by reducing the post-prandial glucose spikes, Starlix could also reduce the risk of mortality in diabetes. Indeed, this was not stated in any of the promotional material. It was, however, suggested that, by including a reference to mortality in a promotional piece for Starlix, even though no direct link was made to Starlix, the reader might mistakenly think Starlix could reduce mortality risk. Thus, in order to clarify this and avoid any potential for confusion, the Starlix promotional material had now been either amended or discontinued accordingly to remove any possible inference that Starlix might reduce the risk of mortality.

The leavepiece that the complainants referred to was no longer in use and was currently being reprinted with the reference to mortality deleted.

Claim that Novartis invented a disease and by inference claimed that Starlix might reduce mortality

Type 2 diabetes was clearly a recognised disease and post-prandial glucose spikes were an acknowledged part of the full glycaemic profile of that condition (Shaw *et al* 1999; Barrett-Conner *et al* 1998; Balkau *et al* 1999). Novartis strongly refuted suggestion that it had 'invented a disease' as the complainants claimed. With regard to the suggestion that there was an inference that Starlix reduced the risk of mortality, the point above referred.

PANEL RULING

The Panel noted Novartis' submission that the organisation of the meeting was the responsibility of the local health care committee. Novartis' representatives had attended and there had been a company stand. The refreshments for the meeting had been provided by Novartis and another pharmaceutical company. The Panel noted that it was unclear from the letter to the BMJ who had made the statement at the meeting that high post-prandial glucose concentrations doubled the risk of death in diabetics. Novartis submitted that the speaker had made this statement. Novartis stated that the DECODE study was provided by its representative to the complainant pursuant to the complainant's request for information about the risk of mortality and post-prandial glucose concentrations. The letter to the BMJ clearly stated that the speaker emphasised the fasting glucose level as the important screening tool in preference to the oral glucose tolerance test. In any event Novartis referred to the DECODE study in its promotional material which had been available at the meeting. The Panel noted that the leavepiece and detail aid had been withdrawn.

The Panel noted the complainant's comments about the DECODE study. The study included 25,364 participants, 1275 of whom had been previously diagnosed as having diabetes, and assessed the risk of death according to the different diagnostic glucose categories. The authors stated that fasting blood glucose alone was not sufficient to predict mortality related to hyperglycaemia. The oral glucose tolerance test provided additional prognostic information and enabled detection of individuals with impaired glucose tolerance, who had the greatest attributable risk of death.

Page 5 of the leavepiece referred to post-prandial glucose (PPG) spikes and included a claim that Starlix was specifically designed to manage PPG spikes. The risks associated with PPG spikes were described on page 6; these were increased atheromatous factors, accelerated deterioration of beta cells and cardiovascular risk and mortality. The DECODE study was cited in support of the statement 'cardiovascular risk and mortality'. A short statement referring to the outcome of the DECODE study read 'PPG spikes >11.0mmol/l vs normal (<7.8mmol/l) = double risk of death'. Page 10 of the detail aid was similar to page 5 of the leavepiece. The effective reduction of PPG spikes was listed as a benefit of Starlix treatment on page 13 of the detail aid.

The Panel considered that the leavepiece and detail aid by linking PPG spikes to an increased risk of death and stating that Starlix managed PPG spikes implied that Starlix reduced cardiovascular risk and mortality. There was no evidence to show that this was so. The Panel considered that the leavepiece and detail aid gave a misleading impression of the effect of Starlix on cardiovascular mortality and risk. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the complainants had queried whether pharmaceutical companies should be able to use notable papers in support of their products, thus gold-stamping them. In the Panel's view it was not unacceptable for companies to refer to published studies in their promotional material provided that such reference was fair and balanced and did not mislead with regard to the clinical significance of the results. Similarly the Panel did not consider it unacceptable *per se* for Novartis to have referred to PPG spikes; in this case, however, a breach of the Code had been ruled because PPG spikes, increased risk of death and treatment of PPG spikes with Starlix had been linked together such that the implication was that Starlix would reduce the risk of death.

Complaint received **28 August 2002**

Case completed **25 November 2002**

GENERAL PRACTITIONER v LUNDBECK

Cipralex discount

A general practitioner complained about Lundbeck's manufacturing discount scheme for Cipralex (escitalopram). Lundbeck also marketed Cipramil (citalopram).

The discount scheme was referred to in a letter from Lundbeck headed 'Cipralex (escitalopram) manufacturing discount schemes to replace Cipramil schemes'. Readers were informed that Cipralex had been launched in June 2002 and that the discount scheme for that product would be better than any discounts previously given for Cipramil. The Cipramil discount schemes would become invalid. Cipralex 10mg was the same price as Cipramil 20mg.

The complainant noted that the penultimate paragraph, which was in bold type, stated 'Please note that this scheme will take the place of all previous Cipramil discount schemes and [free of charge] agreements; as of 30 September 2002 those discount schemes will become invalid'. The complainant considered that the letter was effectively stating 'if you wish to continue to receive a discount which we are currently offering you for the purchase of Cipramil you must change your prescription to Cipralex' ie a blatant attempt to influence prescribing due to financial inducements, or indeed penalties, if one did not comply with its recommendations on changing to Cipralex.

The Panel considered that the letter at issue was promotional and subject to the Code. It referred to the clinical differences between Cipramil and Cipralex and reminded readers of 'Cipralex's key benefits when treating depression'.

Although inducements to prescribe were in general not permitted under the Code, financial discounts having that effect were allowed if they came within the exemption for discounts as set out in the Code. This exemption was included in the Code in conformity with UK and European law. The Panel accordingly ruled that there had been no breach of the Code.

The Panel did not consider that Lundbeck had failed to maintain a high standard; no breach of the Code was ruled.

A general practitioner complained about Lundbeck Ltd's manufacturing discount scheme for Cipralex (escitalopram). Lundbeck also marketed Cipramil (citalopram).

The discount scheme was referred to in a letter (ref 0702/ESC/511/011) from Lundbeck headed 'Cipralex (escitalopram) manufacturing discount schemes to replace Cipramil schemes'. Readers were informed that Cipralex had been launched on 10 June 2002 and that the discount scheme for that product would be better than any discounts previously given for Cipramil. The Cipramil discount schemes would become invalid. Cipralex 10mg was the same price as Cipramil 20mg.

COMPLAINT

The complainant drew attention particularly to the penultimate paragraph which was in bold type and stated 'Please note that this scheme will take the place of all previous Cipramil discount schemes and [free of charge] agreements; as of 30 September 2002 those discount schemes will become invalid'.

The complainant did not object to Lundbeck offering discounts on its new product Cipralex and to it energetically promoting the advantages of its new product. However, the letter was effectively stating 'if you wish to continue to receive a discount which we are currently offering you for the purchase of Cipramil you must change your prescription to Cipralex' ie a blatant attempt to influence prescribing due to financial inducements, or indeed penalties, if one did not comply with its recommendations on changing to Cipralex. The complainant alleged that this was certainly against the spirit of the Code and probably against the actual wording.

When writing to Lundbeck the Authority drew attention to Clauses 9.1 and 18.1 of the Code but noted that discounts were generally excluded from the scope of the Code. Whether the matter was subject to the Code would be decided as a preliminary issue.

RESPONSE

Lundbeck stated that it had written to advise both hospitals and dispensing doctors of the cessation of the current Cipramil discount and about the introduction of a Lundbeck Manufacturing Discount Scheme for Cipralex. The letter in question was one sent out to all dispensing general practitioners.

Lundbeck stated that with the launch of its new antidepressant, Cipralex, it had stopped promoting Cipramil and ended the Cipramil discount scheme. Discount schemes were an example of a trade practice that had been used by pharmaceutical companies for many years and were consequently outside of the Code – reference was made to Clauses 1.2 and 18.1 and their supplementary information. To illustrate this point Lundbeck enclosed a copy of the recent agreement under the Pharmaceutical Price Regulation Scheme (PPRS) relating to hospital discounts, from the Department of Health, which stated 'The Department accepts fully the right of member companies to change discounts allowed on sales to hospitals'. Discounting schemes to various healthcare groups, such as dispensing doctors, were widely accepted. No other package deal had been offered and provision of this commercial information was clearly not an inducement to prescribe.

The decision to switch a discount scheme from one product to another was entirely a commercial one that Lundbeck was entitled to make. Lundbeck disagreed with the interpretation of the letter that prescribers must consequently change their prescribing.

The decision to prescribe any treatment for a patient, on the other hand, was clearly a medical one. Cipramil remained available and doctors could continue to prescribe it after 30 September 2002 if they decided it was the most suitable antidepressant treatment for their patient.

In conclusion therefore, the amending and notification of discount schemes to groups such as dispensing doctors, were common trade practices, which Lundbeck believed did not come under the Code. Lundbeck submitted that the letter was set out clearly and did not breach either Clause 9.1 or Clause 18.1 of the Code.

PANEL RULING

The Panel considered that the letter at issue was promotional and subject to the Code. It referred to the clinical differences between Cipramil and Cipralex and reminded readers of 'Cipralex's key benefits when treating depression'. Prescribing information for Cipralex was printed on the back.

The Panel noted that under Clause 1.2 of the Code the term promotion did not include measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. The supplementary information to Clause 18.1 gave further information in this regard stating that 'Measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 are outside the scope of the Code (see Clause 1.2) and are excluded from the provisions of this clause. Other trade practices are subject to the Code. The terms 'prices', 'margins' and 'discounts' are primarily financial terms'.

The Panel noted that financial discounts were common in the industry and had been in regular use prior to 1 January 1993. There was no reason why a company could not decide to allow a discount on a product or decide to withdraw a discount previously given. It was true that withdrawing the discount on Cipramil and allowing a discount on Cipralex might amount to an inducement to change to Cipralex. This was however not unacceptable. Although inducements to prescribe were in general not permitted under the Code, financial discounts having that effect were allowed if they came within the exemption for discounts in Clause 1.2 of the Code, as set out above. This exemption was included in the Code in conformity with UK and European law.

The Panel accordingly ruled that there had been no breach of Clause 18.1 of the Code. The Panel did not consider that Lundbeck had failed to maintain a high standard and therefore also ruled no breach of Clause 9.1.

Complaint received	**30 August 2002**
Case completed	**26 November 2002**

CASE AUTH/1356/9/02

PHARMACEUTICAL ADVISER & PRESCRIBING TEAM MANAGER v PHARMACIA

Invitation to a concert

A pharmaceutical adviser and prescribing team manager from a primary care trust (PCT) complained about an invitation to attend a concert which had been sent to her and other PCT senior managers by Pharmacia. The invitation stated that Pharmacia was sponsoring the first in a series of orchestral concerts in London. The evening would commence with pre-performance drinks; there would be drinks served in the interval and a light buffet following the performance would also be attended by members of the orchestra.

The complainant stated that as a health professional the remit of her post was to advise other health professionals and PCT management, thus directly falling within the terms of the Code. This invitation to attend a purely social, non-professional, non-clinical event appeared to contravene the Code.

The Panel noted that nearly 600 people (including company personnel) had been invited to the concert which was part of a programme of corporate arts sponsorship by Pharmacia. Almost all of those invited were politicians, policy makers, academics, journalists, patient group executives and members of a variety of pharmaceutical industry and healthcare organisations. Members of staff from The Association of the British Pharmaceutical Industry were invited. Nobody from the Authority had been invited. One member of the Code of Practice Appeal Board had been invited. The invitation list also included staff from the complainant's PCT as well as staff from other PCTs, including pharmaceutical/prescribing advisers, what appeared to be general practitioners and a nurse advisor. Some hospital doctors had also been invited. Pharmacia had listed 23 people who, following notification of the complaint, had had their invitations withdrawn.

The Panel considered that it was inappropriate to invite health professionals in their capacity as prescribers and/or those that recommended medicines to such a corporate event. The invitation to the small group of health professionals identified by Pharmacia brought the arrangements for the meeting within the scope of the Code. It was not relevant that their invitations had been withdrawn before the concert had taken place. The evening was a purely social event. The Panel ruled a breach of the Code.

The Panel noted that it had become apparent that the arrangements for the event had not been reviewed in advance by the company experts on the Code. This was not a requirement of the Code but the guidelines on company procedures relating to the Code advised that procedures should ensure that any item or activity regarded as non-promotional in nature was vetted by an appropriate member of staff familiar with the Code. Pharmacia had stated that its standard operating procedure had not been followed. The Panel considered that Pharmacia had not maintained a high standard and a breach of the Code was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

A pharmaceutical adviser and prescribing team manager of a primary care trust (PCT) complained about an invitation to attend a concert which had been sent to her and other PCT senior managers by Pharmacia Limited.

The invitation stated that Pharmacia was sponsoring the first in a series of orchestral concerts in London. The evening would commence with pre-performance drinks; drinks would be served in the interval and a light buffet following the performance would also be attended by members of the orchestra. The invitation was signed by Pharmacia's director of public affairs.

COMPLAINT

The complainant stated that as a health professional the remit of her post was to advise other health professionals and PCT management, thus directly falling within the terms of the Code. This invitation to attend a purely social, non-professional, non-clinical event appeared to contravene Clauses 15.3, 18.2 and 19.1 of the Code.

The complainant trusted that the Authority would ask Pharmacia to disclose the status and roles of other individuals invited to the concert, and was sure that such disclosure would reveal mostly health professionals on the list. This event could only have been arranged for the main purpose of inviting health professionals, including general practitioners, clinicians and pharmacists, and therefore appeared to directly contravene the Code

When writing to Pharmacia, the Authority asked it to bear in mind the requirements of Clauses 2 and 9.1 of the Code in addition to the clauses referred to by the complainant.

RESPONSE

Pharmacia stated that the invitation had been sent in error to the complainant and a small number of others and the company had already contacted those who had received invitations to withdraw the invitation with an apology and explanation.

The concert in question was part of a programme of corporate arts sponsorship by Pharmacia and the guests were made up of politicians, policy makers, academics, journalists, patient group executives and non-prescribing members of a variety of pharmaceutical industry and healthcare organisations; not the kind of health professionals suggested by the complainant. The list of invitees and their status was provided and Pharmacia had identified those who had been invited inappropriately.

Pharmacia submitted that at a corporate event of this nature there would not be any materials, promotional

or otherwise, displayed or given to the attendees beyond the Pharmacia logos associated with the concert programme materials. The part of the concert hall reserved for hospitality would only be open to those invited by Pharmacia. Those members of the general public attending the concert itself would also only have the opportunity to see the Pharmacia logotype on the programme and on materials produced by the orchestra in connection with the concert.

The tickets were worth £10 each and the estimated cost per head of the catering was not more than £21.

Pharmacia hoped that this would be an acceptable way of resolving the problem from the point of view of the Code. As the event had not yet taken place, Pharmacia considered it had not been in breach of the Code.

Following a request for further information, Pharmacia advised that it had an internal standard operating procedure which covered invitations such as the one in question. However the public affairs department forgot to submit the event and invitations to the internal company Code of Practice review team; had this been done the error of incorrect invitations would have been noticed. The decision to withdraw a number of the invitations was taken when the Authority first wrote to Pharmacia about the matter.

PANEL RULING

The Panel noted that the list provided by Pharmacia showed that nearly 600 people (including company personnel) had been invited to the concert. Job titles included on the list showed that, as submitted by Pharmacia, almost all of those invited were politicians, policy makers, academics, journalists, patient group executives and members of a variety of pharmaceutical industry and healthcare organisations. Members of staff from The Association of the British Pharmaceutical Industry were invited. Nobody from the Authority had been invited. One member of the Code of Practice Appeal Board had been invited.

The Panel noted that the event was part of a programme of corporate arts sponsorship by Pharmacia. Corporate activities, insofar as they were not promotional, were not necessarily covered by the Code; this would depend on the arrangements. The Panel noted that Clause 19.1 applied to hospitality provided to health professionals and appropriate administrative staff. The supplementary information stated that the requirements of the Code did not apply to the provision of hospitality other than to those referred to in Clause 19.1. For example a company could provide hospitality at a meeting of organic chemists. They were neither health professionals nor appropriate administrative staff. The supplementary information to Clauses 19.1 and 15.3 also stated that meetings organised for doctors, other health professionals and/or administrative staff which were wholly or mainly of a social or sporting nature were unacceptable.

The invitation list included staff from the complainant's PCT as well as staff from other PCTs, including pharmaceutical/prescribing advisers, what appeared to be general practitioners and a nurse advisor. Some hospital doctors had also been invited. Pharmacia had listed 23 people who, following notification of the complaint, had had their invitations withdrawn.

The Panel considered that it was inappropriate to invite health professionals in their capacity as prescribers and/or those that recommended medicines to such a corporate event. Other health professionals had been invited but these were in relation to their roles as senior representatives of professional organisations, hospital trusts, PCTs, etc, and not as prescribers or individuals which recommended medicines. The Panel did not consider that the event could be described as one organised for groups of doctors and other health professionals as it was organised for people from a wide range of backgrounds. Nevertheless the Panel considered that the invitation to the small group of health professionals identified by Pharmacia brought the arrangements for the meeting within the scope of the Code. It was not relevant that their invitations had been withdrawn before the concert had taken place. The evening was a purely social event and it was inappropriate to invite prescribers and/or those that recommended medicines. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel did not consider that Clause 15.3 which applied to representatives was relevant here. The complaint had quoted the supplementary information to Clause 15.3 regarding invitations to meetings. The Panel ruled no breach of Clause 15.3. The Panel did not consider that Clause 18 was relevant. The matter was covered by Clause 19. No breach of Clause 18.2 of the Code was ruled.

With regard to Clause 9.1 the Panel noted that the company had withdrawn a number of invitations when it became aware of the situation following notification of the complaint by the Authority. Nevertheless it had become apparent that the arrangements for the event had not been reviewed in advance by the company experts on the Code. This was not a requirement of the Code but the guidelines on company procedures relating to the Code advised that procedures should ensure that any item or activity regarded as non-promotional in nature was vetted by an appropriate member of staff familiar with the Code with a view to determining whether it was indeed non-promotional. Readers were referred to the supplementary information to Clause 14.1 which advised companies to review materials relating to medicines which were not intended to be promotion. The Panel noted that there was no mention of corporate events in the Code. Pharmacia had stated that its standard operating procedure had not been followed.

The Panel considered that Pharmacia had not maintained a high standard and a breach of Clause 9.1 of the Code was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Complaint received **2 September 2002**

Case completed **12 November 2002**

CASE AUTH/1357/9/02

YAMANOUCHI PHARMA v STRAKAN

Zindaclin leavepieces

Yamanouchi Pharma complained about two leavepieces prepared in March and June 2002 for Zindaclin (clindamycin phosphate 1% gel) and issued by Strakan. Yamanouchi supplied Zineryt (erythromycin/zinc acetate alcoholic solution). Both products were indicated for the treatment of acne vulgaris.

The earlier leavepiece included a cost comparison chart headed 'Price comparison for equivalent commonly used treatments' and compared Zindaclin (30g) with Zineryt (30ml), Dalacin T (30ml) and Benzamycin (23.3g). The chart gave the frequency of administration, NHS price per pack, and 'cost per 28 Days *Assumes one gram or ml per application'. The asterisk referred to 'Rates of application may vary. In a controlled trial where the number of applications was the same, the mean amount of Zindaclin used was 25% less than Dalacin T (Cunliffe *et al* unpublished data)'. The layout of the cost comparison chart had been slightly modified in the subsequent leavepiece and the heading changed to omit the word 'equivalent', however Yamanouchi considered that its concerns about the first leavepiece applied equally to the second.

Yamanouchi alleged that the price comparison on the earlier leavepiece was inaccurate, unfair and misleading. The final column of the table showed a 'Cost per 28-day' price comparison between Zindaclin gel and the three other acne preparations. Yamanouchi considered that when comparing the cost per ml of a solution, such as Zineryt, to the cost per gram of a gel, such as Zindaclin, the potential to mislead was great as like was not being compared with like. Yamanouchi noted the use of an asterisk to qualify a claim where differing presentations were compared was not acceptable. The table implied that Zindaclin was considerably cheaper than Zineryt (£8.08 vs £13.23) and that a 30ml bottle of Zineryt would last only 15 days, on average. There was no rational basis for this assumption.

The Panel noted Strakan's submission about the Cunliffe paper and the statement on the leavepiece about the amount of product used when the number of applications were the same. The Panel queried the relevance of this data given that the licensed dose frequencies for the products listed in the chart were different. Zindaclin was licensed for once daily application whereas the other three products were to be used twice daily. There was data to show that patients applied a more generous amount of a product each time they used it if they used it once a day than if they used it twice a day.

The Panel considered that the cost comparison charts were misleading. In the Panel's view the assumption that patients used 1ml/1g of a topical preparation at each application regardless of the number of times a day it had to be applied was too simplistic. A breach of the Code was ruled.

Yamanouchi Pharma Ltd complained about two leavepieces (refs M008/006, prepared March 2002, and M008/033, prepared June 2002) for Zindaclin (clindamycin phosphate 1% gel) issued by Strakan Limited. Yamanouchi supplied Zineryt (erythromycin/zinc acetate alcoholic solution). Both products were indicated for the treatment of acne vulgaris.

The earlier leavepiece, (M008/006), included a cost comparison chart headed 'Price comparison for equivalent commonly used treatments' and compared Zindaclin (30g) with Zineryt (30ml), Dalacin T (30ml) and Benzamycin (23.3g). The chart gave the frequency of administration, NHS price per pack, and 'cost per 28 Days *Assumes one gram or ml per application'. The explanation for the asterisk was given beneath the chart as 'Rates of application may vary. In a controlled trial where the number of applications was the same, the mean amount of Zindaclin used was 25% less than Dalacin T (Cunliffe *et al* unpublished data)'.

The layout of the cost comparison chart had been slightly modified in the subsequent leavepiece (ref M008/033) and the heading changed to omit the word 'equivalent'.

COMPLAINT

Yamanouchi alleged that the price comparison on the earlier leavepiece (ref M008/006) was in breach of Clause 7.2 of the Code. Yamanouchi had tried to resolve the issue directly with Strakan but had been unable to reach a satisfactory outcome.

The final column of the table showed a 'Cost per 28-day' price comparison between Zindaclin gel and three other acne preparations, one of which was Zineryt. In Yamanouchi's view a direct price comparison between a gel, such as Zindaclin, and a solution, such as Zineryt, could not be made when there was no evidence as to comparable usage.

The supplementary information to Clause 7.2 of the Code highlighted the potential to mislead when comparing the cost per ml for topical preparations. That potential to mislead was even greater when comparing the cost per ml of a solution, such as Zineryt, to the cost per gram of a gel, such as Zindaclin, as like was not being compared with like.

The use of an asterisk to qualify a claim where differing presentations (in this case gel vs liquid) were compared was not acceptable. It was a recognised aspect of the Code that a footnote could not be used to correct a misleading presentation.

The table was presented in such a way as to imply that Zindaclin was considerably cheaper than Zineryt (£8.08 vs £13.23). The implication from the table was that a 30ml bottle of Zineryt would last only 15 days, on average. There was no rational basis for this assumption. While Strakan might know from its studies how long a 30g tube of Zindaclin lasted, there was no evidence at all on which to even suggest the implied usage of Zineryt. One ml of a solution might be used to cover a much greater, or lesser, area than

1g of gel/cream/ointment depending on a number of factors, for example its emollient properties.

The difficulties involved in cost comparisons such as the one included in this table had been highlighted in previous cases. In Case AUTH/898/7/99, the Panel expressed the view, in relation to a price comparison between two topical gels, that, 'Given the nature of topical products, usage rates would be imprecise and likely to vary from patient to patient'. This was particularly relevant in the treatment of acne vulgaris where the affected area could vary considerably from a few individual spots to extensive areas of the chest and trunk. In addition, in Case AUTH/1205/7/01, the Panel observed that, 'The Code stated that price comparisons should only be made on the basis of equivalent dosage requirements for the same indication'. With reference to Zindaclin and Zineryt, although the indications were the same, there was no basis on which application rates could be compared for these two products. Comparative application rate data for Zindaclin vs Dalacin T was, however, available as mentioned in the asterisked section of the leavepiece.

Yamanouchi therefore alleged that this price comparison table, by including Zineryt, was in breach of Clause 7.2. It was not accurate (based on zero evidence), not fair (inappropriate comparison) and misled (as the reader was led to believe that the comparison could be made).

Yamanouchi stated that in the course of the inter-company correspondence on the matter, it had been sent a copy of a new version of the Zindaclin leavepiece (M008/033). Yamanouchi did not know if this new version was already in use. Although it contained minor amendments to the price comparison table, it was Yamanouchi's opinion that the points raised above were equally relevant to the new leavepiece.

RESPONSE

Strakan stated that it did not consider that the cost comparison table was in breach of Clause 7.2 of the Code.

Strakan had been guided in its judgement about this price comparison table by the following statement in the supplementary information to Clause 7.2: 'It follows therefore that a price comparison should be made on the basis of equivalent dosage requirement for the same indications. For example, to compare the cost per ml for topical preparations is likely to mislead unless it can be shown that their usage rates are similar or, where this is not possible, for the comparison to be qualified in such a way as to indicate that usage rates may vary.'

Topical therapies were widely prescribed in acne, however they were not all liquids, solutions, lotions, etc, which could be quantified by volume (mls). Many were ointments, gels, etc, which were usually quantified by weight (mg or g). The comparability between topical agents was influenced by a number of variables, which could affect the validity of such a comparison eg viscosity (both liquids and gels might vary in viscosity) and means of application (eg rollerball, applicator pad, fingers, etc).

However, the cost of therapy was an important consideration for all health professionals and where there were a number of different available therapeutic options it was appropriate that an attempt be made to present the available data in a way which helped to rationalise the variables discussed above. Strakan considered that Clause 7.2 of the Code acknowledged these difficulties and allowed for the exercise of some common sense and professional judgement in such comparisons so long as the necessary qualifications were included.

As noted by Yamanouchi, Strakan had data from a controlled study which demonstrated that the use of Zindaclin was less than that of Dalacin T. The medication usage in this study was measured by weighing both the gel and the liquid medications. The results of these measurements were illustrated in the table taken from the report of this study. The comparison of medication usage was conducted on a gram for gram basis for both gel and liquid. When Residerm A (twice daily) and Dalacin T (twice daily) usages were compared it could be seen that Residerm A usage was 75% that of Dalacin T. Thus, Strakan contended that a calculation based on an expectation of Zindaclin usage per application, which was equal to Dalacin T usage on a g for ml basis, was reasonable, conservative and supportable.

Both Zineryt and Dalacin T were topical antibiotic solutions for the treatment of acne. Both were available in 30ml packs with similar applicators which allowed the patient to dab the liquid onto the skin. Thus, for a similar group of patients, using a similar pharmaceutical preparation with a similar applicator, Strakan submitted that it was reasonable to expect that the usage results obtained when comparing Zindaclin with Dalacin T would be replicated when comparing Zindaclin with Zineryt.

It could however be argued that this was not a reasonable assumption to make as there might be factors which would result in a greater usage of Dalacin T than Zineryt. However, in order for Zineryt to achieve parity with Zidaclin in this respect, this excess usage would have to be at least 25%. Strakan was aware of nothing in the summary of product characteristics (SPC) or any data relating to the clinical use of Zineryt and Dalacin T in acne, which would indicate that two such similar liquid, dab-on, topical antibiotics could be used so differently. Once again, Strakan believed that the common sense and professional judgement implied in the supplementary information to Clause 7.2 should be recognised. In addition, recognising the variability, Strakan had included the qualifying statement required by the Code and stated that 'rates of application may vary'.

Strakan had attempted to resolve this issue with Yamanouchi; it had suggested, and implemented, a number of changes to the leavepiece:

1 Zindaclin leavepiece M008/006 was certified for use in March 2002. This piece was intended to summarise the key benefits of Zindaclin discussed with a GP during a visit and was intended to be left with the GP at the end of the visit.

2 Following correspondence with Yamanouchi, leavepiece M008/006 was withdrawn at the end of

August and replaced with M008/033 which was currently being used.

3 During further discussions with Yamanouchi, Strakan proposed replacing M008/033 with M008/036.

In summary, whilst Strakan accepted that usage rates for topical preparations involved a number of variables, it considered that the price comparison table was an acceptable and supportable use of the available data and information on these commonly used topical acne treatments. The price comparisons were based on a gram for ml estimate of liquid and gel usage, the basis of which was the usage data from the study by Cunliffe *et al*; these estimates were based on a conservative interpretation of that data. Strakan believed that it was unreasonable, and clinically unrealistic to expect that Zineryt usage would be so significantly less than that of Dalacin T as to render an extrapolation from the Cunliffe data invalid. Strakan had also included a qualifying statement to indicate that rates of application might vary. It believed that it had complied with both the spirit and the letter of Clause 7.2 of the Code.

PANEL RULING

The Panel noted Strakan's submission about the Cunliffe paper and the statement on the leavepiece about the amount of product used when the number of applications were the same. The Panel queried the relevance of this data given that the licensed dose frequencies for the products listed in the chart were different. Zindaclin was licensed for once daily application whereas the other three products were to be used twice daily. The costs of the treatments listed in the cost comparison chart had been calculated on the assumption that at each application patients would apply 1ml/1g of the medicine. Thus for Zineryt, Dalacin T and Benzamycin, which were all to be applied twice daily, the cost of 56ml or 56g of each was given. As Zindaclin was to be applied only once daily the 28 day cost equated to the cost of 28ml of the solution. The Panel, however, queried the basis of the calculations and noted that the Cunliffe data showed that usage rates of ResiDerm A varied according to whether it was applied once or twice daily. Patients applying the product once daily used 33.7g of the product whereas if it was applied twice daily they used a total of 41.6g, thus they applied a more generous amount of a preparation each time when they used it once daily. The Panel considered that it could not, therefore, be assumed that patients using a product once daily would use half the amount of that product when compared to patients using another product twice daily.

The Panel considered that the cost comparison charts were misleading. In the Panel's view the assumption that patients used 1ml/1g of a topical preparation at each application regardless of the number of times a day it had to be applied was too simplistic. A breach of Clause 7.2 of the Code was ruled.

Complaint received **10 September 2002**

Case completed **13 November 2002**

CASE AUTH/1358/9/02

AVENTIS PASTEUR MSD v GLAXOSMITHKLINE

Havrix Junior Monodose 'Dear Nurse' letter

Aventis Pasteur MSD complained about a 'Dear Nurse' letter for Havrix Junior Monodose (hepatitis A vaccine) sent by GlaxoSmithKline. The letter informed readers that the presentation of Havrix Junior Monodose had been changed, and discussed best vaccination practice. Aventis Pasteur MSD marketed Avaxim and Vaqta Paediatric hepatitis A vaccines.

Aventis Pasteur MSD noted that the claim 'Havrix is the only hepatitis A vaccine recommended for use in an outbreak situation' implied that other hepatitis A vaccines could not be used in outbreak situations. The summary of product characteristics (SPC) for Vaqta Paediatric stated that 'vaccination is recommended in healthy children and adolescents from 2-17 years of age who are at risk of contracting or spreading infection …' and 'Protective efficacy has been demonstrated after a single dose of Vaqta Paediatric in a US community with recurrent outbreaks of hepatitis A'. Aventis Pasteur MSD considered that its SPC clearly covered outbreak situations and noted that much of the data which led to the licensing of Vaqta Paediatric were taken from a clinical trial conducted in a community suffering recurrent outbreaks of hepatitis A (Werzberger *et al* 1992). Aventis Pasteur MSD alleged that a superlative statement had been made which could not be substantiated and was misleading.

The Panel noted that both the Havrix Junior Monodose and the Havrix Monodose SPCs referred to the use of the products during outbreaks of hepatitis A infection. The Panel considered that although there was no direct reference to an outbreak situation, vaccination of 'recent close contacts of infected individuals' indicated that Vaqta Paediatric could be used to control the spread of infection if such a situation arose. The Avaxim SPC referred to the use of the product in the event of case contact. The Panel considered that the claim 'Havrix is the only hepatitis A vaccine recommended for use in an outbreak situation' implied that no other hepatitis A vaccine could be used in such circumstances and that was not necessarily so. Both Vaqta Paediatric and Avaxim could be used pre- or post-exposure. The Panel considered that the claim was misleading and exaggerated as alleged. Breaches of the Code were ruled.

Aventis Pasteur MSD alleged that the claim 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection' was misleading and was not an accurate representation of the SPCs for Havrix Junior Monodose and Havrix. Both SPCs made three points regarding the timing of the booster dose: firstly, in order to obtain more persistent immunity, for at least 10 years, a booster dose was recommended between 6 and 12 months after primary immunisation. Secondly, booster vaccination delayed up to 3 years after the primary dose induced similar antibody levels as a booster dose administered within the recommended time interval and that immunity was also expected to persist for at least 10 years under these conditions. Thirdly, however, to maintain continuous protection, boosting should take place between 6 and 12 months after primary immunisation.

Aventis Pasteur MSD considered that by promoting delayed booster vaccination with Havrix up to 3 years after the primary dose, without mentioning that a booster dose was recommended to be given between 6 and 12 months after primary immunisation, and that to maintain continuous protection boosting should be given between 6 and 12 months, prescribers might be lulled into a false sense of security. A breach of the Code was alleged.

The Panel considered that the claim 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection' was not a fair reflection of the provisions of the SPC regarding booster injections and immunity against hepatitis A infection. 'To provide a *further* (emphasis added) 10 years' protection' gave the impression that 3 years after the initial injection patients were still protected against hepatitis A and that a booster at that point would maintain continuous protection for a further 10 years and that was not so. The Panel did not accept that the matter of continuous protection was sufficiently explained by the subsequent sentence. The claim was misleading as alleged. A breach of the Code was ruled.

Aventis Pasteur MSD objected to the claim 'Delayed boosting – 10 years' protection' which related to the claim 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection' on the grounds that the SPC for Avaxim, together with scientific data, were consistent with the fact that Avaxim might be given as a delayed booster and could also give 10 years' protection.

The Panel noted that the Avaxim SPC stated that to provide long-term protection, a booster should be given 6-12 months after primary immunisation. The long-term duration of serum antibodies to hepatitis A virus was unknown. Long-term antibody persistence data following vaccination with Avaxim was not currently available. It was predicted that antibodies persisted for many years (at least 10) after the booster. In case of doubt the serum hepatitis antibody titre should be determined. The SPC stated that in the event that a booster injection was delayed, there might be a decreased antihepatitis A antibody response. If long term protection was required, the serum antihepatitis A antibody titre might be determined after Avaxim administration.

In the Panel's view there was a possibility that long-term protection could be afforded by a late booster of Avaxim although the serum antihepatitis A antibody titre might have to be determined to establish whether this was so. No mention was made in the Avaxim SPC about the effect of a booster delayed up to 3 years, unlike the Havrix Junior Monodose SPC (referred to above). The claim in question, however, was very specific with

regard to a 3 year gap between the initial vaccination and the booster. In that regard the Panel considered that the claim was not unreasonable. On that narrow point the Panel ruled no breach of the Code.

Aventis Pasteur MSD Ltd complained about a 'Dear Nurse' letter (ref HVX/LTR/02/1955) for Havrix Junior Monodose (hepatitis A vaccine) sent out by GlaxoSmithKline UK Ltd. Havrix Junior Monodose was supplied in a pre-filled 0.5ml syringe. The letter was headed 'Important news about changes to Havrix Junior Monodose' and stated that the presentation had been changed to allow a choice of needle and the product was now provided with both an orange (25G, 5/8") and a blue (23G, 1") needle. The letter also discussed best vaccination practice and made promotional claims. GlaxoSmithKline stated that the letter had been inserted into the polystyrene boxes containing vaccine orders for delivery to practice nurses during May, June and July 2002. There was no envelope.

Aventis Pasteur MSD marketed Avaxim and Vaqta Paediatric hepatitis A vaccines.

1 Claim 'Havrix is the only hepatitis A vaccine recommended for use in an outbreak situation'

COMPLAINT

Aventis Pasteur MSD alleged that this was a superlative statement, clearly designed to imply that other hepatitis A vaccines could not be used in outbreak situations. The summary of product characteristics (SPC) for one of Aventis Pasteur MSD's hepatitis A vaccines, Vaqta Paediatric, stated that 'vaccination is recommended in healthy children and adolescents from 2-17 years of age who are at risk of contracting or spreading infection …'. Aventis Pasteur MSD considered that its SPC clearly covered outbreak situations where persons were, almost by definition, at increased risk of contracting or spreading infection. Aventis Pasteur MSD also noted that much of the data in the regulatory dossier, which led to the licensing of Vaqta Paediatric, were taken from a clinical trial conducted in a community suffering recurrent outbreaks of hepatitis A (Werzberger *et al* 1992). On this basis Aventis Pasteur MSD was absolutely clear that outbreak usage formed part of the Vaqta Paediatric product licence. A statement in the SPC read 'Protective efficacy has been demonstrated after a single dose of Vaqta Paediatric in a US community with recurrent outbreaks of hepatitis A'. Aventis Pasteur MSD also noted that recent guidelines published in Communicable Disease and Public Health regarding the use of hepatitis A vaccine in outbreaks did not make any distinction between the various hepatitis A vaccines available on the market (Crowcroft *et al* 2001).

In intercompany correspondence GlaxoSmithKline had stated that 'demonstration of a vaccine's efficacy in a community prone to recurrent outbreaks of hepatitis A is not comparable' [with demonstrating efficacy in controlling the spread of hepatitis A during outbreak situations] and had declined to comment on the recent UK guidelines on hepatitis A vaccines in outbreaks, as published in Communicable Disease and Public Health.

In light of the above, Aventis Pasteur MSD alleged that GlaxoSmithKline had made a superlative statement regarding the use of Havrix in outbreak situations which could not be substantiated and was misleading, in breach of Clauses 7.2 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline noted that the wording in the Vaqta Paediatric SPC ('… recommended in healthy children and adolescents … who are at risk of contracting or spreading infection') covered outbreak situations and stated that Havrix was the only one of these vaccines that actually had a licensed indication specifically for use in outbreaks. The SPC for Havrix, under Section 4.1 'Therapeutic indications', stated: 'It is also indicated for use during outbreaks of hepatitis A infection'. No such indication appeared in the SPCs for either Vaqta or Avaxim.

In the claim, the word 'recommended' was used in its context meaning 'licensed' or 'indicated' – these terms were often used interchangeably in promotional statements for medicine.

GlaxoSmithKline's licensed indication was obtained on the basis of clinical studies which had demonstrated the efficacy of Havrix in controlling the spread of hepatitis A during outbreak situations. Aventis Pasteur MSD was of the opinion that the study by Werzberger *et al*, which demonstrated the efficacy of Vaqta paediatric in a community prone to recurrent outbreaks of hepatitis A, equated to a licensed indication for use of this vaccine during outbreaks. However, GlaxoSmithKline considered this was not the case, for the following reasons:

– The Werzberger study was a double-blind, placebo-controlled trial, designed to demonstrate the efficacy of Merck's vaccine in the prevention of hepatitis A in children aged 2 to 16 years. It was carried out in a US community with a high rate of childhood hepatitis A; the community was characterised by a high birth rate, and had year-to-year repetition of hepatitis A epidemics at predictable time intervals. It therefore constituted an ideal setting in which to carry out a single-centre, placebo-controlled efficacy study, for licensure purpose.

– This use of a vaccine would be described as pre-exposure prophylaxis; indeed, the vaccination in this study was planned purposely to begin before an expected outbreak, so that as many children as possible on the active treatment arm would seroconvert and be protected from infection before the outbreak began.

– In contrast to this, the specific indication for Havrix was supported by data from studies which showed it to be efficacious in halting the spread of community-wide outbreaks (McMahon *et al* 1996, Prikazsky *et al* 1994). In McMahon *et al*, in those communities where more than 80% of susceptible persons received Havrix during an outbreak, the outbreaks ceased within 4 to 8 weeks. Without vaccination, outbreaks in that region usually lasted for 9 to 12 months.

The wording in the Vaqta SPC ('… recommended in healthy children and adolescents … who are at risk of contracting or spreading infection') thus represented the basic licence for pre-exposure prophylaxis, which would apply to most vaccines.

Aventis Pasteur MSD was attempting to claim a class effect for use of hepatitis A vaccines during outbreak situations, and had cited the guidelines by Crowcroft *et al*, which indeed referred to 'hepatitis A vaccine' in this regard, rather than specifying Havrix by name. However, most of the studies cited in the paper to support use of vaccine to control outbreaks were in fact Havrix studies. It was standard practice for independent reviews of medicines to use generic, rather than brand names. Nonetheless, Havrix was the only one with a specific indication for use during an outbreak situation.

PANEL RULING

The Panel noted that Section 4.1 of the Havrix Junior Monodose SPC referred to the use of the product during outbreaks of hepatitis A infection as did Section 4.1 of the Havrix Monodose SPC.

Section 4.1 of the Vaqta Paediatric SPC stated:

> 'VAQTA Paediatric is indicated for active pre-exposure prophylaxis against disease caused by hepatitis A virus. Vaccination is recommended in healthy children and adolescents 2 years of age up to and including 17 years of age, who are at risk of contracting or spreading infection or who are at risk of life-threatening disease if infected.
>
> Subjects at high risk of hepatitis A infection include those travelling to, or living in, medium or high endemicity areas. Other high risk groups include recent close contacts of infected individuals and potential contacts of cases such as childcare or healthcare workers. In the event of a case contact, human normal immunoglobulin should be given simultaneously with VAQTA Paediatric at different sites. Individuals who potentially play a key role in transmitting infection, eg food-handlers, might also be considered for vaccination.'

The Panel considered that although there was no direct reference to an outbreak situation, vaccination of 'recent close contacts of infected individuals' indicated that Vaqta Paediatric could be used to control the spread of infection if such a situation arose. The product could be used for both pre- and post-exposure prophylaxis. Section 4.2 referred to the concomitant use of Vaqta Paediatric and immunoglobulin after known or presumed exposure. Immediate passive immunity would thus be achieved with the immunoglobulin (ref BNF) while active immunity from the Vaqta Paediatric injection would develop over the next few weeks.

Section 4.1 of the Avaxim SPC stated that the product was indicated for active immunisation against infection caused by hepatitis A virus in susceptible adults and adolescents (of 16 years and over). In the Panel's view such a broad statement could cover many situations where a person might be susceptible to hepatitis A including an outbreak of the disease.

Section 4.2 of the Avaxim SPC referred to the concomitant use of the product with immunoglobulin in the event of case contact.

The Panel considered that the claim 'Havrix is the only hepatitis A vaccine recommended for use in an outbreak situation' implied that no other hepatitis A vaccine could be used in such circumstances and that was not necessarily so. Both Vaqta Paediatric and Avaxim could be used pre- or post-exposure. The Panel considered that the claim was misleading and exaggerated as alleged. Breaches of Clauses 7.2 and 7.10 were ruled.

2 Claim 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection'

COMPLAINT

Aventis Pasteur MSD alleged that this claim was misleading and did not accurately represent GlaxoSmithKline's product licence as laid out in the SPCs for Havrix Junior Monodose and Havrix. Both SPCs made three salient points regarding the timing of the booster dose:

a) In order to obtain more persistent immunity for, at least 10 years, a booster dose was recommended between 6 and 12 months after primary immunisation.

b) Booster vaccination delayed up to 3 years after the primary dose induced similar antibody levels as a booster dose administered within the recommended time interval and that immunity was also expected to persist for at least 10 years under these conditions.

c) However to maintain continuous protection boosting should take place between 6 and 12 months after primary immunisation.

Aventis Pasteur MSD considered that by promoting delayed booster vaccination with Havrix up to 3 years after the primary dose, without also mentioning the other important facts from the SPC, that a booster dose was recommended to be given between 6 and 12 months after primary immunisation, and that to maintain continuous protection boosting should be given between 6 and 12 months, prescribers might be lulled into a false sense of security. The emphasis placed on the fact that boosting might be delayed up to 3 years, without also qualifying that there was a risk that continuous protection would not be maintained in the period between the primary dose and the booster dose, might encourage a *laissez-faire* attitude to recalling patients on time for their 6 to 12 months booster and in doing so could leave patients without protection in the intervening period, thus exposing them to unnecessary risks of contracting hepatitis A.

In intercompany correspondence GlaxoSmithKline had noted that the claim was followed by the sentence 'So even if patients don't come back on time, you still have an opportunity to give them long term protection against hepatitis A'. In GlaxoSmithKline's view, this made it clear that the claim applied only to those patients who presented late for their booster

dose. Aventis Pasteur MSD did not agree that this information was at all clear, and the claim certainly did not serve as a warning that continuous protection might not be maintained. The information GlaxoSmithKline had provided about the use of Havrix in delayed boosting was incomplete and unbalanced when compared with the SPC and as such, misleading, in breach of Clause 7.2 of the Code. In the light of the apparent reassurance given in the mailing, such claims could even expose patients to risks of contracting hepatitis A if a health professional were to relax his/her attitude to calling patients for their booster dose on time.

RESPONSE

GlaxoSmithKline noted that the basis of this complaint was that the claim did not accurately represent the product licence for Havrix. The licence for Havrix, and how this differed from that of Avaxim or Vaqta, could be described as follows:

When an individual received Havrix (or Avaxim/Vaqta) prior to travelling, they could travel again to an at-risk area within the next 6 months, without needing a booster. Between 6 and 12 months, it they wished to travel again, they should present for a booster vaccination, following which they would be protected for up to 10 years.

The difference between the licences of the vaccines became relevant for the patients who did not travel again (or did not present for their booster) until 12-36 months after the first vaccination. If their first vaccination was Havrix, they could be given Havrix again, and be protected for a further 10 years. However, if their first vaccination was Avaxim/Vaqta, they would go 'back to the beginning' – requiring a first vaccination followed by a booster 6-12 months later.

For the reasons Aventis Pasteur MSD had pointed out, a qualifying statement usually accompanied the above claim, ie 'to maintain continuous protection, it is recommended that the booster should be given 6-12 months after the initial vaccination'.

However, in the mailing the claim was followed by the sentence: 'So even if patients don't come back on time, you still have an opportunity to give them long term protection against hepatitis A'.

As GlaxoSmithKline therefore considered it was clear that the claim applied only to those patients presenting late for their booster dose (ie later than the recommended 12 months), the qualifier was not considered necessary in this particular instance.

PANEL RULING

The Panel noted that Section 4.2 of the Havrix Junior Monodose SPC stated that the primary immunisation provided antibodies for at least one year. To obtain persistent immunity for at least 10 years a booster was recommended between 6-12 months after primary immunisation. It was further stated that 'Booster vaccination … delayed up to 3 years after the primary dose induces similar antibody levels as a booster dose administered within the recommended time interval. That is, immunity is also expected to persist for at least 10 years after boosting. However to maintain continuous protection, boosting should take place between 6 and 12 months after primary immunisation'. A similar statement appeared in the Havrix Monodose SPC.

The Panel considered that the claim 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection' was not a fair reflection of the provisions of the SPC regarding booster injections and immunity against hepatitis A infection. 'To provide a *further* (emphasis added) 10 years' protection' gave the impression that 3 years after the initial injection patients were still protected against hepatitis A and that a booster at that point would maintain continuous protection for a further 10 years and that was not so. The Panel did not accept that the matter of continuous protection was sufficiently explained by the subsequent sentence which referred to patients presenting late for their booster dose as submitted by GlaxoSmithKline. The claim was misleading as alleged. A breach of Clause 7.2 of the Code was ruled.

3 Delayed boosting – 10 years' protection

This allegation related to the claim at issue in point 2 that 'Havrix is the only booster for hepatitis A that can be given up to 3 years after the initial vaccination to provide a further 10 years' protection'.

COMPLAINT

Aventis Pasteur MSD objected to the claim on the grounds that the SPC for Avaxim, together with scientific data which GlaxoSmithKline itself had relied upon in the past, were consistent with the fact that Avaxim might be given as a delayed booster and could also give 10 years' protection.

Aventis Pasteur MSD noted that the SPC for Avaxim stated that 'In the event that the booster vaccination has been delayed, there may be a decreased anti-hepatitis A antibody response. If long term protection is required, the serum anti-hepatitis A antibody titre may be determined after Avaxim administration'. Aventis Pasteur MSD considered that its SPC was clearly consistent with the fact that booster vaccination with Avaxim might also be delayed as it was explicitly mentioned. Whilst it was true that the SPC advised prudency through measuring antibody titres if boosting was delayed and if long-term protection was required, this was still not inconsistent with providing 10 years' protection.

There were two general guidelines that were relevant to the late boosting of hepatitis A vaccines:

The Department of Health stated 'if any course of immunisation is interrupted it should be resumed and completed as soon as possible'.

The Advisory Committee on Immunization Practices (ACIP), from the Centre of Disease Control and Prevention in the USA, stated 'an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or the addition of extra doses'.

These guidelines were not specific to Havrix but described a class effect for all hepatitis A vaccines.

Aventis Pasteur MSD noted that a promotional letter from GlaxoSmithKline's medical information department about Havrix clearly stated that 'with regard to the original Havrix vaccine, although there has not been any work carried out on giving the third injection beyond this time, based on experience with other inactivated vaccines, we would still expect it to act as a booster when given beyond this time period. Therefore we recommend that the third injection be given even if this might be quite late with a view that more persistent immunity of up to 10 years will still be attained from when it is given'. Thus, in the past GlaxoSmithKline had considered it acceptable to make a claim for longevity of protection after delayed booster vaccination with Havrix even though it did not have any such data available for Havrix. The basis of its claim at that time was that the experience with other inactivated vaccines was, in effect, a class effect, which was transferable to Havrix. It was thus extremely inconsistent of GlaxoSmithKline to now argue that, having produced data to vary its own licence, such a class effect no longer applied. In fact there were now more data than ever before to support the presence of a strong class effect anamestic response for hepatitis A vaccines as a class. By producing a superlative statement, GlaxoSmithKline was clearly arguing that the data it claimed was once applicable to Havrix as part of a class effect were now not applicable to Avaxim and Vaqta Paediatric.

In intercompany correspondence GlaxoSmithKline had declined to comment about its previous letter, or the change in its interpretation of the data on this subject. Nevertheless, Aventis Pasteur MSD alleged a further breach of Clause 7.2 of the Code.

RESPONSE

GlaxoSmithKline noted that Aventis Pasteur MSD considered that Avaxim could also be given as a delayed booster, to provide a further 10 years' protection.

As discussed, the claim referred specifically to the wording in Section 4.2 of the Havrix SPC, ie: 'Booster vaccination with Havrix … delayed up to 3 years after the primary dose induces similar antibody levels as a booster dose administered within the recommended time interval. That is, immunity is also expected to persist for at least 10 years after boosting'.

This wording was added to the Havrix SPC in May 2001, following a product licence variation supported by published clinical data. There had been no similar amendment to the product licences for either Avaxim or Vaqta – therefore, neither of these vaccines was licensed for boosting beyond 6-12 months following the initial vaccination.

As Aventis Pasteur MSD had noted, the SPC for Avaxim stated that there might be a decreased antibody response if the booster vaccination was delayed, and advised measurement of serum antibody levels if long term protection was required. It was difficult to see how this could equate to a licensed recommendation for delayed boosting, as Aventis Pasteur MSD was claiming.

Once again, Aventis Pasteur MSD was attempting to claim a class effect for hepatitis A vaccines, in an attempt to prevent GlaxoSmithKline from making valid claims relating to the licensed indications for Havrix. Aventis Pasteur MSD had quoted from general guidelines: 'if any course of immunisation is interrupted it should be resumed and completed as soon as possible' (Department of Health, 'Green Book') and 'an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or the addition of extra doses' (ACIP).

However, these guidelines were intended to be used as general advice – they could not supersede specific licensed recommendations for a vaccine. Aventis Pasteur MSD had failed to note that the 'Green Book' statement applied specifically to the paediatric immunisation schedule (which did not include hepatitis A). Furthermore, the ACIP guidelines stated: 'These recommendations are intended for use in the United States because vaccine availability and use … differ in other countries. Individual circumstances might warrant deviations from these recommendations'.

Finally, GlaxoSmithKline noted that Aventis Pasteur MSD had submitted a 'Dear Practice Nurse' letter, which was written by the medical information department at SmithKline Beecham approximately 7 years ago. This letter answered the frequently-asked question 'what course of action should be taken with patients who attend late (after one year) for their booster injections of Havrix …?'.

As noted by Aventis Pasteur MSD, the advice given in the letter was indeed based on experience with other inactivated vaccines. This was necessary at that time, as there were no specific data for boosting of late presenters. Because there was such an obvious need for more specific data, rather than general guidelines or extrapolation from other vaccines, SmithKline Beecham set up and supported Landry *et al*, on which the product licence variation was subsequently granted.

PANEL RULING

The Panel noted that Section 4.2 of the Avaxim SPC stated that to provide long-term protection, a booster should be given 6-12 months after primary immunisation. The long-term duration of serum antibodies to hepatitis A virus was unknown. Long-term antibody persistence data following vaccination with Avaxim was not currently available. It was predicted that antibodies persisted for many years (at least 10 years) after the booster. In case of doubt the serum hepatitis antibody titre should be determined. Section 4.4 of the SPC stated that in the event that a booster injection was delayed, there might be a decreased antihepatitis A antibody response. If long term protection was required, the serum antihepatitis A antibody titre might be determined after Avaxim administration.

In the Panel's view there was a possibility that long-term protection could be afforded by a late booster of Avaxim although the serum antihepatitis A antibody titre might have to be determined to establish whether

this was so. No mention was made in the Avaxim SPC about the effect of a booster delayed up to 3 years unlike the Havrix Junior Monodose SPC (referred to in point 2 above). The claim in question, however, was very specific with regard to a 3 year gap between the initial vaccination and the booster. In that regard the Panel considered that the claim was not unreasonable. On that narrow point the Panel ruled no breach of Clause 7.2 of the Code.

Complaint received **16 September 2002**

Case completed **25 November 2002**

CASE AUTH/1359/9/02

RECKITT BENCKISER HEALTHCARE v NORGINE

Promotion of Movicol

Reckitt Benckiser Healthcare complained about the promotion of Movicol (polyethylene glycol plus electrolytes) by Norgine. A leavepiece and a detail aid each featured the claim 'A clear solution for chronic constipation'. Reckitt Benckiser Healthcare noted that there were a number of claims derived from the modelling study of Movicol versus lactulose in the management of idiopathic constipation (Christie *et al* 2002). The key inputs to the model were efficacy data from a randomised comparative trial (Attar *et al* 1999) and estimates of resource use from a panel of general practitioners and nurses who were interviewed specifically for the purpose. Christie *et al* argued that, despite the higher purchase cost of Movicol, it actually resulted in lower overall costs to the NHS than lactulose. This argument was then used in the detail aid for Movicol.

Reckitt Benckiser Healthcare alleged that the statements by Christie *et al* that the effectiveness measures used in the model might have been too restrictive and the data on which the model was based might not reflect clinical practice meant that the data presented in this paper were unacceptable under the Code.

The Panel noted that it was not stated in either the detail aid or the leavepiece that claims referenced to Christie *et al* were based on a pharmacoeconomic modelling study. The Panel noted the limitations of the Christie data as discussed by the authors, in particular that it might not reflect clinical practice. The Panel noted Norgine's submission in this regard. In the Panel's view the reader would assume that claims and statements referenced to Christie *et al* were based wholly on clinical trial results and that was not so. A breach of the Code was ruled.

Reckitt Benckiser Healthcare noted the claim 'Over twice as many patients were successfully treated with Movicol than with lactulose' which appeared on page 2 of the detail aid. The key outcome measure used for the economic model was a combination of an evacuation score of ≤ 1 and a daily stool frequency of ≥ 1 at 3 months. Christie *et al* argued that this combined measure should relate to 3 month data. However Attar *et al* was not a 3 month study; the extension to the second and third months was not fully randomised and was reported only as a 'follow-up' with considerably less detail than that reported for the first month. The percentage probabilities in Christie *et al* were based on a panel estimate rather than actual data. Reckitt Benckiser Healthcare alleged that the graph and subsequent claim were misleading.

The Panel considered that insufficient information about Christie *et al* had been provided such that the graph and claim at issue gave a misleading impression about the nature of the efficacy data and the products' relative efficacy. A breach of the Code was ruled.

The claims 'Movicol saves time vs lactulose' and 'Potential reduction in consultations' appeared as a heading and subheading respectively on page 2 of the detail aid. Beneath the claim 'Potential reduction in consultations' a bar chart based on Christie *et al* showed the potential reduction in the number of GP consultations in a 3 month period against the number of patients with idiopathic constipation managed by a GP. Beneath the bar chart was the claim 'If you treat 20 patients with Movicol instead of lactulose, you could potentially save 30 consultations over three months'. Reckitt Benckiser Healthcare noted that one additional GP visit was assumed for each patient who discontinued. As with all the resources modelled, additional GP visits were assumed based on panel estimates, not on observation. Reckitt Benckiser Healthcare considered that the graph and subsequent claim were misleading.

The Panel considered that a reader would assume that the potential reduction in consultations and time saved was based upon actual observation rather than a pharmacoeconomic model based on subjective estimates derived from interview and assumptions. The Panel considered that the claims were misleading in this regard. A breach of the Code was ruled.

The claim 'Movicol saves money vs lactulose' appeared as a heading on page 3 of the detail aid which was based on Christie *et al* and featured a bar chart setting out the various components of the NHS cost associated with treating idiopathic chronic constipation with Movicol or lactulose over a 3 month period. A subsequent bullet point read 'Movicol was twice as effective as lactulose' and 'Patients taking Movicol make fewer visits to their GP than those taking lactulose'. Reckitt Benckiser Healthcare stated that the page reiterated and relied upon the claims that Movicol was twice as effective

as lactulose and that patients taking Movicol made fewer visits to their GP. Reckitt Benckiser Healthcare alleged that the overall comparison of NHS costs was misleading.

The Panel considered that its general comments about Christie *et al* above were relevant here. Insufficient information had been provided to place the claim 'Movicol was twice as effective as lactulose' in context; readers would also assume that it related wholly to clinical data collected over a 3 month period. This was not so. The claim was thus misleading and the Panel ruled a breach of the Code in that regard.

In relation to the claim 'Patients taking Movicol make fewer visits to their GP than those taking lactulose', the Panel considered that its previous ruling in relation to the claim 'Potential reduction in consultations' was relevant here and ruled a breach of the Code in that regard.

Reckitt Benckiser Healthcare considered that the data and claims based on Christie *et al* and presented on pages 2 and 3 of the detail aid were at best misleading and at worst the use of this material might bring discredit upon, and reduce confidence in, the pharmaceutical industry.

The Panel did not consider that the material was such as to warrant a ruling of a breach of Clause 2.

Reckitt Benckiser Healthcare noted pages 4, 5 and 10 of the detail aid and pages 1 and 2 of the leavepiece referred to maintenance use of Movicol. Whilst this was listed in the prescribing information in both the detail aid and the leavepiece, it was not supported in the current summary of product characteristics (SPC) which merely talked about extended use in certain patient groups.

The Panel noted that pages 4 and 5 of the detail aid described those patient populations in whom extended use might be necessary, according to the SPC. The Panel did not consider the reference to 'maintenance use' on these pages of the detail aid to be inconsistent with the SPC in this regard; no breach of the Code was ruled. Page 10 of the detail aid and the front side of the leavepiece each referred to 'Maintenance dosage of 1 or 2 sachets per day' but neither gave any information on the patient groups for whom such usage was mentioned in the SPC and were thus inconsistent with the SPC in this regard. A breach of the Code was ruled in respect of each item.

The claim '90% efficacy*' appeared on page 5 of the detail aid headed 'Movicol is now licensed for maintenance use' beneath a list of patient groups in whom it was claimed Movicol was highly effective; patients taking anti-depressants or other drugs (n=296), cancer patients (n=24) and Parkinson's disease (n=20). The asterisk led the reader to a footnote which read 'Overall, over 90% of the doctors rated the efficacy of Movicol as 'good' or 'very good''.

Reckitt Benckiser Healthcare stated that despite the footnote, readers might be misled into believing that the 90% efficacy was based on a direct measurement of efficacy. In addition, the detail aid gave the impression that each of the subgroups demonstrated 90% efficacy. However, the paper on which this data was based (Gruss and Teucher 1999) did not give a breakdown of the number of patients on constipating drugs or with neurological illness who completed the trial successfully. It was not therefore possible to make the 90% efficacy claim for all subgroups based on this data.

The Panel considered that the majority of the readers would gain the impression that the claim related to a clinical measurement of efficacy and that was not so. A breach of the Code was ruled.

The Panel noted that Gruss and Teucher stated that normal stool frequency (> 3 per week) was achieved in 90% of the patients included within a four week observation period. Efficacy was ranked 'as 'very good' to 'good' by 90% (patients) and 92% (doctor) of mentions'. The data on file provided an analyses of sub-groups and demonstrated that the doctor assessment of the percentage of patients whose condition was 'normalised' or 'clearly improved' in each sub-group was: anti-depressants 91%, morphine 96% and Parkinson's disease 89%. The patient numbers in the last two groups were small, 24 and 20 respectively, but were stated on the piece at issue.

The Panel considered that the juxtaposition of the claim '90% efficacy' and the preceding sub-groups created the impression that 90% efficacy was achieved in each patient population mentioned and that was not an accurate reflection of Gruss and Teucher and the data on file. In addition the Panel queried whether data based on small patient groups could in any event give an accurate assessment of percentage efficacy. The Panel considered that the claim for 90% efficacy was also misleading on this point and a further breach of the Code was ruled.

Reckitt Benckiser Healthcare alleged that the claim '… Movicol guarantees a neutral water and electrolyte balance which increases the safety level especially with repeated use or in patients at risk' on page 8 of the detail aid was exaggerated.

The Panel noted that the Movicol SPC stated that 'The electrolytes also present in the formulation ensure that there is virtually no net gain or loss of sodium, potassium or water'. In the Warnings and Precautions for Use section the SPC also gave advice on what to do if a patient developed symptoms indicating shifts of fluid or electrolyles. The Panel considered that 'guarantee' was an absolute term, stronger than 'virtually no' in the SPC and inconsistent with the SPC warning. The Panel ruled a breach of the Code.

Reckitt Benckiser Healthcare stated that the claim 'Movicol efficacy increases with dosage', based on Hammer *et al* (1989), implied that Movicol would be more effective in the treatment of constipation as the amount ingested per 24 hours increased. Hammer *et al* only looked at stool weight in healthy volunteers treated with PEG 3350 plus electrolytes to induce diarrhoea. No measurements of efficacy in the treatment of constipation were made. This claim was misleading as it was based on data from only three healthy volunteers taking doses of up to six times the maximum daily dose recommended on the

SPC. Reckitt Benckiser Healthcare considered that such data could not reliably be extrapolated to efficacy in the treatment of constipation.

The Panel considered that it had not been made clear that the Hammer *et al* study had been conducted in healthy volunteers; readers would assume that the data was based on a study in patients and that was no so. In that regard the Panel noted that the claim referred to 'efficacy' which further implied a clinical context. The Panel considered that the claim was thus misleading and ruled a breach of the Code.

In relation to the allegation that such data could not be extrapolated to the clinical situation the Panel noted Norgine's submission that by demonstrating that faecal water flow was directly proportional to the amount of macrogol administered these data were relevant to the clinical situation. The Panel noted that the licensed dose for Movicol in the treatment of chronic constipation was 1-3 sachets (13.8g/sachet) daily and for faecal impaction, 8 sachets per day. It appeared that increasing doses of Movicol were thus used for increasing effect. The Panel noted Norgine's submission that other laxatives had optimal doses above which the dose response curve was flat. On balance the Panel considered that the data was relevant to the clinical situation and so was not misleading on this narrow point. No breach of the Code was ruled.

Reckitt Benckiser Healthcare noted that the claim of 30% price reduction on pages 1 and 10 of the detail aid and 1 of the leavepiece was relevant at the time the items were produced. However, by continuing to use this claim six months after the price reduction, the historical significance of it was lost.

The Panel considered, on balance, that this was not unreasonable and the detail aid and leavepiece were not misleading in this regard. The Panel ruled no breach of the Code.

The claim 'Over twice as effective as lactulose at a lower total NHS cost' appeared on page 10 of the detail aid and page 1 of the leavepiece. Reckitt Benckiser Healthcare stated that not only was the use of the data from Christie *et al* in this way potentially misleading, but also it might be taken to imply that the actual NHS cost of Movicol was lower than lactulose. This was not the case.

The Panel noted that the items were targeted at GPs, community nurses and hospital doctors. The Panel queried whether, given the intended audience, the meaning of the phrase 'total NHS cost' had been made sufficiently clear. The Panel considered that given the audience the reference to total NHS cost, without further explanation was not sufficiently clear and was misleading in this regard. A breach of the Code was ruled in respect of each item.

Reckitt Benckiser Healthcare (UK) Limited complained about the promotion of Movicol (polyethylene glycol plus electrolytes) for the treatment of chronic constipation by Norgine Limited. There were two items at issue; a leavepiece (ref MO/02/0098 (8079733)) and a detail aid (ref MO/02/0096 (8079725)). Both items featured the claim 'A clear solution for chronic constipation'.

1 Use of data from Christie *et al*

COMPLAINT

Reckitt Benckiser Healthcare noted that there were a number of claims derived from the modelling study of Movicol versus lactulose in the management of idiopathic constipation (Christie *et al* 2002). The key inputs to the model were efficacy data from a randomised comparative trial by Attar *et al* (1999) and estimates of resource use from a panel of six GPs and four nurses who were interviewed specifically for the purpose. Christie *et al* argued that, despite the higher purchase cost of Movicol, it actually resulted in lower overall costs to the NHS than lactulose. This argument was then used in the detail aid for Movicol.

However, as with all models, the results depended on a number of assumptions. Firstly, the use of resources such as GP and nursing time was based on opinions drawn from a small number of panel interviews, not on actual data generated from a trial or audit. This was important because it was the GP time that gave the critical cost advantage claimed for Movicol. The detail aid made a strong point out of 'saving time' – but this was highly dependent on the model's assumptions.

Secondly, the trial data covered only 4 weeks, but with an extension for some patients over a further 2 months. In the extension, no patients aged less than 65 were treated with lactulose. Developing a model for the full 3 months therefore required a key assumption regarding these patients; it was assumed that they would have the same outcomes as patients aged over 65 who received lactulose for the whole 3 month period.

The supplementary information to Clause 7.2 of the Code stated that to be acceptable as the basis of promotional claims the assumptions made in an economic evaluation must be clinically appropriate. However, having made assumptions regarding effectiveness of lactulose in different age groups, the authors admitted that the effectiveness measures used in the model might have been too restrictive. Similarly, they went on to state that the data on which the model was based might not reflect clinical practice, particularly amongst patients managed in the community by their GP. These statements by the authors meant that the data presented in this paper were unacceptable under the Code. Therefore any use of this paper unless appropriately qualified would be in breach of the Clause 7.2 of the Code.

RESPONSE

Norgine stated that the use of pharmacoeconomic modelling was well established in health technology assessments. The fact that all pharmacoeconomic models involved certain assumptions did not prevent them being widely used to inform decisions made by national bodies on the usage, reimbursement and pricing of pharmaceutical products and other health technologies. The use of modelling was no different here to that on a much larger scale at a national level as commonly used by organisations like The National Institute for Clinical Excellence (NICE) in the UK, the Pharmaceutical Benefits Advisory Committee (PBAC)

in Australia and the Transparency Commission in France. Norgine noted that the complaint seemed to be based on the view that economic modelling studies were inherently flawed because they involved a number of assumptions.

Norgine stated that whilst it did not dispute that modelling studies used assumptions which might be a limitation to the interpretation of the results derived, it strongly disputed that the use of comparative data derived from a pharmacoeconomic model was inaccurate or misleading just because it was derived from a model.

All models tested the validity of the assumptions made in a given study by undertaking sensitivity analyses. In the case of Christie *et al*, the sensitivity analyses showed that the model was very robust and that even quite significant changes to the key assumptions would not affect the overall results and conclusions. Furthermore, prospective economic evaluations might not necessarily be superior to modelled evaluations because, as in every study, resource use might well be protocol driven and not reflect that in clinical practice. Consequently, some assumptions might have to be made about whether resource use, such as the number of GP visits, had been driven by the protocol, in which case the number might have to be reduced on the basis of further assumptions. Additionally, there would be admission criteria for patients, even in a prospective study, which would obviously not apply in clinical practice. Hence, the results from a prospective economic evaluation might not be any more robust than those from a modelled evaluation.

Norgine noted that Reckitt Benckiser Healthcare made the point that the comparative phase of the study lasted for only 4 weeks, and that an assumption was made for the 2 month extension of the study that the results for the under 65 age group would show the same outcomes as patients over 65 who were treated with lactulose for the whole 3 month period. This issue was covered in the sensitivity analysis reported in the paper. This showed that the effectiveness of both products at 53% for Movicol and 24% for lactulose was driven by the efficacy of both products seen at the end of the first 2 weeks of treatment (ie 48% for Movicol and 20% for lactulose), in other words during the controlled phase in all age groups.

The sensitivity analysis showed that for the results at 3 months to be based on an incorrect assumption about the behaviour of the patients during the 2 month extension, the efficacy of lactulose would have to increase from 20% to above 50% at week 2 in order to break even with the cost of Movicol. Similarly the efficacy of Movicol would have to decline from 48% to 30% at week 2 in order to break even with the cost of lactulose.

Norgine stated Reckitt Benckiser Healthcare's point that the authors admitted that the effectiveness measures used in the model might have been too restrictive was based on a selective or incorrect reading of the paper. The quotation in full referred to the use of an efficacy score combining stool frequency and ease of evacuation. This therefore meant that the efficacy score was particularly 'rigorous' or 'restricted' and therefore might underestimate the efficacy of the two products. This might well be the case, and it was worth repeating the full quotation from the publication:

'Moreover, the effectiveness measure used to calculate successful resolution of constipation may have been too restrictive, and this would have underestimated the proportion of patients with successful resolution of their constipation. Nevertheless, this would apply equally to both [Movicol] and lactulose and therefore should not affect the assessment of their relative cost effectiveness.'

Norgine noted that Reckitt Benckiser Healthcare also stated that the data on which the model was based might not reflect clinical practice, particularly amongst patients managed in the community by their GP. Presumably the inference here was that the model was not clinically appropriate for a general practice setting and might therefore mislead. Norgine stated that the validity or otherwise of the extrapolation of data from a controlled clinical trial to wider medical practice depended to a large extent on how restrictive the protocol was for the study, particularly in respect of the inclusion and exclusion criteria.

In Attar *et al* on which the Christie *et al* economic model was based, the inclusion and exclusion criteria were not very restrictive at all. The inclusion criteria stated that all patients with fewer than 3 stools a week and difficulty in evacuation, and who had had these symptoms for more than 3 months, were eligible for the study. These were not restrictive inclusion criteria. The Rome II criteria defined chronic constipation as that persisting for 3 months or more, so all patients with chronic constipation were eligible for the study. There were very few exclusion criteria, compared to the number that was commonly seen in a controlled clinical trial. The only significant exclusion criteria were the exclusion of patients with secondary constipation (ie constipation caused by an existing disease), those taking medication which altered bowel transit and those with severely impaired hepatic, renal or cardiac function.

The data on concomitant disease showed that this study was not one with a highly selected group of patients. Analysis of the study population showed that in the Movicol group 43/60 had a concomitant disease, 27% were reported as having cardiovascular disease and 8% a neurological disease. In the lactulose group the figures were 31/54 with a concomitant disease, 14% having cardiovascular disease and 13% neurological disease. This showed that the patients recruited in the study were not those with pure, uncomplicated idiopathic constipation. They were a reasonably typical group of patients that might be seen in a primary care setting with a number of different diseases that might well have contributed to their constipation to a greater or lesser extent. Therefore these patients in Attar *et al* were a relatively heterogeneous group of patients, certainly not untypical of the patients that were seen in general practice, and they were not a highly selected group at all, which made it more likely than not that these results could be justifiably extrapolated to the general practice setting.

PANEL RULING

The Panel noted the supplementary information to Clause 7.2, economic evaluation of medicines, stated, *inter alia*, 'Care must be taken that any claim involving the economic evaluation of a medicine is borne out by the data available and does not exaggerate its significance. To be acceptable as the basis of promotional claims the assumptions made … must be clinically appropriate and consistent with the marketing authorization'.

The Panel noted that Christie *et al* was a decision analytic modelling study which estimated the economic impact (direct healthcare costs) of using PEG+E (Movicol) compared with lactulose in the treatment of idiopathic constipation in ambulant patients at 3 months from the perspective of the NHS. The clinical basis for the economic evaluation was derived from Attar *et al* which compared the efficacy of Movicol and lactulose in 115 patients for the treatment of chronic constipation. Healthcare resource utilisation data were established by interviewing a panel of six GPs, two continence nurse advisors and two district nurses with experience of managing idiopathic constipation. The interviews were semi-structured qualitative discussions. A pharmacoeconomic model was then used to estimate the expected total NHS cost of the two treatments over 3 months. Christie *et al* concluded that the study indicated that managing idiopathic constipation with Movicol instead of lactulose reduced the expected NHS cost by £11 per patient over 3 months and use of Movicol instead of lactulose was expected to double the percentage of patients successfully treated at 3 months.

Attar *et al* compared the efficacy of Movicol and lactulose in chronic constipation. The discussion section stated that the study's main objective was to compare the products' clinical tolerance over a one month period. The results indicated, *inter alia*, that Movicol was significantly more effective than lactulose over a four week treatment period in a total of 99 patients. As the two treatments differed in appearance and taste the study was randomised but not double-blinded. The study authors stated that they could not exclude the possibility that some biases might arise as a result of this methodological limitation. Following the initial four weeks' treatment with either Movicol or lactulose patients were treated for a further two months with open-label Movicol in a follow up phase to evaluate the long-term efficacy and safety of the product. No information was provided by Attar *et al* about the characteristics of these patients.

Christie *et al* stated that the Attar study was divided into part A; the four week study protocol and part B; the eight week extension study during which patients over 65 years of age continued to receive the treatment allocated for part A whilst all patients age 65 or less received Movicol. It was stated that during part B the Movicol dose tended to remain stable whilst the lactulose dose tended to increase and that at the end of three months, in patients over 65 years the efficacy of Movicol was greater than the efficacy of lactulose. This information did not appear in the Attar *et al* publication. The Panel noted Norgine's submission in point 2 below that the authors of Christie *et al* had access to the original Attar *et al* study data.

The Christie *et al* pharmacoeconomic model assumed that patients up to the age of 65 who received lactulose in part A would have the same outcomes as the over 65 year old lactulose-treated patients had they continued to receive lactulose during part B of the study. The pharmacokinetic model considered that a patient was successfully treated if their evacuation score in the study was ≤ 1 and their daily stool frequency was ≥ 1. The clinical effectiveness of Movicol and lactulose was thus calculated as the proportion of patients successfully treated at 3 months. The discussion section stated that the clinical justification for combining these two efficacy outcomes came from the inclusion criteria of Attar *et al* and because a judgement was made as to what degree of improvement in these combined criteria would be of real clinical significance.

The Christie study authors noted its limitations. Most resource utilisation estimates were based on expert opinion rather than published data. Sensitivity analyses showed that the model was mainly sensitive to parameters pertaining to treatment that were derived from Attar *et al* and not to resource use data that was obtained from interviews with the physicians and nurses. The model assumed that the effectiveness of lactulose in patients aged 65 or less would be the same as patients over 65 years. Moreover the effectiveness measure used to calculate successful resolution of constipation might have been too restrictive and this would have underestimated the proportion of patients with successful resolution of their constipation. This would apply to both Movicol and lactulose and should thus not influence their relative cost effectiveness. Furthermore as the study was based on a controlled clinical trial it might not reflect clinical practice with regard to probability of successful treatment and probability of switching laxatives, particularly amongst patients being managed in the community by their GP. The model only considered direct healthcare costs, not direct costs borne by patients or indirect costs borne by society.

The Panel noted that it was not stated in either the detail aid or the leavepiece that claims referenced to Christie *et al* were based on a pharmacoeconomic modelling study. A footnote on page 3 of the detail aid, subheaded 'The economics of treating idiopathic chronic constipation' referred to 'Expected 3 monthly NHS cost per patient …'. Subsequent claims referred to savings on the total NHS treatment cost. However the Panel considered that this was inadequate. The Panel noted the limitations of the Christie data as discussed by the authors, in particular that it might not reflect clinical practice. The Panel noted Norgine's submission in this regard. In the Panel's view the reader would assume that claims and statements referenced to Christie *et al* were based wholly on clinical trial results and that was not so. A breach of Clause 7.2 was ruled.

2 Claim 'Over twice as many patients were successfully treated with Movicol than with lactulose'

This claim appeared on page 2 of the detail aid

beneath a bar chart headed 'Clinical effectiveness' which compared the percentage probability of being successfully treated after 3 months with Movicol (53%) or with lactulose (24%) p=0.001.

COMPLAINT

Reckitt Benckiser Healthcare noted that the claim was based on Christie *et al*. The key outcome measure used for the economic model was a combination of an evacuation score of ≤ 1 and a daily stool frequency of ≥ 1 at 3 months. Christie *et al* argued that this combined measure should relate to 3-month data. However Attar *et al* was not a 3 month study; the extension to the second and third months was not fully randomised and was reported only as a 'follow-up' with considerably less detail than that reported for the first month.

The percentage probabilities in Christie *et al* were based on a panel estimate rather than actual data. In order to arrive at this estimate, having made a general assumption regarding the usage of lactulose in younger patients, it would have been necessary for the panel to estimate outcomes firstly for the 2 month time point and then for the three month time point. Therefore not only was the data based on assumptions, but on three consecutive and therefore potentially compounding assumptions.

As stated above, Christie *et al* admitted that the effectiveness measure used to calculate successful resolution of constipation in their model might be 'too restrictive', and the probabilities used might not reflect clinical practice. These were important qualifications.

Reckitt Benckiser Healthcare alleged that the graph and subsequent claim were potentially misleading, in breach of Clause 7.2.

RESPONSE

Norgine stated that the figures relating to the criteria for successful treatment (lactulose 24% vs Movicol 53%) were not obtained from a panel estimate or any other assumption but from the results obtained in the study. The company responsible for conducting the economic analysis on Norgine's behalf was supplied with the original patient data obtained by Attar *et al* and conducted this combined efficacy analysis itself using this original patient data.

It was decided not to use just stool frequency or just ease of evacuation as the criterion of a successful result as the data was reported in the original trial. It was decided to combine these two outcome measures to produce a measurement of efficacy that was more likely to mirror the real situation where, from an individual patient's perspective, success would be defined as both a daily bowel movement and easy evacuation. This point was covered in the Christie *et al* paper where it was stated:

'In our model, the outcome of clinical effectiveness was defined as the proportion of patients in the study by Attar *et al* who had an evacuation score ≤ 1and a daily stool frequency ≥ 1 at 3 months. The clinical justification for combining these two efficacy outcomes comes firstly from the trial's criteria, in that patients who were recruited into the study could have had either or both infrequent stools and difficult evacuation. The breakdown of symptoms among the trial population at admission was: <3 stools per week (43%), difficult evacuation (12%) and both of the above (45%). Efficacy in the trial was judged both on stool frequency and difficulty of evacuation with both variables being analysed separately. Accordingly, such an analysis would have obscured those patients (if there were any) who may have had an improvement in one outcome, but a worsening of the other. For example, it is possible that patients may have had easier evacuation but were still only passing stools less than 3 times a week. It was therefore considered that the most robust measure of the overall effectiveness of the two laxatives was an improvement in both efficacy variables. Secondly, a judgement as to what degree of improvement in these combined criteria would be of real clinical significance was made and we judged that most patients would consider one bowel movement a day to be the ideal norm; so we therefore set the criteria for stool frequency to be at least one a day. For ease of evacuation, we considered that every patient would want evacuation to be easy. Therefore by combining the two efficacy variables we aimed to produce a rigorous measure of the clinical effectiveness of the two laxatives.'

This combined measurement was therefore a very rigorous measurement of efficacy which would be an underestimate of efficacy but it would apply to both products equally so would not be misleading in biasing towards one product or another.

Norgine stated that Reckitt Benckiser Healthcare's statement that…'Christie *et al* admitted that their effectiveness measure used to calculate successful resolution of constipation in their model might be too restrictive' was based on a very selective quotation from the publication; the quotation in full referred to the point regarding the 'restrictive' or 'rigorous' combined efficacy score as referred to above. It did not mean that the results were not more broadly applicable and therefore potentially misleading. It meant that the use of a very strict criterion of successful treatment might have underestimated efficacy, but this would apply equally to both products as the efficacy measure was applied to both products. Therefore, relatively, the outcome would not be different.

Norgine noted the full quotation from the publication which emphasised the point made above:

'Moreover, the effectiveness measure used to calculate successful resolution of constipation may have been too restrictive, and this would have underestimated the proportion of patients with successful resolution of their constipation. Nevertheless this would apply equally to both [Movicol] and lactulose and therefore should not affect the assessment of their relative cost effectiveness.'

Norgine noted that Reckitt Benckiser Healthcare had questioned the appropriateness of this model for a general practice setting. In point 1 above the company had stated that the data on which the model

was based might not reflect actual clinical practice; in point 2 that the probabilities used might not reflect clinical practice and in point 4 that the data behind these claims was based on assumptions that did not reflect clinical practice.

Norgine stated that it would deal with these essentially similar complaints here rather than reiterating the argument for each in turn.

These complaints all seemed to have as their basis the following quotation from the publication: 'Furthermore, the study was based on a controlled clinical trial and, as such, may not reflect clinical practice with regard to probability of successful treatment and probability of switching laxatives, particularly among patients managed in the community by their GP'.

The allegation seemed in essence to be that these were qualifications that might limit the applicability of the study to a wider spectrum of patients than those actually studied in the trial, and that this fact might make the use of this study in promotional material misleading.

Norgine referred to its comments at point 1 about whether results based on a controlled clinical trial were applicable to general practice.

Norgine noted that a comparative clinical study gave information about the difference between two products in treating a symptom or disease. If this relative difference was maintained across different clinical situations then it was reasonable to extrapolate the comparison. For example, morphine was relatively more effective as an analgesic than paracetamol, irrespective of the cause of the pain.

PANEL RULING

The Panel considered that both its comments and rulings at point 1 about the Christie and Attar studies were relevant here.

The Panel noted that the Attar publication included comparative data for only 4 weeks; upon completion of the 4 week protocol all patients from the Movicol arm of the study and those aged less than 65 years of age from the lactulose arm of the study were given the opportunity to take Movicol for two additional months to evaluate the long-term efficacy and safety of the treatment. Patients aged over 65 who were originally on lactulose stayed on lactulose. Christie *et al* stated that there was a comparative phase of Attar during weeks 4 to 12 but this included only patients over 65. It was assumed that the efficacy of lactulose in this older population would apply to patients aged 65 or less. Components of the measure of successful treatment as defined by Christie were not available in the published Attar paper. The Panel noted Norgine's submission that the Christie *et al* authors had access to the original trial data in Attar *et al*.

The Panel considered that inadequate information was available to substantiate the claim for successful treatment as large amounts of data used were not published in Attar *et al*. Assumptions had been made about the extrapolation of efficacy from one patient group to another. The data was presented beneath a heading 'Clinical effectiveness' which suggested that it was derived wholly from clinical trial data which had compared the products over a 3 month period and that was not so. Insufficient information about Christie *et al* had been provided such that the graph and claim at issue gave a misleading impression about the nature of the efficacy data and the products' relative efficacy. A breach of Clause 7.2 was ruled.

3 Claims 'Movicol saves time vs lactulose' and 'Potential reduction in consultations'

These claims appeared as a heading and subheading, respectively on page 2 of the detail aid. Beneath the claim 'Potential reduction in consultations' a bar chart based on Christie *et al* showed the potential reduction in the number of GP consultations in a 3 month period against the number of patients with idiopathic constipation managed by a GP. Beneath the bar chart was the claim 'If you treat 20 patients with Movicol instead of lactulose, you could potentially save 30 consultations over three months'.

COMPLAINT

Reckitt Benckiser Healthcare noted that one additional GP visit was assumed for each patient who discontinued. As with all the resources modelled, additional GP visits were assumed based on panel estimates, not on observation. It had already been stated that the estimates did not necessarily reflect clinical practice. If this were 1.5 or 2 visits the results would not be so favourable for Movicol.

Reckitt Benckiser Healthcare noted that according to Christie *et al* 11.6% of Movicol patients discontinued treatment in the first month due to adverse events, lack of efficacy and non-compliance compared to only 3.6% of patients on lactulose. Even comparing the two groups with regard to non-compliance, Movicol was substantially worse than lactulose (6.6% versus 3.6%). Discontinuation only moved in favour of Movicol in the second month when 39.4% of patients on it discontinued treatment compared with 51.9% in the lactulose treatment group.

Taking these points into account, the graph and subsequent claim were potentially misleading and therefore in breach of Clause 7.2.

RESPONSE

Norgine stated that this complaint was confusing and it was not clear what points were being made with regard to discontinuation rates at 1 month, and how this might be seen to be a breach of the Code.

The first point to make was that this model was constructed by the authors as a 3 month model, not a 1 month model, therefore discontinuation rates at 1 month were irrelevant.

For the avoidance of doubt, the actual discontinuation rates at 3 months were 28.2% for Movicol and 38.1% for lactulose.

The second point here seemed to be a recycling of the general point that GP visits in the model were based on assumptions not actual data, and thus might not

reflect actual clinical practice. This point was covered in the response to points 1 and 2 above.

PANEL RULING

The Panel noted its comments at point 1 regarding the derivation of the healthcare resource utilisation and clinical data in Christie *et al*. The pharmacoeconomic model incorporated estimates of resource utilisation in relation to, *inter alia*, the number of GP consultations dependent on whether and when the patient experienced successful resolution of their constipation symptoms, discontinuation due to non-compliance or lack of efficacy and adverse events. With regard to efficacy the Panel noted its comments in point 2 above. The efficacy of lactulose in months 2 to 3 in the under 65s had been assumed to be the same as that observed in patients aged over 65. The pharmacoeconomic data indicated that the number of GP consultations was the primary cost driver. The discussion section in Christie *et al* stated that if GPs used Movicol rather than lactulose they could potentially have 30 fewer visits if they managed 20 patients.

The Panel considered that a reader would assume that the potential reduction in consultations and time saved was based upon actual observation rather than a pharmacoeconomic model based on subjective estimates derived from interview and assumptions that efficacy of lactulose in one group of patients could be extrapolated to them all. The Panel considered that the claims were misleading in this regard. A breach of Clause 7.2 was ruled.

4 Page headed 'Movicol saves money vs lactulose'

This claim appeared as a heading on page 3 of the detail aid which was based on Christie *et al* and featured a bar chart setting out the various components of the NHS cost associated with treating idiopathic chronic constipation with Movicol or lactulose over a 3 month period. A subsequent bullet point read 'Movicol was twice as effective as lactulose' and 'Patients taking Movicol make fewer visits to their GP than those taking lactulose'.

COMPLAINT

Reckitt Benckiser Healthcare stated that the page reiterated and relied upon the claims that Movicol was twice as effective as lactulose and that patients taking Movicol made fewer visits to their GP. However, as discussed previously, the data behind these claims was based on assumptions that did not reflect clinical practice and were therefore potentially flawed. Reckitt Benckiser Healthcare alleged that the overall comparison of NHS costs might itself be misleading in breach of Clause 7.2 of the Code.

RESPONSE

Norgine noted that this point seemed to be a repeat of the allegations made in points 1 and 2 regarding the validity of pharmacoeconomic modelling data, and its application to actual clinical practice. The company referred to its responses under points 1 and 2 above.

PANEL RULING

The Panel considered that its general comments about Christie *et al* at point 1 were relevant here. The Panel also noted its ruling at point 2. Insufficient information had been provided to place the claim 'Movicol was twice as effective as lactulose' in context; readers would also assume that it related wholly to clinical data collected over a 3 month period. This was not so. The claim was thus misleading and the Panel ruled a breach of Clause 7.2 in that regard.

In relation to the claim 'Patients taking Movicol make fewer visits to their GP than those taking lactulose' the Panel considered that its ruling at point 3 was relevant here and ruled a breach of Clause 7.2 in that regard.

5 Alleged breach of Clause 2

COMPLAINT

Reckitt Benckiser Healthcare noted that the data and claims presented on pages 2 and 3 of the detail aid were dependent on Christie *et al*. However, as discussed in the various points above, Norgine's use of this study presented a potentially misleading picture of outcomes and resource utilisation for lactulose and Movicol-treated patients. At no point was the fact that the data was driven in large part by assumptions rather than actual observed data noted. The claims made on these pages were therefore at best misleading and at worst could bring the industry into disrepute as the use of this material might discredit and reduce confidence in the pharmaceutical industry. Reckitt Benckiser Healthcare alleged a breach of Clause 2 of the Code.

RESPONSE

Norgine noted that Clause 2 of the Code was reserved for those promotional activities that brought discredit upon, or reduced confidence in, the pharmaceutical industry. Even if it were judged that some of the comparative claims for Movicol against lactulose based on the Christie *et al* study were misleading (which of course Norgine strongly contested), it considered that it was totally out of proportion to suggest that these breaches were of a sufficiently serious nature as to attract the particular censure that a breach of Clause 2 implied.

PANEL RULING

The Panel noted that Clause 2 was used to indicate particular censure and was reserved for such use. Notwithstanding its rulings on the data presented on pages 2 and 3 of the detail aid the Panel did not consider that the material was such as to warrant a ruling of a breach of Clause 2; no breach of that clause was ruled.

6 Maintenance use

COMPLAINT

Reckitt Benckiser Healthcare noted pages 4, 5 and 10 of the detail aid and pages 1 and 2 of the leavepiece

referred to maintenance use of Movicol. Whilst this was listed in the prescribing information in both the detail aid and the leavepiece, it was not supported in the currently published SPC. The SPC merely talked about extended use in certain patient groups. Reckitt Benckiser Healthcare contended that maintenance had a different connotation to extended use and that this claim was therefore in breach of Clause 3.2 of the Code.

RESPONSE

Norgine stated that the licence for the extended use of Movicol in certain patient groups was granted in the UK on 7 March 2002, on the basis of substantial clinical data on several thousand patients treated for up to 2 years, which showed that Movicol was safe and effective for long-term use.

For patients who suffered from conditions like Parkinson's disease or multiple sclerosis, as well as those who were on long-term treatment with medicines which caused constipation, it was important that they were maintained on continuous laxative treatment for as long as was needed. In many cases this might mean life long.

Norgine noted that the issue of the long-term use of Movicol had been the subject of Case AUTH/1290/3/02.

In view of the fact that long-term maintenance of these patients was what actually happened in practice and the use of this term was clearly understood by prescribers, Norgine asserted that the use of the word 'maintenance' was fully compatible with the wording of the SPC where it referred to 'extended use'. Patients were maintained in control of their constipation by the extended use of Movicol over the long-term.

PANEL RULING

The Panel noted that Section 4.2 of the Movicol SPC stated that 'As for all laxatives prolonged use was not usually recommended'. It continued 'Extended use may be necessary in the care of patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's Disease, or induced by regular constipating medicine, in particular opioids and antimuscarinics'.

The Panel noted that in Case AUTH/1290/3/02 it was ruled that, in the context of a letter to a health professional, a three month treatment period was not inconsistent with the SPC which at the relevant time did not include the indication for extended use.

The Panel considered that maintenance implied continued treatment without defined duration and extended use might also cover treatment continued for a significant period of time. On balance the Panel did not consider that use of the word 'maintenance' was in itself necessarily inconsistent with the SPC. The Panel noted that the revised versions of the detail aid (ref MO/02/0157 (8119687)) and leavepiece (ref MO/02/0159 (8119695)) had replaced 'maintenance' with 'long-term use'.

The Panel noted that pages 4 and 5 of the detail aid at issue described those patient populations in whom extended use might be necessary, according to the SPC. The Panel did not consider the reference to 'maintenance use' on pages 4 and 5 of the detail aid to be inconsistent with the SPC in this regard; no breach of Clause 3.2 was ruled. Page 10 of the detail aid and the front side of the leavepiece each referred to 'Maintenance dosage of 1 or 2 sachets per day' but neither gave any information on the patient groups for whom such usage was mentioned in the SPC and were thus inconsistent with the SPC in this regard. A breach of Clause 3.2 was ruled in respect of each item.

7 Claim '90% efficacy*'

This claim appeared on page 5 of the detail aid headed 'Movicol is now licensed for maintenance use' beneath a list of patient groups in whom it was claimed Movicol was highly effective; patients taking anti-depressants or other drugs (n=296), cancer patients (n=24) and Parkinson's disease (n=20). The asterisk led the reader to a footnote which read 'Overall, over 90% of the doctors rated the efficacy of Movicol as 'good' or 'very good''.

COMPLAINT

Reckitt Benckiser Healthcare stated that despite the footnote which was extremely small in comparison to the claim, readers might be misled into believing that the 90% efficacy was based on a direct measurement of efficacy. In addition, the detail aid gave the impression that each of the subgroups demonstrated 90% efficacy in Gruss and Teucher (1999) on which this data was based. However, the paper did not give a breakdown of the number of patients on constipating drugs or with neurological illness who completed the trial successfully. It was not therefore possible to make the 90% efficacy claim for all subgroups based on this data. Reckitt Benckiser Healthcare alleged that the claim was in breach of Clause 7.2 of the Code.

RESPONSE

With regard to the allegation that readers might form the impression that the figure was based on a direct measurement of efficacy, Norgine stated that there was no established 'direct' or 'hard' measurement of efficacy in clinical trials of laxatives in contrast to say hypertension where direct measurement of blood pressure provided a hard endpoint. Endpoints like weekly frequency of bowel movements, assessment of stool form, rating scales for difficulty of evacuation, straining, and hardness of stools had all been used in clinical trials of laxatives, as had investigators' and patients' overall assessment of efficacy and tolerability.

In the absence of any established 'direct' measurement of efficacy, it was perfectly legitimate to quote the result of this study in terms of the investigators' overall assessment of efficacy. The fact that this figure referred to the percentage of doctors involved in the study who rated the efficacy of Movicol as 'good' or 'very good' was clearly noted below the claim. Norgine did not agree that this footnote was extremely small and stated that it was perfectly legible.

The validity of this measurement of efficacy was supported by the measurement of percentage of patients with 3 or more bowel movements per week at 4 weeks (ie not constipated) which also came out at 90% in Gruss and Teucher.

Norgine submitted that the claim of 90% efficacy could be substantiated. The study incorporated a sub-group analysis in the original study report, which would have been provided to Reckitt Benckiser Healthcare if the company had asked for it; a copy of the relevant sections from the study report was provided.

The sub-group analysis showed the efficacy rating by the investigators was as follows: anti-depressants 91%, morphine 96% and Parkinson's disease 89%.

Norgine therefore submitted that in the light of these results the claim was correct and could be substantiated.

In addition the claim of 90% efficacy was further qualified on the page in question by noting the claim was also consistent with the results that were obtained overall for all patients in the study.

The results of the overall rating of efficacy for all patients in the study was 92% which again Norgine believed to be consistent with the claim 'Overall, over 90% of the doctors rated the efficacy of Movicol as 'good' or 'very good''.

PANEL RULING

The Panel considered that the design of the page was such that the reader's eye was drawn from the emboldened subheading 'Movicol is highly effective in:', to the claim '90% efficacy*' which appeared beneath, towards the bottom of the page in a slightly larger emboldened different typeface.

The Panel considered that the majority of the readers would gain the impression that the claim related to a clinical measurement of efficacy and that was not so. The footnote was insufficient to negate this impression. The claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that Gruss and Teucher stated that normal stool frequency (> 3 per week) was achieved in 90% of the patients included within a four week observation period. Efficacy was ranked 'as 'very good' to 'good' by 90% (patients) and 92% (doctor) of mentions'. The data on file provided an analysis of sub-groups and demonstrated that the doctor assessment of the percentage of patients whose condition was 'normalised' or 'clearly improved' in each sub-group was: anti-depressants 91%, morphine 96% and Parkinson's disease 89%. The patient numbers in the last two groups were small, 24 and 20 respectively, but were stated on the piece at issue.

The Panel considered that the juxtaposition of the claim '90% efficacy' and the preceding sub-groups created the impression that 90% efficacy was achieved in each patient population mentioned and that was not an accurate reflection of Gruss and Teucher and the data on file. In addition the Panel queried whether data based on small patient groups could in any event give an accurate assessment of percentage efficacy. The Panel considered that the claim for 90% efficacy was also misleading on this point and a further breach of Clause 7.2 was ruled.

8 Claim '… Movicol guarantees a neutral water and electrolyte balance which increases the safety level especially with repeated use or in patients at risk'

COMPLAINT

Reckitt Benckiser Healthcare noted this claim on page 8 of the detail aid appeared in the form of a quotation from Gruss and Teucher (1999). Quotations must still comply with the Code. Such an implied guarantee was alleged to be in breach of Clause 7.10 which stated that exaggerated or all-embracing claims must not be made and superlatives must not be used except where they related to a clear fact about a medicine.

RESPONSE

Norgine stated that the claim was not misleading as polyethylene glycol plus electrolytes (PEG+E) bowel lavage agents and laxatives (like Movicol) had a unique mode of action not shared by other classes of bowel lavage agents or laxatives.

Inorganic osmotic laxatives (eg sodium phosphate, magnesium hydroxide) and organic osmotic laxatives (eg lactulose) acted by setting up a high osmotic pressure in the lumen of the large bowel. By this osmotic effect water was drawn in from the body which had the effect of bulking the stools, which stimulated peristaltic activity and resulted in laxative action. The water that was drawn in from the body carried with it accompanying electrolytes with the result that removal of a quantity of water with its accompanying electrolyte content was an inherent part of the mode of action of inorganic and organic laxatives.

PEG+E bowel lavage agents and laxatives like Movicol acted in a fundamentally different way. With these products the dose was mixed with a precise volume of water (125ml for each sachet of Movicol) which formed a solution that was in osmotic balance with the extracellular fluid outside the lumen of the large bowel. This resulted in the measure of water in the dose (125ml per sachet) being delivered to the bowel to bulk the faeces and stimulate peristalsis, without the need for this water (with accompanying electrolytes) to be extracted from the total body fluid. This unique mode of action guaranteed that the fluid and electrolyte balance in the body was maintained, which would increase the safety of a laxative especially if used in patients at risk from fluid and electrolyte depletion. The formulation of Movicol could therefore be said to have a special property in its mode of action that was not shared by other laxatives.

In addition, Norgine noted that this claim did not directly refer to Movicol in any way 'guaranteeing' safety. It simply stated the fact that eliminating the loss of body fluid and electrolytes increased the safety of the product. It did not claim a guarantee of absolute safety.

PANEL RULING

The Panel noted that Section 5.1 of the Movicol SPC stated that 'The electrolytes also present in the formulation ensure that there is virtually no net gain or loss of sodium, potassium or water'. Section 4.4 Special Warnings and Precautions for Use stated 'If patients develop any symptoms indicating shifts of fluid/electrolytes (eg oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Movicol should be stopped immediately and electrolytes measured, and any abnormality should be treated appropriately'. The Panel considered that 'guarantee' was an absolute term, stronger than 'virtually no' in the SPC and inconsistent with the SPC warning (Section 4.4). The Panel considered it an exaggerated claim as alleged and ruled a breach of Clause 7.10 of the Code.

During its consideration of this point the Panel noted the use of the phrase '… increases the safety level …' and that Clause 7.9 of the Code stated, *inter alia*, that the word 'safe' must not be used without qualification. The supplementary information to Clause 7.9 stated that the restrictions applied equally to grammatical derivations of the word safe such as safety. Although 'safety' had been used in this instance the Panel nonetheless considered that it should have been qualified; it was not and the Panel requested that Norgine be advised of its concerns in this regard.

9 Claim 'Movicol efficacy increases with dosage'

This claim appeared on page 9 of the detail aid beneath the main heading 'Movicol dose related response' and above a graph which demonstrated a linear relationship between the weight of faeces per 24 hours and the amount of Macrogol ingested. Subsequent claims made reference to the dose of Movicol to be used in constipation or faecal impaction.

COMPLAINT

Reckitt Benckiser Healthcare stated that the claim, based on Hammer *et al* (1989), implied that Movicol would be more effective in the treatment of constipation as the amount ingested per 24 hours increased. Hammer *et al* only looked at stool weight in healthy volunteers treated with PEG 3350 plus electrolytes to induce diarrhoea. No measurements of efficacy in the treatment of constipation were made. This claim was misleading as it was based on data from an extremely small sample of healthy volunteers (n=3) taking doses of up to 6 times the maximum daily dose recommended on the SPC. Reckitt Benckiser Healthcare considered that such data could not reliably be extrapolated to efficacy in the treatment of patients with constipation and alleged that the claim was in breach of Clause 7.2 of the Code.

RESPONSE

Norgine stated that PEG plus electrolyte solutions exhibited a linear dose-response relationship, which was clearly demonstrated by the work of Hammer *et al*. The effect on faecal water flow was directly proportional to the amount of PEG plus electrolyte solution administered, which meant that the effect of this type of product increased with increased dose. Conversely all other classes of laxatives (fibre products, stimulants, osmotics and faecal lubricants) had a ceiling of action above which increasing dosage gave little or no further effect. The result of this was seen in the licensed indications for Movicol which included high-dose use at a dose of 1 litre of solution per day for 3 days to treat faecal impaction, which was the most severe form of constipation seen. Movicol was unique in being the only orally administered product licensed for the treatment of faecal impaction. This gave strong support to the fact that its effect increased in direct proportion to the dose.

It was common practice for dose response relationships for a medicine to be shown in a graphical manner as in the detail aid. The data was usually obtained from dose response studies commonly conducted in healthy volunteers (often in small numbers) as well as in patients. It was not possible in reporting this type of data to confine the results to the licensed dose of a product, as that might be only a single daily dose (eg 5mg daily) or there might be two licensed doses (eg 5mg or 10mg daily). Dose response studies by definition reported the response over a range of doses, so it was usual for this range to include doses significantly higher and/or significantly lower than the final licensed doses as stated in the SPC.

The purpose of the graph was to show a specific response over a given range of doses. The dose was not expressed as the number of sachets of Movicol. It was expressed as grams of macrogol 3350 ingested over a 24 hour period. Therefore, the graph did not directly link the dose in terms of number of sachets of Movicol taken with the efficacy to be expected.

Norgine noted that Reckitt Benckiser Healthcare had stated that the maximum dose used in this study was up to 6 times the maximum daily dose of Movicol as stated in the SPC. This was not so. The maximum licensed dose of Movicol was 8 sachets daily for up to 3 days in the treatment of faecal impaction. This gave a total daily dose of macrogol 3350 of 104.8g per day, ie just under half the maximum dose (250g) used in the dose ranging study and not one sixth.

PANEL RULING

The Panel noted that Hammer *et al* assessed stool weight in healthy volunteers. The claim at issue appeared beneath the heading 'Movicol dose related response'. The supplementary information to Clause 7.2 on 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 in the clinical situation should only be made where there is data to show it is of direct relevance and significance'.

The Panel considered that it had not been made clear that the Hammer *et al* study had been conducted in healthy volunteers; readers would assume that the data was based on a study in patients and that was no so. In that regard the Panel noted that the claim

referred to 'efficacy' which further implied a clinical context. The Panel considered that the claim was thus misleading and ruled a breach of Clause 7.2 of the Code.

In relation to the allegation that such data could not be extrapolated to the clinical situation the Panel noted Norgine's submission that by demonstrating that faecal water flow was directly proportional to the amount of macrogol administered these data were relevant to the clinical situation. The Panel noted that the licensed dose for Movicol in the treatment of chronic constipation was 1-3 sachets (13.8g/sachet) daily and for faecal impaction, 8 sachets per day. It appeared that increasing doses of Movicol were thus used for increasing effect. The Panel noted Norgine's submission that other laxatives had optimal doses above which the dose response curve was flat. On balance the Panel considered that the data was relevant to the clinical situation and so was not misleading on this narrow point. No breach of Clause 7.2 was ruled.

10 Claim '30% price reduction'

COMPLAINT

Reckitt Benckiser Healthcare noted that the claim of 30% price reduction on pages 1 and 10 of the detail aid and 1 of the leavepiece was certainly relevant at the time the items were produced. However, it might be construed that by the continuing use of this claim 6 months after the price reduction, the historical significance of it was lost. Indeed the Code of Practice for Traders on Price Indications issued by the Department of Trade and Industry (DTI) stated that the previous price should be the last price at which the product was available in the previous 6 months and it should have been available to consumers at that price for at least 28 consecutive days in the previous 6 months. If these conditions were not met a clear and positive explanation of the circumstances must be given. The explanation must be given clearly and as prominently as the price indication. The continued use of this claim today did not comply with this Code and might mislead prescribers into believing that a further price reduction had taken place despite the use of a very small footnote to the effect that the reduction was actually in February of this year. Reckitt Benckiser Healthcare alleged that the claim was in breach of Clause 7.2.

RESPONSE

Norgine stated the first mention of this price reduction was in MIMS and Chemist and Druggist in early February 2002. The detail aid and leavepiece in question were first issued on 22 April 2002, and these items were replaced by new items on 9 September 2002. These new items contained no statement about a price reduction. The claim regarding a 30% price reduction was therefore made for a total of 7 months after the price reduction came into effect.

Norgine noted that the claim '30% price reduction' was clearly referenced by the date that the price reduction was made, namely February 2002. Norgine, therefore, did not accept that the claim could mislead in suggesting that a further price reduction had taken place. It was important to publicise this significant price reduction and it was always Norgine's intention to cease to use this claim in September 2002.

Norgine did not believe that the Code of Practice for Traders on Price Indications as issued by the DTI was relevant to this issue. This code of practice was intended for retail outlets that advertised price reductions on individual goods to the general public; it was not intended to apply to the promotion of pharmaceuticals to health professionals.

The ABPI Code did not contain any specific guidance as to what would be the maximum time over which it would be acceptable to advertise a price reduction of a medicine. In respect of the duration of time that any specific claim could be made, the only reference in the Code was in how long a claim of 'new' could be made for a product or for an indication for an existing product. In this case 12 months was the maximum permissible time for which a claim of 'new' could be made. The definition of 'new' did not just refer to a new product but might include, for example, a new pharmaceutical presentation of an existing product which, in some cases, might be a relatively small change. Bearing this in mind, Norgine submitted that a 30% price reduction was a relatively significant change, and to advertise this significant change for a period of 7 months was not unreasonable, especially as it was made clear in a footnote to the claim the date on which the price reduction occurred.

PANEL RULING

The Panel noted that an asterisk adjacent to the claim referred the reader to a footnote which read 'Price reduction 01/02/2002'. The date of preparation of both the detail aid and leavepiece was March 2002. The materials were replaced in September and thus the pieces claimed a price reduction for seven months after it had occurred. The Panel considered, on balance, that this was not unreasonable and the detail aid and leavepiece were not misleading in this regard. The Panel ruled no breach of Clause 7.2 of the Code.

11 Claim 'Over twice as effective as lactulose at a lower total NHS cost'

COMPLAINT

This claim appeared on page 10 of the detail aid and page 1 of the leavepiece. Not only was the use of the data from Christie *et al* in this way potentially misleading as discussed previously, but also it might be taken to imply that the actual NHS cost of Movicol was lower than lactulose. This was not the case. Movicol cost the NHS approximately 50 pence per day based on 2 sachets daily; branded lactulose cost approximately 21 to 28 pence per day based on 15ml twice daily. Reckitt Benckiser Healthcare alleged that the claim was therefore misleading, in breach of Clause 7.2 of the Code.

RESPONSE

Norgine contended that the claim was quite clear in its scope as it stated total NHS cost. This was

different to the NHS price, which was the cost price of an individual product that was quoted in publications like MIMS. The phrase 'total NHS cost' was synonymous with 'total cost to the NHS' and the company believed this would be quite clear to recipients of the leavepiece, who would be in no doubt what was meant by 'total NHS cost' as compared to 'NHS price'.

The total cost to the NHS included all resources used, like GP consultations, special tests, referrals etc, and this was made clear in page 2 of the detail aid where the individual contributions to the total NHS cost of treating the patients in both groups were clearly listed.

To date Norgine had not encountered a prescriber who was in any way confused by this statement.

PANEL RULING

The Panel noted that the items were targeted at GPs, community nurses and hospital doctors. The Panel queried whether, given the intended audience, the meaning of the phrase 'total NHS cost' had been made sufficiently clear.

Information about the components of NHS costs appeared on page 3 of the detail aid. However, the claim at issue appeared on the final page of the detail aid. No information about the various components of NHS costs was provided on the leavepiece. It could not be assumed that all recipients would be aware of the difference between 'total NHS cost' and 'actual NHS price'. This potential confusion was compounded in both the detail aid and the leavepiece by two preceding claims which related to NHS price; '30% price reduction' and 'from 25p per day'. The Panel considered that given the audience the reference to total NHS cost, without further explanation, was not sufficiently clear and was misleading in this regard. A breach of Clause 7.2 of the Code was ruled in respect of each item.

Complaint received **16 September 2002**

Case completed **17 January 2003**

CASE AUTH/1360/9/02

ANONYMOUS DOCTOR v AVENTIS PHARMA

Hospitality at meetings

An anonymous complaint was received about two meetings arranged by Aventis Pharma for a hospital dermatology unit. While the occasional evening out with good food was acceptable, the complainant felt as if (s)he was expected in return to use Aventis' products as a thank you!

The first meeting in question was an evening out in December 2001 at a Chinese restaurant where the wine 'flowed like water,' according to one of the nurses who attended. Then recently, in June, the department was again taken to a public restaurant, with no educational content and at the same level of hospitality. While other companies did this, the events were rarer and instruction was given either prior or after the event. The activity of Aventis, in the complainant's view, seemed out of proportion ie just a booze up.

The Panel noted Aventis' submission that at each event it was invited to join the departmental meeting. The departmental consultant delegated responsibility for the meeting to the nurse administrator; the provision of formal agendas and invitations was not standard practice. It was unclear which party had chosen the venues. The refreshments were paid for by the company. It was beholden upon the company to ensure that the overall arrangements, including the venue, complied with the Code.

The Panel considered that the first meeting had limited educational content; there was no formal presentation, the representative stated that he moved around the table and had individual conversations with each attendee. The Panel did not accept that the nature of the meeting justified the associated hospitality. In the Panel's view, the meeting was inappropriate as it consisted of discussions in a public restaurant and the hospitality was not secondary to the main purpose of the meeting. The Panel queried whether the cost exceeded the level that the recipients would adopt if paying for themselves. A breach of the Code was ruled. The Panel considered that high standards had not been maintained and a further breach of the Code was ruled.

The Panel noted that Clause 2 was used as a sign of particular censure. The Panel considered that the meeting brought discredit upon the pharmaceutical industry and ruled a breach of Clause 2.

The Panel noted that the representative had been asked by the departmental sister, at the last minute, not to proceed with the educational part of the second meeting as one of the attendees had been recently diagnosed with a serious illness and colleagues thought it was best to have a 'light' evening. The Panel appreciated that this had put the representative into a difficult position. From the representative's report, however, it appeared that a presentation on Telfast and Tritace was planned, although the representative's report referred to the first meeting with regard to the agenda structure and formality. The second meeting was to be held in a public restaurant and it appeared that the presentation would have also taken place there. In

the Panel's view the arrangements for the second meeting were little different to those for the first. The Panel considered, therefore, that its rulings above with regard to the first meeting also applied to the prior arrangements for the second. Breaches of the Code including a breach of Clause 2 were ruled. In the circumstances the Panel made no ruling as to what had actually happened at the second meeting.

An anonymous complaint was received about meetings arranged by Aventis Pharma Ltd. The heading to the letter referred to a hospital dermatology unit.

COMPLAINT

The letter of complaint stated that it was written anonymously to protect the complainant from any uncomfortable rebuffs from work colleagues about the company's activities in the hospital.

While the occasional evening out with good food was very acceptable the complainant was concerned over Aventis' activity in this area. It almost felt that the complainant was expected in return to use its products as a thank you!

The specific instances consisted first of an evening out in December 2001 at a Chinese restaurant where the wine 'flowed like water,' according to one of the nurses who attended. Then recently, in June, the department was again taken out to the same type of event, to a public restaurant, with no educational content and at the same level of hospitality.

While other companies did this, the events were rarer and instruction was given either prior or after the event. The activity of Aventis, in the complainant's judgement as a doctor, seemed out of proportion ie just a booze up.

The complainant had thought long and hard before writing to the Authority, but did not want this becoming a potential hazard.

When writing to Aventis Pharma the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Aventis stated that it appeared that its representative followed the procedure in place at the time for educational meetings within the dermatology department. Specifically in the second meeting the representative faced a dilemma when requested, at the start of the evening, not to make the educational presentation he was intending. He then made a judgement call at that time to continue with the meeting given the sensitive nature of the circumstances related to the meeting.

Aventis interviewed the representative concerned and his manager and provided their report of the circumstances relating to both meetings. The report stated that the first meeting took place on 20 December 2001 at a named restaurant and was organised by the departmental nurse administrator. No formal invitation was sent by Aventis, it was invited to join the departmental meeting to present and then discuss its latest data and information on Telfast (fexofenadine). In spite of the fact that Telfast had been marketed in the UK for several years the dermatology unit did not have it on its formulary for the treatment of urticaria. It was standard practice at the hospital for representatives to discuss matters with the consultant and for him to delegate responsibility for the meeting to his nurse administrator. The construction and issuing of formal agendas and invitations was not standard practice within the department. No formal agenda was produced. At 7.30pm everyone met at the venue. The meeting finished at 10.45pm.

The representative could not recall the structure of the meeting in detail and there was no paper record. That being said, the meeting was almost certainly structured around the educational campaign materials available at the time. Copies of these were provided. The educational component would have lasted all evening as the representative moved around the table in order to hold individual conversations with each attendee.

Aventis noted that during the evening the representative had detailed discussions with one of the clinical assistants in dermatology about the writing and production of a dermatology booklet. This had now been published and distributed nationally following financial support received from Aventis.

The total cost had been £346.17, a cost per head of £34.61. A list of those present showed that five clinicians, two nurses and two administrators had attended

Aventis noted that:

- this was the first opportunity to get all key staff within the unit together to discuss the pros and cons of Telfast and to reach a consensus on whether or not Telfast should be considered for inclusion in the unit's formulary;
- the format of the meeting was a round table discussion of Telfast that took place prior to and during the meal. The question and answer session continued throughout the meal with individual attendees; and
- The meal consisted of a set menu with house wine. The attendees drove home at the end of the meeting. No taxis or other forms of transport were offered by Aventis.

Formal feedback on the content and appropriateness of the meeting was not sought, but the representative had been invited back to the unit since and thanked for playing his part in educating the consultant and his team on recent developments in the treatment of urticaria.

The second meeting at issue had taken place at another restaurant on 15 July, 2002. It had been organised by the departmental nurse administrator. No formal invitation was sent by Aventis, it was invited to join the departmental meeting to present and then discuss its latest data and information on Telfast and Tritace (ramipril) due to the high number

of general practitioner clinical assistants present and a cardiologist from a neighbouring hospital.

There had been no formal agenda. Participants arrived at the venue for 7.30pm. The meeting finished at 11pm. Aventis referred to the comments on agenda structure and formality made above for the meeting in 2001. Current campaign material was available.

The total cost had been £673.60, a cost per head of £35.45. A list of those who had attended showed that nine clinicians, eight nurses and one administrator were present.

Aventis noted that:

- A presentation on the benefits and use of Telfast a long acting, non-sedating anti-histamine and Tritace, an ACE inhibitor with unique mortality and morbidity prevention indications, had been planned for this meeting.
- At the last minute on the evening, the representative was asked by the departmental sister not to proceed with the educational and promotional parts of the meeting that had been planned because one of the attendees had been recently diagnosed with a serious illness and his colleagues thought it best to have a 'light' evening and not an educational work evening.
- Due to the late timing of this unprecedented request the representative found himself in an extremely compromised position. He took the decision not to cancel the meeting in the belief that this would not only cause hurt and anguish to the attendee concerned but also in the eyes of the other attendees. The representative regretted the situation, but could see no other honourable way forward when faced with the dilemma.
- The representative had spoken with the departmental sister since receiving this complaint and she was prepared to confirm the position that the representative was placed in regarding their request.
- The representative did his best to hold educational and product related discussions throughout the evening on Telfast and Tritace, as this had been the reason for him agreeing to participate in the meeting. However, he felt that it would be inappropriate to provide too much product related education given the mood of the evening and wishes of the department.
- The menu was a set menu with house wine that was of a standard and cost that the invitees would have arranged and paid for themselves. Attendees drove home at the end of the meeting. Taxis and other forms of transport were not provided by Aventis.

General comments

- All of the meetings were organised locally by the representative.
- The representative had passed his ABPI examination.
- Aventis and, it believed, other pharmaceutical companies, had been involved in this type of evening meeting for the department before the ones in 2001 and 2002 cited in the complaint.
- The level of hospitality for both meetings consisted of set menus and appropriate level of house wine and was of a standard that the participants would have organised and paid for themselves.
- Both meetings were held midweek and most attendees were driving.
- Following the first meeting one of the attendees had gone on to produce an independent guide on the medical aspects of urticaria in which Telfast was listed as a useful treatment.

In response to a request for further information, Aventis confirmed that both meetings took place in the restaurants themselves not in private rooms. The company's understanding of the second meeting was that the group was likely to be the only group in the restaurant that evening.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. 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 supplementary information to Clause 19 which set out certain basic principles for any meeting stated, *inter alia*, that the meeting must have a clear educational content and the hospitality associated with the meeting must be secondary to the nature of the meeting. The supplementary information also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind. Meetings organised for doctors, other health professionals and/or for administrative staff which are wholly or mainly of a social or sporting nature are unacceptable'.

Aventis stated that in relation to each meeting it was invited to join the departmental meeting. The departmental consultant delegated responsibility for the meeting to the nurse administrator; the provision of formal agendas and invitations was not standard practice. It was unclear which party had chosen the venues. The refreshments were paid for by the company. It was beholden upon the company to ensure that the overall arrangements, including the venue, complied with the Code.

The Panel considered that the first meeting had limited educational content; there was no formal presentation, the representative stated that he moved around the table and had individual conversations with each attendee. The Panel did not accept that the nature of the meeting justified the associated hospitality. In the Panel's view, the meeting was inappropriate as it consisted of discussions in a public restaurant and the hospitality was not secondary to the main purpose of the meeting. The Panel queried

whether the cost exceeded the level that the recipients would adopt if paying for themselves. The Panel ruled a breach of Clause 19.1 of the Code.

The Panel also considered that in relation to the requirements of the Code high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was used as a sign of particular censure. The Panel considered that the meeting brought discredit upon the pharmaceutical industry and ruled a breach of Clause 2.

The Panel noted that the representative had been asked, at the last minute, not to proceed with the educational part of the second meeting. The Panel appreciated that this had put the representative into a difficult position. From the representative's report, however, it appeared that a presentation on Telfast and Tritace was planned although the representative's report referred to the first meeting with regard to the agenda structure and formality. The second meeting was to be held in a public restaurant and it appeared that the presentation would have also taken place in the public restaurant. In the Panel's view the arrangements for the second meeting were little different to those for the first meeting. The Panel considered, therefore, that its rulings above with regard to the first meeting also applied to the prior arrangements for the second meeting. Breaches of Clauses 19.1, 9.1 and 2 were ruled. In the circumstances the Panel made no ruling as to what had actually happened at the second meeting.

Complaint received	**19 September 2002**
Case completed	**18 November 2002**

CASES AUTH/1362/9/02 and AUTH/1363/9/02

VOLUNTARY ADMISSIONS BY PFIZER and PHARMACIA

Breach of undertaking

Pfizer advised the Authority that a journal advertisement which it and Pharmacia had undertaken to withdraw in May had appeared in the New England Journal of Medicine in September 2002. The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel noted that there was no documentary evidence of the instructions from Pfizer and Pharmacia to the advertising agency to discontinue use of the advertisement at issue. An email from the agency, dated October 2002, to Pfizer and Pharmacia referred to the request to pull the advertisements. A letter from the agency in October outlined the actions it had taken subsequent to Pfizer and Pharmacia's instruction to discontinue the advertisement at the end of April 2002. It was stated that the relevant account coordinator had contacted all of the journals on the media schedule immediately. The New England Journal of Medicine was instructed to cease using and destroy all forms of the advertisement. The agency had provided the journal with the replacement advertisement although the journal stated that it had not been received. The journal had printed the withdrawn advertisement. The Panel noted that the agency's original copy instructions only referred to one insertion of the advertisement (March 2002) and that for future insertions/repeats the journal was to contact the agency for written confirmation. It appeared that this had not been done. As a consequence of the New England Journal of Medicine's actions, Pharmacia and Pfizer had failed to comply with their undertakings and the Panel ruled a breach of the Code.

The Panel considered that the companies had been let down by the journal. The Panel considered that the companies had endeavoured to comply with their undertakings. It did not consider that the companies had brought discredit upon, or reduced confidence in, the pharmaceutical industry. No breach was ruled.

In Cases AUTH/1293/4/02 and AUTH/1294/4/02 a Celebrex (celecoxib) leavepiece issued by Pharmacia Limited and Pfizer Limited was ruled in breach of the Code. The rulings were accepted. Pfizer and Pharmacia signed an undertaking on 17 May 2002 and withdrew the leavepiece and advertisements containing similar claims. The materials had referred to guidance issued by the National Institute of Clinical Excellence (NICE). On 20 May 2002 Pharmacia and Pfizer received a complaint (Cases AUTH/1321/5/02 and AUTH/1322/5/02) about an advertisement which contained similar claims to those at issue in Cases AUTH/1293/4/01 and AUTH/1294/4/01 and was thus caught by the undertaking given in those cases. The complaint proceeded, however, as it concerned some matters which had not been considered in the previous cases. As a result of the rulings in Cases AUTH/1293/4/01 and AUTH/1294/4/01 the advertisement had nonetheless been withdrawn and had last appeared on 30 May 2002. The time delay between signing the form of undertaking and assurance on 17 May and the advertisement last appearing on 30 May was due to lead times for printing.

COMPLAINT

Pfizer advised the Authority that a journal advertisement (ref CEL061-P7178/01/02 January 2002) which had been withdrawn due to the Panel's

rulings in Cases AUTH/1321/5/02 and AUTH/1322/5/02 had appeared in the New England Journal of Medicine (5, 19 & 26 September).

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review. Pfizer and Pharmacia were asked to comment in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Pfizer and Pharmacia wrote separate but similar responses.

The companies stated that at the end of April 2002 and prior to the ruling in Cases AUTH/1293/4/02 and AUTH/1294/4/02, their advertising agency was instructed to discontinue use of the advertisements in question. The email dated 1 May 2002 from the agency confirmed that these instructions were received.

In addition, Pfizer enclosed a letter from the agency to confirm that it had received the companies' instruction to remove the advertisement referring to the NICE guidance. The letter stated that all of the journals on the media schedule were contacted by the agency. A copy of the media schedule was provided. The New England Journal of Medicine was one of more than 30 journals where the advertisement appeared.

A letter from the agency, dated 9 October 2002, demonstrated that on 30 January 2002 it had instructed the New England Journal of Medicine to run the advertisement in its March editions only. The journal was expressly instructed not to run the advertisement again without the agency's written confirmation. The inclusion in the September editions was a clear breach of this instruction.

In addition, the agency's letter of 9 October included a copy instruction which it had sent to the New England Journal of Medicine on 31 July 2002 enclosing the replacement advertisement for inclusion in the 5 September edition. The journal in its letter of 3 October 2002 stated that the replacement advertisement was never received. Pfizer understood that it was not standard industry practice for receipt of such copy to be acknowledged. The journal printed three editions using the advertisement in question.

Following discussions within Pfizer and Pharmacia about electronic copies of the advertisement, Pharmacia telephoned the agency to request that it remove all electronic versions of the advertisement. The companies believed that this demonstrated their commitment to the undertakings which they had signed. The agency confirmed that the advertisement had been deleted from its server.

In relation to Clause 22, Pfizer and Pharmacia believed that they had acted entirely properly and had taken their undertakings to the Authority seriously. Not only was the agency instructed to ensure that journals ceased to use the advertisement in question, but also to delete the materials from its server so that the advertisement could not be used accidentally. The agency's copy instruction and standard copy procedure demonstrated that the New England Journal of Medicine should only have run the advertisement in March and then requested further instructions. Even if the journal did not receive the replacement advertisement, which was received by every other journal on the media schedule, it was clear that it was acting outside of its instructions.

Pfizer and Pharmacia believed that they had done everything within their power to ensure that the agency acted appropriately. The agency was adamant that the mistake lay with the New England Journal of Medicine, over which Pfizer and Pharmacia had no control. Pfizer firmly believed that they had complied with the undertakings given.

As regards Clause 9.1, the companies believed that the description of their actions showed that they maintained high standards.

Pfizer and Pharmacia took undertakings to the Authority very seriously. It was regrettable that the advertisement had reappeared. The supplementary information to Clause 2 of the Code stated that a ruling of breach of this clause was a sign of particular censure and was reserved for such circumstances. This was inappropriate in the current case for several reasons.

Pfizer and Pharmacia believed that they acted promptly, responsibly and clearly in their communications with the agency. The mistake made was beyond their control and appeared to lie with the New England Journal of Medicine. Neither Pfizer nor Pharmacia acted deliberately in breach of the undertaking. The journal's actions were beyond the companies' control. Pfizer had acted responsibly in bringing this matter to the attention of the Authority when it became aware of it. The companies submitted that a Clause 2 ruling might have been more appropriate if they had found out about this inadvertent breach and waited and hoped that nobody would complain.

For these reasons, Pfizer and Pharmacia submitted that the matter did not warrant the censure of a ruling of a breach of Clause 2.

PANEL RULING

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

The Panel noted that the agency was instructed to discontinue use of the advertisement at issue. There was no documentary evidence of the instructions from Pfizer and Pharmacia to the agency. An email from the agency, dated 4 October 2002, to Pfizer and Pharmacia referred to the request to pull the NICE advertisements. A letter from the agency, dated 7 October, outlined the actions it had taken subsequent to receiving Pfizer and Pharmacia's instruction to

discontinue the advertisement at the end of April 2002. It was stated that the account co-ordinator responsible for the Celebrex business contacted all of the journals on the media schedule immediately. As with all of the other journals the New England Journal of Medicine was instructed to cease using the advertisement referring to NICE and to destroy all disk, film and proof copies. The agency had provided the journal with the replacement advertisement although the journal stated that it had not been received. The journal had printed the withdrawn advertisement. The Panel noted that the agency's original copy instructions regarding the advertisement at issue referred to one insertion only (March 2002) and that for future insertions/repeats the journal was to contact the agency for written confirmation. It appeared that this had not been done.

As a consequence of the New England Journal of Medicine's actions, Pharmacia and Pfizer had failed to comply with their undertakings and the Panel ruled a breach of Clause 22 of the Code.

The Panel considered that the companies had been let down by the journal. The Panel considered that the companies had endeavoured to comply with their undertakings. It did not consider that the companies had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

Proceedings commenced 30 September 2002

Case completed 21 November 2002

CASE AUTH/1364/10/02

ASTRAZENECA v NOVARTIS

Femara journal advertisement

AstraZeneca complained about a Femara (letrozole) journal advertisement issued by Novartis. Femara was indicated for the treatment of breast cancer. The advertisement was headed 'Are all aromatase inhibitors equal?' and featured a stylised drawing of the upper body of a woman with a breast tumour highlighted. AstraZeneca considered that this image gave the impression that the question was being set in a clinical context. The claim 'In two separate clinical trials Femara has shown superior results to anastrozole' was beneath the drawing. Beneath the Femara product logo at the bottom of the advertisement was the strapline 'Time to make a difference'. AstraZeneca marketed Arimidex (anastrozole).

AstraZeneca stated that the claim, together with the overall theme of the advertisement, portrayed a very clear and strong message that Femara was clinically superior to anastrozole in the treatment of breast cancer. The claim was referenced to Thomas *et al* and Rose *et al* but AstraZeneca considered that neither study substantiated it. Rose *et al* failed to show any statistically significant difference between letrozole and anastrozole for the primary endpoint of time to progression, and the only secondary endpoint that showed any difference in favour of letrozole was objective response. Time to progression was one of the more meaningful measurements in breast cancer trials. Conversely, objective response was a much softer measure and could be open to bias.

Thomas *et al* did not assess clinical efficacy and therefore the results would not be able to demonstrate any clinical advantage for either medicine. AstraZeneca considered that given the clinical theme of the advertisement, the results of this patient preference study had been misapplied, resulting in an inaccurate claim which was likely to mislead.

AstraZeneca considered that the strapline 'Time to make a difference' only added to the impression that Femara was clinically superior to anastrozole by suggesting that if health professionals prescribed Femara instead of anastrozole they would see a positive change in the prognosis of their breast cancer patients. AstraZeneca stated that in the absence of robust conclusive evidence this message was inaccurate and likely to mislead.

The Panel noted that the question 'Are all aromatase inhibitors equal' and the claim 'In two separate clinical trials Femara has shown superior results to anastrozole' were followed by two further claims each referring separately to the results of Rose *et al* and Thomas *et al*.

Rose *et al* was a comparison of Femara and anastrozole in the second-line treatment of post-menopausal women with advanced breast cancer. The primary endpoint was time to progression in which no difference was shown between the two medicines. Secondary endpoints included, *inter alia*, objective response, duration of response, duration of clinical benefit and time to treatment failure. Advantages for Femara were shown in terms of objective response (p=0.014) and response rate (p=0.218;ns). There were no differences in time to progression, time to treatment failure, duration of response or duration of clinical benefit. Rose *et al* was cited in support of the claim 'A large scale study of 713 postmenopausal women, who had progressed on tamoxifen showed significantly greater objective response rate (ORR) with Femara compared to anastrozole'.

Thomas *et al* compared the tolerability, quality of life and patient preference of Femara and anastrozole. The study did not measure clinical response to either medicine. Thomas *et al* was cited in support of the claim 'Results from a randomised crossover study showed 68% of patients preferred to stay on Femara at the end of the study compared to 32% on anastrozole'.

The Panel considered that although the claim 'In two separate clinical trials Femara has shown superior results to anastrozole' was qualified by the claims which referred separately to the results of Rose *et al* and Thomas *et al*, it nonetheless implied that better clinical results were achieved with Femara than with anastrozole; this was not borne out by the data cited. In the Panel's view the question about equality, the image of the woman and the strapline 'Time to make a difference' added to the impression of clinical superiority for Femara created by the claim. The Panel considered that the advertisement was misleading as alleged and not capable of substantiation. Breaches of the Code were ruled.

The Panel considered that while the advertisement exaggerated the clinical significance of the data cited, and so was misleading in that regard, it had not included an exaggerated claim *per se*. No breach of the Code was ruled.

AstraZeneca UK Limited complained about a Femara (letrozole) advertisement (ref FEM/02/45) issued by Novartis Pharmaceuticals UK Limited which had appeared in a number of issues of the BMJ including 22 June. Femara was indicated for the treatment of breast cancer. The advertisement was headed 'Are all aromatase inhibitors equal?' and featured a stylised drawing of the upper body of a woman with a breast tumour highlighted. The claim beneath the drawing, 'In two separate clinical trials Femara has shown superior results to anastrozole' was referenced to a poster presentation by Rose *et al* (2002) and an abstract by Thomas *et al* (2002). Each of these references in turn supported separate claims of greater objective response rate (Rose *et al*) and patient preference (Thomas *et al*) for Femara compared with anastrozole. Beneath the Femara product logo at the bottom of the advertisement was the strapline 'Time to make a difference'.

AstraZeneca marketed Arimidex (anastrozole).

COMPLAINT

AstraZeneca noted that directly beneath the question 'Are all aromatase inhibitors equal?' appeared the image of a woman with her breast cancer tumour illuminated. This image was the focal point of the advertisement and immediately gave the impression that the question was being set very much in a clinical context. Underneath the visual was the claim 'In two separate clinical trials Femara has shown superior results to anastrozole'. This claim, together with the overall theme of the advertisement, portrayed a very clear and strong message that Femara was clinically superior to anastrozole in the treatment of breast cancer.

AstraZeneca noted that the claim was referenced to Thomas *et al* and Rose *et al*. However, the company considered that neither study was in any way capable of substantiating the claim. The significance of both study results had been exaggerated and misapplied. The resulting claim was therefore alleged to be inaccurate and misleading.

AstraZeneca noted that Rose *et al* was a head-to-head open-label study which compared letrozole with anastrozole in the second-line treatment of advanced breast cancer ie in patients who had subsequently progressed whilst being treated with tamoxifen. The study failed to show any statistically significant difference between the two medicines for the primary endpoint of time to progression. Further, of seven of the secondary endpoints (including overall survival), the only one that showed any difference in favour of letrozole was objective response.

Time to progression amongst the medical community was one of the more meaningful measurements in breast cancer trials particularly in advanced breast cancer. The same could be said for overall survival. Conversely, objective response was viewed as a much softer measure and could be open to bias due to intra-observer variation. In isolation the significance of these results was questionable and needed to be viewed in the context of other well-established parameters for a more accurate assessment of the true clinical efficacy of a particular medicine.

AstraZeneca stated that the results of this study were totally insufficient to support a superiority claim for Femara over anastrozole; AstraZeneca was concerned about the implications such a claim would have on the target audience. In AstraZeneca's view the claim represented an exaggeration of the clinical significance of the cited data. The resulting message was inaccurate and likely to mislead. Breaches of Clauses 7.2, 7.4 and 7.10 were alleged.

AstraZeneca noted that Thomas *et al* compared tolerability, quality of life and patient preference of anastrozole and letrozole. The study did not involve any measurement for clinical efficacy for either medicine and therefore the results would not be able to demonstrate any clinical advantage for either medicine. In addition the trial was flawed in its methodology. In summary, the main areas of concern were:

- The Functional Assessment of Cancer Therapy – Endocrine Subscale Quality of Life (FACT-ES QoL) instrument had been used incorrectly. FACT-ES was not a valid endpoint used alone. It should be used in the context of a more general QoL scale. Contacting the originator of the FACT-ES instrument had confirmed AstraZeneca's opinion that in this instance it had not been applied in an appropriate manner.
- The trial was an open-label study leading to a risk of patient bias.
- The sample size was small (n=65).
- Each treatment period was very short (4 weeks was too short to measure quality of life changes effectively).
- The washout period was too short to be sure that there was no carry over.
- The patient preference was not measured at baseline or at the end of the first treatment period.

AstraZeneca considered that the claim 'In two separate clinical trials Femara has shown superior results to anastrozole', together with the context in which it had been set, suggested that Femara had been shown to have a clinical advantage over anastrozole. The results of this patient preference

study had therefore been grossly and deliberately misapplied resulting in an inaccurate claim, which was likely to mislead the intended audience. AstraZeneca alleged breaches of Clauses 7.2 and 7.4.

In summary, AstraZeneca considered that the data being used to substantiate the superiority claim for letrozole were inadequate and inappropriate. The significance of these results had been exaggerated, taken out of context and misapplied. The overall message was that Femara was clinically superior to anastrozole. The fact that the advertisement concluded with the strapline 'Time to make a difference' only added to this impression by suggesting that if health professionals prescribed Femara instead of anastrozole they would see a positive change in the prognosis of their breast cancer patients. AstraZeneca stated that in the absence of robust conclusive evidence this message was inaccurate and likely to mislead. Breaches of Clauses 7.2 and 7.4 on two accounts each and a breach of Clause 7.10 were alleged.

RESPONSE

Novartis noted that the advertisement was subjected to routine scrutiny by the Medicines Control Agency (MCA); the MCA had requested copies of the substantiating data on the 6 August. No further action was required by the company as a result of the MCA's review.

Novartis noted that the data presented in the advertisement appeared under the main heading 'Are all aromatase inhibitors equal?' This question was of particular interest to health professionals working in this area. Below the heading appeared a stylised image of a woman with an area of her breast highlighted by the bracket of the product logo. Novartis agreed with AstraZeneca that this image clearly defined the therapeutic area of the product and the fact that clinical evidence would be presented. Novartis disagreed however with AstraZeneca's assertion that the two trial statements in association with the visual exaggerated the clinical significance of the data presented. Every effort had been taken to define very clearly the two areas of superiority from the studies cited, namely the objective response from the first and the patient preference from the second.

Novartis noted that the abstract by Rose *et al* reported the results of a company sponsored phase IIIb clinical study involving 713 postmenopausal women with breast cancer who had progressed on tamoxifen. One of the clearly defined secondary endpoints of this study was objective response. This was a widely used endpoint in such studies and was a very important one from both the patient's and clinician's perspectives representing tangible evidence of effect. In this study Femara was found to be superior to anastrozole in terms of objective response. The statement in the advertisement did not suggest that every endpoint in the study was favourable for letrozole but identified the specific endpoint which was. This was not an ad hoc analysis but a pre-defined endpoint and there was nothing in the study results that might present any conflict with the finding. The study was large and the result statistically significant and relevant.

Novartis noted that AstraZeneca had suggested that such an outcome might be open to bias because of the open-label design of the trial. However, a blinded independent peer review by committee on the results of the study came to the same overall conclusions as that of the original authors in terms of objective response, the concordance being 83% and the statistical significance retained.

Novartis noted that the advertisement was aimed at a specialist target audience who would fully appreciate the significance of objective response rates in relation to the management of patients with advanced breast cancer.

Thomas *et al* was an independently conducted clinical study with three clear endpoints: tolerability, quality of life and patient preference. It was this third element – patients' preference for Femara – which was referred to by the claim in the advertisement.

Novartis disagreed that in the context of the study the sample size (n=65) was too small. This was not an inconsiderable number of patients for such a study in this indication and had clearly been calculated by the authors as being sufficient to provide the statistical power required. The fact that a statistical difference was shown, for each endpoint individually, suggested that the study was adequately powered.

Novartis noted that AstraZeneca had suggested that having been an open-label study the trial risked patient bias and that patients' preference for medication should have been measured at baseline or at the end of a treatment period. Novartis disagreed that it would have been logical or valid to measure patients' preference for one of two medicines before they had received them. It would also be hard to see how being open to patients about the identity of their medicine could influence their preference given that during the trial patients would have the opportunity to receive both. In general, breast cancer patients could not be expected to be aware, let alone knowledgeable of, endocrine cancer therapies prior to receiving them, so it was not clear why they would be expected to have an impression of them prior to the trial, or why knowing the names of the medicines would bias them at this point. Novartis considered that the authors were correct in carrying out the preference analysis at the end of the study after both medicines had been received.

Novartis noted that AstraZeneca had also suggested that the washout period between medicines was too short to be sure that there was no carry over, and that the treatment periods were too short to measure quality of life changes effectively. Novartis noted that no claims had been made in the advertisement in relation to the quality of life aspects of this study. Given that each patient had received both medicines during the study Novartis did not consider that the washout period was relevant in terms of their expressed preference for one of the two treatments.

The main issue which AstraZeneca had presented in relation to the use of this study appeared to relate to a difference of opinion between the authors and the originator of the FACT-ES instrument to measure quality of life. Specifically AstraZeneca had provided an extensive prompted letter from the person

concerned in which the use of a particular quality of life instrument was criticised. Novartis stated that it became aware that this difference of opinion existed after it had developed this advertisement. Novartis noted, however, that the advertisement did not refer to the quality of life endpoint of the study, so the way in which the FACT-ES QoL instrument had been employed by the authors appeared to be irrelevant to this complaint.

Novartis did not consider that it was in a position to arbitrate in this matter; any disagreements about the quality of life scales employed in this study should be more appropriately resolved through discussion between these two respected experts.

PANEL RULING

The Panel noted that the question 'Are all aromatase inhibitors equal' and the claim 'In two separate clinical trials Femara has shown superior results to anastrozole' were followed by two further claims each referring separately to the results of Rose *et al* and Thomas *et al*.

The study by Rose *et al* was a comparison of Femara and anastrozole in the second-line treatment of post-menopausal women with advanced breast cancer. The primary endpoint was time to progression in which no difference was shown between the two medicines. Secondary endpoints included, *inter alia*, objective response, duration of response, duration of clinical benefit and time to treatment failure. Advantages for Femara were shown in terms of objective response (p=0.014) and response rate (p=0.218;ns). There were no differences in time to progression, time to treatment failure, duration of response or duration of clinical benefit. Rose *et al* was cited in support of the claim 'A large scale study of 713 postmenopausal women, who had progressed on tamoxifen showed significantly greater objective response rate (ORR) with Femara compared to anastrozole'.

Thomas *et al* compared the tolerability, quality of life and patient preference of Femara and anastrozole. The study did not measure clinical response to either medicine. Thomas *et al* was cited in support of the claim 'Results from a randomised crossover study showed 68% of patients preferred to stay on Femara at the end of the study compared to 32% on anastrozole'.

The Panel considered that although the claim 'In two separate clinical trials Femara has shown superior results to anastrozole' was qualified by the claims which referred separately to the results of Rose *et al* and Thomas *et al* it nonetheless implied that better clinical results were achieved with Femara than with anastrozole; this was not born out by the data cited. In the Panel's view the question about equality, the image of the woman and the strapline 'Time to make a difference' added to the impression of clinical superiority for Femara created by the claim. The Panel considered that the advertisement was misleading as alleged and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel considered that while the advertisement exaggerated the clinical significance of the data cited, and so was misleading in that regard, it had not included an exaggerated claim *per se*. No breach of Clause 7.10 was ruled.

Complaint received **3 October 2002**

Case completed **25 November 2002**

CASE AUTH/1365/10/02

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE CONSUMER HEALTHCARE

Breach of undertaking

GlaxoSmithKline Consumer Healthcare advised the Authority that as a result of its own investigations into the circumstances which led to the ruling of a breach of the Code in Case AUTH/1348/8/02 for failing to comply with an undertaking, it had discovered that the advertisement for NiQuitin CQ Lozenges which had been ruled in breach of the Code in another case, Case AUTH/1272/1/02, had been republished in error.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel noted that Case AUTH/1272/1/02 had concerned an advertisement for NiQuitin CQ Lozenges which was ruled in breach of the Code by the Panel; GlaxoSmithKline Consumer Healthcare provided the requisite form of undertaking and assurance in April 2002. The advertisement had, however, appeared again in the June/July 2002 edition of Northern Ireland Medicine Today and as a consequence the company had failed to comply with its undertaking. A breach of the Code was ruled in the present case, Case AUTH/1365/10/02, as acknowledged by GlaxoSmithKline Consumer Healthcare.

The Panel noted that in Case AUTH/1348/8/02 GlaxoSmithKline Consumer Healthcare had been ruled in breach of the Code because an advertisement for NiQuitin patches, which had been ruled in breach of the Code, had been published again. GlaxoSmithKline Consumer Healthcare had submitted that this had occurred as a result of human error and because an electronic copy of the advertisement had been issued despite the job bag being archived and 'no longer current'. In Case AUTH/1348/8/02 the Panel had considered that it was beholden upon a company to ensure that its procedures for the withdrawal of material pursuant to the provision of an undertaking encompassed all forms in which it was stored. It appeared that at the time GlaxoSmithKline Consumer Healthcare's withdrawal procedures did not specifically address the matter of material stored electronically independently of the job bag.

GlaxoSmithKline Consumer Healthcare had been advised of the complaint in Case AUTH/1348/8/02 in August 2002. Since then it had reviewed its procedures. The advertisement now at issue in Case AUTH/1365/10/02 had appeared in the June/July edition of Northern Ireland Medicine Today as a result of the journal using an electronic version of the advertisement which had been supplied to it in December 2001. The brand manager in the Republic of Ireland agreed that the advertisement could be run but had not contacted the UK media buying agency or the advertising agency. These errors had already occurred by the time GlaxoSmithKline Consumer Healthcare received the complaint in Case AUTH/1348/8/02.

The Panel noted that the reuse of an advertisement previously ruled in breach of the Code which had occurred in this case, Case AUTH/1365/10/02, was, as in Case AUTH/1348/8/02, due to human error and GlaxoSmithKline Consumer Healthcare's failure to expressly request the destruction or return of electronically stored images. The Panel considered that GlaxoSmithKline Consumer Healthcare had failed to maintain a high standard and a breach of the Code was ruled in the case now before it, Case AUTH/1365/10/02. The Panel decided that although a breach of undertaking was a serious matter, taking all the circumstances into account it would rule no breach of Clause 2.

In Case AUTH/1348/8/02 GlaxoSmithKline Consumer Healthcare had been ruled in breach of Clause 22 of the Code for failing to comply with its undertaking given in Case AUTH/1253/11/01 and allowing the further publication of an advertisement for NiQuitin patches (ref NCQ/PWT/0901/002). The company was also ruled in breach of Clause 2. These rulings were not appealed.

COMPLAINT

GlaxoSmithKline Consumer Healthcare advised the Authority that as a result of its own investigations into the circumstances which led to the breach of Clause 22 of the Code in Case AUTH/1348/8/02, it had discovered that the advertisement for NiQuitin CQ Lozenges (ref NCQ/PWT/1101/001) which had been ruled in breach of the Code in Case AUTH/1272/1/02 had also been republished in error in the June/July edition of Northern Ireland Medicine Today.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Authority requested that, when considering the matter, GlaxoSmithKline Consumer Healthcare respond in relation to the provisions of Clauses 2, 9.1 and 22 of the Code.

Case AUTH/1272/1/02 was completed on 12 April 2002.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that when it was advised of the Panel's rulings in Case AUTH/1272/1/02, relevant materials were recalled from representatives and destroyed. There was no field force in Northern Ireland, so no recall of material was required from them. The media schedule for Northern Ireland, agreed between GlaxoSmithKline

Consumer Healthcare and the media buying agency, did not have any prescription advertisements for NiQuitin CQ Lozenge booked to run at the time until December 2002, when the new campaign would start. The advertising agency archived its job bag in line with its policy to ensure only 'live' job bags were used.

General process for the placement of advertisements in Northern Ireland

GlaxoSmithKline Consumer Healthcare stated that advertisements for its products in Northern Ireland were arranged by the GlaxoSmithKline Ireland business. When GlaxoSmithKline Ireland wished to place an advertisement or generate any promotional material in Northern Ireland, GlaxoSmithKline Ireland would book space via the UK media buying agency and go through the UK advertising agency which provided it with currently approved copy.

GlaxoSmithKline Consumer Healthcare submitted that as the UK advertising agency and the UK media agency had been informed that the relevant advertisement could no longer be used, this procedure should have ensured that no problems would arise.

Discovery of publication of advertisement after Panel ruling

GlaxoSmithKline Consumer Healthcare stated that having been informed in August 2002 of a breach of undertaking for a separate advertisement (Case AUTH/1348/8/02), that had originally been found in breach in February (Case AUTH/1253/11/01), it overhauled its processes as it was clear from this first breach that it needed to be explicit in reference to the destruction of films and electronic files held by agencies and publications. The company undertook a review to elicit a list of all agencies and publications that might have held electronic copies of its advertisements so that it could ensure their destruction. As part of that review it included Northern Ireland and discovered that an unscheduled advertisement had run in the June/July edition of Northern Ireland Medicine Today.

It appeared that the process outlined above was not followed in respect of this advertisement. Instead, the Northern Ireland Medical Times rang GlaxoSmithKline Ireland to ask if it could use the NiQuitin Lozenge advertisement that it had run previously, as it was doing a feature on the top 100 pharmacy brands. The publication had been supplied with an electronic version of the advertisement on 3 December 2001, before it was subject to complaint. As GlaxoSmithKline Consumer Healthcare had not expressly requested destruction of electronic files by this time, the publication still held this electronic file. Without contacting either the UK media buying agency or the advertising agency, the brand manager in Ireland agreed that the publication could run the advertisement.

Steps taken upon discovery of error

GlaxoSmithKline Consumer Healthcare stated that it would ensure that, in future, GlaxoSmithKline Ireland and any other part of GlaxoSmithKline that could authorise advertisements within the UK and Northern Ireland were informed immediately of the outcome of complaints.

GlaxoSmithKline Consumer Healthcare submitted that the changes it made to its recall process as a result of Case AUTH/1348/8/02, if implemented initially, would in any event have prevented this error from occurring: if the publication had been requested to destroy the electronic file, then the brand manager would have had to contact the advertising agency to be supplied with a new copy that was not subject to a Code of Practice ruling.

GlaxoSmithKline Consumer Healthcare stated that it hoped that the Authority would take into consideration both its voluntary admission of this error and the fact that it was discovered as a result of the company correcting the flaw in its recall process highlighted by Case AUTH/1348/8/02, and which occurred as a result of the same flaw; not expressly requesting deletion of electronic files. GlaxoSmithKline Consumer Healthcare acknowledged that there was breach of undertaking (Clause 22), but this was reported to the Authority as a result of the company taking its undertakings extremely seriously and being rigorous in its determination to maintain high standards and promote confidence in the pharmaceutical industry.

PANEL RULING

The Panel noted that the advertisement at issue had been placed in a Northern Ireland journal by GlaxoSmithKline Ireland in the Republic of Ireland. The Code covered the promotion of medicines in the UK, which included Northern Ireland. It was, however, an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas divisions. GlaxoSmithKline Consumer Healthcare in the UK was therefore responsible under the Code for the advertisement.

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

With regard to the case now before it, the Panel noted that Case AUTH/1272/1/02 concerned an advertisement for NiQuitin CQ Lozenges which was ruled in breach of the Code by the Panel; these rulings were accepted by GlaxoSmithKline Consumer Healthcare which provided the requisite form of undertaking and assurance on 12 April 2002. The advertisement had, however, appeared again in the June/July 2002 edition of Northern Ireland Medicine Today and as a consequence the company had failed to comply with its undertaking. A breach of Clause 22 of the Code was ruled as acknowledged by GlaxoSmithKline Consumer Healthcare.

The Panel noted that the breach of the undertaking given in Case AUTH/1272/1/02 had come to light as a result of GlaxoSmithKline Consumer Healthcare's

investigation into the breach of the undertaking it had given in Case AUTH/1253/11/01 which gave rise to Case AUTH/1348/8/02. In Case AUTH/1348/8/02 GlaxoSmithKline Consumer Healthcare had been ruled in breach of Clause 22 because an advertisement for NiQuitin patches, which had been ruled in breach of the Code in Case AUTH/1253/11/01, had been published again. GlaxoSmithKline had submitted that this had occurred as a result of human error and the fact that a copy of the advertisement which had been stored electronically had been issued despite the fact that the job bag was archived and 'no longer current'.

In Case AUTH/1348/8/02 the Panel had considered that it was beholden upon a company to ensure that its procedures for the withdrawal of material pursuant to the provision of an undertaking encompassed all forms in which it was stored, including the electronic version of the material. It appeared that at the time GlaxoSmithKline Consumer Healthcare's procedures did not specifically address the withdrawal of material stored electronically independently of the original job bag.

The Panel noted that GlaxoSmithKline Consumer Healthcare was advised of the complaint in Case AUTH/1348/8/02 on 1 August 2002. Since then it had reviewed its procedures and recognised that it needed to be explicit in reference to the destruction of electronic files held by agencies and publications. The advertisement now at issue had appeared in the June/July edition of Northern Ireland Medicine Today as a result of the journal using an electronic version of the advertisement which had been supplied to it in December 2001. The brand manager in Ireland had agreed that the advertisement could be run but had not contacted the UK media buying agency or the advertising agency as (s)he should have done according to established procedures. These errors had already occurred by the time GlaxoSmithKline Consumer Healthcare received the complaint in Case AUTH/1348/8/02 and knew there was a problem regarding electronically stored material held by third parties.

The Panel noted that the reuse of an advertisement previously ruled in breach of the Code which had occurred in this case, Case AUTH/1365/10/02, was, as in Case AUTH/1348/8/02, due to human error and GlaxoSmithKline Consumer Healthcare's failure to expressly request the destruction or return of electronically stored images. The publication of the advertisement had occurred before GlaxoSmithKline Consumer Healthcare had been informed of Case AUTH/1348/8/02. The Panel considered that GlaxoSmithKline Consumer Healthcare had failed to maintain a high standard and a breach of Clause 9.1 of the Code was ruled in the case now before it. The Panel noted that Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel decided that although a breach of undertaking was a serious matter, taking all the circumstances into account it would rule no breach of Clause 2 in the case now before it. In that regard the Panel noted that GlaxoSmithKline Consumer Healthcare had accepted a ruling of a breach of Clause 2 in Case AUTH/1348/8/02.

Proceedings commenced 1 October 2002

Case completed 21 November 2002

CASE AUTH/1367/10/02

PHARMACIST v OTSUKA

Hospitality for accompanying partners

A pharmacist from a primary care trust complained about an invitation to a meeting which he had received from Otsuka. The meeting, entitled 'Northwest Claudication Consensus Guidelines Forum', was scheduled to start at 6.30pm one Friday evening and finish with lunch the next day. There were four hours of presentations spread over the two days. The invitation stated 'Should you wish to bring your partner to stay at the Hotel, a partner fee of £20 will be payable directly to the [named] Hotel. Please advise in advance'.

The complainant stated that although participants were being asked to pay for their partners, the fee of £20 was considerably less than the cost of hospitality provided. The complainant alleged that this was in breach of the Code which stated that 'hospitality should only be available for health professionals'.

The Panel considered that the educational content of the meeting and the hospitality for those attending were not unreasonable. The Panel considered, however, that the wording on the invitation did not explain that the £20 requested only covered the cost of the partner's dinner on the Friday evening. Delegates should have been told that all additional expenses incurred as a result of their partner being present were their responsibility. In the Panel's view the wording of the invitation suggested that inappropriate hospitality for partners was being offered. High standards had not been maintained. Breaches of the Code were ruled.

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

A pharmacist from a primary care trust, complained about an invitation to a meeting which he had received from Otsuka Pharmaceuticals (UK) Ltd. The meeting, entitled 'Northwest Claudication Consensus Guidelines Forum', was scheduled to start at 6.30pm one Friday evening and finish with lunch the next day. There were four hours of presentations spread over the two days. The invitation stated 'Should you wish to bring your partner to stay at the Hotel, a partner fee of £20 will be payable directly to the [named] Hotel. Please advise in advance'.

COMPLAINT

The complainant stated that although participants were being asked to pay for their partners, the fee of £20 was considerably less than the cost of hospitality provided. The complainant alleged that this was in breach of the Code which stated that 'hospitality should only be available for health professionals'.

When writing to advise Otsuka of the complaint the Authority requested that it should respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Otsuka noted that the meeting in question did not take place. Upon review, its approval process had identified an issue with the meeting invitation, specifically in relation to the potentially misleading description of the arrangements for payment of partner costs. The invitation was withdrawn and the meeting cancelled.

Otsuka did not consider that it was in breach of Clause 19.1 of the Code. The objective of the meeting was to develop intermittent claudication guidelines and shared-care protocols for both primary and secondary care. It was planned that a number of experts in the area would present relevant topics as described in the invitation. Only health professionals would join the meeting and be provided hospitality. All hospitality was secondary to the meeting and was at an appropriate level. The offer of accommodation was due to the geographic spread of the audience, some of whom would have had to travel 2-3 hours to reach the venue. The hotel offered three star accommodation and the delegate rate would have been £139 including VAT for dinner, overnight stay, breakfast and lunch. Otsuka did not consider this would have exceeded the level which the recipients would normally adopt when paying for themselves.

The intention was not to invite partners of delegates to attend the meeting or receive hospitality. The charge of £20 was requested to cover a separate partners' dinner on the Friday night should a delegate be accompanied by their partner. In the case of an accompanying partner, all other costs incurred by them were to be paid by the delegate. As a consequence of the delegate rate there was no additional accommodation charge for the partner.

With respect to Clause 9.1, Otsuka believed that the planned meeting was consistent with the Code. The content was very clearly directed at the health professions and the meeting was prepared bearing in mind the special nature of medicines and the profession.

Otsuka did not consider that its actions represented a breach of Clause 2. As a responsible company, Otsuka took appropriate steps to avoid any possible discredit by withdrawing the invitation and cancelling the meeting once the issue relating to the wording of the invitation had been identified. Otsuka had reviewed and improved its approval process and reinforced its guidance to its representatives to ensure that this situation could not occur in the future.

PANEL RULING

The Panel noted that the supplementary information to Clause 19.1 of the Code did not preclude spouses and accompanying persons being invited to events. Such persons must not attend the meeting unless they qualified as a proper delegate in their own right and must not receive any associated hospitality at the

company's expense. The entire costs which their presence involved was the responsibility of those they accompanied.

The Panel considered that the educational content of the meeting and the hospitality for those attending were not unreasonable. It was noted that some delegates would have had a two or three hour journey to the venue. It was not unreasonable to provide overnight accommodation in such circumstances. The Panel considered, however, that the wording on the invitation did not explain the position of the accompanying partners; the £20 as requested only covered the cost of their dinner on the Friday evening. In the Panel's view delegates should have been told that all additional expenses incurred as a result of their partner being present were their responsibility. The invitation gave the impression that delegates would have to pay only £20 in order for their partner to accompany them. This was not so. The Panel noted the supplementary information to Clause 19.1 which stated, *inter alia*, that the impression created by the arrangements for any meeting must be kept in mind. In the Panel's view the wording of the invitation suggested that inappropriate hospitality for partners was being offered. High standards had not been maintained. Breaches of Clauses 19.1 and 9.1 were ruled.

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

Complaint received **4 October 2002**

Case completed **18 November 2002**

CASE AUTH/1368/10/02

ORTHO BIOTECH v ROCHE

NeoRecormon journal advertisement

Ortho Biotech, a division of Janssen-Cilag, complained about a two page advertisement for Roche's product NeoRecormon (epoetin beta) which appeared in the NHS Journal of Healthcare Professionals. The advertisement took the form of an advertorial and assessed the evidence for once weekly epoetin beta dosing in the treatment of anaemia associated with chronic renal failure in predialysis patients. The advertisement summarised the results of two studies sponsored by Roche. Ortho Biotech marketed epoetin alpha (Eprex).

Ortho Biotech alleged that the advertisement was in breach of the Code, since prescribing information was not included.

The Panel noted that Roche had been approached by the NHS Journal of Healthcare Professionals for information on the use of epoetin beta in predialysis patients. It appeared that the journal wanted Roche to sponsor the article. Roche supplied camera ready copy and submitted that the journal had full editorial control over the feature, although in fact no changes were made to the camera ready copy supplied by Roche other than the addition of the word 'Advertisement' on the top right hand corner of the left hand page. Roche had paid for the publication and sponsorship of the piece.

The Panel did not accept that the matter was outside the scope of the Code as submitted by Roche. The company had in effect provided camera ready copy which discussed Roche's product and paid for the placement of the article. The Panel considered that the arrangements were such that the article constituted an advertisement subject to the Code and ought to have included prescribing information. A breach of the Code was ruled.

Ortho Biotech, a division of Janssen-Cilag Limited, complained about a two page advertisement for Roche Products Limited's product NeoRecormon, (epoetin beta) which appeared in the NHS Journal of Healthcare Professionals, September 2002.

The advertisement took the form of an advertorial and assessed the evidence for once weekly epoetin beta dosing in the treatment of anaemia associated with chronic renal failure in predialysis patients. The advertisement summarised the results of two studies sponsored by Roche.

Ortho Biotech marketed epoetin alpha (Eprex).

COMPLAINT

Ortho Biotech alleged that the advertisement was in breach of Clause 4.1 of the Code, since prescribing information for NeoRecormon was not included. It did not fulfil the criteria for an abbreviated advertisement under Clause 5 of the Code.

RESPONSE

Roche stated that it received a telephone call from the editor of the NHS Journal of Healthcare Professionals who wanted to write a sponsored feature article on epoetin beta in predialysis patients and requesting information if Roche agreed. As a consequence Roche provided the journal with a summary of the clinical trial work performed in this area. Roche understood that this was common practice. The information provided was factual and balanced according to Clause 20.2.

The journal had full editorial control over the feature. Unfortunately due to circumstances entirely out of

Roche's control, the feature appeared with the word 'advertisement' at the top of the page. This had led, understandably, to Ortho Biotech believing that this feature was indeed a promotional piece without prescribing information.

Roche denied a breach of Clause 4.1 for the following reasons: the sponsored feature was the initiative of and under the editorial control of, the journal – Roche provided information and sponsorship following a request from the journal. The word 'advertisement' appeared inadvertently under conditions that were entirely out of Roche's control. Roche provided a copy of relevant correspondence with the journal.

As such the article did not fall under the scope of the Code as set out in Clause 1.1 as Roche was not promoting NeoRecormon.

In response to a request for further information Roche stated that it had provided the NHS Journal of Healthcare Professionals with an encapsulated post script image file of the article. This was a file that could be used by publishers. This was the only printed or electronic information provided by Roche. The journal sent an email to Roche with the article prior to publication, which was in a pdf format and this did not include the heading 'Advertisement' or any other indication that it would be published as an advertisement.

No amendments were made by the journal to the original submitted by Roche, apart from the words relating to advertisement. Roche paid £3,500 in relation to the publication and sponsorship.

The journal was independent of Roche. The journal approached Roche for the article. A photocopy of the issue of the journal in question was provided. There were many sponsored features on various products. Some were clearly headed 'advertisements' of which some included prescribing information but others were features, which were identified as being sponsored by a particular company. In addition, there were other articles which were not attributed to any company.

Roche expected that as the article was not requested as an advertisement, it would have been used either as an editorial or as a sponsored feature similar to others in the journal where the sponsor was acknowledged.

PANEL RULING

The Panel noted that the journal was divided into five main sections; Current Issues, Management, Health Promotion, Clinical and Childcare. The advertisement at issue appeared within the Clinical section.

The Panel noted that there were important differences between the advertisement complained of and the editorial which appeared throughout the journal. The advertisement at issue was not listed on the contents page of the journal and its typeface and layout was different to that of the editorial.

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

The Panel noted that Roche had been approached by the NHS Journal of Healthcare Professionals for information on the use of epoetin beta in predialysis patients. It appeared that the journal wanted Roche to sponsor the article. Roche submitted that the journal had full editorial control over the feature although in fact no changes were made to the camera ready copy supplied by Roche other than the addition of the word 'Advertisement' on the top right hand corner of the left hand page. Roche had paid £3,500 in relation to the publication and sponsorship of the piece.

The Panel noted that companies could provide materials to journalists for their use in articles editorials, etc. This was usually done in the form of a press release or press pack. Any articles which appeared as the result of material given to the press must be printed at the publisher's expense. The payment of monies in such circumstances would render the article an advertisement.

The Panel did not accept that the matter was outside the scope of the Code as submitted by Roche. The company had in effect provided camera ready copy which discussed Roche's product and paid for the placement of the article. The Panel considered that the arrangements were such that the article constituted an advertisement subject to the Code and ought to have included prescribing information. A breach of Clause 4.1 was ruled.

Complaint received **7 October 2002**

Case completed **6 December 2002**

CASE AUTH/1371/10/02

PRIMARY CARE TRUST PROGRAMME DIRECTOR v ASTRAZENECA

Symbicort journal advertisement

The programme director of a primary care trust complained about an advertisement issued by AstraZeneca for Symbicort (budesonide/eformoterol) which appeared in Nursing Times. The advertisement took the form of an advertorial headed 'Asthma action plans and adjustable dosing is efficacious and cost effective, using less drug than fixed dosing'. The text referred to personalised asthma action plans (PAAPs) and the use of Symbicort in such plans. A recent study (ASSURE) had shown that patients using adjustable dosing of Symbicort with a PAAP used less doses of the medicine over 12 weeks compared to fixed dosing. It was stated that this could result in considerable cost-savings to the NHS.

The complainant alleged that the claim 'Research suggests that written personalised asthma action plans (PAAPs) are an effective intervention in the routine management of asthma' was misleading and not a fair representation of the evidence base. The complainant cited Jones *et al* 2002 which suggested that personalised plans were not always successful.

The Panel noted that Jones *et al* concluded that attempts to introduce self-guided management plans in primary care were unlikely to be successful. However, a Cochrane Review (Gibson *et al* 2002) had concluded that self-management education of adults with asthma resulted in clinically important improvements in asthma health outcomes. This was most apparent with interventions involving a written action plan, self-monitoring and regular medical review. The Panel considered the balance of the evidence lay as reported in the Cochrane review. The Panel did not consider that the claim was misleading as alleged or that it was an unfair representation of the evidence base. No breach of the Code was ruled.

The complainant noted that the reference cited in support of the statement 'The latest guidelines recommend that written PAAPs should now be offered to all asthma patients' was to draft guidelines, not yet fully agreed and published. The Panel considered that 'The latest guidelines' implied that the guidelines being referred to had been accepted; this was not so. The Panel considered that the statement was misleading and ruled a breach of the Code.

A graph entitled 'Patients in the adjustable dosing group used less treatment overall' showed the mean daily number of inhalations (y-axis) over time (x-axis). The y-axis had been shortened between 0 and 3 and then had points for 3, 3.5 and 4 inhalations daily. The complainant stated that the abbreviated y-axis overstated the benefits of adjustable dosing.

The Panel considered that the use of a suppressed zero on the y-axis exaggerated the benefits of adjustable dosing by making the line for that arm of the study appear closer to baseline, ie no inhalations per day, than was the case. The Panel considered that the graph was misleading in that regard and ruled a breach of the Code.

The claim 'This new data supports the role of Symbicort in encouraging the use of guided PAAPs' appeared as part of the conclusion. The complainant stated that he could see no evidence that the use of Symbicort increased the likelihood of a self-management plan being followed.

The Panel noted that the ASSURE study had shown that Symbicort was a suitable treatment option when using guided PAAPs. In the Panel's view, however, the claim in question went further by implying that Symbicort, as opposed to other medicines, encouraged the use of guided PAAPs. There was no evidence in this regard. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

The programme director at a primary care trust, complained about an advertisement (ref 11026A) issued by AstraZeneca UK Limited for Symbicort (budesonide/eformoterol) which appeared in Nursing Times, 1 October 2002. The advertisement, and an alternative version of it, also appeared in other nursing journals; the alternative version had also appeared in Pulse, 14 October 2002.

The advertisement at issue took the form of an advertorial headed 'Asthma action plans and adjustable dosing is efficacious and cost effective, using less drug than fixed dosing'. The text referred to personalised asthma action plans (PAAPs) and the use of Symbicort in such plans. A recent study (ASSURE) had shown that patients using adjustable dosing of Symbicort with a PAAP used less doses of the medicine over 12 weeks compared to fixed dosing. It was stated that this could result in considerable cost-savings to the NHS.

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.8 of the Code.

1 Claim 'Research suggests that written personalised asthma action plans (PAAPs) are an effective intervention in the routine management of asthma'

COMPLAINT

The complainant stated that the first sentence of the summary was misleading and not a fair representation of the evidence base. The complainant cited Jones *et al* 2002 which, although an observational study, suggested that personalised plans were not always successful.

RESPONSE

AstraZeneca stated that it was not entirely clear what the complainant meant by 'the first sentence of the

summary', however the company assumed it to be the first sentence of the opening paragraph of the advertisement as quoted above. This claim was referenced to Beasley *et al* (1989) and accurately reflected the authors' work which clearly demonstrated the clinical benefits to asthma patients when using self-management plans as part of their treatment.

AstraZeneca provided an expert report on the matter written by Professor Martyn Partridge, Chief Medical Adviser for the UK National Asthma Campaign, who led the Executive Committee on the patient education and compliance section of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Asthma Guidelines. The report discussed the recent Cochrane Review of 24 randomised controlled trials, involving over 2800 asthma patients, which demonstrated that guided self-management plans when used to treat asthma were associated with significant clinical benefits such as reductions in patient hospitalisation visits, emergency room visits, time off work or school, and night-time symptoms. On the strength of this data, the BTS/SIGN Executive Committee had recommended that in the new guidelines, all asthma patients should be offered an asthma action plan by their health care provider.

AstraZeneca refuted the allegation that the claim was misleading or unfair or that there had been a breach of Clause 7.2 of the Code.

PANEL RULING

Clause 7.2 of the Code required, *inter alia*, claims to be based upon an up-to-date evaluation of all the evidence and reflect that evidence clearly. The complainant had cited one paper, Jones *et al* which had concluded that attempts to introduce self-guided management plans in primary care were unlikely to be successful. More recently however, a Cochrane Review (Gibson *et al* 2002) had concluded from a number of papers that self-management education of adults with asthma resulted in clinically important improvements in asthma health outcomes. This was most apparent with interventions involving a written action plan, self-monitoring and regular medical review. The British Guidelines on Asthma Management (1997) referred to patient education and guided self-management plans and stated that giving those with asthma written self management plans so that they might adjust treatment to keep themselves well, reduced morbidity and health costs.

The Panel considered that although Jones *et al* had shown otherwise the balance of the evidence lay as reported in the Cochrane review. The Panel did not consider that the claim was misleading as alleged or that it was an unfair representation of the evidence base. No breach of Clause 7.2 was ruled.

2 Statement 'The latest guidelines recommend that written PAAPs should now be offered to all asthma patients'

This statement appeared as the first sentence of the final 'Conclusion' paragraph.

COMPLAINT

The complainant noted that the reference cited in support of this statement was to draft guidelines, not yet fully agreed and published.

RESPONSE

AstraZeneca noted that the cited reference was the soon to be published new BTS/SIGN guidelines. This draft document had been in the public domain since October 2001. The guidelines had been used by AstraZeneca and other companies such as GlaxoSmithKline in promotional and educational material when discussing asthma treatment.

AstraZeneca noted that the expert report stated that it was not possible to pre-empt what would be in the final published version of the BTS/SIGN guidelines, but given the weight and strength of evidence, recommendations for offering personal written asthma action plans would be included as in the draft guidelines.

AstraZeneca did not consider that the statement was misleading or incapable of substantiation.

PANEL RULING

The Panel considered that 'The latest guidelines' implied that the guidelines being referred to had been accepted; this was not so. The cited reference to the draft guidelines did not negate this impression. The Panel considered that the statement was misleading and ruled a breach of Clause 7.2 of the Code.

3 Alleged misleading use of abbreviated y-axis

A graph entitled 'Patients in the adjustable dosing group used less treatment overall' showed the mean daily number of inhalations (y-axis) over time (x-axis). The y-axis had been shortened between 0 and 3 and then had points for 3, 3.5 and 4 inhalations daily. Patients taking fixed doses of medication had between 3.5 and 4 inhalations a day whereas those on flexible dosing had between 3 and 3.5 inhalations a day.

COMPLAINT

The complainant stated that the abbreviated y-axis overstated the benefits of adjustable dosing.

RESPONSE

AstraZeneca stated that the graph presented the results of the ASSURE study which were recently presented at the European Respiratory Society conference in Stockholm, September 2002. The ASSURE study involved 1539 asthma patients from the UK with the primary objective of comparing adjustable (as part of an agreed management plan) and fixed (2 inhalations bd) dosing of Symbicort. The results demonstrated that when compared with fixed doses of Symbicort, patients using adjustable dosing used significantly less medicine ($p<0.05$). There were no differences between treatment arms with regard to the level of asthma control. The y-axis of the graph depicted the mean daily number of inhalations and used a scale of 0-4 which included a suppressed zero.

AstraZeneca noted that the supplementary information to Clause 7.8, Artwork, did not categorically prohibit the use of suppressed zeros in promotional material. Instead it advised that 'Particular care should be taken with graphs and tables to ensure that they do not mislead, for example by their incompleteness or by the use of suppressed zeros or unusual scales'.

Owing to the fact that the difference between the two treatment arms reached statistical significance, AstraZeneca did not consider that using a graph with a suppressed zero scale to present the results exaggerated or over-stated the advantage of one arm over the other in this instance. The use of the suppressed zero was purely for presentational reasons.

AstraZeneca stated that in its opinion presenting the results in this manner did not constitute a breach of Clause 7.8.

PANEL RULING

The Panel considered that the use of a suppressed zero on the y-axis exaggerated the benefits of adjustable dosing by making the line for that arm of the study appear closer to baseline, ie no inhalations per day, than was the case. The Panel considered that the graph was misleading in that regard and ruled a breach of Clause 7.8 of the Code.

4 Claim 'This new data supports the role of Symbicort in encouraging the use of guided PAAPs'

This claim appeared as part of the conclusion.

COMPLAINT

The complainant stated that he could see no evidence that the use of Symbicort increased the likelihood of a self-management plan being followed.

RESPONSE

AstraZeneca stated that the claim was based on the results of the ASSURE study which demonstrated that adjustable dosing with Symbicort was as effective as fixed dosing in certain efficacy parameters. These included significant improvements in symptom control, preventing asthma exacerbations and improving quality of life scores throughout the 12-week study period.

However, differences between the groups were seen as shown by the relative amount of asthma medication used in the trial. In the adjustable dosing group, patients used significantly less Symbicort and reliever treatment than fixed therapy despite a similar level of asthma control. This was in line with international asthma guidelines which endorsed the maintenance of optimal asthma control together with using the lowest possible inhaled steroid dose. These results therefore supported the use of Symbicort as a suitable medicine when using guided PAAPs by not only gaining and maintaining asthma control but also by using a lower overall amount of medication than fixed therapy.

Furthermore, data had shown that asthma patients expressed a greater level of enablement in the adjustable Symbicort arm when following a PAAP compared with the fixed dosing Symbicort arm. A subgroup of 228 patients from the ASSURE trial were asked to complete a validated Patient Enablement Instrument questionnaire. This set out to record how patients felt about their own level of asthma control. Patients' responses were scored 0 ('same or less' or 'not applicable') to 2 (much better). A mean difference in total scores ≥ 0.8 between groups, or an individual's total score ≥ 6 was considered to reflect a clinically relevant treatment benefit. The study showed that a statistically greater proportion of patients receiving adjustable dosing had a score ≥ 6 compared with fixed dosing (57% vs 43%, p=0.04) meaning that guided self-management with Symbicort provided a greater level of patient enablement than fixed dosing.

AstraZeneca stated that these results supported the use of Symbicort as a suitable treatment option for use in guided PAAPs. In addition Symbicort Turbohaler, a single combination inhaler, allowed the patient to adjust the dose of their maintenance treatment in response to breakthrough symptoms in order to maintain asthma control and therefore was particularly suitable for an agreed personalised asthma plan.

AstraZeneca did not consider the claim was misleading or incapable of substantiation; it denied breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that the ASSURE study had shown that Symbicort was a suitable treatment option when using guided PAAPs. In the Panel's view, however, the claim in question went further by implying that Symbicort, as opposed to other medicines, encouraged the use of guided PAAPs. There was no evidence in this regard. The Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **10 October 2002**

Case completed **2 December 2002**

CASE AUTH/1372/10/02

ANONYMOUS DOCTOR v DERMAL LABORATORIES

Promotional Aid

An anonymous doctor questioned how a sticky roller, offered via a mailing by Dermal Laboratories, was relevant to the practice of medicine. The reply paid card included in the mailing had the headline 'spruce up with this handy sticky roller' and stated that 'This handy 'sticky' roller will remove fluff, lint, pet hairs and almost anything else from almost any surface!'. The revolving drum of the roller had two product logos printed on it. The mailing had been sent to GPs and consultant dermatologists.

The Panel noted that the sticky rollers were acceptable on the grounds of cost as each one had cost the company £1.40. However, the Panel did not consider that the sticky roller was sufficiently relevant to the practice of medicine. It was to be used to keep the surgery clean or to aid personal grooming. The Panel ruled that the item was in breach of the Code.

An anonymous doctor wrote to the Authority about a sticky roller offered by Dermal Laboratories Ltd; in accordance with established practice the letter was accepted as a complaint under the Code and dealt with in the usual way.

The sticky roller had been offered via a mailing (ref CAP187/AUG02) on the use of Capasal Shampoo and Betacap Scalp Application in the treatment of psoriasis. The reply paid card included in the mailing (ref CAP188/AUG02) had the headline 'spruce up with this handy sticky roller' and stated that 'This handy 'sticky' roller will remove fluff, lint, pet hairs and almost anything else from almost any surface!'. The revolving drum of the roller had Capasal and Betacap product logos printed onto it. The mailing had been sent to GPs and consultant dermatologists.

COMPLAINT

The complainant questioned how the sticky roller was relevant to the practice of medicine. The complainant stated that (s)he was sent it that morning.

RESPONSE

Dermal pointed out that when the complainant stated that (s)he 'was sent it that morning' (s)he was presumably referring to the mailing offering the sticky roller, not to the roller itself. Dermal wanted to make clear that it had not mailed out unsolicited rollers.

Dermal stated that the roller was of relevance to the practice of medicine as it could be used by the doctor either in the surgery or in the course of home visits.

In the course of a day's surgery, the average doctor would receive a steady stream of patients wearing a variety of apparel and suffering from a variety of conditions. As a result, the surface of his/her patients' chairs and, more particularly, examination couches, could often become littered, if not contaminated, by a variety of matter. This would include hair, skin debris, wound exudate, dandruff, psoriatic scales and fluff. Some of these were readily visible, some not. The sticky roller was such that it would pick up virtually everything in a quick, comprehensive and hygienic manner. It was much more convenient than washing a surface, for which there was not always time and, in the case of fabric surfaces, might be inadvisable.

Home visits might be a bit of a rarity these days, but they still happened. Not all homes visited were the cleanest imaginable – pets of all descriptions abounded. If a doctor was seated in a chair recently vacated by a cat or dog or by someone munching crisps, their next patient might not be impressed by the unprofessional image conveyed by a suit transporting the evidence from the previous visit.

Dermal stated that the roller was not expensive each one had cost £1.40. To be relevant to the practice of medicine whilst also satisfying low-cost criteria, a promotional aid could rarely be a medical device – but it could still be a very useful item for doctors in the course of their work. Dermal considered the roller was exactly that and was surprised that anyone would see fit to complain about it. Presumably the anonymity of the complainant reflected their lack of conviction. Dermal trusted the Authority would agree that this complaint was without merit.

PANEL RULING

The Panel noted that Clause 18.2 required gifts in the form of promotional aids to health professionals to be inexpensive and relevant to the practice of their profession or employment. Inexpensive was defined as costing the donor company no more than £6 excluding VAT. The Panel noted that the sticky rollers were acceptable on the grounds of cost as each one had cost the company £1.40. The Panel did not consider that the sticky roller was sufficiently relevant to the practice of medicine. It was to be used to keep the surgery clean or to aid personal grooming. The Panel ruled that the item, by not meeting the provisions of Clause 18.2, was in breach of Clause 18.1 of the Code.

Complaint received	**10 October 2002**
Case completed	**19 November 2002**

ANONYMOUS DOCTOR v GLAXOSMITHKLINE

'Diabetes First' journal advertisements

An anonymous doctor complained that 'Diabetes First' advertisements issued by GlaxoSmithKline were backdoor promotion of Avandia. The advertisements featured close up photographs of type 2 diabetics. Text superimposed on one of the photographs described the patient as being uncontrolled on monotherapy. Text below the photograph explained that tight, sustained control of glycaemia was essential to avoid vascular complications of type 2 diabetes and readers were reminded of the value of using combination therapy early in this regard. The patient in the other advertisement was described as looking fine but 'He could die tomorrow'. Text below his photograph stated that good glycaemic control could not be assessed by looking at a patient; the only reliable way was to measure HbA1c levels every 2-6 months. The 'Diabetes First' logo appeared in the bottom right hand corner of each advertisement and each carried a statement regarding GlaxoSmithKline's sponsorship.

Neither advertisement referred to a specific medicine. Although one advertisement referred to combination therapy, Avandia was not the only medicine which could be used in this regard. The Panel did not consider that the advertisements promoted Avandia. No breaches of the Code were ruled.

An anonymous doctor wrote to the Authority about 'Diabetes First' advertisements issued by GlaxoSmithKline UK Ltd; in accordance with established practice the letter was accepted as a complaint under the Code and dealt with in the usual way.

GlaxoSmithKline provided two advertisements. One of the advertisements (ref DFT/ADO/02/2712) featured a close up photograph of a woman and the headline 'This woman has type 2 diabetes. She's on monotherapy'. In the bottom right-hand corner of the photograph was the statement 'And she's out of control'. Text below the photograph explained that tight and sustained control of glycaemia was essential in order to avoid the vascular complications associated with type 2 diabetes. Readers were reminded of the value of using combination therapy early in this regard. The 'Diabetes First' logo appeared in the bottom right-hand corner of the advertisement. Small print at the bottom of the advertisement stated that 'Diabetes First' was a trademark of the GlaxoSmithKline Group of companies and that Diabetes First was sponsored by an educational grant from GlaxoSmithKline.

The second advertisement (ref DFT/ADO/02/2736) featured the close up photograph of a man. The headline stated 'He has type 2 diabetes. He looks fine'. In the bottom right-hand corner of the photograph was the statement 'He could die tomorrow'. Text below the photograph stated that good glycaemic control could not be assessed just by looking at a patient; the only reliable way was to measure HbA_{1c} levels. It was recommended that HbA_{1c} levels should be measured every 2-6 months and kept below 7%. The 'Diabetes First' logo appeared in the bottom right-hand corner of the advertisement and the statement regarding 'Diabetes First' being a trade mark and GlaxoSmithKline's sponsorship of the initiative, was along the bottom edge.

GlaxoSmithKline marketed Avandia (rosiglitazone) which was indicated for use either with metformin or a sulphonylurea in the management of type 2 diabetes.

The advertisements had appeared in Practice Nurse and Pulse.

COMPLAINT

The complainant alleged that the 'Diabetes First' advertisements were backdoor promotion of Avandia. If GlaxoSmithKline was promoting combination therapy in asthma, then the complainant would expect to see Seretide information on the equivalent advertisement, or Symbicort if they were AstraZeneca advertisements. The complainant did not provide copies of the advertisements.

When writing to inform GlaxoSmithKline of the complaint the Authority asked it to bear in mind the requirements of Clauses 4.1 and 10.1 of the Code.

RESPONSE

GlaxoSmithKline noted that the advertisements were solely concerned with increasing awareness of the need to monitor HbA1c regularly in type 2 diabetes and of the importance of rigorous blood glucose control. These priorities were fully in line with the findings of the United Kingdom Prospective Diabetes Study and with the guidelines issued by the National Institute for Clinical Excellence and those contained in the National Service Framework for Diabetes. No specific product or product class was mentioned, explicitly or implicitly, in either item. As such, GlaxoSmithKline believed that neither could be considered as promotional, and that therefore the company was not in breach of the Code.

PANEL RULING

Neither advertisement referred to a specific medicine. The advertisement featuring the photograph of a man made no reference to treatment of any kind; the advertisement featuring the photograph of a woman referred to combination therapy. Although GlaxoSmithKline marketed Avandia, a thiazolidinedione for use in combination with metformin or a sulphonylurea in the management of type 2 diabetes uncontrolled by monotherapy, it was not the only medicine in its therapeutic class and nor

were thiazolidinedione combinations the only ones which could be used in such circumstances. The Panel did not consider that the advertisements promoted Avandia. The advertisements thus did not constitute disguised promotion for the product nor did they require prescribing information for Avandia. No breach of Clauses 4.1 and 10.1 was ruled.

Complaint received **10 October 2002**

Case completed **25 October 2002**

CASE AUTH/1374/10/02

GLAXOSMITHKLINE v NEOLAB

Promotion of BDP Neo-Haler

GlaxoSmithKline complained about a detail aid and an advertisement issued by Neolab promoting beclometasone dipropionate (BDP) Neo-Haler. The Neo-Haler was a metered-dose inhaler (MDI) with a vortex generating actuator which acted to reduce the velocity of the emitted dose. Compared with a standard MDI the Neo-Haler decreased the proportion of non-respirable drug particles within the emitted dose cloud whilst achieving a similar respirable fraction.

GlaxoSmithKline stated that it had requested evidence to support the claim 'Local side effects in oropharynx with steroids may reduce compliance', however Neolab's response was that the claim was self-evident. In particular, Neolab referred to the British National Formulary (BNF) as it offered advice on corticosteroids with regard to oral candidiasis without any reference. GlaxoSmithKline did not know to what extent oral candidiasis was a problem for patients and, therefore, how much of a benefit this would be. There was also no evidence of which GlaxoSmithKline was aware which reported reduced compliance because of local side effects from inhaled medications.

The Panel noted that Neolab had not produced any evidence to show that local side effects in the oropharynx with steroids might reduce compliance. Companies needed to have specific data to support particular claims, it was not sufficient to state that the claim was self evident. The Panel ruled a breach of the Code.

The claim 'The Neo-Haler device gives equivalent efficacy to standard MDI and large volume spacer' appeared on page 4 which was headed 'Fundamental advantages of Neo-Haler device' and was referenced to Gunawardena *et al* (1997). GlaxoSmithKline stated that Gunawardena *et al* compared the bronchodilator effect of 200mcg salbutamol administered by a [Neo-Haler] with the same dose of salbutamol administered by an MDI plus Volumatic spacer device and found them to be equivalent. However, the detail aid in question was solely about the delivery of beclometasone via the Neo-Haler. The above claim therefore implied that the Neo-Haler gave equivalent efficacy to a standard MDI and large volume spacer for beclometasone. GlaxoSmithKline alleged that the claim was inaccurate, misleading and was not capable of substantiation.

In the Panel's view the results from Gunawardena *et al* applied to only salbutamol and could not be assumed to apply to beclometasone as submitted by Neolab. The data could not be extrapolated to beclometasone. The Panel considered that the claim was misleading and had not been substantiated. Breaches of the Code were ruled.

The claim 'May help reduce local and systemic side effects compared to conventional MDI' appeared on page 5 which was headed 'Potential benefits for the patient'. GlaxoSmithKline stated that the claim was referenced to Gunawardena *et al*. Gunawardena *et al* had only considered the proportion of the dose deposited in the oropharynx. The study did not evaluate the impact on local or systemic side effects. Furthermore the study compared the delivery of salbutamol not beclometasone. GlaxoSmithKline alleged that the claim was misleading and not supported by the reference.

The Panel noted that the paper cited was Newman *et al* (1999) and not Gunawardena *et al*. Newman *et al* was a randomised cross-over study on 12 asthmatic patients to compare the deposition of a single dose of radiolabelled beclometasone 250mcg administered via a [Neo-Haler] or conventional MDI. Although one of the conclusions of the study was that the Neo-Haler reduced the risk of local and systemic side effects there was no clinical data presented to show that this was the case. The Panel noted that the claim at issue was more circumspect than the study authors had been in that it stated 'May help reduce local and systemic side effects compared to conventional MDI'. Nonetheless, in the Panel's view, most readers would expect that the claim was based on data from a study which reflected the clinical usage of the product and this was not so. The Panel considered that the claim was misleading and that it had not been substantiated. Breaches of the Code were ruled.

The claim 'A cost-effective generic alternative' was the first of three which appeared on page 6 below the heading 'Beclomethasone 50, 100 and 250 microgram inhaler with Neo-Haler actuator offers'. GlaxoSmithKline considered that the claim implied that an economic evaluation had been carried out. No such evaluation had taken place. Accordingly GlaxoSmithKline alleged that the claim was misleading. Furthermore as the claim stated that the product was a cost-effective generic alternative,

without stating with which medicine it was an alternative to, GlaxoSmithKline alleged that this was a hanging comparison.

The Panel noted that the term 'cost effective' related to the economic evaluation of medicines. Cost-effectiveness took into account more than the acquisition cost and efficacy. Other costs were relevant. Neolab had not provided any economic evaluation data. The Panel considered that the claim was misleading as alleged and a breach of the Code was ruled. The Panel did not consider that the claim was a hanging comparison as alleged. It was clear that the comparison was with branded beclometasone and no breach of the Code was ruled in this regard.

The claim 'Equivalent efficacy to standard MDI with reduction in local and systemic side effects' also appeared on page 6 and was referenced to Newman and Clarke (1993).

GlaxoSmithKline stated that Newman and Clarke considered the radioaerosol deposition pattern and bronchodilator response following inhalation of 100mcg of salbutamol. The above claim implied that equivalent efficacy had been demonstrated for beclometasone, across the dose range when only one study at 100mcg salbutamol was referenced. GlaxoSmithKline alleged that the claim was misleading and unsupported by the evidence.

The Panel noted that the Newman and Clarke study was carried out on salbutamol. The results could not be assumed to apply to a beclomethasone Neo-Haler. The Panel considered that the claim was misleading and had not been substantiated by the studies referred to by Neolab. Breaches of the Code were ruled.

GlaxoSmithKline noted that the section titled 'Precautions' in the prescribing information included a statement 'May induce systemic corticosteroid effects … and adrenal suppression (above 2,000 micrograms daily) …'. GlaxoSmithKline alleged that this did not reflect the summary of product characteristics (SPC), which stated that 'Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression …'. GlaxoSmithKline's view was that the prescribing information gave the impression that adrenal suppression could only occur at doses above the maximum licensed dose.

The prescribing information made no mention of the recommendation in the SPC that the height of children receiving prolonged treatment with inhaled corticosteroids was regularly monitored. GlaxoSmithKline alleged that these were serious omissions.

The Panel considered that the prescribing information on the detail aid did not give the substance of the relevant information in the SPC. The Panel considered that Neolab had failed to meet the requirements of the Code and a breach was thus ruled.

GlaxoSmithKline also complained about a journal advertisement. A number of allegations were similar to those for the detail aid and the Panel referred to its rulings made above.

GlaxoSmithKline considered that the tone of the claim 'Everything you'll ever need in Generic Pharmaceutical Products' was not in keeping with the special nature of medicines and the professional standing of the audience to which it was directed.

The Panel did not consider that the claim failed to recognise the special nature of medicines or the professional standing of the audience as alleged. The Panel ruled no breach of the Code.

GlaxoSmithKline UK Ltd complained about the promotion of beclometasone dipropionate (BDP) Neo-Haler by Neolab Limited. The Neo-Haler was a metered-dose inhaler (MDI) with a vortex generating actuator which acted to reduce the velocity of the emitted dose. Compared with a standard MDI the Neo-Haler decreased the proportion of non-respirable drug particles within the emitted dose cloud whilst achieving a similar respirable fraction. GlaxoSmithKline marketed beclometasone (Becotide) in a standard MDI.

The materials at issue were a detail aid and an advertisement.

A Detail Aid

1 Claim 'Local side effects in oropharynx with steroids may reduce compliance'

Page 2 of the detail aid was headed 'Basic problems of conventional MDI' one of which was stated to be that most of the dose was deposited on the oropharynx. It was stated on page 3 (facing) that one of the 'Potential problems for the patient' was that 'Local side effects in oropharynx with steroids may reduce compliance'.

COMPLAINT

GlaxoSmithKline stated that it had requested evidence to support the claim, however Neolab's response was that the claim was self-evident. In particular, Neolab referred to the British National Formulary (BNF) as it offered advice on corticosteroids with regard to oral candidiasis without any reference.

GlaxoSmithKline did not know to what extent oral candidiasis was a problem for patients (much of the candidiasis reported in clinical trials was sub-clinical, ie found on mouth swabs, but not seen on examination by the clinician or reported by the patient) and, therefore, how much of a benefit this would be. There was also no evidence of which GlaxoSmithKline was aware, which reported reduced compliance because of local side effects from inhaled medications.

GlaxoSmithKline alleged that the claim was inaccurate in breach of Clause 7.2 of the Code.

RESPONSE

In Neolab's opinion the claim was still self-evident.

Any medication which was associated with uncomfortable or distressing side effects was less likely to be taken as directed. Neolab had mentioned, as an example, the oral candidiasis advice in the BNF. GlaxoSmithKline claimed not to know to what extent oral candidiasis was a problem for patients and, therefore, how much of benefit this might be.

Asymptomatic oral candidiasis might well be no problem for patients – self-defined by the word 'asymptomatic'. But the wording to which GlaxoSmithKline took exception was 'local side effects …' which by definition would not be asymptomatic.

Although not mentioned in GlaxoSmithKline's own literature for its beclometasone pressurised inhaler, sore mouth was a known side effect to steroid-containing inhalers. Neolab quoted from the 'Action Asthma' website sponsored by Allen & Hanburys: 'Some people find that their preventer can cause a sore mouth.', which then gave the usual advice for avoiding this side effect.

GlaxoSmithKline also stated that there was no evidence of which it was aware, which reported reduced compliance because of local side effects from inhaled medications. Neolab asked if one was supposed to take it that because GlaxoSmithKline did not know of any evidence, the company actually believed that local side effects would not affect compliance to inhaled medications. In the section on 'Guidance on Prescribing' the BNF listed a series of factors which might affect compliance to therapy:

'TAKING MEDICINES TO BEST EFFECT. Difficulties in compliance with drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

Prescription not collected or not dispensed
Purpose of medicine not clear
Perceived lack of efficacy
Real or perceived side-effects
Instructions for administration not clear
Physical difficulty in taking medicines (eg with swallowing the medicine, with handling small tablets, or with opening medicine containers)
Unattractive formulation (eg unpleasant taste)
Complicated regimen'

Amongst the factors listed were 'real or perceived side-effects'. In Neolab's view it was hardly necessary to continue.

PANEL RULING

The Panel noted that Neolab had not produced any evidence to show that local side effects in the oropharynx with steroids might reduce compliance. A general reference was made to factors contributing to poor compliance listed in the BNF; one of these was real or perceived side effects. Under the Code, however, companies needed to have specific data to support particular claims, it was not sufficient to state that the claim was self evident. The Panel ruled a breach of Clause 7.2 of the Code.

2 Claim 'The Neo-Haler device gives equivalent efficacy to standard MDI and large volume spacer'

The claim appeared on page 4 which was headed 'Fundamental advantages of Neo-Haler device'. The claim was referenced to a study by Gunawardena *et al* (1997).

COMPLAINT

GlaxoSmithKline stated that Gunawardena *et al* compared the bronchodilator effect of 200mcg salbutamol administered by a [Neo-Haler] with the same dose of salbutamol administered by an MDI plus Volumatic spacer device and found them to be equivalent. However, the detail aid in question was solely about the delivery of beclometasone via the Neo-Haler. The above claim therefore implied that the Neo-Haler gave equivalent efficacy to a standard MDI and large volume spacer for beclometasone.

Neolab's response was that this double page spread (pages 4 and 5) was referring to the Neo-Haler device rather than to beclometasone. However, GlaxoSmithKline considered that as the canister shown in the picture was clearly beclometasone there was no doubt that the customer was intended to read the claim as referring to beclometasone. One could not extrapolate data evaluating the effectiveness of salbutamol in improving lung function, to the effectiveness of beclometasone delivered through the same device. There were clear differences between salbutamol and beclometasone in pharmacotherapeutic and pharmacokinetic effects.

GlaxoSmithKline alleged that the claim was inaccurate, misleading and was not capable of substantiation, in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Neolab stated that the claim was indeed referenced to a paper which used a salbutamol MDI with and without a Volumatic spacer to evaluate the Neo-Haler device (called Spacehaler in the paper). The action of a spacer was based on the physical nature of aerosol sprays delivered from a conventional MDI into the enclosed volume of the spacer device. The two benefits spacers offered were to avoid co-ordination problems in some patients and also to reduce the large particle fraction which was what tended to be deposited in the oropharynx.

Neolab noted that the BNF stated: 'The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx. In addition the device allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs'. This referred to spacers and inhalers without mentioning a specific therapeutic agent. Neolab emphasised that the spacer was used irrespective of the active medication when a pressurised inhaler was taken by the patient. Neolab noted that the BNF did not give any references either.

In Neolab's opinion, it was ingenuous to say that one could not extrapolate data from the efficacy of one medicine comparing the use of two particular devices to the efficacy of another medicine using the same two devices. Gunawardena *et al* used clinical efficacy of a salbutamol MDI as a measure of the comparative

effectiveness of the Neo-Haler and a spacer. As a choice of an indicating model, a quick acting bronchodilator was clearly superior to a slow acting anti-inflammatory. Neolab accepted that there were pharmacotherapeutic and pharmacokinetic differences between salbutamol and beclometasone but stated that this was not the matter in question. The point here was whether or not the Neo-Haler device gave equivalent efficacy to standard MDI and large volume spacer.

Neolab considered that GlaxoSmithKline was being deliberately obtuse and was deliberately invoking spurious claims that were not in the detail aid.

PANEL RULING

In the Panel's view the results from Gunawardena *et al* applied to only salbutamol and could not be assumed to apply to beclometasone as submitted by Neolab. The Panel noted Neolab's reference to the BNF which gave general information about the effect of using a spacer. The BNF was not evaluating the similarities or otherwise between the Neo-Haler device and a standard MDI and large volume spacer. The page of the detail aid in question clearly related to BDP. The data could not be extrapolated to beclometasone.

The Panel considered that the claim was misleading and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Claim 'May help reduce local and systemic side effects compared to conventional MDI'

The claim appeared on page 5 which was headed 'Potential benefits for the patient'. The claim was referenced to a study by Newman *et al* (1999).

COMPLAINT

GlaxoSmithKline stated that the claim was referenced to Gunawardena *et al* (point A2 above). Gunawardena *et al* had only considered the proportion of the dose deposited in the oropharynx. The study did not evaluate the impact on local or systemic side effects. Furthermore the study compared the delivery of salbutamol not beclometasone.

GlaxoSmithKline had requested evidence to support the claim. However Neolab had not addressed this concern in its response. GlaxoSmithKline considered that where such a claim or statement was made, supporting evidence should be made available. Accordingly GlaxoSmithKline alleged that the claim was misleading and not supported by the reference in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Neolab stated that the claim was clearly referenced to Newman *et al* (1999). The reason that Neolab might have appeared not to respond to GlaxoSmithKline's concern was that it could not believe that any reasonably informed person could misinterpret the message from the correct reference as supporting the claim.

Neolab noted that in the final paragraph of the Newman *et al* study the authors stated: 'On the basis of this study, the Spacehaler [Neo-Haler] represents an improvement over conventional MDIs. It provides more efficient delivery of drug to the lungs, reduces the risk of local and systemic side-effects from the oropharyngeal deposition and results in a lower total dose of drug being delivered to the patient'.

Neolab stated that this paragraph, particularly the last sentence, was entirely compatible with the claim that the Neo-Haler 'May help reduce local and systemic side effects compared to conventional MDI'.

PANEL RULING

The Panel noted that GlaxoSmithKline was incorrect with regard to the reference cited in support of the claim. The paper cited was Newman *et al* (1999) and not Gunawardena *et al*. Newman *et al* was a randomised cross-over study on 12 asthmatic patients to compare the deposition of a single dose of radiolabelled beclometasone 250mcg administered via a [Neo-Haler] or conventional MDI. The study concluded that the [Neo-Haler] represented an improvement over conventional MDIs. It provided more efficient delivery of medicine to the lungs, reduced the risk of local and systemic side effects from oropharyngeal deposition and resulted in a lower total dose of medicine being delivered to the patient.

Although one of the conclusions of the study was that the Neo-Haler reduced the risk of local and systemic side effects there was no clinical data presented to show that this was the case. The Panel noted that the claim at issue was more circumspect than the study authors had been in that it stated 'May help reduce local and systemic side effects compared to conventional MDI'. Nonetheless, in the Panel's view, most readers would expect that the claim was based on data from a study which reflected the clinical usage of the product and this was not so. The Panel also noted that the use of the word 'may' in a claim rarely negated the impression that a product 'would' do something.

The Panel considered that the claim was misleading and that it had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

4 Claim 'A cost-effective generic alternative'

This claim was the first of three which appeared on page 6 below the heading 'Beclomethasone 50, 100 and 250 microgram inhaler with Neo-Haler actuator offers'.

COMPLAINT

GlaxoSmithKline stated that no cost-effectiveness data were presented to support the claim. There was no reference and no further explanation was given. GlaxoSmithKline had requested supporting evidence from Neolab, but it had responded that in its opinion this was not a claim for cost effectiveness, merely a statement as it was not stated that the product or the device was more effective than any other.

GlaxoSmithKline considered that the claim implied that an economic evaluation had been carried out. No such evaluation had taken place. Accordingly GlaxoSmithKline alleged that the claim was misleading in breach of Clause 7.2 of the Code.

Furthermore as the claim stated that the product was a cost-effective generic alternative, without stating with which medicine it was an alternative to, GlaxoSmithKline alleged that this was a hanging comparison in breach of Clause 7.2 of the Code.

RESPONSE

Neolab stated that this continued mis-interpretation of a simple statement of fact that the Neo-Haler offered 'a cost-effective generic alternative' was laughable. Again, the letter from GlaxoSmithKline stated that: Neolab had responded that in its opinion this was not a claim for cost effectiveness, merely a statement as it was not stated that the product or the device was more effective than any other was. Did GlaxoSmithKline perhaps not understand Neolab's reply that 'There is no hanging comparison because there is no comparison being made, merely a statement that it is cost-effective.'?

The continued complaint that there was a hanging comparison relating to the phrase 'generic alternative' could not really be a serious attempt at critical and informed debate to maintain high standards of promotional literature. Did GlaxoSmithKline really disagree that a generic product was not an alternative to a branded product?

PANEL RULING

The Panel noted that the term 'cost effective' related to the economic evaluation of medicines. Cost-effectiveness took into account more than the acquisition cost and efficacy. Other costs were relevant. Neolab had not provided any economic evaluation data. The Panel considered that the claim was misleading as alleged and a breach of Clause 7.2 of the Code was ruled.

The Panel did not consider that the claim was a hanging comparison as alleged. It was clear that the comparison was with branded beclometasone and no breach of Clause 7.2 of the Code was ruled in this regard.

5 Claim 'Equivalent efficacy to standard MDI with reduction in local and systemic side effects'

This was the second claim which appeared on page 6. The claim was referenced to Newman and Clarke (1993).

COMPLAINT

GlaxoSmithKline stated that Newman and Clarke considered the radioaerosol deposition pattern and bronchodilator response following inhalation of 100mcg of salbutamol from a metered dose inhaler and the Gentlehaler [low velocity MDI]. The above claim implied that equivalent efficacy had been demonstrated for beclometasone, across the dose range when only one study at 100mcg salbutamol was referenced.

GlaxoSmithKline raised this concern with Neolab, which responded that as the referenced paper stated '… this device appears to offer potential advantages for inhaler therapy' the claim did not imply any more than stated in the study. GlaxoSmithKline disagreed and considered that the claim extrapolated from a potential advantage suggested by the authors for another medicine and could not be considered to be supported by the evidence.

GlaxoSmithKline alleged that the claim was misleading and unsupported by the evidence in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Neolab stated that it could be argued that the Newman and Clarke paper used to support the claim was inappropriate. Indeed the other Newman *et al* (1999) quoted in point A3 above might well appear to be a better justification for a beclometasone containing MDI. Maybe it should have been used and it could even be a misprint in the original printing that should have been picked up.

However, Newman and Clarke's opinion was that: '... this device appears to offer several potential advantages for inhaler therapy: (1) a reduction in the incidence of 'cold Freon' problems when using MDIs; … (2) a reduction in the incidence of the local and systemic side effects associated with high-dose inhaled corticosteroids, which are probably related chiefly to high oropharyngeal deposition; …'.

It appeared to Neolab that the claim echoed Newman and Clarke.

PANEL RULING

The Panel noted that Newman and Clarke stated that the Gentlehaler appeared to offer several potential advantages for inhaler therapy. One of the listed potential advantages was a reduction in local and systemic side-effects associated with high dose inhaled corticosteroids which were probably related chiefly to high oropharyngeal deposition. The claim was not similarly qualified.

The Panel noted that the Newman and Clarke study was carried out on salbutamol. The results could not be assumed to apply to a beclomethasone Neo-Haler. This was similar to point A2 above. The Panel noted its comments about Newman *et al* (1999) in point A3 above. The Panel considered that the claim was misleading and had not been substantiated by the studies referred to by Neolab. Breaches of Clauses 7.2 and 7.4 were ruled.

6 Prescribing Information

COMPLAINT

GlaxoSmithKline noted that the section titled 'Precautions' in the prescribing information included a statement 'May induce systemic corticosteroid

effects … and adrenal suppression (above 2,000 micrograms daily) …'.

GlaxoSmithKline alleged that this did not reflect the summary of product characteristics (SPC), which stated that 'Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression …'. GlaxoSmithKline's view was that the prescribing information gave the impression that adrenal suppression could only occur at doses above the maximum licensed dose.

The prescribing information made no mention of the recommendation in the SPC that the height of children receiving prolonged treatment with inhaled corticosteroids was regularly monitored. This was of special concern as Neolab included the statement 'Growth retardation in children is not usually associated with inhaled steroids' in its 'Formulary Facts Inhaled Beclometasone' insert in the 22 May issue of Chemist and Druggist.

GlaxoSmithKline alleged that these were serious omissions in breach of Clause 4.2 of the Code.

RESPONSE

Neolab submitted that prescribing information was of course required in all promotional material (except abbreviated advertisements) and must be consistent with the SPC. It did not have to contain all of the advice in the SPC, so that some of the new complaints made by GlaxoSmithKline not included in its original letter to Neolab would seem to be unjustified, eg recommendation that children's height was regularly monitored. It should also be noted that the prescribing information also did not include warnings of decreases of bone mineral density, cataracts or glaucoma.

It was a matter of interpretation whether the prescribing information gave the impression that adrenal suppression could only occur at doses above the maximum licensed dose. Since the prescribing information contained the standard advice to refer to the SPC before prescribing, one would not assume that this should be the only information available to a prescriber before he or she treated a patient.

PANEL RULING

The Panel noted Clause 4.2 which required, *inter alia*, that the prescribing information was a succinct statement of the side effects, precautions and contraindications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the SPC.

The SPC stated:

> 'Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.
>
> It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.
>
> Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.'

The prescribing information on the piece in question stated:

> '**Precautions:** Patients should be instructed in the correct use of inhalers. May induce systemic corticosteroid effects (with reduction in plasma cortisol levels) and adrenal suppression (above 2,000 micrograms daily) – monitor adrenal function and provide systemic steroid in appropriate cases of stress. Caution in patients with history of, or active pulmonary tuberculosis. Avoid sudden cessation of treatment. Not for relief of acute symptoms.'

The Panel considered that the prescribing information on the detail aid did not give the substance of the relevant information in the SPC. In this regard the SPC did not link adrenal suppression to a particular steroid dose whereas the prescribing information stated that it might happen at above 2000mcg daily and there was no mention in the prescribing information of the recommendation to regularly monitor the height of children receiving prolonged treatment.

The Panel considered that the prescribing information failed to include the elements required by Clause 4.2 of the Code and therefore Neolab had failed to meet the requirements of Clause 4.1 of the Code and a breach was thus ruled.

The Panel noted that there was no formal complaint under the Code about the 'Formulary Facts Inhaled Beclometasone' insert so it did not consider the document.

B Beclometasone Inhaler advertisement

GlaxoSmithKline also complained about a journal advertisement. A number of allegations were similar to those for the detail aid.

1 Claim 'A cost effective generic alternative'

As Point A4 above.

2 Claim 'Equivalent efficacy to standard MDI with reduction in local and systemic side effects'

As Point A5 above.

3 Claim 'The Neo-Haler device gives equivalent efficacy to standard MDI and large volume spacer'

As Point A2 above.

4 Prescribing Information

As Point A6 above.

5 Claim 'Everything you'll ever need in Generic Pharmaceutical Products'

This claim appeared at the bottom of the advertisement, just above the Neolab company logo.

COMPLAINT

GlaxoSmithKline considered that the tone of this claim was not in keeping with the special nature of medicines and the professional standing of the audience to which it was directed. It would seem to be an exaggeration and to be more in keeping with a supermarket or DIY store than a medical advertisement. GlaxoSmithKline alleged a breach of Clause 9.1 of the Code.

RESPONSE

Neolab understood that this advertisement was directed to retail and wholesale pharmacists. The claim could be considered to be a statement of fact or justified hyperbole in an advertisement. It was a matter of interpretation as to what the reader might infer from this claim and whether the phrase demeaned the professional standing of the target audience or was likely to cause offence.

PANEL RULING

The Panel did not consider that the claim failed to recognise the special nature of medicines or the professional standing of the audience as alleged. It was unclear whether it referred to the Neo-Haler range as being everything that was ever needed in generic pharmaceutical products or whether Neolab produced everything that was ever needed in generic pharmaceutical products. The Panel ruled no breach of Clause 9.1 of the Code.

Complaint received **10 October 2002**

Case completed **6 December 2002**

CASE AUTH/1375/10/02

PHARMACIA v ALLERGAN

Sampling of Lumigan

Pharmacia complained about the way in which representatives of Allergan had been distributing samples of Lumigan. Pharmacia alleged that members of its sales team noted that at two meetings in October Allergan representatives were allowing visitors to their stands to take bottles of Lumigan in a poorly regulated manner. The meetings were held in a hotel in Scotland and a hospital in Birmingham.

The bottles of Lumigan were not labelled as samples. Dated signatures, whilst collected from some delegates, were not a prerequisite before release. Pharmacia's representatives attending the Scottish meeting (neither of whom were health professionals) had helped themselves to two bottles in an attempt to provide evidence. The representatives took photographs of Allergan's stand; copies of these were provided. Pharmacia stated that an Allergan regional manager was present at the Scottish meeting and so this did not simply reflect the activities of an inexperienced representative.

The Panel noted that at the meeting held in Scotland, samples of Lumigan had been given to two people, a nurse and a vet, neither of whom were health professionals qualified to prescribe the product. A breach of the Code was ruled.

The Panel noted that Pharmacia had stated that at the Scottish meeting its representatives had helped themselves to two bottles of Lumigan without the need to sign and date a request form. Allergan had stated that the only samples of Lumigan given out were those that had been signed for. The company had, however, also stated that there were no records to reconcile the number of samples of Lumigan taken to the meeting, the number given out and the number left. The Panel considered that the balance of probability, given that Allergan had no system to account for samples, was that some samples of Lumigan were taken without the required written request which had been signed and dated; a breach of the Code was ruled.

The samples of Lumigan distributed at the meeting in Scotland had not been marked 'free medical sample – not for resale' or similar. A breach of the Code was ruled.

The Code required that samples distributed by representatives must be handed direct to health professionals requesting them or persons authorized to receive them on their behalf. At the meeting in Scotland samples had been given to a nurse and a vet. The Panel considered, however, that its first ruling above covered this alleged breach of the Code.

With regard to the meeting held in the Midlands the signed and dated requests for samples of Lumigan had all come from health professionals qualified to

prescribe the product. The Panel ruled no breach of the Code. Allergan had stated that the only samples given out were in response to signed and dated requests; Pharmacia had submitted no evidence that samples had been taken without such requests. The Panel ruled no breach of the Code. The bottles of Lumigan had been labelled with a sticker which read 'Free medical sample – not for re-sale'. The Panel considered that there was no evidence that the samples distributed by the representatives at the meeting had not been handed directly to the health professionals requesting them. No breaches of the Code were ruled.

With regard to both meetings the Panel noted that Allergan had stated that it did not hold records to reconcile the number of samples of Lumigan taken to each meeting, the number given out and the number left. Allergan did not have adequate systems of control and accountability for the samples of Lumigan distributed by its representatives. A breach of the Code was ruled.

COMPLAINT

Pharmacia Limited complained about the way in which representatives of Allergan Ltd had been distributing samples of Lumigan.

Pharmacia had contacted Allergan on 18 September regarding the delivery of 12 bottles of Lumigan to a hospital pharmacy. Pharmacia stated that it was also aware of other instances throughout the UK of sampling regulations being ignored by Allergan representatives, and hoped that a formal reminder by senior management would rectify this. Allergan's reply dated 27 September, whilst contestable with regard to the hospital, initially provided Pharmacia with the reassurance sought, notably: 'The Sales Team have been made aware of the importance of adhering to the Code of Practice and that failure to do so will have severe implications for the individual involved'. However, members of Pharmacia's sales team noted that at two meetings on Friday, 4 October, Allergan representatives were allowing visitors to their stands to take bottles of Lumigan in a very poorly regulated manner. The meetings were the Scottish Ophthalmology Club Autumn Meeting and the Midlands Ophthalmology Society Meeting.

Pharmacia stated that the bottles of Lumigan were not labelled as samples. Dated signatures, whilst collected from some delegates, were not a prerequisite before release. Pharmacia's representatives attending the Scottish meeting (neither of whom were health professionals) had helped themselves to two bottles in an attempt to provide evidence. The representatives at this meeting also bought a disposable camera and took photographs of Allergan's stand; copies of these were provided. Pharmacia stated that an Allergan regional manager was present at the Scottish meeting and so this did not simply reflect the activities of an inexperienced representative. Breaches of Clauses 17.1, 17.3, 17.5, 17.7 and 17.9 of the Code were alleged.

Pharmacia stated that it accepted that an individual could let a company down, however the company was particularly concerned that two representatives in different parts of the country had committed the same offence so soon after a warning from their Managing Director. Pharmacia noted that it did not receive a copy of the communication to the sales force, despite requesting it in its letter to Allergan of 18 September.

RESPONSE

Allergan stated that the attendance list for the Scottish Ophthalmology Club Autumn Meeting, provided by the organisers, included the names of 53 ophthalmologists or doctors with an interest in ophthalmology, all of whom were qualified to prescribe Lumigan. The company did not have details of actual attendance at the meeting, however its representative considered that not all doctors listed attended, and some doctors who were not listed did. In addition, the company was aware that 20-30 nurses also attended the meeting but it had no details of these.

The Allergan stand was manned by two representatives, one of whom was an area sales manager. Samples of Lumigan were available from the stand in response to signed written and dated requests. Such requests were received from two individuals (copies of the signed/dated request forms were provided). Regrettably, it appeared on examining these requests that one was from a nurse, who received six samples, and the other was from a vet, who received one sample. Neither of these was qualified to prescribe Lumigan. Allergan therefore accepted a breach of Clause 17.1 of the Code.

It was also regrettable that the bottles of Lumigan which were supplied in response to these requests were normal stock and were not labelled as samples. The representative concerned was unable to explain, other than by a lapse in attention to detail, why normal stock was available at the stand instead of correctly labelled samples. Allergan therefore accepted a breach of Clause 17.5 of the Code.

The representative concerned had passed the ABPI representatives' examination. He was experienced, conscientious, and normally punctilious. Clearly, however, on this occasion his conduct fell considerably short of acceptable standards. He would be disciplined and re-training would be arranged as soon as possible.

The attendance list for the Midlands Ophthalmology Society Meeting, provided by the organisers, included over 100 names, but there was no indication whether these were doctors, qualified to prescribe Lumigan. Again, Allergan did not have details of actual attendees but it was aware that a number of nurses had also attended at least part of the meeting.

The Allergan stand was manned by three representatives. Samples of Lumigan were available from the stand and were provided in response to signed, written and dated requests from doctors. Seven requests were received (copies of the signed/dated request forms were provided), all of which had been verified as requests from doctors qualified to prescribe Lumigan.

Doctors were provided with the number of bottles of Lumigan specified on the signed request forms. Two doctors received 10 samples each, one received 6, and

four received one. No doctor received more than ten samples. A total of 30 samples were therefore supplied. All samples provided were labelled with the statement 'Free Medical Sample – Not For Re-Sale'.

The three representatives concerned had passed the ABPI representatives' examination.

Allergan denied any breach of the Code in relation to the provision of samples at this meeting.

Allergan stated that it was fully committed to abiding by the requirements of the Code in all areas of promotion, including the provision of samples by sales representatives. A copy of the guidelines issued to representatives in this regard was provided together with a memorandum reinforcing these guidelines which was issued following a recent complaint from Pharmacia about sampling in hospitals.

In response to a request for further information Allergan stated that at both meetings, the only bottles of Lumigan given out were those given in response to signed, written and dated requests. No other samples were supplied at either meeting. The company did not hold records to reconcile the number of samples of Lumigan taken to each meeting, the number given out and the number left. At each meeting at any one time there was a small display of approximately 12 samples.

Allergan stated that it was aware of some shortfalls in its current system for sampling and was currently reviewing its procedures for the provision of samples by representatives. The company had stopped sampling of all products until it was sure that a robust system was in place and all the representatives had been trained in the revised procedure. This revised system would include a procedure to reconcile the number of samples taken to meetings, given out and taken back by the representatives.

PANEL RULING

The Panel noted that at the meeting held in Scotland, samples of Lumigan had been given to two people, a nurse and a vet, neither of whom were health professionals qualified to prescribe the product. A breach of Clause 17.1 was ruled. Allergan had acknowledged this breach of the Code.

The Panel noted that Pharmacia had stated that at the Scottish meeting its representatives had helped themselves to two bottles of Lumigan without the need to sign and date a request form. Allergan had stated that the only samples of Lumigan given out were those that had been signed for. The company had, however, also stated that there were no records to reconcile the number of samples of Lumigan taken to the meeting, the number given out and the number left. The Panel considered that although it was not able to determine precisely what had happened, the balance of probability, given that Allergan had no system to account for samples, was that some samples of Lumigan were taken without the required written request which had been signed and dated. A breach of Clause 17.3 was ruled.

The samples of Lumigan distributed at the meeting in Scotland had not been marked 'free medical sample – not for resale' or similar. A breach of Clause 17.5 was ruled. Allergan had acknowledged this breach of the Code.

Clause 17.7 of the Code required that samples distributed by representatives must be handed direct to health professionals requesting them or persons authorized to receive them on their behalf. At the meeting in Scotland samples had been given to a nurse and a vet. The Panel considered, however, that its ruling of a breach of Clause 17.1 above covered the alleged breach of Clause 17.7.

During its consideration of the events which had occurred at the meeting in Scotland, the Panel noted that the Allergan representative had been accompanied by an area sales manager. The Panel was concerned that despite the presence of a senior member of the sales team the distribution of samples at the meeting had not been in accordance with the requirements of the Code. The Panel requested that Allergan be advised of its concerns.

With regard to the meeting held in the Midlands the signed and dated requests for samples of Lumigan had all come from health professionals qualified to prescribe the product. The Panel ruled no breach of Clause 17.1. Allergan had stated that the only samples given out were in response to signed and dated requests; Pharmacia had submitted no evidence that samples had been taken without such requests. The Panel ruled no breach of Clause 17.3.

The bottles of Lumigan distributed at the meeting in the Midlands had been labelled with a sticker which read 'Free medical sample – not for re-sale'. The Panel ruled no breach of Clause 17.5. The Panel considered that there was no evidence that the samples distributed by the representatives at the meeting had not been handed directly to the health professionals requesting them. No breach of Clause 17.7 was ruled.

With regard to both meetings the Panel noted that Allergan had stated that it did not hold records to reconcile the number of samples of Lumigan taken to each meeting, the number given out and the number left. Clause 17.9 of the Code required companies to have adequate systems of control and accountability for samples which they distributed and for all medicines handled by representatives. Allergan had no such system for the samples of Lumigan distributed by its representatives. A breach of Clause 17.9 was ruled.

Complaint received **14 October 2002**

Case completed **9 December 2002**

MERCK SHARP & DOHME v ASTRAZENECA and TAKEDA

Amias leavepiece

Merck Sharp & Dohme complained about an Amias (candesartan cilexetil) leavepiece entitled 'SCOPE study in focus' issued jointly by AstraZeneca and Takeda. The SCOPE study (Study on Cognition and Prognosis in the Elderly) had compared the effects of Amias and placebo on cardiovascular events and cognitive function in elderly patients (70-89 years) with mild hypertension. Page 2 of the leavepiece discussed the incidence and economic impact of stroke and introduced the SCOPE study. Page 3 of the leavepiece claimed that 'For the primary endpoint, major cardiovascular events (CV death, non-fatal myocardial infarction, non-fatal stroke), there was a trend towards a reduction of events in the Amias group compared to the control group (10.9%, p=0.19)' and that 'For non-fatal stroke, there was a significant risk reduction with the Amias group compared to the control group (p=0.04)'. Page 3 also featured a large downward arrow marked '28% (p=0.04)' which was labelled 'Risk reduction in non-fatal stroke with the Amias group compared to the control group'.

Merck Sharp & Dohme marketed Cozaar (losartan).

Merck Sharp & Dohme was aware from previous cases that promotion of a clinical benefit of treatment might be acceptable, provided the benefits were set clearly in the context of the licensed indication. Amias was licensed in the UK for the treatment of hypertension. The benefits of reduction in non-fatal stroke in SCOPE were not set adequately in the context of treating hypertension. Merck Sharp & Dohme alleged that this amounted to promotion of an unlicensed indication.

In relation to Cases AUTH/1342/7/02 and AUTH/1343/7/02, which concerned a press release issued by AstraZeneca and Takeda about the SCOPE trial, Merck Sharp & Dohme, the complainant, had noted that non-fatal stroke was considered by the Panel to be pre-specified, based on the confidential statistical analysis plan which was not available to it. However, Merck Sharp & Dohme still considered that undue prominence was being placed on this one positive secondary outcome on page 3 of the leavepiece now at issue, which misled the reader into thinking that it was the main result of the study.

Merck Sharp & Dohme considered that the leavepiece failed to set the SCOPE study clearly in the context of treating elderly hypertensives and misled by giving undue prominence to a secondary endpoint while glossing over the negative primary endpoints.

Finally, Merck Sharp & Dohme was concerned that the leavepiece might encourage prescribers to use 8-16mg in elderly patients when the summary of product characteristics (SPC) indicated 2-4mg might be more appropriate.

The Panel noted that in Cases AUTH/1342/7/02 and AUTH/1343/7/02 the Panel had considered that the press release was misleading, unbalanced and did not accurately reflect the evidence. The results referred to in the press release had not been placed in the context of the overall study results such that readers could assess their clinical significance. The press release also implied that Amias could be beneficial in delaying the onset of type 2 diabetes which was not a licensed indication for the product. Breaches of the Code had been ruled.

Turning to the cases now before it, Cases AUTH/1377/10/02 and AUTH/1378/10/02, the Panel noted the layout of the leavepiece. The front page read 'SCOPE study in focus'. Page 2 featured five bullet points. The first three gave details about the incidence and cost of stroke. The fourth and fifth bullet points mentioned the aim of the SCOPE study, to evaluate Amias in elderly patients with mild hypertension and that such treatment demonstrated beneficial outcomes. The Panel considered that the leavepiece gave undue emphasis to stroke and the findings of SCOPE with regard to non-fatal stroke without placing these results sufficiently within the context of treating essential hypertension such that the leavepiece appeared to promote Amias for its effects on stroke reduction. A breach of the Code was ruled.

The Panel considered that the leavepiece was misleading about the SCOPE data and that the prominence given to non-fatal stroke (a secondary outcome) was such that the leavepiece would mislead readers into thinking that the assessment of the risk of non-fatal stroke was a primary objective of the SCOPE study and this was not so. A breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about a four page Amias (candesartan cilexetil) leavepiece (ref TA 020712/AMS 10879) issued jointly by AstraZeneca UK Limited and Takeda UK Ltd. The leavepiece was entitled 'SCOPE study in focus'. The SCOPE study (Study on Cognition and Prognosis in the Elderly) compared the effects of Amias and placebo on cardiovascular events and cognitive function in elderly patients (70-89 years) with mild hypertension. Page 2 of the leavepiece discussed the incidence and economic impact of stroke and introduced the SCOPE study. Page 3 of the leavepiece claimed that 'For the primary endpoint, major cardiovascular events (CV death, non-fatal myocardial infarction, non-fatal stroke), there was a trend towards a reduction of events in the Amias group compared to the control group (10.9%, p=0.19)' and that 'For non-fatal stroke, there was a significant risk reduction with the Amias group compared to the control group (p=0.04)'. Page 3 also featured a large downward arrow marked '28% (p=0.04)' which was labelled 'Risk reduction in non-fatal stroke with the Amias group compared to the control group'.

Merck Sharp & Dohme marketed Cozaar (losartan).

COMPLAINT

Merck Sharp & Dohme stated that in light of the Panel's recent decisions in Cases AUTH/1342/7/02 and AUTH/1343/7/02, in which breaches of Clauses 7.2 and 20.2 were ruled, it had asked AstraZeneca to confirm that the leavepiece in question was to be withdrawn as part of the undertaking; AstraZeneca had indicated that this was not the case.

Merck Sharp & Dohme stated that it had three main concerns about the leavepiece which appeared to principally promote the as yet unpublished SCOPE study and stroke reduction rather than the reduction of blood pressure.

1 Merck Sharp & Dohme was all too aware from previous cases, Case AUTH/1340/7/02 and Case AUTH/1262/12/01, that promotion of a clinical benefit of treatment might be acceptable, provided the benefits were set clearly in the context of the licensed indication. Merck Sharp & Dohme's understanding in this regard was that promotion of stroke reduction (where such a reduction had been unequivocally demonstrated) might be part of a promotional piece provided the initial and main focus was on the lowering of blood pressure.

Amias was licensed in the UK for the treatment of hypertension. The benefits of reduction in non-fatal stroke in SCOPE were not set adequately in the context of treating hypertension. Merck Sharp & Dohme alleged that this amounted to promotion of an unlicensed indication (reduction in non-fatal stroke) in breach of Clause 3.2.

2 In relation to Cases AUTH/1342/7/02 and AUTH/1343/7/02, Merck Sharp & Dohme noted that non-fatal stroke was considered by the Panel to be pre-specified, based on the confidential statistical analysis plan which was not available to it. However, Merck Sharp & Dohme still considered that undue prominence was being placed on this one positive secondary outcome on page 3 of the leavepiece, which misled the reader into thinking that it was the main result of the study. Merck Sharp & Dohme alleged a breach of Clause 7.2.

3 Merck Sharp & Dohme was concerned that, on page 4 of the leavepiece, there were inconsistencies between the dosing in SCOPE and the UK summary of product characteristics (SPC). The SCOPE study treated an elderly (70-89 years) population with 8mg of Amias, increasing to 16mg if needed. The licensed treatment regimen for Amias in the elderly was a starting dose of 4mg in those with normal renal and hepatic function, and in the presence of renal or hepatic impairment, an initial dose of 2mg was recommended. The leavepiece was a focus on SCOPE and, as such, should focus on doses in the elderly. Instead, it downplayed initiation at lower doses which was required by the current SPC which should be of equal prominence as the higher doses. Merck Sharp & Dohme alleged that this was a breach of Clause 4.1.

In summary, Merck Sharp & Dohme considered that the leavepiece failed to set the SCOPE study clearly in the context of treating elderly hypertensives and misled by giving undue prominence to a secondary endpoint while glossing over the negative primary endpoints.

Finally, Merck Sharp & Dohme was concerned that the leavepiece might encourage prescribers to use 8-16mg in elderly patients when the SPC indicated 2-4mg might be more appropriate.

RESPONSE

AstraZeneca responded on behalf of both companies.

AstraZeneca expressed concern that Merck Sharp & Dohme was unable to resolve this on an inter-company level after initial conversations on the telephone and went directly to the Authority before it or Takeda had had an opportunity to address these concerns.

As a result of the Panel's rulings in Cases AUTH/1342/7/02 and AUTH/1343/7/02, referred to by Merck Sharp & Dohme, AstraZeneca confirmed that the companies had fully complied with the undertakings not to issue any similar material with unbalanced data, as ruled by the Panel.

AstraZeneca addressed each of the points raised in turn.

1 The SCOPE study

The SCOPE study was the largest ever study of mild hypertension in the elderly using an angiotensin II receptor antagonist (AIIRA), candesartan. It involved almost 5,000 patients followed up for a period of 3-5 years. The leavepiece in question was primarily to inform health professionals of the SCOPE study and the predominant outcomes. This was clear from the front page.

From the description of the study design it was quite clear that Amias was evaluated in elderly patients with mild hypertension, for which it was licensed.

The cases which Merck Sharp & Dohme had mentioned (Case AUTH/1340/7/02 and Case AUTH/1262/12/01) referred to the LIFE and RENAAL studies, respectively. The LIFE study involved 9193 patients with essential hypertension and left ventricular hypertrophy (LVH). The aim of the LIFE study was to establish whether the selective blocking of angiotensin II improved LVH beyond reducing blood pressure and consequently reduced cardiovascular morbidity and death. The RENAAL study looked at the effects of losartan on renal and cardiovascular outcomes in 1513 patients with type 2 diabetes and nephropathy.

AstraZeneca noted Merck Sharp & Dohme's reference to Case AUTH/1340/7/02 and considered that the SCOPE leavepiece should be viewed on the basis that it explained the SCOPE study design and outcomes in the context of the licensed indication for Amias.

AstraZeneca stated that according to Case AUTH/1262/12/01, the Appeal Board had ruled a breach of Clause 3.2 for promoting losartan outside of its licence, since the renoprotective effects had not been placed sufficiently within the context of treating hypertension. The SCOPE study only involved elderly patients with mild hypertension, which was

within the current marketing authorization for Amias. AstraZeneca submitted that Case AUTH/1262/12.01 was distinct from the use of Amias in the SCOPE study and should be considered as such.

The final bullet point on the second page of the leavepiece in question stated 'SCOPE has shown that actively lowering blood pressure with Amias in elderly patients with mild hypertension has beneficial outcomes'. It was evident within the SCOPE study that Amias was only used within its licensed indication and not in patients or a group of patients not specifically mentioned in the SPC for Amias. Both the primary and secondary endpoints were listed and it was quite clear that the indication for use of Amias in the study was hypertension and the results were presented entirely within this context.

AstraZeneca did not consider that the presentation of the results in an important study of mild hypertension in the elderly could be construed as promoting Amias outside its licence. AstraZeneca refuted the allegation of a breach of Clause 3.2 of the Code.

2 Reduction in non-fatal stroke

It was established in Cases AUTH/1342/7/02 and AUTH/1343/7/02 that non-fatal stroke was considered a pre-specified endpoint. Since non-fatal stroke was considered the largest single cause of severe disability in the UK, AstraZeneca considered it was appropriate to inform health professionals of available medicines, which through effective blood pressure control, could potentially reduce the risk of such a disability.

A review by MacMahon and Rodgers (1994) had demonstrated that a reduction in blood pressure could lead to significant reductions in non-fatal strokes. Treating risk factors such as hypertension in the SCOPE study and demonstrating the potential benefits of treating an asymptomatic disease such as this, in balance with the other primary and secondary endpoints, was considered entirely appropriate. AstraZeneca did not consider that its presentation of this data was misleading. The results for the reduction in non-fatal stroke were clinically significant and AstraZeneca refuted the allegation of a breach of Clause 7.2.

3 Presence of prescribing information

AstraZeneca did not understand the relevance of the allegation of a breach of Clause 4.1 of the Code, since that clause stated that prescribing information must be provided in a clear and legible manner in all promotional material. This was quite clearly the case as the prescribing information for Amias was printed in a clear and legible manner on the back page. AstraZeneca therefore did not believe the leavepiece was in breach of Clause 4.1 of the Code.

However to address the issue with respect to treating hypertension in the elderly, the leavepiece stated that the 'Usual maintenance dose' of Amias was 8mg once daily. Most health professionals would recognise the relevance of the use of a maintenance dose once a treatment regimen had been established. It was also stated in the Amias SPC that the usual maintenance dose was 8mg once daily. A starting dose of 4mg was suggested in the Amias SPC and this was stated immediately below the usual maintenance dose within the leavepiece. A dose of 2mg was only recommended in patients with severe renal impairment and in mild to moderate hepatic impairment. This was stated in the prescribing information included in the leavepiece. However, the patients in the SCOPE study did not have renal or hepatic impairment.

In summary, AstraZeneca considered that the leavepiece was sufficiently balanced in informing health professionals of the results of the SCOPE study, including all primary and secondary endpoints and indicating the potential benefits of treatment within the context of hypertension. The leavepiece did not promote Amias outside its product licence and included clear and legible prescribing information. AstraZeneca therefore refuted the alleged breaches of Clauses 3.2, 4.1 and 7.2.

PANEL RULING

The Panel noted that Cases AUTH/1342/7/02 and AUTH/1343/7/02 concerned a press release issued about the outcome of the SCOPE study.

The description of the SCOPE study published in 1999 stated that the primary objective was to assess the effect of candesartan on major cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension. The secondary objectives were to assess the effects on a number of factors including cardiovascular mortality, fatal and non-fatal myocardial infarction and fatal and non-fatal stroke.

The Panel noted that the statistical analysis plan stated that the results of the analysis of the secondary variables would not automatically be considered as confirmatory but rather as exploratory in the sense that they might support the results from the confirmatory analyses or indicate other effects of treatment.

In Cases AUTH/1342/7/02 and AUTH/1343/7/02 the Panel had considered that the press release was misleading, unbalanced and did not accurately reflect the evidence. The results referred to in the press release had not been placed in the context of the overall study results such that readers could assess their clinical significance. Readers were not told what the primary and secondary endpoints of the trial had been. Much had been made of the reduction in non-fatal stroke which was not the primary endpoint. Although readers were told of the non-significant risk reduction in major cardiovascular events they were not told that this was the primary composite endpoint which included non-fatal stroke. The press release did not state that the total number of strokes was not significantly reduced. Given the reduction in non-fatal stroke and the fact that total stroke stayed roughly constant the Panel queried whether this meant there had been an increase in the number of fatal strokes. Although the non-significant risk reduction in major cardiovascular events was reported in the press release no mention was made of the similarly non-significant increase in non-fatal

myocardial infarction. The press release implied that Amias could be beneficial in delaying the onset of type 2 diabetes which was not a licensed indication for the product. No details about the comparator were given. At enrolment all patients on current antihypertensive therapy had their medication standardized to hydrochlorothiazide after an appropriate reduction of prior treatment. The Panel had considered that the press release failed to meet the requirements of Clause 20.2 and a breach of that clause was ruled. The Panel also considered that the press release failed to meet the requirements of Clause 7.2 as alleged and a breach of that clause was ruled.

Turning to the cases now before it, Cases AUTH/1377/10/02 and AUTH/1378/10/02, the Panel noted the layout of the leavepiece. The front page read 'SCOPE study in focus'. Page 2 featured five bullet points. The first three gave details about the incidence and cost of stroke. The fourth and fifth bullet points mentioned the aim of the SCOPE study, to evaluate Amias in elderly patients with mild hypertension and that such treatment demonstrated beneficial outcomes. A simple linear representation of a brain, above 'SCOPE', appeared in a prominent size and logo format adjacent to the bullet points. The Panel considered that page 2 established the context within which the subsequent material would be interpreted.

The Panel considered that the leavepiece gave undue emphasis to stroke and the findings of SCOPE with regard to non-fatal stroke without placing these results sufficiently within the context of treating essential hypertension such that the leavepiece appeared to promote Amias for its effects on stroke reduction. A breach of Clause 3.2 of the Code was ruled.

The Panel considered that the leavepiece was misleading about the SCOPE data. Although it was stated that the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) showed a trend towards a reduction of events it was not made clear that this had been driven mainly by the reduction in non-fatal stroke. The secondary endpoints were listed in the leavepiece but only the risk reduction for non-fatal stroke was referred to. No mention was made with regard to the fact that total stroke stayed roughly constant. The Panel considered that the prominence given to non-fatal stroke (a secondary outcome) was such that the leavepiece would mislead readers into thinking that the assessment of the risk of non-fatal stroke was a primary objective of the SCOPE study and this was not so. A breach of Clause 7.2 of the Code was ruled.

With regard to the alleged breach of Clause 4.1, the Panel noted that prescribing information had been included in the leavepiece. The allegation was that the leavepiece down played initiation at lower doses. In the Panel's view this was not a matter that was covered by Clause 4.1 and thus no breach of that clause was ruled.

Complaint received **15 October 2002**

Case completed **12 December 2002**

GLAXOSMITHKLINE CONSUMER HEALTHCARE v PHARMACIA

Alleged breach of undertaking

GlaxoSmithKline Consumer Healthcare complained that Pharmacia had breached the undertaking it had given in Case AUTH/1329/6/02 which concerned the promotion of Nicorette Patch (16 hour nicotine replacement patch). GlaxoSmithKline Consumer Healthcare referred to a Nicorette patch advertisement in Pulse, October 2002, and a detail aid for the product. GlaxoSmithKline Consumer Healthcare marketed NiQuitin CQ.

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

GlaxoSmithKline Consumer Healthcare noted that in Case AUTH/1329/6/02 the Panel had ruled breaches of the Code because it 'considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better while using Nicorette as opposed to other nicotine patches'.

In the present case the advertisement at issue was headed 'Nicorette patch can protect patients from unnecessary sleep disturbance' and the detail aid was headed 'Help protect your patients from unnecessary sleep disturbance'. The advertisement and detail aid gave the overall impression was that 24 hour patches caused more sleep disturbance than Nicorette patches. This appeared to disregard the Panel's rulings.

The advertisement stated:

> **'… it avoids the nocturnal nicotine dosing often associated with sleep disturbance.**
>
> **In fact, Nicorette 16 hour Patch is the only one not shown to increase levels of sleep disturbance over and above placebo levels …**
>
> **So to help them beat cigarettes all day – while minimising the risk of sleep disturbance prescribe Nicorette 16 hour Patch.'**

The detail aid stated:

> **'– helps avoid the sleep disruption associated with nocturnal nicotine administration**
>
> **– not shown to cause sleep disturbance over placebo levels …**
>
> **– No other nicotine patch works harder at beating cigarettes whilst minimising the risk of sleep disturbance.'**

Case AUTH/1329/6/02 concerned a journal advertisement for Nicorette Patch which featured the claim 'For patients who want to give up smoking, not their sleep' above a photograph of a woman sleeping in a bed beneath which was a figure representing a cigarette. Text read '… It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers don't smoke while they sleep. In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance. So help them beat cigarettes all day – and then look forward to a comfortable night's sleep – prescribe Nicorette 16 hour Patch'.

The Panel had considered that most readers would gain the impression that patients using the Nicorette patch would not suffer sleep disturbance at all. Although Nicorette would not result in night-time nicotine dosing, which in itself was associated with sleep disturbance, it would not avoid the sleep disturbance caused by lack of nicotine. The Panel had considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better, while using Nicorette as opposed to other nicotine patches. Breaches of the Code had been ruled.

Turning to the case now before it, Case AUTH/1380/10/02, the Panel noted that the NiQuitin (a 24 hour patch) summary of product characteristics (SPC) mentioned abnormal dreams and insomnia as systemic effects found in clinical studies. The Nicorette Patch (16 hour patch) SPC did not list similar features in the list of undesirable effects. The Panel considered that the material was sufficiently different to that previously at issue. The material now at issue referred to minimising the risk of unnecessary sleep disturbance. The Panel considered that neither the advertisement nor the detail aid were in breach of the undertakings given in Case AUTH/1329/6/02 and no breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare complained that Pharmacia Limited had breached the undertaking it had given in Case AUTH/1329/6/02 which concerned the promotion of Nicorette Patch (16 hour nicotine replacement patch).

GlaxoSmithKline Consumer Healthcare referred to a Nicorette patch advertisement (ref P/8395/09/02) in Pulse, 7 October 2002, and a detail aid (ref P 8175-08-02) for the product. GlaxoSmithKline Consumer Healthcare marketed a 24 hour nicotine transdermal patch – NiQuitin CQ.

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

COMPLAINT

GlaxoSmithKline Consumer Healthcare noted that in Case AUTH/1329/6/02 the Panel had ruled breaches of Clauses 7.2 and 7.3 of the Code because it

'considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better while using Nicorette as opposed to other nicotine patches'.

In the present case the advertisement at issue was headed 'Nicorette patch can protect patients from unnecessary sleep disturbance' and the detail aid was headed 'Help protect your patients from unnecessary sleep disturbance'. The advertisement and detail aid differed slightly in their body text wording. However, the overall impression was that 24 hour patches caused more sleep disturbance than Nicorette patches. This appeared to disregard the Panel's rulings.

The advertisement stated:

> '… it avoids the nocturnal nicotine dosing often associated with sleep disturbance.
>
> In fact, Nicorette 16 hour Patch is the only one not shown to increase levels of sleep disturbance over and above placebo levels …
>
> So to help them beat cigarettes all day – while minimising the risk of sleep disturbance prescribe Nicorette 16 hour Patch.'

The detail aid stated:

> '– helps avoid the sleep disruption associated with nocturnal nicotine administration
>
> – not shown to cause sleep disturbance over placebo levels …
>
> – No other nicotine patch works harder at beating cigarettes whilst minimising the risk of sleep disturbance.'

The Authority asked Pharmacia to respond in relation to the requirements of Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Pharmacia submitted that it had not breached its undertaking and that the amended material was in compliance with the ruling in Case AUTH/1329/6/02.

A Advertisement

1 Claim '… it avoids the nocturnal nicotine dosing often associated with sleep disturbance'

Pharmacia pointed out that based on the data provided for the previous ruling, the Panel accepted that sleep disturbance during smoking cessation could also be caused by night-time dosing if a patient used a 24 hour patch. The Panel had considered that Pharmacia had not made it sufficiently clear in the previous advertisement that it was sleep disturbance associated with nocturnal nicotine dosing that was the subject of the advertisement and that most readers would gain the impression from the advertisement that a patient using Nicorette Patch would not suffer any sleep disturbances at all. However in this amended advertisement the headline 'Nicorette patch can protect patients from unnecessary sleep disturbance' clearly indicated that some sleep disturbance could be avoided and that this was the sleep disturbance associated with nocturnal dosing with nicotine as stated in the first sentence of the text.

2 Claim 'In fact, Nicorette 16 hour Patch is the only one not shown to increase levels of sleep disturbances over and above placebo levels'

Pharmacia pointed out that again, based on the data provided for the previous case, the Panel accepted that several studies had shown that sleep disturbance was not reported more frequently in patients using an active 16 hour patch compared to placebo. The Panel also agreed that 16 hour patches did not cause sleep disturbances *per se*. In addition, as a simple statement of fact, Nicorette Patch was the only 16 hour patch; all other patches were designed for 24 hour administration. The Panel ruling stated that sleep disturbance during smoking cessation could also be caused by night-time dosing if a patient used a 24 hour patch. Pharmacia therefore understood that the Panel accepted the data provided for the previous ruling which showed the increased incidence of sleep disturbances with 24 hour patches when compared to placebo and that insomnia and abnormal dreams were listed as potential adverse effects with NiQuitin CQ patches whereas they were not listed for Nicorette Patch.

In the previous case, the issue was that Pharmacia had not made it clear that there could be sleep disturbances as a consequence of nicotine withdrawal. However the headline 'Nicorette patch can protect patients from unnecessary sleep disturbance' made it clear that the subject of the advertisement was avoidable sleep disturbances. This was supported by the amended statement which did not claim that there were no sleep disturbances but that there was no increase in sleep disturbances over placebo levels using 16 hour patches. This was in contrast to 24 hour patches where the Panel had accepted that nocturnal nicotine dosing could cause sleep disturbances over placebo levels.

3 Claim 'So to help them beat cigarettes all day – while minimising the risk of sleep disturbance prescribe Nicorette 16 hour Patch'

Pharmacia pointed out that as stated above, the Panel had accepted that several studies had shown that sleep disturbances were not reported more frequently in patients using an active 16 hour patch compared to placebo. Since Nicorette Patch did not increase sleep disturbances over placebo levels the prescribing of it would therefore minimise the risk of unnecessary sleep disturbances associated with nocturnal nicotine dosing which was the subject of the advertisement. Again the use of the expression 'minimise the risk' clearly indicated that a patient could suffer sleep disturbances and that unlike the previous advertisement Pharmacia did not claim that there would be no sleep disturbances.

B Detail Aid

1 Claim 'helps avoid the sleep disruption associated with nocturnal nicotine administration'

Pharmacia submitted that this claim was essentially a re-wording of point A1 above.

2 Claim 'not shown to cause sleep disturbance over placebo levels'

Pharmacia submitted that this claim was essentially the same as point A2 above.

3 Claim 'No other nicotine patch works harder at beating cigarettes whilst minimising the risk of sleep disturbance'

Pharmacia submitted that this claim was similar to point A3 above. Also as stated in point A2, Nicorette was the only 16 hour patch available and therefore the only one that minimised the risk of sleep disturbances.

In summary, Pharmacia submitted that it had taken into account the previous ruling when developing the revised copy. The subject of the advertisement was very clear; it was about unnecessary sleep disturbance associated with nocturnal nicotine dosing which was avoided by the use of Nicorette 16 hour Patch. All the claims in this respect could be substantiated and had been previously sanctioned in the Panel ruling in Case AUTH/1329/6/02.

PANEL RULING

The Panel noted that it was not in a position to approve material and activities.

Case AUTH/1329/6/02 had concerned a journal advertisement for Nicorette Patch which featured the claim 'For patients who want to give up smoking, not their sleep' above a photograph of a woman sleeping in a bed beneath which was a figure representing a cigarette. Text read '… It's the only patch specifically designed to mimic your patient's regular smoking pattern by avoiding the nocturnal nicotine dosing commonly associated with sleep disturbance – useful as smokers don't smoke while they sleep. In fact, when compared to placebo, Nicorette 16 hour Patch is the only nicotine patch which has not been shown to cause sleep disturbance. So help them beat cigarettes all day – and then look forward to a comfortable night's sleep – prescribe Nicorette 16 hour Patch'.

The Panel had noted that for patients giving up smoking sleep disturbance was a likely consequence of nicotine withdrawal. Several studies had shown that sleep disturbances were not reported more frequently in patients using an active 16 hour patch compared to placebo. It appeared therefore that although a 16 hour patch did not cause sleep disturbance *per se* it did not prevent the sleep disturbance which resulted from total nicotine withdrawal.

Sleep disturbance during smoking cessation could also be caused by night-time nicotine dosing if a patient used a 24-hour patch. The Panel had noted Pharmacia's submission that it was this effect on sleep which was the subject of the advertisement and not the sleep disturbance caused by the lack of nicotine. In the Panel's view this had not been made sufficiently clear.

The Panel had considered that most readers would gain the impression from the advertisement that patients using the Nicorette Patch would not suffer sleep disturbance at all. One of the claims at issue 'For patients who want to give up smoking, not their sleep' was the headline to the advertisement and the picture was of a woman fast asleep in bed. Although Nicorette would not result in night-time nicotine dosing which in itself was associated with sleep disturbance, it would not avoid the sleep disturbance caused by lack of nicotine. The Panel had considered that the advertisement was misleading with regard to a patient being able to sleep well, or any better while using Nicorette as opposed to other nicotine patches. Breaches of Clauses 7.2 and 7.3 had been ruled.

Turning to the case now before it, Case AUTH/1380/10/02, the Panel noted that the NiQuitin (a 24 hour patch) summary of product characteristics (SPC) mentioned abnormal dreams and insomnia as systemic effects found in clinical studies. The Nicorette Patch (16 hour patch) SPC did not list similar features in the list of undesirable effects. Although it stated that Nicorette Patch might cause adverse reactions similar to those associated with nicotine administered by other means. The Panel considered that the material was sufficiently different to that previously at issue. The previous material implied that patients using the Nicorette Patch would not suffer sleep disturbance at all. Patients would not avoid the sleep disturbance caused by lack of nicotine. The material now at issue referred to minimising the risk of unnecessary sleep disturbance. The Panel considered that neither the advertisement nor the detail aid were in breach of the undertakings given in Case AUTH/1329/6/02 and no breach of Clause 22 was ruled. The Panel also ruled no breach of Clauses 9.1 and 2.

During its consideration of the case, the Panel queried whether the material was sufficiently clear regarding the sleep disturbance caused by withdrawal of nicotine. There was no allegation in this regard. The Panel also noted that the only date of preparation given on the detail aid, at the end of the prescribing information, was February 2002. As this predated the undertaking given in Case AUTH/1329/6/02 the Panel assumed that the date referred to the date on which the prescribing information was prepared. Since the ruling in Case AUTH/1329/6/02 Pharmacia had revised its copy. Clause 4.9 of the Code required 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. Further, the Panel noted that the section of the prescribing information in the detail aid entitled 'Package Quantities and Cost' stated 'all trade prices correct at time of printing'. In the Panel's view this was not sufficient. The cost had to be correct at the time of use in order to comply with the requirements of Clause 4.1 of the Code. The Panel requested that Pharmacia be advised of its concerns.

Complaint received **22 October 2002**

Case completed **10 December 2002**

PRESCRIBING ADVISER v GLAXOSMITHKLINE

Avandia journal advertisement

A primary care trust prescribing adviser complained about a journal advertisement for Avandia (rosiglitazone) issued by GlaxoSmithKline which appeared in Primary Care. The complaint concerned a claim 'When you need additional therapy for obese patients not controlled on metformin monotherapy*, why choose anything else?' The asterisk referred to a footnote just below the claim which read 'maximal tolerated dose'.

The complainant stated that the claim and the inference that rosiglitazone should be added to metformin as first-choice additional therapy was at odds with both the National Institute for Clinical Excellence (NICE) guidance and a recent NICE Clinical Guideline.

The NICE guidance on the use of rosiglitazone specifically recommended that patients with inadequate blood glucose control on oral monotherapy with either metformin or a sulphonylurea should first be offered metformin and sulphonylurea combination therapy (unless there were contraindications or tolerability problems) before considering use of rosiglitazone. The NICE Clinical Guideline recommended that thiazolidinediones (such as rosiglitazone) should be used if: patients were unable to take metformin and insulin secretagogues (including sulphonylureas) as combination therapy, or HbA1c remained unsatisfactory despite an adequate trial of metformin with insulin secretagogues.

The complainant stated that the combination of metformin with an insulin secretagogue was the preferred option for patients whose blood glucose control remained unsatisfactory on monotherapy with either agent. The thiazolidinediones (rosiglitazone and pioglitazone) should be reserved for use in those patients who were unable to use a metformin and insulin secretagogue combination. The complainant alleged that the advertisement was misleading.

The Panel noted that according to its summary of product characteristics (SPC) Avandia could be used in combination with metformin in obese type 2 diabetic patients whose blood glucose levels had not been adequately controlled on maximal tolerated doses of metformin alone. The NICE guidance stated that it should only be used in patients who had not been controlled on a combination of metformin and insulin secretagogues (including sulphonylureas). The Panel considered that although NICE had added a restriction to the use of Avandia, in effect advising that the product should be used as a third line agent, GlaxoSmithKline was nonetheless entitled to promote it as a second line agent, within the terms of its marketing authorization.

The Panel noted that the difference between the indications listed in the Avandia SPC and the NICE guidance as to how the product should be used appeared to have given rise to the complainant's concerns. In the Panel's view the claim in the advertisement 'When you need additional therapy for obese patients not controlled on metformin monotherapy, why choose anything else?' was consistent with the indication for Avandia given in the SPC as submitted by GlaxoSmithKline. The Panel did not consider that the advertisement was misleading as alleged and ruled no breach of the Code.

A primary care trust prescribing adviser complained about a journal advertisement for Avandia (rosiglitazone) (ref AVD/DPS/02/4027) issued by GlaxoSmithKline UK Ltd. The advertisement appeared in Primary Care, 13 November 2002. The complaint concerned a claim 'When you need additional therapy for obese patients not controlled on metformin monotherapy*, why choose anything else?' The asterisk referred to a footnote just below the claim which read 'maximal tolerated dose'.

COMPLAINT

The complainant stated that the claim in question and the inference that rosiglitazone should be added to metformin as first-choice additional therapy was at odds with both the National Institute for Clinical Excellence (NICE) guidance on rosiglitazone for type 2 diabetes (Technology Appraisal Guidance Number 9, August 2000) and the recent NICE Clinical Guideline: Management of type 2 diabetes: Management of blood glucose (issued September 2002).

The NICE guidance on the use of rosiglitazone specifically recommended that patients with inadequate blood glucose control on oral monotherapy with either metformin or a sulphonylurea should first be offered metformin and sulphonylurea combination therapy (unless there were contraindications or tolerability problems) before considering use of rosiglitazone.

The NICE Clinical Guideline recommended (point 3.9) that thiazolidinediones (such as rosiglitazone) should be used if: patients were unable to take metformin and insulin secretagogues (including sulphonylureas) as combination therapy, or HbA1c remained unsatisfactory despite an adequate trial of metformin with insulin secretagogues. This was also highlighted in the treatment algorithm included with the clinical guideline.

The complainant stated that the combination of metformin with an insulin secretagogue was the preferred option for patients whose blood glucose control remained unsatisfactory on monotherapy with either agent. The thiazolidinediones (rosiglitazone and pioglitazone) should be reserved for use in those patients who were unable to use a metformin and insulin secretagogue combination. The complainant alleged that the advertisement for Avandia was thus misleading.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clause 7.2 of the Code.

RESPONSE

GlaxoSmithKline considered that the complainant had misunderstood the company's obligations under the

Code. Under Clause 3.2 of the Code the company was obliged to promote Avandia (rosiglitazone) in accordance with the terms of its marketing authorization. Insofar as it related to the combination of Avandia with metformin – the subject of the advertisement in question – the Avandia summary of product characteristics (SPC) indicated its use in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with…metformin…; in combination with metformin only in obese patients. Every element of this rather complex indication had been duly incorporated into the body text of the advertisement which as a whole therefore complied in full with the terms of the Avandia marketing authorization.

GlaxoSmithKline's understanding was that the existence of national or local guidelines that might seek to expand, restrict or otherwise modify a medicine's licensed indications did not, and could not, release the company from its primary obligation to promote in accordance with the licence, nor did it prohibit it from so doing. That said, GlaxoSmithKline believed that the NICE guidance and clinical guidelines referred to by the complainant were generally consistent with the Avandia licence. Thus, NICE guidance stated that 'patients with inadequate blood glucose control on oral monotherapy with either metformin or a sulphonylurea should first be offered metformin and sulphonylurea combination therapy (unless there are contraindications or tolerability problems) before considering use of rosiglitazone'. It was a clinical decision as to whether the presence of significant obesity represented a tolerability problem for sulphonylureas; and, in such patients, Avandia might legitimately be considered, in accordance with both the terms of its licence and of NICE guidance.

In one respect, however, the NICE clinical guideline appeared to position Avandia outside its licence. As noted by the complainant, the guideline recommended that thiazolidinediones, such as Avandia, be used if 'HbA1c remains unsatisfactory despite an adequate trial of metformin with insulin secretagogues'. This opinion could be inferred as an endorsement of the use of triple therapy with Avandia in certain circumstances, whereas the Avandia SPC ('Special warnings and special precautions for use') stated 'There is no clinical experience with rosiglitazone in triple combination with other oral anti-diabetics'. This discrepancy was the subject of continuing correspondence between the company and NICE; but, were GlaxoSmithKline to promote Avandia in accordance with the NICE clinical guideline, it could be held to be promoting outside the Avandia licence, and thus be in breach of Clause 3.2 of the Code.

GlaxoSmithKline maintained that the advertisement in question, inasmuch as it was entirely consistent with the Avandia licence, was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that according to its SPC Avandia could be used in combination with metformin in obese type 2 diabetic patients whose blood glucose levels had not been adequately controlled on maximal tolerated doses of metformin alone. The NICE guidance stated that it should only be used in patients who had not been controlled on a combination of metformin and insulin secretagogues (including sulphonylureas). The Panel considered that although NICE had added a restriction to the use of Avandia, in effect advising that the product should be used as a third line agent, GlaxoSmithKline was nonetheless entitled to promote it as a second line agent, within the terms of its marketing authorization.

The Panel noted that the difference between the indications listed in the Avandia SPC and the NICE guidance as to how the product should be used appeared to have given rise to the complainant's concerns. In the Panel's view the claim in the advertisement 'When you need additional therapy for obese patients not controlled on metformin monotherapy, why choose anything else?' was consistent with the indication for Avandia given in the SPC as submitted by GlaxoSmithKline.

The Panel did not consider that the advertisement was misleading as alleged and ruled no breach of Clause 7.2 of the Code.

Complaint received **14 November 2002**

Case completed **19 December 2002**

CASE AUTH/1391/11/02

PHARMACIA v ALLERGAN

Lumigan leavepiece

Pharmacia complained about a Lumigan (bimatoprost) leavepiece issued by Allergan for use with ophthalmologists. Page 2 of the leavepiece was headed 'Glaucoma Management Goal'. Two groups were identified; new patients and uncontrolled patients. Beneath these two groups was the word 'Monotherapy'. A downward arrow led the reader to 'Choice of Monotherapy?' next to which was a list of factors to consider; efficacy, tolerability, side-effects and cost-effectiveness, each of which was ticked.

Pharmacia marketed Xalatan (latanoprost).

Pharmacia considered that the flowchart presented Lumigan as a choice of therapy for new patients. It was not licensed for first-line use, as the 'monotherapy' in 'new patients' wording suggested. The company alleged that the flowchart was misleading in promoting an unauthorised indication.

Pharmacia noted that the 'Choice of monotherapy?' section at the bottom of the page listed four factors that should be considered. The company alleged that 'side-effects' followed by a tick was misleading as there was no clarification as to what level of side-effects this related to; it could be interpreted as an annotation representing 'safe'.

The Panel noted that newly diagnosed patients could only be treated first-line with Lumigan if they were known to have contraindications to other first-line therapies. Thus it was a specific sub-set of newly diagnosed patients who were suitable for Lumigan monotherapy. The Panel considered that by not making this clear the impression given was misleading and inconsistent with the particulars listed in the summary of product characteristics (SPC). Breaches of the Code were ruled.

In relation to the list of positive product attributes including the statement 'side-effects' followed by a tick, the Panel did not consider that it would be interpreted as meaning that Lumigan was 'safe'. No breach of the Code was ruled.

The claim 'Twice as many patients to target IOP [intraocular pressure] ≤ 15mmHg vs latanoprost' appeared on page 3 of the leavepiece beneath the sub-heading 'Lower is better in the fight to save sight'. Pharmacia noted the claim was based on a sub-group analysis of Gandolfi *et al* (2001) and was not the stated endpoint. The study was designed to assess a difference in the rates of patients achieving an IOP ≤ 18mmHg, not IOP ≤ 15mmHg. There was no difference between latanoprost and Lumigan in this respect, and it was only selected sub-group analysis at lower target pressures that had shown any statistically significant differences. The clinical relevance of lower target pressures was unknown, and the validity of any differences identified in Gandolfi *et al* when this was not a pre-defined endpoint was questionable. Pharmacia alleged that clinicians were left with the clear message that Lumigan was more efficacious than latanoprost and this was misleading.

The Panel noted that Gandolfi *et al* had originally set out to assess the percentage of patients who achieved an IOP of ≤ 17mmHg which showed no difference between the products. Subsequent sub-group analysis had, however, assessed the percentage of patients who achieved a lower target IOP of ≤ 15mmHg. This result was statistically significant in favour of Lumigan. The Panel considered that the use of a sub-group analysis in the leavepiece gave a misleading impression of the comparative efficacy of Lumigan and latanoprost. A breach of the Code was ruled.

Page 3 of the leavepiece featured a table comparing the various attributes of Lumigan and latanoprost. The first line read 'Low BAK–0.005%' and was followed by a tick for Lumigan and a cross for latanoprost. Pharmacia stated that such a comparison of the different concentrations of the preservative benzalkonium chloride was meaningless unless it could be linked with some practical advantage. The company was not aware of any. The rates of hyperaemia were higher in the Lumigan arm of Gandolfi *et al* than in the latanoprost arm. Pharmacia considered that the comparison was designed to mislead.

The Panel noted that the issue of the concentration of BAK was related to possible toxicity. The concentration of BAK in Lumigan was 0.005% while in Xalatan eye drops it was 0.02%. The SPCs for the two products, however, showed that ocular side-effects for Lumigan and Xalatan were of a similar type and incidence. The Panel considered that although the statement 'Low BAK–0.005%' followed by a tick for Lumigan and a cross for latanoprost was true, the cross for latanoprost gave a negative impression of the product and implied that it had more ocular side-effects than Lumigan which was not so and that the effects of BAK had been firmly established. The Panel considered that the information given was misleading. A breach of the Code was ruled.

The second line of the table on page 3 comparing the attributes of Lumigan and latanoprost read 'No refrigeration' followed by a tick for Lumigan and a cross for latanoprost. Pharmacia stated that contrary to the impression given, latanoprost did not need refrigeration once opened. Doctors' main concern when reading this line would be the ease of storage for their patients. There was anecdotal evidence from doctors that Allergan's representatives were claiming that 'the need for refrigeration' created problems for patients going on holiday. Once opened, both Lumigan and latanoprost must be used within 4 weeks and kept below 25°C. Pharmacia stated that the cross next to 'No refrigeration' was an absolute that required appropriate qualification and alleged that without it the claim was misleading.

The Panel noted that while Lumigan had to be stored in a refrigerator, once it was in use it could be stored in temperatures of up to 25°C and used within four weeks. Although the statement in the leavepiece, 'No refrigeration' followed by a tick for Lumigan and a cross for latanoprost, was true it did not accurately reflect the whole situation and was

misleading in that regard. Readers would assume that Xalatan had to be kept in the refrigerator at all times and that was not so. A breach of the Code was ruled.

Pharmacia Limited complained about a four page Lumigan (bimatoprost) leavepiece (ref ACA 084/02) issued by Allergan Ltd for use with ophthalmologists. Lumigan was indicated to lower elevated intraocular pressure (IOP) in chronic open-angle glaucoma and ocular hypertension. As monotherapy in patients insufficiently responsive or intolerant or contraindicated to first-line therapy. As adjunctive therapy to beta-blockers.

Pharmacia marketed Xalatan (latanoprost) which was also licensed to reduce elevated IOP in patients with open-angle glaucoma and ocular hypertension. There were no restrictions as to the patient groups in whom the product could be used.

1 Flow chart – page 2

Page 2 of the leavepiece was headed 'Glaucoma Management Goal'. Two groups of patients were identified; new patients and uncontrolled patients. Beneath these two groups was the word 'Monotherapy'. A downward arrow led the reader to 'Choice of Monotherapy?' next to which was a list of factors to consider; efficacy, tolerability, side-effects and cost-effectiveness, each of which was ticked.

COMPLAINT

Pharmacia considered that the flowchart presented Lumigan as a choice of therapy for new patients. Lumigan was indicated 'To lower elevated intraocular pressure (IOP) in chronic open-angle glaucoma and ocular hypertension. As monotherapy in patients insufficiently responsive or intolerant or contraindicated to first-line therapy, and as adjunctive therapy to beta-blockers'. It was not licensed for first-line use, as the 'monotherapy' in 'new patients' wording suggested. The company alleged that the flowchart was misleading in promoting an unauthorised indication in breach of Clauses 3.2 and 7.2.

Pharmacia noted that the 'Choice of monotherapy?' section at the bottom of the page listed four factors that should be considered. The company alleged that 'side-effects' followed by a tick was misleading as there was no clarification as to what level of side-effects this related to; it could be interpreted as an annotation representing 'safe', which was alleged to be in breach of Clause 7.9.

RESPONSE

Allergan did not consider that the page was misleading. It was clearly headed 'Glaucoma Management Goal' and provided background as to the factors relevant to the choice of monotherapy. The list at the bottom of the page outlined factors that needed to be considered when choosing a monotherapy one of which was the side-effect profile of the product. There was no claim made for any specific monotherapy, including Lumigan.

Allergan did not agree with the suggestion that a tick next to side-effects could be considered to represent 'safe'. Similarly as there was no claim for any specific product, there could be no implication that Lumigan, or any other monotherapy, was 'safe'.

Allergan noted that, on the basis of the licensed indications for Lumigan, Pharmacia had stated that the product was not licensed for first-line use. However Lumigan could be used as monotherapy in 'patients … contraindicated to first-line treatment' which constituted, by definition, an indication for the use of Lumigan first-line in such patients eg where a beta-blocker was contraindicated, Lumigan could be considered by a physician as a potential first-line treatment.

Allergan did not consider that the flowchart was in breach of Clauses 3.2, 7.2 or 7.9 of the Code.

PANEL RULING

The Panel considered that within the context of a leavepiece for Lumigan the statements on page 2 would be seen to relate to that product. Page 1 referred to new Lumigan. It appeared that Lumigan monotherapy could be used to treat newly diagnosed patients or those uncontrolled on other therapies. The Panel noted that one of the licensed indications for Lumigan monotherapy was use in patients insufficiently responsive to first-line therapy. With regard to newly diagnosed patients, however, they could only be treated first-line with Lumigan if they were known to have contraindications to other first-line therapies. Thus it was a specific sub-set of newly diagnosed patients who were suitable for Lumigan monotherapy. The Panel considered that by not making this clear within the leavepiece the impression given was misleading and inconsistent with the particulars listed in the summary of product characteristics (SPC). Breaches of Clauses 3.2 and 7.2 of the Code were ruled.

The list of positive product attributes included the statement 'side-effects' adjacent to which was a tick. The Panel did not consider that this would be interpreted as meaning that Lumigan was 'safe'. No breach of Clause 7.9 was ruled.

2 Claim 'Twice as many patients to target IOP ≤ 15mmHg vs latanoprost'

This claim appeared on page 3 of the leavepiece beneath the sub-heading 'Lower is better in the fight to save sight'.

COMPLAINT

Pharmacia stated that Allergan had agreed to withdraw this leavepiece by 9 December having accepted that 'this statement, in isolation, might be considered misleading without further contextualisation'. However, Pharmacia questioned Allergan's 'right to use this statement in the fuller context' in any replacement materials.

The claim was based on a sub-group analysis of Gandolfi *et al* (2001) and was not the stated endpoint for the study. The study was designed to assess a difference in the rates of patients achieving an IOP ≤

18mmHg, not IOP ≤ 15mmHg. There was no difference between lantanoprost and Lumigan in this respect, and it was only selected sub-group analysis at lower target pressures that had shown any statistically significant differences. 18mmHg was taken as the aim for therapy in glaucoma. This target was supported by the Advanced Glaucoma Intervention Study (AGIS) 7, which showed that patients with an IOP ≤ 18mmHg had no progression of visual deterioration. The clinical relevance of lower target pressures was unknown, and the validity of any differences identified in Gandolfi *et al* when this was not a pre-defined endpoint was highly questionable. Pharmacia noted that the more cuts of the data performed, the greater the likelihood of obtaining a p value less than 0.05.

Pharmacia stated that in summary, clinicians were left with the clear message that Lumigan was more efficacious than latanoprost. This was misleading, in breach of Clause 7.3.

RESPONSE

Allergan submitted that the claim was based on the results of Gandolfi *et al* in which 29% of patients reached ≤ 15mmHg with Lumigan, compared to 14% with latanoprost (p=0.009). These data were given in figure 2 of the paper. However, as this was not a stated endpoint of the study and as the data were based on a sub-group analysis, Allergan accepted that use of this statement, in isolation, might be considered misleading without further contextualisation. Allergan confirmed that it had already agreed to withdraw the leavepiece.

PANEL RULING

Gandolfi *et al* had compared the safety and efficacy of Lumigan and latanoprost in patients with glaucoma or ocular hypertension. The authors had originally set out to assess the percentage of patients who achieved an IOP of ≤ 17mmHg. Subsequent sub-group analysis had, however, assessed the percentage of patients who achieved a lower target IOP of ≤ 15mmHg. The Panel noted that Allergan had accepted that these results were based on a sub-group analysis and that the company had already agreed to withdraw the leavepiece. The primary outcome measure, target IOP ≤ 17mmHg, showed no difference between the products. The Panel noted Pharmacia's comment that 18mmHg was taken as the target IOP for glaucoma therapy. The Panel considered that the use of a sub-group analysis in the leavepiece had given a misleading impression of the comparative efficacy of Lumigan and latanoprost. A breach of Clause 7.3 was ruled.

3 Concentration of benzalkonium chloride (BAK)

Page 3 of the leavepiece featured a table comparing the various attributes of Lumigan and latanoprost. The first line read 'Low BAK–0.005%' and was followed by a tick for Lumigan and a cross for latanoprost.

COMPLAINT

Pharmacia stated that such a comparison of the different concentrations of the preservative benzalkonium chloride was meaningless unless it could be linked with some practical advantage. The company was not aware of any. The rates of hyperaemia were higher in the Lumigan arm of Gandolfi *et al* than in the latanoprost arm. Pharmacia considered that the comparison was designed to mislead, rather like claims of superior potency. A breach of Clause 7.2 was alleged.

RESPONSE

Allergan did not consider that the information provided on BAK was misleading. Lumigan contained a low concentration of BAK (0.005%), whilst latanoprost contained a higher concentration (0.02%). The table illustrated that fact.

Allergan noted that Pharmacia did not challenge the accuracy of the statement but stated that it was unaware of any practical advantage of a low concentration of BAK.

Noecker (2001a) discussed the effects of common ophthalmic preservatives on ocular health. BAK was the most commonly used antimicrobial preservative and was found in nearly all glaucoma medications because it was highly efficacious against numerous microbes. BAK worked by denaturing protein and causing lysis of cytoplasmic membranes. In antiglaucoma preparations BAK did not alter the medicine's ability to lower intraocular pressure but had been found to modify the ocular surface with long-term use. Choosing eye drops with lower concentrations of preservatives could be beneficial to the patient.

Noecker (2001b) also discussed the considerations that needed to be taken into account concerning ophthalmic preservatives in the long-term use of glaucoma medications. The author stated that the concentration of BAK was a critical concern, especially if adjunctive medications were being added to existing therapy. He concluded that to reduce possible toxicity, it might be best for eye-care providers to recommend products with the lowest concentration of BAK.

Allergan therefore considered that the concentration of BAK was of clinical relevance and that it was not therefore misleading to include a comparison of this feature. The company denied that this was in breach of Clause 7.2.

PANEL RULING

The Panel noted that Noecker had written two papers on the effects of common ophthalmic preservatives on ocular health. The author stated that in chronic diseases, such as glaucoma or dry eye syndrome, high concentrations of preservative or repeated exposure to preserved medications increased the likelihood of adverse effects. BAK was a commonly used preservative in antiglaucoma preparations and its concentration in those medicines was of concern especially if adjunctive therapy was added to existing therapy. Noecker stated that to reduce possible toxicity it might be best for eye-care providers to recommend products with the lowest concentration of BAK. BAK had been shown to induce ocular surface

damage caused by a decrease in the aqueous layer production rate and impaired tear film mucus layer. In addition patients using BAK-combination glaucoma medicines, alone or in combination, had a statistically significant degree of conjunctional metaplasia compared to patients not using topical treatment. Further, long-term use of antiglaucoma medicines containing BAK had been shown to change the conjunctival surface and tear film function.

The Panel noted that the issue of the concentration of BAK was related to possible toxicity. The concentration of BAK in Lumigan was 0.005% while in Xalatan eye drops it was 0.02%. The SPCs for the two products, however, showed that ocular side-effects for Lumigan and Xalatan were of a similar type and incidence. The Panel considered that although the statement 'Low BAK–0.005%' followed by a tick for Lumigan and a cross for latanoprost was true, the cross for latanoprost gave a negative impression of the product and implied that it had more ocular side-effects than Lumigan which was not so and that the effects of BAK had been firmly established. The Panel considered that information given was misleading in that regard. A breach of Clause 7.2 was ruled.

4 No refrigeration

The second line of the table on page 3 comparing the attributes of Lumigan and latanoprost read 'No refrigeration' followed by a tick for Lumigan and a cross for latanoprost.

COMPLAINT

Pharmacia stated that contrary to the impression given, latanoprost did not need refrigeration once opened. Doctors' main concern when reading this line would be the ease of storage for their patients. There was anecdotal evidence from doctors that Allergan's representatives were claiming that 'the need for refrigeration' created problems for patients going on holiday. Once opened, both Lumigan and latanoprost must be used within 4 weeks and kept below 25°C.

Pharmacia stated that the cross next to 'No refrigeration' was an absolute that required appropriate qualification. Without it, the company considered the claim was misleading, in breach of Clause 7.2 of the Code.

RESPONSE

Allergan did not consider that the information provided on refrigeration was misleading. There were no special precautions for the storage of Lumigan. However, the SPC for Xalatan stated 'Store at 2-8°C (in a refrigerator). Keep the container in the outer carton in order to protect from light. After first opening the container: do not store above 25°C and use within four weeks'. Therefore, before opening, latanoprost must be stored in a refrigerator by both health professionals and patients.

Clearly it was therefore accurate to state that Lumigan required no refrigeration, but it was inaccurate to state that latanoprost required no refrigeration. This was the information that was conveyed in the table. Allergan did not consider that this was misleading or in breach of Clause 7.2.

PANEL RULING

The Panel noted that while Lumigan had to be stored in a refrigerator, once it was in use it could be stored in temperatures of up to 25°C and used within four weeks. Although the statement in the leavepiece, 'No refrigeration' followed by a tick for Lumigan and a cross for latanoprost, was true it did not accurately reflect the whole situation and was misleading in that regard. Readers would assume that Xalatan had to be kept in the refrigerator at all times and that was not so. A breach of Clause 7.2 was ruled.

Complaint received **20 November 2002**

Case completed **14 January 2003**

CASE AUTH/1396/12/02

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Malarone mailing

A general practitioner complained about a Malarone (atovaquone/prognanil) mailing he had received from GlaxoSmithKline. The mailing envelope stated 'this is important information, do not discard'. Inside was promotional material for Malarone which did not contain any significant safety information. The complainant alleged that this was misleading, unjustified and diminished the impact of genuine important prescribing information.

The Panel considered that recipients of the mailing in question, on reading the statement on the envelope 'Important Information: MALARIA PROPHILAXIS [sic] Do not discard', would not expect its contents to be promotional. The Panel considered that the promotional nature of the mailing was thus disguised and a breach of the Code was ruled.

A general practitioner complained about a Malarone (atovaquone/prognanil) mailing sent by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant noted that the envelope clearly stated 'this is important information, do not discard'. Inside was promotional material for Malarone which did not contain any significant safety information. The complainant alleged that this was misleading, unjustified and diminished the impact of genuine important prescribing information.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to the requirements of Clause 10.1 of the Code.

RESPONSE

GlaxoSmithKline stated that the mailing was sent to practice nurses and general practitioners between 20 and 30 November 2002 to notify them of the availability of Malarone Paediatric tablets (a newly licensed formulation of Malarone specifically formulated for children). The information contained related to dosage, efficacy and tolerability as well as including prescribing information for Malarone tablets (for adults) and Malarone Paediatric tablets.

The envelope in which the mailing was sent was printed with the following:

Important Information:
MALARIA PROPHYLAXIS
Do not discard

GlaxoSmithKline did not consider that the envelope was misleading, or designed to disguise the promotional nature of its contents.

Clause 9.7 of the Code stated 'Envelopes must not carry matter which might be regarded as advertising to the general public'. Therefore the company considered that it was inappropriate to have the brand name on the envelope and that it would be more appropriate to include information relating to the indication of the product.

The back of the envelope stated 'If undelivered return to: GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex, UB11 IBT'. GlaxoSmithKline considered that this statement made it clear that the envelope was from a pharmaceutical company.

GlaxoSmithKline considered that the notification of the availability of Malarone Paediatric tablets was important, considering that they were the first antimalarial tablets specifically formulated for children. Malarone tablets (licensed in May 2001) were only licensed for adults weighing 40kg and over. The recent launch of Malarone Paediatric tablets would enable children weighing 11-40kg to receive prophylaxis for *Plasmodium falciparum malaria* (the most deadly type of malaria). The launch of this product was significant, as other prophylactic antimalarials that were recommended for travellers to areas where Malarone was appropriate, were either not licensed for children less than 12 years of age or required tablets to be broken which could make accurate dosing difficult.

Malarone Paediatric was the first malarial prophylaxis for children that could be taken up to a day before entering a malaria endemic area and for 1 week after leaving it. All other antimalarials needed to be taken for longer periods: 1 week (or more) before entering the malaria endemic area and for four weeks after leaving it.

The content of the envelope included important information regarding tolerability, which was of particular concern when launching a paediatric product. The dosage and other relevant information were contained in the prescribing information.

GlaxoSmithKline noted that it was standard practice to notify health professionals about the launch of a new product or formulation. The company considered that this information was important in order for health professionals to keep abreast of new developments, especially since the majority of GPs and nurses were actively involved in advising travellers on malarial prophylaxis.

PANEL RULING

The Panel acknowledged that it was acceptable to notify health professionals about the launch of a new medicine or formulation providing all the material, including the envelopes for mailings, complied with the Code.

The Panel considered that recipients of the mailing in question, on reading the statement on the envelope 'Important Information: MALARIA PROPHILAXIS [sic] Do not discard', would not expect its contents to

be promotional. The Panel considered that the promotional nature of the mailing was thus disguised and a breach of Clause 10.1 of the Code was ruled.

Complaint received **2 December 2002**

Case completed **16 January 2003**

CODE OF PRACTICE REVIEW – FEBRUARY 2003

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1299/4/02	**TKT-5S v Genzyme**	**Promotion of Fabrazyme**	**Breach Clause 3.2 Two breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.4**	**Appeal by respondent**	**Page 3**
1318/5/02	**Social Audit v GlaxoSmithKline**	**Promotion of Seroxat**	**Breaches Clauses 7.2, 7.9 and 20.2**	**Appeal by complainant**	**Page 26**
1320/5/02	**Anonymous Health Professional v Aventis Pharma**	**Cardiology meetings**	**Breaches Clauses 2, 9.1 and 19.1 Audits of Aventis Pharma's procedures required by Appeal Board**	**Appeal by respondent Report from Panel to Appeal Board**	**Page 38**
1349/8/02	**GlaxoSmithKline v Takeda**	**Promotion of Actos**	**Two breaches Clause 3.2 Five breaches Clause 7.2 Three breaches Clause 7.3**	**No appeal**	**Page 44**
1350/8/02	General Practitioner v Novartis	Stepwise campaign	No breach	Appeal by complainant	Page 53
1351/8/02	**AstraZeneca v Sanofi-Synthelabo**	**Promotion of Solian**	**Two breaches Clause 7.2 Breach Clause 7.4**	**Appeals by complainant and respondent**	**Page 60**
1352/8/02	**Media/Director v Schering Health Care**	**Promotion of Yasmin**	**Four breaches Clause 7.2 Breach Clause 7.3 Four breaches Clause 7.2 Two breaches Clause 20.2**	**Appeals by complainant and respondent**	**Page 67**
1353/8/02	**General Practitioner v Novartis**	**Promotion of Starlix**	**Breach Clause 7.2**	**No appeal**	**Page 77**
1355/8/02	General Practitioner v Lundbeck	Cipralex discount	No breach	No appeal	Page 80
1356/9/02	**Pharmaceutical Adviser & Prescribing Team Manager v Pharmacia**	**Invitation to a concert**	**Breaches Clauses 9.1 and 19.1**	**No appeal**	**Page 82**
1357/9/02	**Yamanouchi Pharma v Strakan**	**Zindaclin leavepieces**	**Breach Clause 7.2**	**No appeal**	**Page 84**
1358/9/02	**Aventis Pasteur MSD v GlaxoSmithKline**	**Havrix Junior Monodose 'Dear Nurse' letter**	**Two breaches Clause 7.2 Breach Clause 7.10**	**No appeal**	**Page 87**

1359/9/02	**Reckitt Benckiser Healthcare v Norgine**	**Promotion of Movicol**	**Breach Clause 3.2 Eight breaches Clause 7.2 Breach Clause 7.10**	**No appeal**	**Page 92**
1360/9/02	**Anonymous v Aventis Pharma**	**Hospitality at meetings**	**Breaches Clauses 2, 9.1 and 19.1**	**No appeal**	**Page 104**
1362/9/02 & 1363/9/02	**Voluntary admissions by Pfizer and Pharmacia**	**Breach of undertaking**	**Breach Clause 22**	**No appeal**	**Page 107**
1364/10/02	**AstraZeneca v Novartis**	**Femara journal advertisement**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 109**
1365/10/02	**Voluntary admission by GlaxoSmithKline Consumer Healthcare**	**Breach of undertaking**	**Breaches Clauses 9.1 and 22**	**No appeal**	**Page 113**
1367/10/02	**Pharmacist v Otsuka**	**Hospitality for accompanying partners**	**Breaches Clauses 9.1 and 19.1**	**No appeal**	**Page 116**
1368/10/02	**Ortho Biotech v Roche**	**NeoRecormon journal advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 117**
1371/10/02	**Primary Care Trust Programme Director v AstraZeneca**	**Symbicort journal advertisement**	**Breaches Clauses 7.2, 7.3, 7.4 and 7.8**	**No appeal**	**Page 119**
1372/10/02	**Anonymous Doctor v Dermal Laboratories**	**Promotional aid**	**Breach Clause 18.1**	**No appeal**	**Page 122**
1373/10/02	Anonymous Doctor v GlaxoSmithKline	'Diabetes First' journal advertisements	No breach	No appeal	Page 123
1374/10/02	**GlaxoSmithKline v Neolab**	**Promotion of BDP Neo-Haler**	**Breach Clause 4.1 Five breaches Clause 7.2 Three breaches Clause 7.4**	**No appeal**	**Page 124**
1375/10/02	**Pharmacia v Allergan**	**Sampling of Lumigan**	**Breaches Clauses 17.1, 17.3, 17.5 and 17.9**	**No appeal**	**Page 130**
1377/10/02 & 1378/10/02	**Merck Sharp & Dohme v AstraZeneca and Takeda**	**Amias leavepiece**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 133**
1380/10/02	GlaxoSmithKline Consumer Healthcare v Pharmacia	Alleged breach of undertaking	No breach	No appeal	Page 137
1388/11/02	Prescribing Adviser v GlaxoSmithKline	Avandia journal advertisement	No breach	No appeal	Page 140
1391/11/02	**Pharmacia v Allergan**	**Lumigan leavepiece**	**Breach Clause 3.2 Three breaches Clause 7.2 Breach Clause 7.3**	**No appeal**	**Page 142**
1396/12/02	**General Practitioner v GlaxoSmithKline**	**Malarone mailing**	**Breach Clause 10.1**	**No appeal**	**Page 146**

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).