PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW
NUMBER 31 FEBRUARY 2001

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

Complaints in 2000 slightly down on 1999

There were 121 complaints under the Code of Practice in 2000 as compared with 127 in 1999. There were 144 in 1998 and 145 in 1997.

The number of cases arising from the complaints was however higher in 2000 than in 1999. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because complaints sometimes do not become cases at all, usually because no *prima facie* breach is established. There were 135 cases in 2000 as compared with 128 in 1999.

The number of complaints from health professionals exceeded the number of complaints from other pharmaceutical companies, 57 coming from health professionals and 51 from pharmaceutical companies. It is generally the case that the greatest number of complaints come from health professionals, though this was not so in 1996 and 1999.

Of the remainder of the complaints, three were anonymous, one came from the Medicines Control Agency, one from a charity and one from a company supplying devices. Seven complaints were nominally made by the Director of the Authority, two arising from voluntary admissions, two relating to breaches of undertaking, one concerning media criticism and two dealing with further matters noted during the consideration of complaints.

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

Further consultation on proposed changes to Code and Constitution

In July of last year, proposals for amendment of the Code of Practice for the Pharmaceutical Industry and the Constitution and Procedure for the Prescription Medicines Code of Practice Authority were circulated for comment to the chief executives of ABPI member companies and those non-member companies which had agreed to comply with the Code of Practice and accept the jurisdiction of the Code of Practice Authority. The British Medical Association, the Medicines Control Agency, the Office of Fair Trading and the Royal Pharmaceutical Society of Great Britain were also consulted. The Authority was grateful to all those who submitted comments.

In the light of the comments which were received, the ABPI Board of Management decided upon a number of changes to the proposals. The revised proposals have now been sent out again for consultation as before and further comments invited.

It is hoped that it will be possible to put the final proposals before member companies at the ABPI Annual General Meeting in April with a view to a new edition of the Code taking effect on 1 July. During a transitional period from 1 July to 30 September, no promotional material or activity would be regarded as being in breach of the Code if it failed to comply only because of requirements newly introduced.

Taking the examinations for representatives

Clause 16.2 of the Code of Practice stipulates that representatives must pass the appropriate one of the ABPI's examinations before they have been engaged in such employment for more than two years, continuous or otherwise.

The Director regularly receives requests from companies for the exercise of the discretion allowed by the supplementary information to Clause 16.2 so that in extenuating circumstances a representative can continue in employment beyond the end of the two years allowed, subject to the representative passing the examination within a reasonable time.

Although such requests are always accompanied by hard luck stories and they are viewed sympathetically where possible, the basic cause of most such requests is that the representative concerned was not first entered for the examination at the earliest opportunity. The supplementary information to Clause 16.3 of the Code says that normally representatives should be entered for the appropriate examination within their first year of employment. If this is not done, and personal difficulties subsequently ensue, no margin of time is available.

It is in everyone's interests for the requirement to pass the examinations being met as early as possible and companies are requested to ensure that new representatives are entered as soon as is reasonably practicable.

Numbering is helpful

When multi-issue complaints are made under the Code of Practice, it is helpful if the issues are numbered in a logical manner in the letter of complaint and if the same numbering system is used by the respondent.

The assistance of companies on this point would greatly assist the Authority in the resolution of complaints.

CODE OF PRACTICE TRAINING

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

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

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

Friday, 18 May

Friday, 1 June

Monday, 2 July

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1022/5/00

JANSSEN-CILAG v LILLY

Promotion of Zyprexa

Janssen-Cilag complained about the promotion of Zyprexa (olanzapine) by Lilly. Janssen-Cilag supplied Risperdal (risperidone). The material at issue was a mailing sent to UK psychiatrists.

Janssen-Cilag noted that the claim 'In the UK more patients with schizophrenia are switched to Zyprexa than any other antipsychotic' was based on a dataset of 46 psychiatrists in September 1999 reporting switches for patients from their last two consecutive outpatient clinics. Whilst analyses of larger datasets from this source could be taken to be robust, the smaller dynamic datasets were more subject to variation. The most recent figures for January 2000 showed the addition of 'late events' in the September dataset. The additional six switch events had the effect of reversing the position so that risperidone was the most switched to antipsychotic in September 1999. It was alleged that the claim was inconsistent with the most up-to-date information and incapable of substantiation for the lifetime of the piece. The Panel noted that the data to which the claim was referenced was supplied in October 1999 and showed Zyprexa sustaining the highest monthly percentage switch rates since shortly after its launch. The Panel noted Lilly's submission regarding the reason for the corrected switch data from September 1999 which appeared in the January 2000 report. The percentage switch rate for olanzapine had decreased from 28.3% to 25% whilst risperidone had increased from 26.1% to 28.8%. Taking the amended data into account, from January 1997 to January 2000 the median switch rate for olanzapine was still greater than that for risperidone (38.5% versus 19.55%). The Panel did not consider the sample size of 46 specialists unreasonable. The September data had not been corrected at the time of distribution in November and December. The corrected data was issued in February 2000 and included data for January 2000. The Panel did not consider it unreasonable to rely on the data at issue nor did it consider the claim to be inconsistent with the most up-to-date information and incapable of substantiation at the time it was used. No breach of the Code was ruled.

Janssen-Cilag stated that in relation to the claims 'For example, your choice could affect your patients' risk of unpleasant side effects such as movement related disorders or hormonal imbalance' and 'Significantly fewer elevations of prolactin than risperidone (p<0.001)', the implication that 'hormonal imbalance' was an 'unpleasant side effect' was vague. In this context hormonal imbalance was intended to mean sex hormone changes leading to side effects such as gynaecomastia, galactorrhoea, amenorrhoea etc. Hormonal imbalance itself was not a side effect; it might be an effect. Elevation of prolactin due to antipsychotic medicines was not by mechanism of balance, unlike other hormonal effects that were part of biochemical feedback mechanisms. There could be no claim for 'hormonal imbalance'. The piece posed a question about choice of atypical antipsychotic, with just two choices presented, risperidone or olanzapine. The further implication was that plasma prolactin elevation was a hormonal imbalance that was an 'unpleasant side effect', and the claim 'significantly fewer elevations of prolactin than risperidone', inferred that olanzapine caused fewer 'unpleasant side effects'. It was alleged that the confusing representation of biochemical events as side effects, in vague terms with inferred consequences, was not fair or balanced. The Panel did not consider that the claim ' … your choice could affect your patients' risk of unpleasant side effects such as …hormonal imbalance' created the impression that with regard to hormonal imbalance risperidone had an unfavourable side effect profile compared to olanzapine. It was a general statement relating to the choice of newer atypical antipsychotics, a topic discussed in the preceding paragraphs. Whilst the final paragraph inferred that Zyprexa would be a good choice, the Panel did not consider the phrase was unacceptable and ruled no breach of the Code. The Panel considered that most readers would assume that 'significantly fewer elevations of prolactin than risperidone (p<0.001)' meant that olanzapine had a significantly better prolactin mediated side effect profile than risperidone. The Panel noted that the claim appeared beneath a graph from Tran *et al* favourably comparing the extra-pyramidal symptoms (EPS) of Zyprexa with risperidone. The Zyprexa summary of product characteristics (SPC) referred to the clinical manifestations eg gynaecomastia, galactorrhoea and breast enlargement and stated that these were rare. The Risperdal SPC did not quantify the clinical manifestations of increased prolactin levels. The Panel considered that the impression given by the statement was that there was a significant difference between the products. This was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels. A breach of the Code was ruled.

Janssen-Cilag pointed out that no mention was made of other 'unpleasant side effects', such as weight gain. The balance of published literature showed that more patients receiving olanzapine would experience weight increase and patients experiencing weight gain had a greater increase in weight than those receiving Risperdal. In addition Janssen-Cilag drew attention to the SPC for Zyprexa where weight gain was described as 'undesirable' and 'frequent', and especially noted this for an initial starting dose of 15mg or greater, the only dose mentioned in the leaflet being a 15mg starting dose. The suggestion in the leaflet that risperidone was less appropriate than olanzapine when considering 'unpleasant side effects' and the omission of weight gain, an unpleasant side effect with long term sequelae, was alleged to be selective and unbalanced. The Panel noted that the Zyprexa SPC stated that the only frequent (10%) undesirable effects associated with the use of olanzapine were somnolence and weight gain. Weight gain was related to a lower pre-treatment body mass index and initial starting dose of 15mg or greater. The Panel considered that the promotional item did not

purport to summarise all of the side effects associated with Zyprexa. On balance the Panel did not accept that the omission of weight gain was selective and unbalanced. No breach of the Code was ruled. Upon appeal by Janssen-Cilag, the Appeal Board noted the frequent undesirable side effects listed in the Zyprexa SPC. In general terms the Appeal Board did not consider it necessary to mention in promotional material each side effect listed on an SPC; the selection and discussion of side effects had to comply with the Code. The Appeal Board considered that the intended audience, all UK psychiatrists, would not gain the impression that movement related disorders and hormonal imbalance were the only side effects of atypical antipsychotics. The Appeal Board did not consider the omission of weight gain misleading as alleged and upheld the Panel's ruling of no breach of the Code.

The claim 'Significantly lower EPS than risperidone' appeared above a bar chart which compared Zyprexa (10-20mg/day) and risperidone (4-12mg/day) with regard to the percentage of patients with specific types of EPS (Barnes Akathisia, Simpson Angus and AIMS) at week 28 LOCF (last observation carried forward analysis). Janssen-Cilag stated that the graph presented comparison between olanzapine and risperidone at doses of risperidone not used in normal clinical practice and at variance to the SPC for Risperdal. When considering the use of Risperdal in most patients, there had been a number of published criticisms of this study highlighting the point about dose. Since March 1999 the Risperdal SPC included statements about its dose, indicating that most patients would respond to 4-6mg/day, and that EPS might be more likely at doses above 10mg/day. The leaflet implied that there was an unfavourable incidence of EPS for risperidone compared to olanzapine across the selected high dose ranges for most patients stated in the piece.

4-12mg was not the recommended dose range for Risperdal and this was clear from the SPC. The leaflet was misleading as it described a range of doses used, which were inconsistent with the normal use of risperidone in the UK. In addition (when risperidone was used in accordance with UK practice and consistent with the SPC recommendations), a large randomised double-blind study, Conley *et al*, comparing risperidone and olanzapine showed no statistically significant difference in movement disorders (based on ESRS (Extrapyramidal Symptom Rating Scale)) between risperidone and olanzapine. Janssen-Cilag alleged that the comparison was not based on an up-to-date evaluation of the evidence and was not a fair comparison. The graph represented LOCF analysis on a subset of patients rather than the Intention To Treat (ITT) population. LOCF was generally accepted to be a tool to facilitate the reporting on the ITT population, whereby data for all patients that were originally randomised could be included. The reporting on all patients randomised in a clinical trial was of particular importance when reporting side effects, given that side effects were the most common cause for drop-out from trials. The reference Tran *et al* used to support the graph stated that all analyses were done on the ITT population, however, the ITT population was not represented on the graph. From the reference it could not be determined that the ITT analysis gave the same statistically significantly different result between the treatment groups seen from the subset presented. Tran *et al* stated that 172 patients were randomised to receive treatment with olanzapine, 167 to receive treatment with risperidone. The title of the graph stated that it was LOCF. The numbers of patients presented in the graph were clearly lower than the number randomised to treatment, and these numbers were not present in the cited reference. The reference also reported that there were no statistically significant differences in extrapyramidal symptoms between the risperidone and olanzapine groups for solicited adverse events, and that the two groups were comparable for reporting of the treatment emergent adverse events 'akathisia' and 'dyskinetic events', two types of EPS represented in the graph. Janssen-Cilag stated that Lilly had implied that the results presented were from an ITT analysis. The cited reference also stated that an ITT analysis was performed. However, since sub-sets of patients were shown on the graph, then the graph could not be presenting ITT results. This was alleged to be misleading. Separately, the graph implied a difference in EPS profile between the products whilst the solicited EPS were comparable. This was also alleged to be misleading.

The Panel noted that according to the Zyprexa SPC the recommended starting dose was 10mg/day. Daily dosage could be subsequently adjusted on the basis of individual need within the range of 5-20mg daily. An increase to a dose greater than 10mg/day was recommended only after appropriate clinical reassessment. The Risperdal SPC stated that all adult patients should start with 2mg/day. The dosage might be increased to 4mg/day on the second day. Thereafter the dosage might be maintained unchanged or further individualised if needed. Most patients would benefit from daily doses between 4 and 6mg/day although in some an optimal response might be obtained at lower doses. Doses above 10mg/day generally had not been shown to provide additional efficacy to lower doses and might increase the risk of extrapyramidal symptoms. In the Tran *et al* study patients started risperidone titration at a dosage of 1mg twice daily on day one, 2mg twice daily on day two and then 3mg twice daily on days three through seven. After the first week investigators could adjust the daily risperidone dosage upward or downward by 2mg daily every seven days within the approved range of 4 to 12mg/day. The mean modal dose for the risperidone treatment group was 7.2 ± 2.7mg/day. The study authors noted that had a lower dose for risperidone been used it might be speculated that there would have been a reduced incidence of EPS. Given the dosage recommendation in the product's SPC and the stated association between EPS and doses above 10mg/day, the Panel considered the comparison unfair in this regard and ruled a breach of the Code. Upon appeal by Lilly, the Appeal Board noted the dosage recommendations in the Risperdal SPC. The Appeal Board noted that Tran *et al* was a double

blind parallel group 28 week prospective study in 339 patients. The Appeal Board considered that it was a well designed study, the mean modal dose for the risperidone treatment group was 7.2 ± 2.7mg/day which was within the recommendations in the Risperdal SPC. The Appeal Board did not consider the data unfair as alleged and ruled no breach of the Code.

The Panel did not accept the allegation that there was an implication that the results presented were from an ITT analysis. It was clearly stated that the data on the graph was from an LOCF analysis. The Panel did not consider that the methodology utilised or the presentation of the LOCF data were misleading and ruled no breach of the Code in that regard. In considering the allegation that the graph implied a difference in EPS profile between products whilst solicited EPS were comparable, on balance the Panel did not accept that the failure to include the spontaneously reported EPS data in itself rendered the graph misleading as alleged and ruled no breach in that regard.

Janssen-Cilag pointed out the starting dose of olanzapine used in the Tran *et al* study and quoted on the leaflet was 15mg. This was not a licensed starting dose of olanzapine in the UK. It was alleged that this was misleading and inconsistent with the SPC. The Panel noted that the Zyprexa SPC stated that its recommended starting dose was 10mg/day. Daily dosage might subsequently be adjusted on the basis of individual need within the range 5-20mg/day. In the Tran *et al* study patients started olanzapine therapy at 15mg/day for the first seven days. Thereafter investigators could adjust the daily olanzapine dosage upward or downward by 5mg every 7 days (range 10-20mg). The Tran *et al* study had started when the starting dose of olanzapine had not been decided. The starting doses used in the study were clearly stated beneath the graph. Nonetheless the Panel considered that given the licensed starting dosage of olanzapine the graph was misleading as alleged and ruled a breach of the Code.

Janssen-Cilag Ltd complained about a mailing (ref ZY468) for Zyprexa (olanzapine), sent by Eli Lilly and Company Limited in November 1999 to all UK psychiatrists. Janssen-Cilag also alleged that similar misleading claims were made in other promotional items, for example another mailing (ref ZY469) sent to the same audience. The mailings had not been used since then. Janssen-Cilag marketed Risperdal (risperidone).

The mailing primarily at issue (ref ZY468) consisted of a four page leaflet entitled 'Thanks to you the voices have gone' with the follow up question 'Now what are you going to do about his shaking?' Page 2 was headed 'Are you happy with your choice of atypical?' Page 3 included a bar chart comparing the incidences of extra pyramidal symptoms (EPS) between Zyprexa and risperidone using data from three studies. The page also included a claim 'Significantly fewer elevations of prolactin than risperidone ($p<0.001$)'. The other mailing (ref ZY469) was similar in format and entitled 'Thanks to you he no longer frightens his mother' with the follow up 'But you are concerned that he never leaves the house'.

1 Claim 'In the UK more patients with schizophrenia are switched to Zyprexa than any other antipsychotic'

This claim appeared on page two in both leaflets and was referenced to HMSL Psychotrak Neuroleptics. September 1999 (Data on file).

COMPLAINT

Janssen-Cilag stated that the supporting evidence for this was based on a dataset of 46. These data were from a panel of psychiatrists reporting switches for patients from their last two consecutive outpatient clinics. Whilst analyses of larger datasets from this source could be taken to be robust, the smaller dynamic datasets were more subject to variation. The most recent HMSL Psychotrak figures for January 2000 showed the addition of 'late events' in the September dataset. The additional 6 switch events had the effect of reversing the position so that risperidone was the most switched to antipsychotic in September 1999. The claim was inconsistent with the most up-to-date information, and incapable of substantiation for the lifetime of the piece. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Lilly stated that up-to-date data on switch prescribing up to and including September 1999 were supplied to Lilly in good faith by HMSL Psychotrack in October 1999. These four monthly data as supplied in October showed that since shortly after its launch olanzapine had consistently been the antipsychotic enjoying the highest percentage of switches – between January 1997 and September 1999 the switch rate for olanzapine had ranged from 26.1% to 47.6% (median = 39.5%) whilst over the same period the switch rate for risperidone (its nearest rival) had ranged from 11.9% to 26.1% (median = 20.9%) and no other agent had come top in any four month period. A copy of the data was provided.

It was therefore clear that the switch prescribing data over the last 3 years had shown a consistent pattern with olanzapine being the antipsychotic agent with most switches in all periods between January 1997 and September 1999.

These data were the best available in November 1999 when the leaflets were designed and approved. Item ZY468 was then distributed as a one off mailing in November 1999 and item ZY469 was distributed as a one off mailing in December 1999. At that time the data were still the most up-to-date information available.

After the two mailings had been distributed by Lilly, HMSL Psychotrack issued its report for the period up to and including January 2000, a copy of which was provided. This new report contained updated data from September 1999 due to the late arrival of information from physicians involved in the care of the elderly and the new data for January 2000.

The new (February 2000) HMSL Psychotrack report showed that between January 1997 and January 2000 the switch rate for olanzapine had ranged from 25% to 47.6% (median = 38.5%) whilst over the same period the switch rate for risperidone (its nearest

rival) had ranged from 11.9% to 28.8% (median = 19.55%). In only one of the ten four month periods under review did olanzapine fail to come top in terms of switch rate, and in the most recent period it was again in first place. Thus, for almost all of the time since it was launched olanzapine was the most switched antipsychotic, which meant that overall it was the most switched antipsychotic.

Even taking account of the revised data for September 1999, the data up to January 2000 showed that the claim made by Lilly was still true, not misleading and capable of substantiation. Indeed it would require risperidone to move into top place for several four month periods in a row for this situation to change and its median switch rate to overtake that of olanzapine. As a result of these facts, these mailings were not in breach of Clause 7.2 even several months after they were distributed and were unlikely to become so during the foreseeable future. For the lifetime of these mailings the data were in accordance with the best available data.

Janssen-Cilag also made reference to the small sample size of the survey (46 prescribers) used to collect the Psychotrack data. The sample size represented about one specialist for every 20 acute NHS trusts in the UK. Lilly submitted that this was not unreasonable and gave the same sort of ratio of subjects studied to total population as the GPRD data base used for epidemiological research.

PANEL RULING

The Panel noted that the Psychotrak data to which the claim was referenced, was supplied in October 1999 and comprised a series of quarterly data sheets which had consistently shown Zyprexa sustaining the highest monthly percentage switch rates since shortly after its launch. The Panel noted Lilly's submission regarding the reason for the corrected switch data from September 1999 which appeared in the January 2000 report; the percentage switch rate for olanzapine had decreased from 28.3% to 25% whilst risperidone had increased from 26.1% to 28.8%. The Panel noted that taking the amended data into account, from January 1997 to January 2000 the median switch rate for olanzapine was still greater than that for risperidone (38.5% versus 19.55%). Further the Panel did not consider the sample size of 46 specialists unreasonable given the therapy area, the total population of psychiatrists in the UK and the mode of research. The Panel noted that the September data had not been corrected at the time when the promotional items were distributed as one-off mailings in November and December. The corrected data was issued in February 2000 and included data for January 2000. The Panel did not consider it unreasonable to rely on the data at issue nor did it consider the claim to be inconsistent with the most up-to-date information and incapable of substantiation at the time it was used. No breach of Clause 7.2 of the Code was ruled.

2 Presentation of side effects

a) Prolactin

Item ZY468 featured the claim on page 2 that 'For example, your choice could affect your patients' risk of unpleasant side effects such as movement-related disorders or hormonal imbalance'. The bullet point 'Significantly fewer elevations of prolactin than risperidone ($p<0.001$)' appeared on page three, referenced to Tran *et al* (1997).

COMPLAINT

Janssen-Cilag alleged that the implication that 'hormonal imbalance' was an 'unpleasant side effect' was vague. In this context hormonal imbalance was intended to mean sex hormone changes leading to side effects such as gynaecomastia, galactorrhoea, amenorrhoea etc. Hormonal imbalance itself was not a side effect; it might be an effect. Elevation of prolactin due to antipsychotic medicines was not by mechanism of balance, unlike other hormonal effects that were part of biochemical feedback mechanisms. There could be no claim for 'hormonal imbalance'. The piece posed a question about choice of atypical, with just two choices presented, risperidone or olanzapine. The suggestion that risperidone had an unfavourable side effect profile compared to olanzapine when considering 'hormonal imbalance' was contrary to Clause 7.2 of the Code.

The further implication was that plasma prolactin elevation was a hormonal imbalance that was an 'unpleasant side effect', and the claim 'significantly fewer elevations of prolactin than risperidone', inferred that olanzapine caused fewer 'unpleasant side effects'.

Janssen-Cilag stated that the published literature recognised that there was poor correlation between raised plasma prolactin and clinical symptoms, as did its own pharmacovigilance monitoring. Kleinberg *et al* (1999) described the reporting of prolactin mediated side effects and plasma prolactin elevation, with data taken from risperidone double-blind trials. In addition there were two large randomised risperidone and olanzapine comparative studies available (Tran *et al* 1997, Conley *et al* 1999). Neither found significant differences between groups receiving treatment with olanzapine or risperidone for side effects related to prolactin elevation. Tran *et al* (1997) found no difference between the olanzapine and risperidone patient groups for reporting of prolactin mediated side effects such as gynaecomastia and galactorrhoea. Indeed, on examination of the summary of product characteristics (SPC) for side-effects of Risperdal and olanzapine there was little qualitative difference with respect to their particular side effects, in spite of reporting differences in prolactin elevation between the groups.

When considering treatment choice from this aspect prolactin mediated side effects would be treated, or treatment altered, however elevated plasma prolactin in the absence of side effects would not be reason for intervention. In short, elevated plasma prolactin levels did not necessarily result in side effects.

The confusing representation of biochemical events as side effects, in vague terms with inferred consequences was not fair, balanced and contrary to Clause 7.2 of the Code as shown by inspection of the respective SPCs.

RESPONSE

Lilly stated that Janssen-Cilag suggested that the claim about hormonal imbalance was vague, nevertheless it stated that hormonal imbalance implied sex hormone changes leading to gynaecomastia, galactorrhoea, amenorrhoea etc. Certainly such adverse events were observed in patients receiving antipsychotic agents and many of them were thought to be due to alterations in prolactin levels. Alteration in the relative levels of hormones was often described as hormonal imbalance.

Lilly stated that although the text did not state it, Janssen-Cilag asserted that the choice of atypical antipsychotic agents posed by the piece lay between olanzapine and risperidone (the examples given were based on this comparison). If this was the case, an important factor in making a choice between the two medicines might well be the extent to which prolactin levels were altered by each medicine. The adverse events proposed by Janssen-Cilag as resulting from altered prolactin levels were 'gynaecomastia, galactorrhoea, amenorrhoea etc' (this list should probably include sexual dysfunction). These were adverse events which many patients would find unpleasant.

In this context, in both leaflets Lilly cited the study by Tran *et al* (1997) which showed that olanzapine gave rise to significantly fewer elevations of prolactin than risperidone in a head-to-head comparison in a large randomised controlled trial.

Lilly stated that Janssen-Cilag had gone to considerable lengths to cast doubt on the validity of the findings of Tran *et al*. However, it was interesting to note that a number of publications reporting studies sponsored by both companies reported similar safety and side effect findings. Furthermore the results of PEM studies on both drugs and the UK Yellow Card data in the ADROIT database indicated quite clearly that adverse events such as gynaecomastia, galactorrhoea and amenorrhoea were reported more frequently with risperidone than with olanzapine.

The paper by Tran *et al* had been published in a peer reviewed journal. It reported a randomised controlled trial of olanzapine and risperidone sponsored by Lilly. The study was conducted in patients with a DSM IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder. The study had three periods: a run-in period sufficient to allow typical oral or depot antipsychotic medication to be washed out from the system, a 28 week double blind treatment period (olanzapine 10-20mg/day, risperidone 4-12mg/day), and a tapering or down titration run-out period.

The results for prolactin levels were analysed in patients whose prolactin had been normal at base line. Of those randomised to receive risperidone 94.4% of patients developed levels above the normal range compared to only 51.2% of patients receiving olanzapine ($p<0.001$). This effect was more persistent on risperidone than on olanzapine and was significant at the final visit as well as overall.

In addition to a battery of efficacy measures, adverse events were detected by clinical evaluation, spontaneous reports and by the 40 item AMDP-5 questionnaire. Extra-pyramidal signs were evaluated using Simpson-Angus Scale, the Barnes Akathisia Scale and Abnormal Involuntary Movement Scale. Laboratory testing was carried out for, amongst other things, prolactin levels. Data were analysed on an intention to treat basis using the last observation carried forward (LOCF) method for missing data (methodology which was consistent with the current ICH and EU guidance note on Biostatistical Methodology in Clinical Trials 1993).

One reproductive system adverse event (delayed ejaculation) was reported so much more frequently on risperidone than on olanzapine that the difference reached statistical significance. Lilly stated that this was an especially interesting finding given that the study was powered not to detect differences in adverse event rates but to detect equivalent or superior efficacy of olanzapine over risperidone.

Lilly stated that the data from Conley *et al* (1999) had appeared in the public domain as a short abstract and as a poster. The study was sponsored by Janssen-Cilag – the company had recently issued a corrected version of the results following an audit of two study centres. It was likely that the poster represented the most recent version of the results. Of particular interest were the safety data for reproductive system disorders, which were given in a two section table, which highlighted prolactin related adverse events.

Lilly reproduced a table from the poster by Conley *et al* which compared risperidone and olanzapine with regard to prolactin-related adverse events and adverse events related to prolactin or to other factors. Lilly submitted that these data showed that risperidone was associated with 'prolactin related' adverse events three times more often than olanzapine (18 versus 6).

The meta-analysis by Kleinberg *et al* (1999), sponsored by Janssen-Cilag, pooled data from a number of comparative studies involving risperidone. A clear dose response for 'prolactin related' adverse events was shown indicating that there was a clear biological basis for risperidone causing such effects. The failure of the meta-analysis to find a clear association with prolactin levels might reflect either the wide normal range and standard deviation for prolactin levels or the problems of obtaining consistent and accurate values for hormones which were released in a pulsatile manner. Lilly submitted, however, it might be unwise to put too much credence on meta-analyses of risperidone data since the recent Cochrane review of this medicine found evidence of publication bias in the risperidone literature (Kennedy *et al* 2000). This evidence was obtained using the funnel plot method described in Egger *et al* (1997).

The recent abstract by Knegtering (1999) reported on prolactin levels and the prevalence of sexual dysfunction in patients taking various antipsychotic agents. The abstract reported on the findings of a questionnaire completed during a survey of patients using classical antipsychotics, risperidone and olanzapine. The abstract highlighted the following results:

		Sexual dysfunction rate	*Prolactin levels (ME/L[SD])*
Classical antipsychotic	n=45	50%	750 *[721]*
Risperidone	n=30	67%	1235 *[929]*
Olanzapine	n=15	27%	255 *[258]*

Lilly stated that clearly these data needed to be treated with circumspection even though the findings were in keeping with all of the other adverse event data presented above. The sizes of the standard deviations for the prolactin levels made it clear why the meta-analysis by Kleinberg was unable to demonstrate an association between prolactin levels and adverse event rates in patients on risperidone.

Data on the absolute rate of 'prolactin related adverse events' were available for both risperidone and olanzapine – the risperidone data had been published (Mackay *et al* 1998) whilst the olanzapine data was currently available in a confidential DSRU report sent to Lilly.

Prescription Event Monitoring (PEM) studies looked at the frequencies of medical events (incidence densities) in the month immediately after the index prescription was issued and compared them with the frequencies in months 2-6 post index prescription. By comparing the two rates per month those events associated with starting the medicine could be identified.

Lilly reproduced data from Mackay (1998) and Olanzapine PEM Report, (DSRU) 2000 which compared incidence densities (events per 1000 patient months) of the top 30 ranked events on risperidone with the incidence densities for the same events on olanzapine. These data confirmed that prolactin related events were seen more frequently per 1000 patient months of risperidone treatment than with olanzapine. Thus there was an absolute excess of events with risperidone.

Lilly referred to data from the Medicines Control Agency (MCA) ADROIT database. A table derived from Drug Analysis Prints (DAPs) in which the relative frequency with which prolactin related adverse events had been reported on Yellow Cards for risperidone and olanzapine was provided. Lilly stated that although these data must be considered with care, they might be useful in comparing medicines with similar indications. MCA guidance on the interpretation of DAP was provided. From the DAP it could be calculated that the proportion of risperidone adverse events related to the reproductive system taken as a whole was about three times that observed for olanzapine.

The suggestion that risperidone was associated with unpleasant side effects which might be prolactin related was well founded. There was nothing confusing about the link between biochemical events (raised prolactin levels) and adverse effects related to the reproductive system.

Lilly submitted that as a result, the claims made were fair, balanced and not in breach of Clause 7.2 of the Code.

Furthermore, the use of terms such as 'hormonal imbalance' and 'prolactin' would be readily understood by psychiatrists as referring to those adverse events observed in the reproductive system which were possibly related to elevated prolactin levels. Psychiatrists were familiar with prolactin changes due to experience with typical antipsychotics. The usage was therefore neither vague nor misleading.

If the 'vague' reference to prolactin levels and hormonal imbalance amounted to the representation of biochemical events as side effects, as claimed by Janssen-Cilag, then the frequency with which such side effects were seen in the UK in routine clinical practice certainly pointed to a greater problem with risperidone than with olanzapine. This was true as shown above both based on PEM data and on Yellow Card data, as well as on the results of comparator controlled trials.

Lilly submitted that the data put forward by Janssen-Cilag in its argument that prolactin related adverse events were not seen more frequently with risperidone did not stand serious scrutiny.

PANEL RULING

The Panel noted that Lilly had referred to both leaflets in its response. Mailing ZY469 neither mentioned prolactin levels nor side effects. The Tran *et al* study was used as a reference to a claim 'Superior to risperidone in treating negative symptoms' Janssen-Cilag however had only mentioned item ZY468 in its complaint on this point. The Panel did not consider that it had a complaint about item ZY469 on this point.

The Panel noted that the 'Undesirable effects' section of the Zyprexa SPC stated under the subheading 'Other findings' that plasma prolactin levels were sometimes elevated, but associated clinical manifestations (eg gynaecomastia, galactorrhoea and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment. The 'Undesirable Effects' section of the Risperdal SPC stated that 'Risperdal can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.'

The Panel noted that the item was mailed to psychiatrists. The Panel considered that, in general terms, the effect of various antipsychotic agents on prolactin levels and adverse events in the reproductive system would be familiar to such a specialist audience. The Panel noted Janssen-Cilag's view that hormonal imbalance itself was not a side effect; it might be an effect. The Panel noted the submission that there was poor correlation between raised plasma prolactin and clinical symptoms; elevated plasma prolactin levels did not necessarily result in side effects. The Panel noted the wording in the respective products' SPCs in this regard. Nonetheless given the intended audience the Panel did not accept the allegation that the implication that 'hormonal imbalance' was an unpleasant side effect was vague. Given the nature of the side effects

associated with raised prolactin levels the Panel did not consider it unreasonable to describe them as unpleasant. No breach of Clause 7.2 of the Code was ruled.

The Panel did not consider that the phrase on page two of the mailing '…your choice could affect your patients' risk of unpleasant side effects such as … hormonal imbalance', created the impression that with regard to hormonal imbalance risperidone had an unfavourable side effect profile compared to olanzapine. It was a general statement relating to the choice of newer atypical antipsychotics, a topic discussed in the preceding paragraphs. Whilst the final paragraph inferred that Zyprexa would be a good choice, the Panel did not consider the phrase was unacceptable and ruled no breach of Clause 7.2 of the Code.

The Panel noted that Tran *et al* (1997) was designed to evaluate the effectiveness and safety of olanzapine versus risperidone during double blind therapy. The study authors reported that a statistically significantly greater proportion of men receiving risperidone experienced treatment emergent adverse events, including abnormal ejaculation. The clinical laboratory evaluation section stated that a statistically significantly ($p<0.001$) lower proportion of patients in the olanzapine treatment group experienced an elevation above standard reference ranges in prolactin concentration at any time during the study (51.2% vs 94.4%). Moreover fewer olanzapine-associated elevations were persistent. At endpoint the proportion of risperidone treated patients still elevated remained significantly higher ($p<0.001$) than the proportion of olanzapine treated patients still elevated (90.3% vs 36%). Because of abnormal baseline prolactin concentrations, 45% of olanzapine treated patients and 55% of risperidone treated patients were excluded from the analysis. The discussion section mentioned the possible consequences of chronic prolactin elevation including gynaecomastia, galactorrhoea, amenorrhoea, sexual dysfunction and predisposition to osteoporosis. The authors noted that subjects treated with olanzapine experienced a significantly lower incidence of prolactin elevation and that olanzapine was associated with statistically significantly less sexual dysfunction as assessed by treatment-emergent and solicited adverse events than risperidone. It was stated that this 'may be related to its effect on prolactin.' Another possible explanation mentioned was the differential blocking effect of the α adrenergic receptors. The Panel noted that the only prolactin mediated adverse event mentioned in the data was abnormal/delayed ejaculation. The Panel could find no express mention of data relating to the incidence of gynaecomastia and galactorrhoea as inferred by Janssen-Cilag. The Panel noted the comments by both parties with regard to the comparative data derived from Conley *et al*, Kleinberg *et al* and Knegtering *et al*. The Panel noted that the Kleinberg *et al* study was an analysis of all data from randomized double-blind studies of risperidone in patients with chronic schizophrenia. The review concluded that a risperidone associated increase in serum prolactin levels was not significantly correlated to the emergence of possible prolactin related side effects. The Panel noted that the Conley *et al* study reported that more patients exceeded the laboratory normal limit for serum prolactin on risperidone than olanzapine. There was no statistically significant difference between treatment groups in the rate of prolactin related adverse events. Less than 2% of patients had adverse events clearly attributable to prolactin elevation (galactorrhoea or gynaecomastia). The study gave details of some adverse events that could be caused by prolactin elevation but were frequently attributable to a variety of other medical and psychiatric conditions. These included decreased libido, breast pain, abnormal sexual function, ejaculation failure, anorgasmia, ejaculation disorder, dysmenorrhoea and impotence. Numerically more adverse events were attributed to patients on risperidone than olanzapine except for dysmenorrhoea which was reported by more patients on olanzapine. The Panel noted that Knegtering *et al* (1999) was an evaluation of sexual dysfunction in an open ongoing study which concluded, *inter alia,* that higher prolactin levels were associated with more sexual dysfunctions occurring most frequently in patients using classical antipsychotics or risperidone.

The Panel noted that the data derived from DAPs and noted that whilst such data might be useful it should be treated with caution. There was a difference between the actual level of side effects and the level of reported side effects. In this regard the Panel noted the MCA guidance on the interpretation of reaction analysis prints which stated 'numerical comparisons should not be made between reactions associated with different products on the basis of the data in these prints alone. Comparisons can be misleading unless they take account of variations in the level of reporting, the extent of use of the products and a number of other confounding variables.'

The Panel considered that most readers would assume that 'significantly fewer elevations of prolactin than risperidone ($p<0.001$)' meant that olanzapine had a significantly better prolactin mediated side effect profile than risperidone. The Panel noted that the claim appeared beneath a graph from Tran *et al* favourably comparing the extra-pyramidal symptoms of Zyprexa with risperidone. The Panel noted its comments on the relevant data above and that the Zyprexa SPC referred to the clinical manifestations eg gynaecomastia, galactorrhoea and breast enlargement and stated that these were rare. The Risperdal SPC did not quantify the clinical manifestations of increased prolactin levels. The Panel considered that the impression given by the statement was that there was a significant difference between the products. This was not a fair reflection of the totality of the data regarding the effect of raised prolactin levels. A breach of Clause 7.2 of the Code was ruled.

b) Body weight

COMPLAINT

Janssen-Cilag noted that no mention was made of other 'unpleasant side effects', such as weight gain. The balance of published literature showed that more patients receiving olanzapine would experience weight increase and patients experiencing weight gain

had a greater increase in weight than those receiving Risperdal. This was clear in the published comparison by Tran *et al*. In addition Janssen-Cilag drew attention to the SPC for Zyprexa where weight gain was described as 'undesirable' and 'frequent', and especially noted this for an initial starting dose of 15mg or greater, the only dose mentioned in the leaflet being 15mg starting dose.

The leaflet proposed a question about choice of atypical, with just two choices presented, risperidone or olanzapine. The suggestion was that risperidone was less appropriate than olanzapine when considering 'unpleasant side effects', the omission of weight gain, an unpleasant side effect with long term sequelae, was selective and unbalanced, contrary to Clause 7.2.

RESPONSE

Lilly stated that the front cover of the leaflet (ZY468) posed a simple question: 'Now what are you going to do about his shaking?'. Page 2 continued this theme 'for example your choice could affect your patients' risk of unpleasant side effects such as movement disorders or hormonal imbalance'. Page 3 showed data on treatment induced movement disorders from the paper by Tran *et al* (1997). The balance of the piece turned around whether Lilly had addressed this issue of movement disorder fairly. It was recognised that new atypical antipsychotics (including both olanzapine and risperidone) had a lower EPS (extra-pyramidal symptoms) risk and minimal elevation of prolactin compared to older 'typicals'. Answering the question posed on the front cover had nothing to do with discussing all of the possible pros and cons of the two medicines.

The unpleasant side effects hinted at on page 2 of the leaflet included hormonal ones and the hormone in question was identified as prolactin in the stab point on page 3. For Janssen-Cilag to raise the issue of weight gain was to introduce an irrelevant factor into the examination of the marketing message. The abbreviated prescribing information on page 4 of the piece highlighted weight gain as a frequent adverse effect of olanzapine.

Based on the PEM studies and Yellow Card data for the two medicines the most common adverse events were summarised in tables by Lilly in order of frequency. The first table, derived from Mackay *et al* (1998) PEM study, reproduced the risperidone incidence densities for common adverse events for the first month ranked 1-30. The second table, from the DSRU report on olanzapine PEM study, reproduced incidence densities for the first month ranked 1-30. The third table, from the DSRU report on olanzapine PEM study, provided the incidence densities for olanzapine in the first month for those risperidone events ranked 1-30.

The fourth table provided risperidone – ADEs accounting for 1% or more of Yellow Card reports extracted from a DAP dated 5 May 2000. The final table provided the olanzapine – ADEs accounting for 1% or more of Yellow Card reports extracted from a DAP dated 25 April 2000.

Lilly pointed out that these data showed that both prolactin related adverse events (ie various types of sexual dysfunction) and 'shaking' related adverse events (tremor and Parkinsonian symptoms) featured prominently in the adverse event profile of risperidone but were less of an issue with olanzapine. Thus the comparison made was fair and balanced and was not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the Zyprexa SPC stated that the only frequent (>10%) undesirable effects associated with the use of olanzapine were somnolence and weight gain. Weight gain was related to a lower pre-treatment body mass index (BMI) and initial starting dose of 15mg or greater. The Panel considered that the promotional item did not purport to summarise all of the side effects associated with Zyprexa. Page 2 of the mailing described movement disorders and hormonal imbalance as examples of unpleasant side effects associated with atypical antipsychotics; the Panel noted its comments at 2a above on this point. The Panel did not accept that page 2 of the leaflet created the impression that risperidone had an unfavourable side effect profile compared to Zyprexa. On balance the Panel did not accept that the omission of weight gain was selective and unbalanced. No breach of Clause 7.2 of the Code was ruled. This ruling was appealed by Janssen-Cilag.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag stated that it disagreed that the 'balance of the piece turned around whether Lilly had addressed the issue of movement disorder fairly'.

The issue at stake was whether Lilly, when addressing the general issue of choice of atypical in this piece, had selectively focused on a set of side effects, which were potentially favourable to the company, and omitted a major side effect, namely weight gain and its associated consequences, which was not.

The statement 'Now what are you going to do about his shaking' could not be used to justify selective focusing on EPS, as in the piece hormone imbalance (and specifically prolactin elevation) was clearly referred to. These side effects were quite distinct and separate from one another and highlighted areas where olanzapine had a perceived advantage over Janssen-Cilag's product risperidone.

Janssen-Cilag would assert that it was misleading to imply that only these two side effects were important in the choice of atypical. Choice of atypical depended upon a wide range of factors with weight gain being as important as any other side effect. A recent survey by the National Schizophrenia Fellowship ranked it as the side effect which troubled patients the most. The problem of weight gain was well documented for olanzapine with the balance of comparative evidence favouring risperidone.

Janssen-Cilag thus believed it misleading for the piece to include reference to EPS on the front and then to expand the debate into 'hormonal imbalance', as factors pertaining to choice of atypical, but to deliberately exclude mention of weight gain and it was therefore in breach of Clause 7.2 of the Code.

RESPONSE FROM LILLY

Lilly stated that with regard to Janssen-Cilag's allegation that it had selectively focussed on a set of side effects, it was unrealistic to expect that any item of promotional material, let alone a brief leaflet, could possibly address all the issues pertaining to a medicine. It was the nature of promotional material that a medicine's strengths in comparison with its competitors were highlighted, but comprehensive information regarding undesirable effects of a marketed product was nevertheless freely available to all prescribers in the form of the SPC, prescribing information and patient information leaflet, in order that a balance of information was presented. It would be noted that the prescribing information for Zyprexa covered one quarter of the surface area of the leaflet.

Janssen-Cilag's suggestion that because weight gain was listed as 'undesirable' and 'frequent' in the Zyprexa SPC, Lilly should be required to include a reference to this adverse event in the leaflet in question (presumably in addition to its appearance in the prescribing information), and presumably in all Lilly's other Zyprexa-related materials as well was plainly absurd and quite clearly not reflective of current practice within the industry. As an example, Lilly referred to the current Risperdal SPC and an item of Janssen-Cilag's promotional material for Risperdal (a leavepiece, code 605102). The Risperdal SPC listed insomnia, agitation, anxiety and headache as common and frequent undesirable effects of Risperdal. Apart from the mandatory prescribing information, however, the leavepiece devoted only one panel to tolerability-related issues, where it stated that 'Risperdal has a low propensity for weight gain'. If Janssen-Cilag's arguments were taken to their logical conclusion, insomnia, agitation, anxiety and headache (which were, after all, common, undesirable effects of Risperdal) should be given equal prominence to 'Low propensity for weight gain' in this leavepiece and indeed in all promotional material for Risperdal in order that Janssen-Cilag was not seen to have, in its own words, 'selectively focussed on a set of side effects which are potentially favourable to the company'. This was of course not the case – no reference was made to these common and frequent effects of Risperdal other than in the prescribing information. As Janssen-Cilag obviously felt strongly about this issue, Lilly would urge it to address it in its own materials prior to presenting it as a cause for complaint in Lilly's.

Lilly said that with regard to EPS and hormonal imbalance, Janssen-Cilag's assertion that 'it was misleading to imply that only these two side effects were important in the choice of an atypical' was puzzling. At no point in the material in question, nor indeed at any other time, had Lilly stated or implied that this was the case. There were many factors involved in the choice of an atypical antipsychotic, with patient acceptability being an important but by no means exclusive factor. Again using Janssen-Cilag's own leavepiece as an example, the logical extension of its argument would be that it itself was implying that efficacy against positive and negative symptoms together with a low propensity for weight gain were the only factors important in the choice of an atypical, constituting a breach of the Code.

It was furthermore a cause for concern that the material referenced by Janssen-Cilag as purported evidence for its argument, namely the press release from the National Schizophrenia Fellowship, was released into the public domain long after the material in question had ceased to be in use, and also some time after Janssen-Cilag's original complaint. For this reason, Lilly felt it wholly inappropriate that this reference should be considered in relation to this particular complaint.

In summary, Lilly fully supported the Panel's ruling of no breach. The effect of a ruling against Lilly on this point would in effect have also rendered the Janssen-Cilag leavepiece, and indeed the vast majority of materials in current use from all pharmaceutical companies, in breach of the Code. A reversal of the ruling would fly in the face of common sense, and Lilly trusted that the Panel's ruling of no breach on this point would be upheld.

FURTHER COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag stated that it was interested to receive the response to its appeal from Lilly and stated that it did not disagree with the general thrust of Lilly's submission: namely that it was unrealistic to expect any promotional material to fully address all relevant issues pertaining to the medicine. Janssen-Cilag asserted, however, that Lilly had misunderstood the point of its argument and it was happy to clarify this.

In this particular piece Lilly had chosen to address the general issue of choice of atypical using the issue of unpleasant side effects as a factor for consideration. In doing this it had used a comparative study (Tran *et al*) to draw distinctions between risperidone and olanzapine. Janssen-Cilag had already drawn attention to the shortcomings of using this particular study but Janssen-Cilag fully supported the general principle that comparative claims should be supported by comparative studies.

Tran *et al* provided support for the areas of EPS and prolactin elevation as shown but the findings on EPS were not borne out by the Conley *et al* study and elevations of prolactin *per se* were poorly correlated with clinical side effects and were potentially misleading in this context. The point Janssen-Cilag wished to emphasise was that there was another significant finding from the Tran *et al* study that was absolutely relevant to any discussion of unpleasant side effects in the choice of an atypical, but this had been omitted. The study clearly demonstrated that there was a greater degree of weight gain with olanzapine than with risperidone and indeed this was the only consistent major finding across the two main studies (Tran *et al* and Conley *et al*).

Hence, the major points as Janssen-Cilag saw them were that the piece discussed choice of atypical in the context of unpleasant side effects and used a major comparative trial (Tran *et al*) to draw distinctions between risperidone and olanzapine; this same study also showed that weight gain (an unpleasant side effect) was higher with olanzapine than risperidone but this fact was omitted; the other major comparative study (Conley *et al*) provided confirmation of the difference in weight gain but did not support the

difference in EPS claimed by Tran *et al*; a difference in weight gain was absolutely relevant to the subject of the piece as it had been shown to be of major clinical concern as evidenced by the National Schizophrenia Fellowship's press release.

Janssen-Cilag would thus still contend that the omission of this in this piece constituted an unbalanced representation of the known data and was in breach of the Code.

Lilly's contention that the inclusion of the National Schizophrenia Fellowship press release was invalid was frankly perverse. The discovery of new and pertinent information was often the central tenet of most appeal processes and Janssen-Cilag strongly felt that this survey supported its contentions.

In concluding, Janssen-Cilag agreed with Lilly's assertion that it was not realistic to expect a leaflet to 'address all the issues pertaining to a medicine'. However, Janssen-Cilag's contention was that where reference was made to differential side effects, it would expect that piece to refer to weight gain.

APPEAL BOARD RULING

The Appeal Board noted the frequent undesirable side effects listed in the Zyprexa SPC. In general terms the Appeal Board did not consider it necessary to mention in promotional material each side effect listed on an SPC; the selection and discussion of side effects had to comply with the Code. The Appeal Board noted that the intended audience comprised all UK psychiatrists and considered that such an audience would not gain the impression that movement related disorders and hormonal imbalance were the only side effects of atypical antipsychotics. The Appeal Board did not consider the omission of weight gain misleading as alleged and upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal was unsuccessful.

c) Claim that Zyprexa 'Significantly lower EPS than risperidone'

The claim 'Significantly lower EPS than risperidone' appeared above a bar chart which compared Zyprexa (10-20mg/day) and risperidone (4-12mg/day) with regard to the percentage of patients with specific types of EPS (Barnes Akathisia, Simpson Angus and AIMS) at week 28 LOCF (last observation carried forward analysis). The claim and bar chart were referenced to Tran *et al* (1997).

COMPLAINT

Janssen-Cilag stated that the graph presented comparison between olanzapine and risperidone at doses of risperidone not used in normal clinical practice and at variance to the SPC for Risperdal.

When considering the use of Risperdal in most patients, there had been a number of published criticisms of the study by Tran *et al* highlighting the point about dose. Since March 1999 the Risperdal SPC included statements about its dose, indicating that most patients would respond to doses between 4 and 6mg/day, and that EPS might be more likely at doses above 10mg/day.

The leaflet implied that there was an unfavourable incidence of EPS for risperidone compared to olanzapine across the selected high dose ranges for most patients stated in the piece. 4-12mg was not the recommended dose range for Risperdal and this was clear from the SPC. The leaflet was misleading as it described a range of doses used, which were inconsistent with the normal use of risperidone in the UK.

In addition (when risperidone was used in accordance with UK practice and consistent with the SPC recommendations), a large randomised double-blind study, Conley *et al*, comparing risperidone and olanzapine showed no statistically significant difference in movement disorders (based on ESRS (Extrapyramidal Symptom Rating Scale)) between risperidone and olanzapine.

Janssen-Cilag alleged that the comparison was not based on an up-to-date evaluation of the evidence and was not a fair comparison, contrary to Clause 7.2 of the Code.

The graph represented a LOCF analysis on a subset of patients rather than the intention to treat (ITT) population. LOCF was generally accepted to be a tool to facilitate the reporting on the ITT population, whereby data for all patients that were originally randomised could be included. The reporting on all patients randomised in a clinical trial was of particular importance when reporting side effects, given that side effects were the most common cause for drop-out from trials.

Janssen-Cilag stated that the reference Tran *et al* used to support the graph stated that all analyses were done on the ITT population, however the ITT population was not represented on the graph. From the reference it could not be determined that the ITT analysis gave the same statistically significantly different result between the treatment groups seen from the subset presented. Tran *et al* stated that 172 patients were randomised to receive treatment with olanzapine, 167 to receive treatment with risperidone. The title of the graph stated that it was LOCF. The numbers of patients presented in the graph were clearly lower than the number randomised to treatment, and these numbers were not present in the cited reference. The reference also reported that there was no statistically significant difference in extrapyramidal symptoms between the risperidone and olanzapine groups for solicited adverse events, and that the two groups were comparable for reporting of the treatment emergent adverse events 'akathisia' and 'dyskinetic events', two types of EPS represented in the graph.

Janssen-Cilag stated that Lilly had implied that the results presented were from an ITT analysis. The cited reference also agreed that an ITT analysis was performed. However, since sub-sets of patients were shown on the graph, then the graph could not be presenting ITT results. This was alleged to be misleading in breach of Clause 7.2 of the Code.

Separately, the graph implied a difference in EPS profile between the products whilst the solicited EPS were comparable. This was alleged to be misleading in breach of Clause 7.2.

RESPONSE

Lilly stated that there was no doubt that movement disorders were amongst the more prominent side effects of risperidone as illustrated by the data presented in parts 2a and 2b. Since PEM and Yellow Card data were derived from routine clinical use there could be no complaint about the doses on which such data were based. Comparison of the PEM study results and the Yellow Card data for risperidone and olanzapine showed that movement disorders were more common with risperidone than with olanzapine.

The specific allegations about the doses used in the study by Tran had been answered in letters published in response to the original article. Furthermore the doses used for both medicines were within the ranges described in the SPC.

In Lilly's letter of 19 January to Janssen-Cilag prior to submission of the complaint it answered this point as follows:

> '[The study by Tran] is a double blind trial looking at a large number of schizophrenic patients. Risperidone was therefore blindly up-titrated from 1mg bd consistent with labelling to give maximum response. The mean modal dose of 7.2 mg/day of risperidone is consistent with Janssen-sponsored studies in Europe (n=1362), Canada (n=135) and the USA (n=388). Conclusions were 'doses of 4mg and 8mg seem optimal' and 'optimal therapeutic dose is 6mg/day'. In Tran *et al* over 50% of risperidone patients had a modal dose of 6mg/day, or less. Olanzapine was also blindly titrated. At these doses, the differences in movement side effects were found to be significantly different between risperidone and olanzapine. The body of evidence, as set out in one of your own risperidone product monographs, citing major studies of risperidone in schizophrenia, looks at studies using risperidone dose ranges of 1-10mg, 2-16mg, 1-16mg, 4-12mg, 5-15mg, 2-10mg, 2-20mg, therefore often using much higher doses than Tran *et al*.'

Clearly there could be no reasonable grounds for concern about the choice of dose for the study or the fairness of the comparison since the mean modal dose was indeed the one Janssen-Cilag recommended in the SPC for risperidone. Therefore, the choice of dose was not an issue in respect to a breach of Clause 7.2.

The analysis was designed to attribute EPS to treatment and in this respect the graphs and analyses were correct – Lilly would not want to consider EPS that was happening anyway when comparing the two medicines. In the statistical methods section of Tran it stated:

> 'To assess treatment-associated pseudo-parkinsonism, the proportion of patients with a Simpson-Angus scale total score >3 at any post-baseline visit was calculated among those with a total score of<=3 at baseline'.

This meant that patients who had no baseline measure were excluded, patients who had no post-baseline data at all were excluded, and patients who had a baseline score >3 were excluded when computing total scores. If any of the individual items were missing then the total score was considered missing. However this set of rules merely defined the ITT population in whom the analysis of emergent EPS was possible (ie those with data and those without EPS at baseline). This meant that the number included in the analysis would be less than the number randomised.

Similar statements were made regarding the Barnes and AIMS scales. This meant that the graph was showing data on a subset of patients – those with no EPS at baseline. Since it was treatment emergent events that were being considered one could only look at patients who had no events (ie score <=3) at baseline: a consideration of the complete randomised population would not allow you to do this. Therefore, one could apply LOCF to this population in order to make the best use of the available data on the particular population of interest so the analysis was valid.

The very last paragraph of the statistical methods section in Tran *et al* specifically defined what was meant by ITT in this publication (patients analysed in the group they were randomised to) – there was no other claim that the analyses all had to include all randomised patients. In order to do a LOCF analysis the patients would have to have had at least one post-baseline assessment (it could not be called an endpoint) – therefore, the analyses would necessarily exclude patients who had no post-baseline measurements. When computing total scores, if any of the individual items were missing then the total score was considered missing (paragraph 2 of the statistical methods section in Tran *et al*.). All of these reasons could lead to a reduced 'n' in the analysis for legitimate reasons and this was displayed on the graph.

Lilly further submitted that there was nothing written on the graph to imply a difference in EPS profile between the products whilst solicited EPS were comparable.

From these comments it could be seen that the graph was not misleading and was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that according to its SPC the recommended starting dose for olanzapine was 10mg/day. Daily dosage could be subsequently adjusted on the basis of individual clinical status within the range of 5-20mg daily. An increase to a dose greater than the routine therapeutic dose of 10mg/day ie, to a dose of 15mg/day or greater, was recommended only after appropriate clinical reassessment. The Risperdal SPC stated that all adult patients should start with 2mg/day. The dosage may be increased to 4mg/day on the second day. Thereafter the dosage may be maintained unchanged or further individualised if needed. Most patients would benefit from daily doses between 4 and 6mg/day although in some an optimal response may be obtained at lower doses. Doses above 10mg/day generally had not been shown to provide additional

efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10mg/day should only be used in individual patients if the benefit was considered to outweigh the risk. The section headed 'Undesirable Effects' stated that the incidence and severity of extrapyramidal symptoms were significantly less than haloperidol. However the following EPS symptoms might occur: tremor, rigidity, hypersalivation, bradykinesia and acute dystonia. If acute in nature, these symptoms were usually mild and reversible upon dose reduction and/or administration of antiparkinson medication.

The Panel noted that the Conley *et al* study showed no statistically significant difference between risperidone and olanzapine in the rate of adverse events related to extrapyramidal symptoms or on the magnitude of improvement in extrapyramidal symptoms.

The Panel noted that in the Tran *et al* study patients started risperidone titration at a dosage of 1mg twice daily on day one, 2mg twice daily on day two and then 3mg twice daily on days three through seven. After the first week investigators could adjust the daily risperidone dosage upward or downward by 2mg daily every seven days within the approved range of 4 to 12mg /day. The mean modal dose for the risperidone treatment group was 7.2 ± 2.7mg/day. The study authors noted that had a lower dose for risperidone been used it might be speculated that there would have been a reduced incidence of EPS. Given the dosage recommendation in the product's SPC and the stated association between EPS and doses above 10mg/day, the Panel considered the comparison unfair in this regard and ruled a breach of Clause 7.2 of the Code. This ruling was appealed by Lilly.

The Panel then considered the study methodology. All endpoint analyses used an LOCF algorithm; the last available visit served as endpoint. The study further stated that all analyses were done on the intent-to-treat population; all patients were included in the groups to which they were randomly assigned. The Panel noted that the graph presented a LOCF rather than an ITT analysis. The Panel noted Lilly's submission that since it was treatment emergent events that were being considered one could only look at patients who had no events at baseline; a consideration of the complete randomised population would not allow you to do this. The Panel was concerned that patient population numbers on the graph were not stated in Tran *et al* and noted Lilly's explanation for the reduced patient population in the LOCF analysis which was presented in the graph. It was clearly stated that the data on the graph was from a LOCF analysis. The Panel did not accept the allegation that there was an implication that results presented were from an ITT analysis. The Panel did not consider the methodology utilised or presentation of the LOCF data misleading as alleged and ruled no breach of Clause 7.2 of the Code.

The Panel then considered the allegation that the graph implied a difference in EPS profile between products whilst solicited EPS were comparable. The Panel noted that no mention was made on the graph that the data related to treatment emergent EPS. The Panel noted its comments on Tran *et al* above. Adverse events were detected by clinical evaluation and spontaneous report at each visit. The incidence of EPS based on rating scales was clinically evaluated using the Simpson – Angus scale, Barnes Akathisia scale and AIMS; this data was depicted on the graph at issue using LOCF analysis. With reference to spontaneously reported treatment emergent extrapyramidal adverse events, the proportions of patients with events, parkinsonian events or with any extrapyramidal event were significantly lower in the olanzapine than in the risperidone group (p=0.042, p=0.022 and p=0.008 respectively). The proportions of patients experiencing treatment spontaneously reported emergent akathisia events, dyskinetic events and residual events were comparable (p=NS) between groups. The study authors concluded that olanzapine treatment resulted in significantly fewer EPS than treatment with risperidone on both self reported treatment emergent adverse events and categorical changes on objective rating instruments. The Panel considered that there were differences between spontaneously reported events and those clinically evaluated with a recognised rating scale. On balance the Panel did not accept that the failure to include the spontaneously reported EPS data in itself rendered the graph misleading as alleged and ruled no breach of Clause 7.2 of the Code in that regard.

APPEAL BY LILLY

Lilly noted that Janssen-Cilag had alleged that a comparison of Zyprexa and Risperdal with regard to the percentage of patients with specific types of EPS presented in the form of a bar chart was unfair because the doses of risperidone used in the comparison were not in accordance with UK practice and not consistent with SPC recommendations. Janssen-Cilag cited a study by Conley *et al* which claimed to show no statistically significant difference in movement disorders between risperidone and olanzapine as evidence for its arguments. The Panel noted the results from Conley *et al*, accepting that the study showed no statistically significant difference between risperidone and olanzapine in the rate of adverse events related to extrapyramidal symptoms, before concluding that, given the dosage recommendation in the risperidone SPC and the stated association between EPS and doses above 10mg/day, the comparison was unfair and in breach of Clause 7.2 of the Code.

Lilly disagreed with the conclusions of the Panel with regard to this particular aspect of the ruling for the following reasons. Firstly the Risperdal SPC stated that 'Patients should be titrated to 6mg/day gradually over three days'. The methodology employed by Tran *et al* was consistent with this recommendation. The SPC went on to state that 'Doses above 10mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16mg/day have not been extensively evaluated for safety and therefore should not be used'. As the dose of risperidone employed by Tran *et al* was in the range of 4-12mg/day, it could not be argued that its use was outside that recommended in the SPC, especially as the mean modal dose for the risperidone group was 7.2mg ±2.7mg/day, less than the

recommended 10mg/day 'cut-off point' for individual patient use. Furthermore, more than 50% of risperidone-treated patients had a modal dose of 6mg/day or less. Much had been made of the upper end of the dose range exceeding 10mg/day, but in practice the majority of patients were taking doses significantly less than this.

Janssen-Cilag stressed than once the patients in the risperidone group had been titrated up to a dose of 6mg/day as recommended in the risperidone SPC, the decision of whether to increase or decrease a patient's dose was left entirely up to the clinician in order to optimise patient outcome, ie the decision to alter the dose of either medicine was clinical and not determined by a fixed dosing regimen or other artificial means. Any argument that the range of doses used was inconsistent with the normal use of risperidone in the UK or anywhere else was therefore spurious as the doses received by patients at the 28-week endpoint were determined on clinical grounds alone.

Lilly stated that its second reason for disagreeing with the Panel's ruling was that Janssen-Cilag used the results of a study by Conley *et al* to support its argument. It was claimed that 'this large randomised double-blind study comparing risperidone and olanzapine showed no statistically significant difference in movement disorders (based on ESRS) between risperidone and olanzapine' and the Panel appeared to have taken this into account in arriving at its conclusions.

Lilly referred to Case AUTH/858/3/99, a complaint by Lilly about the promotion of Risperdal by Janssen-Cilag. Many aspects of this earlier complaint revolved around the promotional use of data from the same Conley study described previously. Lilly alleged that the safety data relating to EPS presented by Conley *et al* was highly misleading since the number of patients dropping out of the study was different in the risperidone and olanzapine treatment groups, and that patients might have dropped out due to EPS, rendering the data table misleading and the analysis not statistically valid. The Panel ruling on this complaint included the conclusion that 'The Panel considered that the omission of patients who had dropped out of the study … could have influenced the data. The Panel considered the page [containing the data table] was misleading and ruled a breach of Clause 7.2 of the Code'.

Lilly was most concerned that not only had Janssen-Cilag submitted data which had previously been ruled to be misleading to the Panel in order to support its argument, but that in addition to this the Panel had used this same flawed and misleading data as evidence against Lilly. This data formed a significant part of Janssen-Cilag's argument as it was being used to support its contention that at lower doses, risperidone did not cause more EPS than olanzapine. Without the Conley data, however, Janssen-Cilag had little support for its case in the literature.

In summary, the doses of risperidone used in the Tran study were chosen in order to optimise clinical outcomes on a patient by patient basis. Those patients on risperidone were initially titrated up to a dose of 6mg/day as recommended in the SPC and the dose was then tailored according to individual patient response. The dose ranges used in the study for both olanzapine and risperidone were clearly stated on the graph, allowing the readers to make their own minds up as to the validity of the comparison. Furthermore, the mean modal dose of risperidone (7.2 mg/day ±2.7mg) was well within recommended SPC limits. Finally, and critically, the Janssen-Cilag argument that a lower dose of risperidone would have yielded significantly different results in a comparison with olanzapine hinged to a significant extent on data from Conley *et al* which had already been ruled as misleading in a previous ruling and which was generally accepted to be critically flawed.

APPEAL BOARD RULING

The Appeal Board noted the dosage recommendations in the risperidone SPC. The Appeal Board noted that Tran *et al* was a double-blind parallel group 28 week prospective study in 339 patients. The Appeal Board considered that it was a well designed study, the mean modal dose for the risperidone treatment group was 7.2 ± 2.7mg/day which was within the recommendations in the Risperdal SPC. The Appeal Board did not consider the data unfair as alleged and ruled no breach of Clause 7.2. The appeal was successful.

3 Starting dose of olanzapine

COMPLAINT

Janssen-Cilag pointed out the starting dose of olanzapine used in the Tran *et al* study and quoted on the leaflet was 15mg. This was not a licensed starting dose of olanzapine in the UK. This was misleading and inconsistent with the SPC. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Lilly stated that its comments at point 2b above and from its previous letter to Janssen-Cilag at point 2c above regarding dose also applied here, and demonstrated that there was no breach. These data were clearly taken from a published study as discussed above. At the time of the study, the starting dose of olanzapine had not been decided (Lilly referred to published correspondence). It might also be noted that the higher doses would be more likely to cause adverse effects than lower doses.

PANEL RULING

The Zyprexa SPC stated that its recommended starting dose was 10mg/day. Daily dosage might subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. The Panel noted that in the Tran *et al* study patients started olanzapine therapy at 15mg/day once daily for the first seven days. Thereafter investigators could adjust the daily olanzapine dosage upward or downward by 5mg every 7 days (range 10-20mg). The Tran *et al* study had started when the starting dose of olanzapine had not been decided. The Panel noted

that the starting doses used in the study were clearly stated beneath the graph. Nonetheless the Panel considered that given the licensed starting dosage of olanzapine the graph was misleading as alleged and ruled a breach of Clause 7.2 of the Code.

Complaint received **22 May 2000**

Case completed **2 November 2000**

CASE AUTH/1043/6/00

GLAXO WELLCOME v ELAN PHARMA

Promotion of Migramax

Glaxo Wellcome complained about claims made by Elan Pharma for Migramax (lysine acetylsalicylate/metoclopramide) which appeared in a journal advertisement and in a voiceover on a Telemed GP CD. Most of the claims at issue were based on the one study which directly compared Migramax with oral sumatriptan 100mg (Tfelt-Hansen *et al* 1995). Glaxo Wellcome produced Imigran (sumatriptan).

The claims 'New Migramax changes the face of migraine therapy' and 'Migramax just may be the biggest news in migraine since triptans were first launched in the early 90s' appeared in the advertisement and the claim 'New Migramax, it changes the face of migraine therapy' was in the CD voice-over. Glaxo Wellcome stated that Migramax was not the first analgesic/antiemetic combination to be marketed for migraine and it was unlikely that its management would be changed dramatically by Migramax. The Panel considered that these claims would give readers the impression that Migramax represented a significant change in migraine therapy and that was not so. It was not the first analgesic/antiemetic combination to be marketed, although it was the first lysine acetylsalicylate to be introduced to the UK. Elan had submitted that this would increase the rate of absorption but the Panel noted that there was limited comparative data. The Panel considered the impression created by the claims misleading as alleged and ruled a breach of the Code in respect of each. Upon appeal by Elan, the Appeal Board upheld the Panel's rulings of breaches of the Code.

The claim 'After all, Migramax is as effective as sumatriptan 100mg in migraine headaches' appeared in the advertisement and the claim 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache …' was in the CD voiceover. Glaxo Wellcome stated that in the one study which compared Migramax with oral sumatriptan 100mg there was no significant difference between the two treatments for the primary end point ie headache relief at two hours for the first migraine attack. This study also failed to show a statistically significant difference for either treatment compared to placebo. Whereas there was evidence that showed sumatriptan 100mg to be superior to placebo for headache relief at two hours; therefore this study did not reflect the balance of evidence for sumatriptan 100mg. It was alleged that the claims were misleading. The Panel considered that the claim in the advertisement was too broad. The data was limited and insufficient to support a general claim about the comparability of Migramax and sumatriptan. The claim was not sufficiently qualified and was thus not a fair reflection of the balance of the evidence and was misleading in this regard. A breach of the Code was ruled. Upon appeal by Elan, the Appeal Board noted that there was only one comparative study available. It was a large study and it had been published in a peer review journal. The Appeal Board was slightly concerned that the study had been powered to detect a difference between the products, it had not been powered to demonstrate equivalence. Nevertheless the study was on a large number of patients. The claim referred to Migramax being as effective as sumatriptan 100mg. On balance the Appeal Board considered that the claim was a fair reflection of the evidence and was not misleading. The Appeal Board ruled no breach of the Code. The Panel considered that the claim in the voiceover that 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache …' was suitably qualified and an accurate reflection of the study. The Panel did not consider the claim misleading as alleged and ruled no breach of the Code.

The claim 'Significantly more effective than sumatriptan 100mg in nausea after first attack' appeared in the advertisement and the claim '… more effective against nausea …' was in the CD voiceover. Glaxo Wellcome stated that the claim in the advertisement should be qualified as it only referred to the one clinical study. The results for nausea after the first attack showed statistical significance between Migramax and sumatriptan but a greater number of patients in the Migramax group had nausea before treatment started, compared to those in the placebo and sumatriptan groups. After the first attack the results were 44% of patients in the Migramax group had nausea four hours after treatment compared to 48% in the sumatriptan group. Migramax was not significantly more effective than sumatriptan 100mg in treating nausea after the second attack (49% vs 47%) in this study. There was no clinical relevance in a one-off significant difference result, especially as there was only a 4% marginal difference in just one attack in one study. It was alleged that the claim was misleading. The Panel noted that the claim in the advertisement was referenced to Tfelt-Hansen *et al* (1995) wherein the effect on nausea and vomiting was a secondary endpoint. Migramax was statistically significantly better than sumatriptan in

the treatment of nausea at two hours after medicine intake for the first attack; 44% versus 48% p<0.0001. For the second attack there was no statistically significant between group difference. The Panel noted that whilst the presence of nausea in the two groups differed numerically at baseline (77% for Migramax and 69% for sumatriptan) this difference did not achieve statistical significance. The Panel considered that the claim on the CD voiceover was not a fair reflection of the study. Migramax was more effective than sumatriptan against nausea with regard to the first attack only. The Panel considered the claim '… more effective against nausea …' was not sufficiently qualified. It was not a fair reflection of the study and was thus misleading. The Panel noted that the claim in the advertisement 'Significantly more effective than sumatriptan 100mg in nausea after first attack' referred to the initial migraine attack. The data was derived from one study. The Panel queried whether the statistically significant difference of 4% would be of general clinical significance. On balance the Panel considered that there was insufficient evidence to support such a general claim and it was misleading in this regard. Each claim was ruled in breach of the Code. Upon appeal by Elan, the Appeal Board considered that there was sufficient evidence in the Tfelt-Hansen study to support the claim in the advertisement that Migramax was 'significantly more effective than sumatriptan 100mg in nausea after the first attack'. It was sufficiently qualified and no breach of the Code was ruled. The Appeal Board considered that the claim on the CD voiceover was not a fair reflection of the study with regard to nausea; Migramax was more effective than sumatriptan against nausea with regard to the first attack only. The Appeal Board considered the claim '… more effective against nausea …' was not sufficiently qualified. It was not a fair reflection of the study and was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The claim 'Has a significantly lower incidence of adverse effects than sumatriptan 100mg' appeared in the advertisement and '… with fewer adverse effects' was on the CD voiceover. Glaxo Wellcome stated that there was a lack of long term safety data as only two attacks were monitored in just one study. Therefore this statement implied tolerability but it was well documented that metoclopramide had an extensive list of interactions and adverse events, which might be different to those with sumatriptan but equally might be important. The Panel noted that the Migramax SPC stated that the most common side effects occurring with therapeutic doses of salicylates were gastrointestinal disturbances. Effects associated with aspirin and hypersensitivity associated with salicylates were mentioned. A low incidence of side effects had been associated with metoclopramide. Symptoms which could occur especially with chronic use included endocrine disorders, tardive dyskinesia and spasms of the facial muscles. Raised serum prolactin levels had been observed during metoclopramide therapy. The incidence of such side effects was not stated. The Panel noted that in Tfelt-Hansen *et al* (1995) Migramax had an incidence of side effects comparable to placebo and significantly lower than sumatriptan 100mg. In the Panel's view the claims in the advertisement and the voiceover implied a greater tolerability in general whereas the comparative data was limited to one study evaluating two attacks. The claims were misleading in this regard and each was ruled in breach of the Code. Upon appeal by Elan, the Appeal Board noted that the study related to two consecutive attacks. Nevertheless, the Appeal Board considered that the two claims relating to adverse events were not unreasonable. The Appeal Board ruled no breach of the Code.

Glaxo Wellcome UK Limited complained about claims made by Elan Pharma Limited for its product Migramax (lysine acetylsalicylate/metoclopramide) which appeared in an advertisement in GP on 7 April (ref EL/MM-029) and in a voiceover on Telemed GP CD April 2000.

The advertisement featured the heading 'New Migramax changes the face of migraine therapy' above a row of seven photographs of a woman's face depicting the progression from a migraine attack to relief of migraine. Text stated 'Migramax just may be the biggest news in migraine since triptans were first launched in the early 90s' and compared Migramax with sumatriptan 100mg.

The advertisement on the Telemed CD comprised a series of sequential images. It featured a similar depiction of a woman's face progressing from pain to relief followed by an image of a glass of water adjacent to a patient pack. The advertisement then returned briefly to an image of the woman's face depicting migraine relief finishing with a display of all six facial images on the screen above the claim 'Changes the face of migraine therapy'. There was a direct link above each screen dump to the CD index for prescribing information. The accompanying voiceover stated, *inter alia*, 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache, more effective against nausea and with fewer adverse events. New Migramax, it changes the face of migraine therapy'.

Glaxo Wellcome produced Imigran (sumatriptan).

1 Claims 'New Migramax changes the face of migraine therapy' (advertisement)
'New Migramax, it changes the face of migraine therapy' (CD voiceover)
'Migramax just may be the biggest news in migraine since triptans were first launched in the early 90s' (advertisement)

COMPLAINT

Glaxo Wellcome stated that Migramax was a new presentation that contained lysine acetylsalicylate and metoclopramide. It was not the first analgesic/antiemetic combination product to be marketed for migraine therapy and therefore it was unlikely that the management of migraine would be changed dramatically by Migramax. Glaxo Wellcome recognised the play on words with the faces in the advertisement that represented a progression from

painful to complete relief of migraine. The claim implied that this transformation was something new in the treatment of migraine. Whereas since the early 1990s Glaxo Wellcome had introduced three formulations of Imigran (tablets, injection, nasal spray) as well as Naramig tablets. Glaxo Wellcome alleged that the claims were in breach of the Code as they were misleading and exaggerated (Clauses 7.2 and 7.8).

RESPONSE

Elan Pharma stated that Migramax was a new formulation containing lysine acetylsalicylate and metoclopramide. The addition of lysine to acetylsalicylate increased the rate of absorption. Migramax might not be the first analgesic/antiemetic combination to be marketed for the treatment of migraine, but it represented the first introduction of lysine acetylsalicylate to the UK. The introduction of a previously unavailable treatment obviously represented a change to the migraine therapy armamentarium. The statement 'Changes the face of migraine therapy' reflected this fact without qualifying the magnitude or impact of this change.

The introduction of the triptan class of medicines was indisputably a major advance in the treatment of migraine. Several triptans were now available in a variety of presentations but none had demonstrated superior efficacy to sumatriptan injection introduced in 1991. The only non-triptan acute treatments introduced since 1991 were tolfenamic acid, a paracetamol/domperidone combination, dihydroergotamine nasal spray and Migramax. Of these, only tolfenamic acid and Migramax included previously unavailable active ingredients and were the subject of published data demonstrating comparable efficacy with sumatriptan 100mg. Elan agreed that it would be unacceptable to state that Migramax was the biggest news in migraine therapy as this was subjective. However, to state that Migramax just might be the biggest news in migraine therapy left it to the reader to make a judgement and was reasonable and consistent with the facts.

PANEL RULING

The Panel considered that the claim in the advertisement 'New Migramax changes the face of migraine therapy' was a strong claim. The Panel did not accept the submission that the claim reflected a change to the migraine therapy armamentarium without qualifying the magnitude or impact of this change. It would also be read in light of the second claim at issue; 'Migramax just may be the biggest news in migraine since triptans were first launched in the early 90s.' The Panel considered that these claims would give readers the impression that Migramax represented a significant change in migraine therapy and that was not so. It was not the first analgesic/antiemetic combination to be marketed although it was the first lysine acetylsalicylate to be introduced to the UK. Elan submitted that this would increase the rate of absorption. The Panel noted that there was limited comparative data. The Panel noted that the visual offered another interpretation, ie from pain to relief, but did not consider that this would negate the overall impression given that Migramax represented a significant change in migraine therapy. The Panel considered the impression created by each claim at issue in the advertisement misleading as alleged and ruled a breach of Clause 7.2 in respect of each claim. The Panel considered the alleged breach of Clause 7.8 was covered by this ruling.

The Panel considered that the claim on the CD voiceover was similarly misleading. It gave the impression that Migramax represented a significant change in migraine therapy and that was not so. A breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 7.8 was covered by this ruling.

Elan appealed the rulings of breaches of Clause 7.2.

2 Claims 'After all, Migramax is as effective as sumatriptan 100mg in migraine headaches' (advertisement)
'In a clinical study it was as effective as sumatriptan 100mg against the initial headache…' (CD voiceover)

COMPLAINT

Glaxo Wellcome stated that it was aware of one study only (Tfelt-Hansen *et al* 1995) comparing directly with oral sumatriptan 100mg, and there was no significant difference between the two treatments for the primary end point ie headache relief at 2 hours for the first migraine attack. This study also failed to show a statistically significant difference for either treatment compared to placebo. Whereas there was evidence that showed sumatriptan 100mg to be superior to placebo for headache relief at 2 hours; therefore this study did not reflect the balance of evidence for sumatriptan 100mg. There was also one study to show Migramax to be superior to placebo. The results showed that sumatriptan was numerically better than Migramax for the second migraine attack. The response to Migramax appeared to decline for the second attack (57% and 43%) whereas the response to sumatriptan was constant for both attacks (53% and 55%). Only two consecutive migraine attacks were monitored in this study, hence there was no evidence to show continuing long term efficacy.

Glaxo Wellcome alleged that the claims in the advertisement and voiceover were misleading in breach of Clause 7.2. The claim in the advertisement should be qualified, ie it should state that it was based on one study and both the claim in the advertisement and voiceover should state that only two migraine attacks were monitored in the clinical study.

RESPONSE

Elan stated that a well designed and conducted double-blind, randomised, placebo controlled study in 385 patients showed comparable efficacy for Migramax and sumatriptan 100mg in the treatment of migraine headache over two consecutive attacks according to efficacy criteria endorsed by the International Headache Society (Tfelt-Hansen *et al* 1995). There was no statistically significant difference in terms of headache relief between either treatment for both attacks. Contrary to Glaxo Wellcome's

assertion, both treatments were statistically significantly superior to placebo. For an episodic condition such as migraine and for a treatment promoted for first line use, this study was sufficient to support the claim that Migramax was as effective as sumatriptan 100mg in migraine headaches. The efficacy of sumatriptan demonstrated in this study was consistent with that seen in other studies (Tfelt-Hansen 1993). Supporting evidence was provided by a review of clinical studies involving Migramax and conventional aspirin/metoclopramide combinations (Chabriat 1997) which concluded, '…efficacy is comparable with that of oral sumatriptan…'.

PANEL RULING

The Panel noted that the claim 'After all, Migramax is as effective as sumatriptan 100mg in migraine headaches' was referenced to Tfelt-Hansen *et al* (1995). This study was an 8 week double-blind, randomized three parallel group study of oral sumatriptan 100mg, Migramax and placebo in patients with migraine. Two consecutive attacks were evaluated. The primary efficacy parameter was the number of migraine attacks with a decrease in headache grade to 0 or 1 at two hours after treatment of the first attack. A secondary endpoint was the decrease of headache grade for the second treated attack. The study was powered to detect a 15% difference between treatments. Primary endpoint data showed there was no statistically significant difference between sumatriptan and Migramax with regard to the first attack. Both active medications were statistically significantly superior to placebo; $p<0.0001$. The secondary endpoint data showed that both Migramax and sumatriptan were superior to placebo with regard to treating the second attack; $p=0.006$ and $p<0.0001$ respectively. However, although there was a numerical difference between the products (Migramax 43% versus sumatriptan 55%) this difference did not achieve statistical significance. In this regard the Panel noted that the study was statistically designed to detect a difference of 15% between treatments. The study authors concluded that there was no difference in primary or secondary efficacy between Migramax and sumatriptan.

The Panel noted that Tfelt-Hansen (1993) was a review of controlled clinical trials for sumatriptan in the treatment of migraine attacks. The study authors noted one study which compared oral sumatriptan with metoclopramide plus aspirin wherein the between group difference in response rates was not statistically significant for the first attack, but was for the second and third attacks. The review authors concluded that in general sumatriptan was superior to placebo in providing relief from the associated symptoms of the migraine attack.

Chabriat *et al* (1997) was a review of nine trials evaluating the efficacy of combined aspirin and metoclopramide in the acute treatment of migraine attacks. Data derived from the Oral Sumatriptan and Aspirin Plus Metoclopramide Comparative Study Group (1992) and Tfelt-Hansen *et al* (1995) were presented. In the former sumatriptan was superior to Migramax in headache relief in the second and third attacks, but not in the first attack; overall the authors concluded that the efficacy of Migramax was comparable with that of oral sumatriptan.

The Panel considered that the claim 'After all Migramax is as effective as sumatriptan 100mg in migraine headaches' was too broad. The data was limited and insufficient to support a general claim about the comparability of Migramax and sumatriptan. The claim was not sufficiently qualified and was thus not a fair reflection of the balance of the evidence and was misleading in this regard. A breach of Clause 7.2 was ruled. This ruling was appealed by Elan.

The Panel considered that the claim in the voiceover that 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache …' was suitably qualified and an accurate reflection of Tfelt-Hansen *et al* (1995). The Panel did not consider the claim misleading as alleged and ruled no breach of Clause 7.2 of the Code.

3 Claims 'Significantly more effective than sumatriptan 100mg in nausea after first attack' (advertisement)
'…more effective against nausea…' (CD voiceover)

COMPLAINT

Glaxo Wellcome stated that this statement should be qualified in the advertisement, as it referred to only one clinical study. The results for nausea after the first attack showed statistical significance between Migramax and sumatriptan but a greater number of patients in the Migramax group were suffering with nausea before treatment started, compared to those in the placebo and sumatriptan patient groups. After the first attack the results were 44% of patients in the Migramax group had nausea 2 hours after treatment compared to 48% in the sumatriptan group. Migramax was not significantly more effective than sumatriptan 100mg in treating nausea after the second attack (49% vs 47%) in this one study. There was no clinical relevance in a one-off significant difference result, and especially as there was only a 4% marginal difference in just one attack in one study. Glaxo Wellcome alleged that this claim was in breach of Clause 7.2 of the Code as it was misleading.

RESPONSE

Elan stated that the sumatriptan comparative study (Tfelt-Hansen *et al* 1995) revealed a statistically significant difference in terms of relief of nausea in favour of Migramax after the first of the two treated attacks, but not after the second. The proportion of patients reporting nausea before treatment was greater in the Migramax group than in the sumatriptan group but this difference was not statistically significant. The reduction in the proportion of patients reporting nausea after treatment of the first attack was significantly greater in Migramax treated patients, however. This was explicit in the claim that Migramax was superior to sumatriptan in this regard after the first attack (advertisement) and in treating nausea associated with the initial headache (voiceover). Elan did not

accept that a statistically significant difference after one attack could not have a clinical relevance.

PANEL RULING

The Panel noted that the claim at issue in the advertisement was referenced to Tfelt-Hansen *et al* (1995) wherein the effect on nausea and vomiting was a secondary endpoint. Migramax was statistically significantly better than sumatriptan in the treatment of nausea at 2 hours after medicine intake for the first attack; 44% versus 48% $p<0.0001$. For the second attack there was no statistically significant between group difference. The Panel noted that whilst the presence of nausea in the two groups differed numerically at baseline (77% for Migramax and 69% for sumatriptan) this difference did not achieve statistical significance.

The Panel considered that the claim on the CD voiceover that 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache, more effective against nausea' was not a fair reflection of Tfelt-Hansen *et al* (1995) with regard to nausea; Migramax was more effective than sumatriptan against nausea with regard to the first attack only. The Panel listened to the CD. The Panel considered that the voiceover reference on the CD to 'the initial headache' appeared to refer to the efficacy claim only. The Panel considered the claim '… more effective against nausea …' was not sufficiently qualified, it was not a fair reflection of the study and was thus misleading. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the claim in the advertisement 'Significantly more effective than sumatriptan 100mg in nausea after first attack' referred to the initial migraine attack. The data was derived from one study. The Panel queried whether the statistically significant difference of 4% would be of general clinical significance. On balance the Panel considered that there was insufficient evidence to support such a general claim and it was misleading in this regard. A breach of Clause 7.2 was ruled.

Elan appealed the rulings of breaches of Clause 7.2.

4 Claims 'Has a significantly lower incidence of adverse events than sumatriptan 100mg' (advertisement)
'… and with fewer adverse effects' (CD voiceover)

COMPLAINT

Glaxo Wellcome stated that there was a lack of long term safety data as only two attacks were monitored in just one study. Therefore this statement implied tolerability but it was well documented that metoclopramide had an extensive list of interactions and adverse events, which might be different to those with sumatriptan but equally might be important (eg extrapyramidal effects of metoclopramide were very distressing in some patients over the age of 20 years). Glaxo Wellcome concluded that this statement was also in breach of the Code in that it should be qualified, ie it should state that it was based on one study that monitored only two migraine attacks (Clause 7.2).

RESPONSE

Elan stated that migraine was an episodic condition which usually required discreet treatment episodes. Long term safety data, therefore, had less relevance than for chronic treatments taken on a daily basis. In the case of migraine, acute tolerability had much greater relevance. The sumatriptan comparative study (Tfelt-Hansen *et al* 1995) showed clearly that the incidence of adverse events associated with Migramax was comparable with that associated with placebo and significantly lower than that associated with sumatriptan 100mg. Comparable low rates of adverse effect reporting were found in a placebo-controlled study (Chabriat *et al* 1994) and an open-label study (Hughes *et al* 1997). The claim relating to the comparative incidence of adverse events was, therefore, a fair interpretation of the data. Elan agreed that metoclopramide could be associated with adverse effects, including rare extrapyramidal side effects. However, they tended to occur mostly with continuous use which was inconsistent with the episodic administration of a migraine therapy. Extrapyramidal effects tended to occur in young adults, especially female patients under 20 years of age (Bateman *et al* 1985) and the use of Migramax in patients under 20 years of age was clearly contraindicated in the summary of product characteristics (SPC).

PANEL RULING

The Panel noted that section 4.8 of the Migramax SPC headed 'Undesirable Effects' stated that the most common side effects occurring with therapeutic doses of salicylates were gastrointestinal disturbances such as gastric irritation with blood loss, nausea, dyspepsia, vomiting and gastric ulceration. Effects associated with aspirin and hypersensitivity associated with salicylates were mentioned. A low incidence of side effects had been associated with metoclopramide. Symptoms which could occur especially with chronic use included, *inter alia*, endocrine disorders, tardive dyskinesia, spasms of the facial muscles. Raised serum prolactin levels had been observed during metoclopramide therapy. The incidence of such side effects was not stated. Section 4.3 of the SPC stated that Migramax was not recommended for patients under 20 years of age in view of the particular risk of dystonic reactions in young adults and children.

The Panel noted that in Tfelt-Hansen *et al* (1995) Migramax had an incidence of side effects comparable to placebo and significantly lower than sumatriptan 100mg.

The Panel noted that Hughes *et al* (1997) was an open label non-comparative study designed to evaluate the effects of second and third doses of Migramax when the first dose was ineffectual. Acknowledging the limitations of this kind of trial the study authors noted that only a few minor or transient side effects were reported throughout the trial.

The Panel noted Elan's submission regarding the occurrence of extrapyramidal side effects and the relevant comments in the Migramax SPC. The Panel noted that the reference used to support this, Bateman *et al* (1985), showed that although the rate of extrapyramidal reactions was significantly higher in

12-19 year olds, this could partly be explained by the frequency of therapeutic over-dosage in this group and in terms of the numbers of reactions; 48% of the reactions studied occurred in patients 20 years and older. Reactions often developed within 24 hours of starting treatment and 94% occurred within 72 hours. The paper stated that although these reactions were 'self limiting and rarely caused permanent damage their morbidity was high and many patients … were admitted to hospital'. In the Panel's view Bateman was inconsistent with Elan's submission that EPS reactions were not an issue for patients on Migramax.

In the Panel's view the claims in the advertisement and the voiceover implied a greater tolerability in general whereas the comparative data was limited to one study evaluating two attacks. The claims were misleading in this regard and each was ruled in breach of Clause 7.2.

Elan appealed the rulings of breaches of Clause 7.2.

APPEAL BY ELAN PHARMA

Elan stated that it remained of the opinion that the claims made were fair, balanced and in compliance with the Code. It appealed all of the Panel's rulings of breaches.

Migraine was a serious, debilitating condition that affected around eight million people in the UK. The cost of treating migraine was around £30 million per year; the wider costs to society were considerably higher. Compared with non-migraineurs, migraineurs reported compromised physical, mental and social functioning, and cormorbid depression was common (Terwindt *et al* and Lipton *et al*). Effective treatment required the administration of an appropriate agent as soon as possible. An important pathophysiological feature of a migraine attack was gastric stasis. This might slow the absorption of migraine treatments and impair their ability to control symptoms rapidly and effectively. Alternative routes of administration such as parenteral, nasal or rectal were sometimes employed, but these were not always convenient. Metoclopramide combined centrally acting dopaminergic anti emetic properties with anticholinergic effects that improved gastric motility. Metoclopramide or similar medicines were available in combination with analgesics to overcome the gastric stasis associated with migraine and improve the absorption of the analgesic. Aspirin was an effective analgesic often used to treat the headache associated with migraine. The addition of lysine to acetylsalicylate increased solubility 140 fold and both significantly increased the rate of absorption, and reduced gastric mucosal damage. The combination of metoclopramide and lysine acetylsalicylate in Migramax represented the first time two medicines, which both addressed the problem of absorption, had been brought together in proprietary form in the UK to treat the symptoms of migraine.

Tfelt-Hansen *et al* described a placebo controlled, randomised, double blind comparator study in which 385 patients received Migramax, sumatriptan 100mg or placebo for the treatment of two consecutive migraine attacks. Migramax was found to be as effective as sumatriptan in treating headache associated with both attacks. Migramax was more effective than sumatriptan in treating nausea after the first attack. The Panel was correct to point out that the difference in the incidence of nausea after the first treated attack in patients who received Migramax and patients who received sumatriptan was only 4%. The Panel was mistaken, however, in considering the clinical significance of this difference in relation to the claims. The reduction in the incidence of nausea from baseline (42% in patients who received Migramax and 31% in patients who received sumatriptan) was statistically significant and clinically relevant.

The Panel was mistaken to conclude that data from the Oral Sumatriptan and Aspirin Plus Metoclopramide Comparative Study Group (Chabriat *et al*) indicated that sumatriptan was superior to Migramax in the treatment of the second and third attacks. The analgesic/antiemetic combination used in this study was standard aspirin and metoclopramide, not Migramax. In fact, the efficacy of sumatriptan and Migramax (not standard aspirin and metoclopramide in combination) demonstrated by Tfelt-Hansen *et al* was consistent with that seen in other studies. The placebo-level of adverse events associated with Migramax was also consistent with that seen in other studies. The Panel listed the adverse effects appearing under Section 4.8 of the Migramax SPC. It must be noted, however, that these were the adverse effects known to be associated with aspirin and metoclopramide when used in all circumstances, and not the adverse effects related causally to Migramax in clinical studies. The treatment of acute migraine attacks required short, discreet episodes of therapy. The adverse effect profile of lysine acetylsalicylate and metoclopramide used in this way would differ from that seen when the individual components were administered repeatedly. The placebo-level of adverse effects associated with metoclopramide when combined with other analgesics for the treatment of migraine provided yet further support for the findings of Tfelt-Hansen (Dexter *et al* 1985).

This study was reported in The Lancet, one of the UK's premier peer reviewed journals. In conclusion, the author stated that '[Migramax] is as effective as sumatriptan in the treatment of migraine attacks. It is also much cheaper.' The claims regarding efficacy against headache, nausea and tolerability were clearly supported by the data. However, the issue appeared to be whether these claims were too broad when based on only one comparative study. This depended upon the quality of that study, and data derived from other studies. The study by Tfelt-Hansen *et al* was well designed and robust. The data were consistent with those from other studies. There were no published data suggesting that Migramax was less effective than sumatriptan against headache, no more effective against nausea after the first treated attack, or not associated with placebo-level adverse effects.

The claims based upon these data were fair reflection of the balance of evidence.

To summarise, a clinical study conducted according to a 'gold standard' design and published in a highly reputable journal demonstrated that a new and novel treatment was as effective as the 'gold standard' oral therapy. The fact that this treatment was cheaper than

the gold standard (a single dose of Migramax cost £1.17, a single dose of sumatriptan 100mg cost £8.00) did not form part of any claim, but was an important issue nonetheless. The claims regarding efficacy and tolerability were not only supported clearly by the data presented by Tfelt-Hansen *et al*, but were also consistent with the findings of other studies. These claims were not based on unreliable findings from one inadequate study.

Overall, Elan believed that Migramax did, therefore, 'change the face of migraine therapy' and represented an important and newsworthy addition to the migraine treatment armamentarium. Elan believed the wording of the claims regarding efficacy and tolerability were a fair and accurate reflection of the facts.

APPEAL BOARD RULING

1 Claims 'New Migramax changes the face of migraine therapy' (advertisement)
'New Migramax, it changes the face of migraine therapy' (CD voiceover)
'Migramax just may be the biggest news in migraine since triptans were first launched in the early 90s' (advertisement)

The Appeal Board noted that Migramax was not the first analgesic/antiemetic combination to be marketed although it was the first lysine acetylsalicylate to be introduced to the UK. The Appeal Board considered that the impression of each of the three claims at issue was that Migramax represented a significant change in migraine therapy and that was not so. The Appeal Board upheld each of the Panel's three rulings of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

2 Claims 'After all, Migramax is as effective as sumatriptan 100mg in migraine headaches' (advertisement)
'In a clinical study it was as effective as sumatriptan 100mg against the initial headache…' (CD voiceover)

The Appeal Board examined the Tfelt-Hansen *et al* 1995 study. It was a double blind randomised, placebo controlled study in 385 patients published in The Lancet. The study evaluated two consecutive attacks. The Appeal Board noted the study results.

Primary endpoint data showed there was no statistically significant difference between sumatriptan and Migramax with regard to the first attack. Both active medications were statistically significantly superior to placebo; $p<0.0001$. The secondary endpoint data showed that both Migramax and sumatriptan were superior to placebo with regard to treating the second attack; $p=0.006$ and $p<0.0001$ respectively. However, although there was a numerical difference between the products (Migramax 43% versus sumatriptan 55%) this difference did not achieve statistical significance. The study was statistically designed to detect a difference of 15% between treatments. The study authors concluded that there was no difference in primary or secondary efficacy between Migramax and sumatriptan.

The Appeal Board noted that Tfelt-Hansen (1993) was a review of controlled clinical trials for sumatriptan in the treatment of migraine attacks. The study authors noted one study which compared oral sumatriptan with metoclopramide plus aspirin wherein the between group difference in response rates was not statistically significant for the first attack, but was for the second and third attacks. The Appeal Board noted that this was not a comparison of sumatriptan and Migramax.

The Appeal Board noted that the Tfelt-Hansen *et al* 1995 study was the only comparative study available. The Appeal Board considered that it was a large study and noted that it had been published in a peer review journal. The Appeal Board was slightly concerned that the study had been powered to detect a difference between the products, it had not been powered to demonstrate equivalence. Nevertheless the study was on a large number of patients. The claim referred to Migramax being as effective as sumatriptan 100mg. On balance the Appeal Board considered that the claim was a fair reflection of the evidence and was not misleading. The Appeal Board ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

3 Claims 'Significantly more effective than sumatriptan 100mg in nausea after first attack' (advertisement)
'…more effective against nausea…' (CD voiceover)

The Appeal Board noted its general comments about the Tfelt-Hansen *et al* 1995 study in point 2 above.

The Appeal Board noted that the effect on nausea and vomiting was a secondary endpoint in the Tfelt-Hansen study. Migramax was statistically significantly better than sumatriptan in the treatment of nausea at 2 hours after medicine intake for the first attack; 44% versus 48% $p<0.0001$. For the second attack there was no statistically significant between group difference. The presence of nausea in the two groups differed numerically at baseline (77% for Migramax and 69% for sumatriptan), the difference did not achieve statistical significance.

The Appeal Board noted that after the first attack the reduction of nausea from baseline was 42% for patients receiving Migramax and 31% in patients receiving sumatriptan. For the second attack there was no statistically significant between group difference.

The Appeal Board considered that there was sufficient evidence in the Tfelt-Hansen study to support the claim in the advertisement that Migramax was 'significantly more effective than sumatriptan 100mg in nausea after the first attack'. It was sufficiently qualified and no breach of Clause 7.2 of the Code was ruled. The appeal on this point was successful.

The Appeal Board considered that the claim on the CD voiceover that 'In a clinical study it was as effective as sumatriptan 100mg against the initial headache, more effective against nausea' was not a fair reflection of Tfelt-Hansen *et al* (1995) with regard to nausea; Migramax was more effective than sumatriptan against nausea with regard to the first attack only. The reference on the CD to 'the initial

headache' appeared to refer to the efficacy claim only. The Appeal Board considered the claim '… more effective against nausea …' was not sufficiently qualified, it was not a fair reflection of the study and was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

4 Claims 'Has a significantly lower incidence of adverse events than sumatriptan 100mg' (advertisement)
'… and with fewer adverse effects' (CD voiceover)

The Appeal Board noted its comments regarding the Tfelt-Hansen *et al* (1995) study made in point 2. It noted that the study related to two consecutive attacks. Nevertheless the Appeal Board considered that the two claims relating to adverse events were not unreasonable. The Appeal Board ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

Complaint received **26 June 2000**

Case completed **1 November 2000**

CASE AUTH/1054/7/00

GENERAL PRACTITIONER v ASTRAZENECA

Imdur mailing

A general practitioner complained about an Imdur (sustained release isosorbide mononitrate – ISMN) mailing sent by AstraZeneca alleging that a histogram entitled 'Risk of angina', which showed the number of ischaemic episodes throughout a twenty-four hour period, was incomprehensible. The Panel ruled a breach of the Code as the title of the histogram was misleading; the histogram showed both symptomatic and asymptomatic ischaemia and angina only related to symptomatic episodes.

The complainant alleged that the argument in the mailing assumed a direct relationship between plasma concentration and effectiveness which might be true but was not actually demonstrated. The Panel noted that a graph which compared the plasma profiles of Imdur 60mg od and isosorbide mononitrate (ISMN) 20mg bd was adapted from Olsson and Allgén (1992). It was concluded that six characteristics of a treatment regimen were desirable to optimise oral prophylactic nitrate therapy including a 24 hour plasma concentration profile resulting in avoidance of both development of nitrate tolerance and the suggested rebound phenomenon seen during nitrate-free intervals. The Panel noted that the graph at issue showed that the plasma concentration of ISMN abruptly peaked shortly after administration before falling. The Panel considered that it was not unreasonable to juxtapose the histogram showing ischaemic episodes with the graph showing plasma concentration profiles. In the opinion of the Panel plasma profile was a relevant factor and no breach of the Code was ruled.

The complainant alleged that the use of clockfaces to present the duration of antianginal effect was a complicated way of showing a simple point and the sample size in one of the studies referenced, Thadani *et al* (1987), appeared to be minute. The Panel noted that the clock face ISMN 20mg bd showed a 2 hour duration of antianginal effect. The data had been taken from Thadani *et al* in which the duration of activity of single oral doses of ISMN 20mg had been compared with that after one week of twice daily dosing (8am and 8pm). The authors reported that after a single dose exercise duration increased at 2 hours and 6 hours post-dose but after one week's twice daily therapy exercise duration was only increased at 2 hours but not at 6. It was concluded that tolerance to the antianginal effects of ISMN had occurred during the twice daily therapy. The Panel noted that nitrate tolerance involved a combination of reduced dose-effect relationship as well as a reduced duration of action of a given dose (Olsson and Allgén). The Panel noted that if tolerance occurred then tablets could be dosed asymmetrically. In this regard the Panel noted that in the graph showing the plasma concentration profile of ISMN 20mg bd the second dose had been given only six hours after the first – not twelve hours. The Panel considered that it was thus unfair to show a duration of effect of only two hours for ISMN 20mg bd when the medicine had been dosed twelve hourly and subsequent tolerance, involving reduced duration of action, had been demonstrated. A breach of the Code was ruled.

On appeal by AstraZeneca, the Appeal Board noted that the claim above the clock faces stated 'The effectiveness of twice daily nitrate regimens may diminish after only 2 hours'. With regard to ISMN 20mg bd only that segment of the clock face between 12 o'clock and 2 o'clock was highlighted. The Appeal Board considered that the implication was that at more than 2 hours post-dose ISMN was no longer effective. Both the claim and the clock face were referenced to Thadani *et al* which the Appeal Board noted had involved only 9 patients. Thadani *et al* had measured exercise tolerance at 2 and 6 hours post-dose and shown that when given ISMN every 12 hours patients could exercise for longer before the onset of pain at 2 hours post-dose but not at 6. The antianginal effects of ISMN were thus still evident at 2 hours but not at 6. Exercise tolerance had, however, only been measured at these two times and so it was impossible to tell when, between 2 and 6 hours post-dose, ISMN was no longer effective. The Appeal Board considered that

the presentation of the data was misleading and upheld the Panel's ruling of a breach of the Code.

A general practitioner complained about a mailing which he had received from AstraZeneca in relation to Imdur (sustained release isosorbide mononitrate – ISMN). The mailing consisted of a 'Dear Doctor' letter, a six page leaflet and a reply paid card, all bearing the reference IMD6097.

The leaflet was entitled 'Once-daily Imdur. Why expose your patients to the uncertainties of twice-daily nitrates?' The second page, headed 'The need for angina protection varies throughout the day', featured a histogram, entitled 'Risk of angina', which showed the number of asymptomatic and symptomatic ischaemic episodes throughout a twenty-four hour period. The page was referenced to Carboni *et al* (1987).

The third page compared the plasma profile of Imdur with a twice daily nitrate in relation to the pattern of ischaemic risk. The claim 'The effectiveness of twice daily nitrate regimens may diminish after only 2 hours' appeared on page four above two clock faces which depicted the duration of antianginal effects (hours) of ISMN 20mg bd (two hours) (Thadani *et al* 1987) and Imdur 60mg od (twelve hours) (Parker *et al* 1989). The 'Dear Doctor' letter similarly compared the plasma profile, in relation to pattern of ischaemic risk, of ISMN 20mg bd and Imdur. The page was referenced to Olsson and Allgén (1992).

COMPLAINT

The complainant was concerned that the histogram in the leaflet labelled 'Risk of angina' was completely incomprehensible. The number of ischaemic episodes did not convert to a risk. The complainant could not work out what the colour scheme meant or indeed exactly what it was that was being measured. Consequently, he could not establish what the message was intended to be.

The complainant stated that the argument assumed a direct relationship between plasma concentration and effectiveness, which might well be true but was not actually demonstrated. The clock presentation of the duration of antianginal effect was a very complicated way of showing a simple point, and the sample size of the study by Thadani *et al* appeared minute.

The overall argument appeared to be constructed from independent and unrelated links, each of which might stand up, but unfortunately were not scientifically connected to each other. The complainant did not consider the art work, illustrations and graphs complied with the Code and did not think the logic of AstraZeneca's argument did either.

RESPONSE

AstraZeneca stated that the mailing, which was sent to general practitioners in the UK, was designed to remind prescribers of a number of aspects pertinent to the use of nitrates in the prophylaxis of angina. The intention was to highlight succinctly the ways in which AstraZeneca's product addressed some of the issues involved. These being that: episodes of angina were more likely to occur during the patient's waking/active hours; they did not occur with a uniform distribution throughout the day; nitrates were effective in preventing such attacks.

AstraZeneca submitted that the pharmacokinetic properties of the nitrate formulation used influenced its performance in relation to certain well recognised practical issues. These being duration of effect of the nitrate, potential for development of tolerance, requirement for dosage regimen to provide a 'nitrate poor' period to avoid tolerance, patient compliance with therapy.

1 Histogram depicting 'risk of angina'

AstraZeneca disagreed with the complainant's view that the histogram was not readily comprehensible. The histogram had been adapted from a paper by Carboni *et al* which was clearly referenced. This paper described a study in which 59 patients with chronic stable reproducible effort angina pectoris underwent 24-hour ambulatory ST-segment monitoring; the patients also kept diaries in which time and duration of episodes of anginal pain were recorded. The data were analysed and presented graphically to show, for all patients in this part of the study, the number of asymptomatic and symptomatic anginal episodes occurring in a 24-hour period, as identified from ST-segment monitoring and patient diary results. A similar graphical presentation appeared in the paper. AstraZeneca's purpose in using the histogram was to demonstrate that episodes of angina were clustered around certain parts of the day. The study showed that numbers of episodes of both asymptomatic and symptomatic ischaemia plateaued and then tailed off during a 24-hour period. This was emphasised via the page heading, which clearly stated 'The need for angina protection varies throughout the day'. The chart legend made it clear that the darker colour related to asymptomatic episodes of angina and the lighter colour to symptomatic episodes, the number of patients in the study was stated and both axes were clearly labelled. AstraZeneca therefore believed that the message was clearly conveyed and self-explanatory and derived from a robust and clinically relevant study.

2 Graph depicting plasma profiles of different nitrate formulations

AstraZeneca stated that the page immediately adjacent to the histogram depicted data discussed in a review by Olsson and Allgén. This paper provided an overview of some of the problems encountered with nitrate therapy and graphically presented data showing the plasma concentrations of Imdur 60mg once daily compared to ISMN tablets 20mg twice daily. As was apparent from a visual inspection of the two graphs, the sustained release properties of Imdur provided a smooth plasma profile, in which nitrate levels rose to a peak and then gradually subsided over a period of hours. Such a regimen had been shown to be beneficial in avoiding development of nitrate tolerance (Olsson and Allgén). It was relatively more difficult to reproduce this profile with a twice daily nitrate regimen using a conventional tablet formulation, as the graph illustrated.

Twice daily formulations might produce sharper peaks and troughs of nitrate levels within the 24-hour period. If the first dose of conventional ISMN tablet was taken first thing in the morning it was conceivable that there would be a period during the daytime (depending upon the timing of the second nitrate dose) when a relatively abrupt drop in the levels of ISMN could occur. This could be viewed as disadvantageous and was avoided with the Imdur formulation.

AstraZeneca believed this message was clearly conveyed by the graph. The relationship between nitrate levels and clinical effectiveness was well recognised by the medical profession, hence the widespread adoption of glyceryl trinitrate for acute anginal episodes. Clearly, in the context of anginal prophylaxis any such relationship was complex, due to the issues of nitrate tolerance, as the evidence quoted below illustrated. However, it was apparent that given that episodes of angina were more frequent during the patient's waking hours (as indicated in the histogram), it was rational to utilise a formulation which provided elevated plasma levels during the daytime, without precipitate falls. Relatively low levels of nitrate were present during the night-time hours, when episodes of angina were less likely to occur. Again, AstraZeneca believed the graph was self-explanatory.

3 Duration of antianginal effect

AstraZeneca stated that the use of the clock faces to indicate duration of antianginal effect was to provide further evidence as to why a general practitioner might wish to adopt the use of a sustained release preparation such as Imdur, in preference to a twice daily regimen. The two studies cited used exercise testing in patients with angina to assess the impact of nitrate therapy in comparison to placebo. The study by Thadani *et al* was a randomised, double-blind crossover study where nine patients received a bd nitrate regimen. Following one week of therapy it was shown that an anti-anginal effect was present 2 hours after nitrate dosing, but not at 6 hours or 10 hours. Due to the practicalities of exercise testing, such studies did not tend to involve large patient numbers, however the results obtained showed statistically significant differences between groups. Parker *et al* studied a larger patient population with stable angina and utilised treadmill testing to assess the antianginal properties of sustained release ISMN 60mg compared to isosorbide dinitrate (ISDN) 30mg in four daily doses or placebo. This confirmed that the antianginal properties of sustained release ISMN were maintained over 12 hours. The clock faces were used to provide a visual representation of the data from the two studies, further explanatory information appeared in the legends and the page headings.

In summary, AstraZeneca believed that the mailing item presented a series of key points regarding the use of Imdur Durules in angina in an abbreviated but readily understandable fashion. These being that episodes of angina were not uniformly distributed throughout a 24-hour period, but were concentrated during the waking hours; the sustained release properties of Imdur Durules allowed levels of nitrate to plateau during the daytime, when anginal episodes were likely to occur; studies had shown that the antianginal properties of Imdur, as demonstrated by exercise testing, were still present 12 hours after dosing, in contrast to a conventional bd formulation where development of nitrate tolerance might lead to loss of antianginal effect.

Whilst AstraZeneca acknowledged that the evidence presented was derived from a number of sources, it firmly believed that the leavepiece provided a coherent rationale for the use of Imdur and provided robust evidence in each instance. The issues were further clarified in the accompanying letter. In AstraZeneca's view, the separate points were 'scientifically connected' and it believed that the points made were both coherent as they stood and in relation to the overall issues as noted previously The company did not believe that it had in any way been misleading in its use of data. AstraZeneca regretted the fact that the complainant had difficulties of interpretation with the piece, however it denied any breach of Clauses 7.2, 7.3 or 7.6 of the Code on the grounds that:

- it had not attempted to mislead the reader, the data quoted were from robust, clinically relevant sources and were used in a logical and balanced fashion to support the claims made (Clause 7.2);
- references were cited which provided substantiation of all claims made (Clause 7.3);
- the two graphs used had been taken directly from published sources and minimally adapted by AstraZeneca; the adaptations that had been made were with the aim of enhancing clarity; the graphs had been included to illustrate clear points of fact concerning occurrences of angina and the pharmacokinetic profiles of ISMN formulated in Durules and conventional tablets; all axes and legends had been clearly labelled and the graphs were fully referenced. (Clause 7.6).

PANEL RULING

The Panel noted that whilst the complainant had provided a copy of each promotional item in the mailing the specific allegations appeared to refer to the leaflet and the Panel thus considered the complaint in relation to this item.

The Panel noted that Imdur was indicated for the prophylactic treatment of angina pectoris. The histogram at issue was adapted from Carboni *et al* which examined the relationship between heart rate and ischaemic ST-segment depression in patients with documented obstructive coronary artery disease and reproducible effort angina. The original histogram recorded the mean hourly number of ischaemic episodes during 24 hour ambulatory ST-segment monitoring and showed that most episodes occurred during the period of peak daily activity when heart rate was highest.

The Panel noted that in the histogram at issue asymptomatic (painless) ischaemic episodes were recorded in dark green; these constituted the majority of episodes at every time period throughout the 24 hour period. Superimposed on the dark green bars

were light green bars depicting the number of symptomatic (painful) ischaemic episodes. The graph thus showed the 24 hour profile of ischaemic burden; the incidence of painful episodes more or less mirroring the greater incidence of painless ischaemia. There were periods of the day, however, when patients recorded asymptomatic ischaemia but no painful ischaemia. The Panel noted that the term angina only related to painful episodes of ischaemia. The study by Carboni *et al*, from which the histogram was taken, showed that asymptomatic and symptomatic ischaemia might be caused by different mechanisms. The Panel considered that the title of the histogram 'Risk of angina' was misleading as alleged as it showed both symptomatic and asymptomatic ischaemia and angina only related to symptomatic episodes. A breach of Clause 7.2 was ruled.

The Panel noted that the graph on page 3 which compared the plasma profiles of Imdur 60mg od and ISMN 20mg bd was adapted from Olsson and Allgén, an article entitled 'Prophylactic nitrate therapy in angina pectoris – is there an optimal treatment regimen?' which primarily discussed Imdur. It was concluded that six characteristics of a treatment regimen were desirable to optimise oral prophylactic nitrate therapy including a plasma concentration profile over 24 hours resulting in avoidance of both development of nitrate tolerance and the suggested rebound phenomenon seen during nitrate-free intervals. The Panel noted that the graph at issue showed that the plasma concentration of ISMN 20mg bd abruptly peaked shortly after administration before falling. The Panel considered that it was not unreasonable to juxtapose the histogram showing ischaemic episodes with the graph showing plasma concentration profiles. The Panel did not accept the allegation that the argument presented in the leaflet assumed a direct relationship between plasma concentration and effectiveness which might well be true but was not actually demonstrated. In the opinion of the Panel plasma profile was a relevant factor. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that the clock face for twice daily ISMN 20mg showed a 2 hour duration of antianginal effect. The data had been taken from a study by Thadani *et al* in which the duration of activity of single oral doses of ISMN 20mg had been compared with that after one week of twice daily dosing (8am and 8pm). The authors reported that after a single dose exercise duration increased at 2 hours and 6 hours post-dose but after one week's twice daily therapy exercise duration was only increased at 2 hours but not at 6. It was concluded that tolerance to the antianginal effects of ISMN had occurred during the twice daily therapy. The Panel noted that nitrate tolerance involved a combination of reduced dose-effect relationship, as well as a reduced duration of action of a given dose (Olsson and Allgén). The Panel noted that if tolerance occurred then tablets could be dosed asymmetrically. In this regard the Panel noted that in the graph showing the plasma concentration profile of ISMN 20mg bd (page 3 of the leaflet) the second dose had been given only six hours after the first – not twelve hours. The Panel considered that it was thus unfair to show a duration of effect of only two hours for ISMN 20mg bd when the medicine had been dosed twelve hourly and subsequent tolerance, involving reduced duration of action, had been demonstrated. A breach of Clause 7.2 was ruled.

APPEAL BY ASTRAZENECA

AstraZeneca appealed the ruling relating to the duration of antianginal effect. AstraZeneca stated that tolerance was a well-recognised consequence of prophylactic treatment of angina with nitrates and resulted in reduced efficacy and shortened duration of response. Tolerance could be avoided by ensuring that there was a relatively nitrate-poor period during each day's treatment. This nitrate-poor period was conveniently provided by the use of once daily modified-release preparations of ISMN such as Imdur. Short-acting preparations of ISMN, unless dosed asymmetrically, could lead to the development of nitrate tolerance as outlined by Thadani *et al* and quoted in the mailing. As the Panel pointed out, this showed tolerance developing when ISMN was dosed twice daily with 12 hours in between each dose. Ideally therefore patients should be dosed asymmetrically, however this was not stipulated in the summaries of product characteristics for the various versions of short acting ISMN and AstraZeneca considered that it was questionable how often this was practised. Furthermore the paper by Olsson and Allgén described a study in which 81 patients who had been prescribed an asymmetric dosing regimen were questioned as to their adherence to it. The second dose was taken anywhere between 4 and 12 hours after the first with a fairly even spread.

AstraZeneca submitted that it was quite reasonable to state that 'The effectiveness of twice-daily nitrate regimens may diminish after only 2 hours' because in the real world an asymmetric dosing regime was frequently not complied with even if it was prescribed.

Finally AstraZeneca stated that whilst the graph of plasma profiles showed optimal dosing the clocks below demonstrated what might happen in clinical practice. The company considered this was relevant information to give clinicians and did not mislead given what was known about patient compliance with these medicines. AstraZeneca denied a breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the claim above the clock faces stated 'The effectiveness of twice-daily nitrate regimens may diminish after only 2 hours'. With regard to ISMN 20mg bd only that segment of the clock face between 12 o'clock and 2 o'clock was highlighted. The Appeal Board considered that the implication was that at more than 2 hours post-dose ISMN was no longer effective. Both the claim and the clock face were referenced to Thadani *et al* which the Appeal Board noted had involved only 9 angina patients. Thadani *et al* had measured exercise tolerance at 2 and 6 hours post-dose and shown that when given ISMN every 12 hours patients could exercise for significantly longer before the onset of

pain, compared to placebo ($p<0.02$), at 2 hours post-dose but not at 6. The antianginal effects of ISMN were thus still evident at 2 hours but not at 6. Exercise tolerance had, however, only been measured at these two times and so it was impossible to tell when, between 2 and 6 hours post-dose, ISMN was no longer effective. The Appeal Board considered that the presentation of the data was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

Complaint received **21 July 2000**

Case completed **4 January 2001**

CASE AUTH/1057/7/00 *NO BREACH OF THE CODE*

PROCTER & GAMBLE v MERCK SHARP & DOHME

Fosamax exhibition panel

Procter & Gamble alleged that claims on a Fosamax (alendronate) exhibition panel, used by Merck Sharp & Dohme, of a 59% reduction in painful vertebral fractures at 12 months and a 63% reduction in hip fractures at 18 months in women with osteoporosis in the Fracture Intervention Trial (FIT) were false and misleading as they relied on statistical analyses and data that did not support the claimed therapeutic benefit.

FIT was designed to test the hypothesis that alendronate would reduce the rate of fractures in women aged 55-80 years with low hip bone mineral density (BMD) at the femoral neck. The women were assigned to one of two sub-studies. FIT 1 (vertebral fracture arm) was a study in patients with low femoral neck BMD and a pre-existing vertebral fracture confirmed by radiography prior to randomisation to alendronate or placebo. The primary end point was vertebral fractures confirmed by radiography after three years. FIT 2 (clinical fracture arm) was a study in patients with low femoral neck BMD T-score ≤ – 1.6. The T-score related to the number of standard deviations (SD) below the mean BMD of a young adult woman but without a pre-existing vertebral fracture prior to randomisation to alendronate or placebo. The primary end point was clinical fractures after four years.

Procter & Gamble stated that Merck Sharp & Dohme had previously acknowledged the different patients included in FIT 1 and FIT 2 by stating in the publication describing the FIT design (Black) that 'an assessment will be made separately of the effect of alendronate in two distinct populations …. The possibility of stopping the Clinical Fracture Study on the basis of the observation of an early positive result in the Vertebral Deformity Study is obviated by the different populations and end points studied in the two trials'. Procter & Gamble was therefore surprised that, despite this, Merck Sharp & Dohme had subsequently chosen to pool data from the two studies. Specifically, Procter & Gamble alleged that Merck Sharp & Dohme had inappropriately pooled fracture data from different subgroups of FIT. It had combined a subgroup of patients with T-scores below – 2.5 SD from FIT 2 (37% of the overall population) with the entire population from FIT 1, who had a T-score of ≤ – 1.6 SD. The populations were clearly different and such a combination analysis was methodologically flawed. Further, the combined population was inconsistent with the CPMP and WHO definitions of osteoporosis (T-score ≤ – 2.5 SD). The Panel noted that there was a difference between the two populations. Patients in FIT 1 had pre-existing vertebral fracture whereas those in FIT 2 did not. Both populations were at risk of fracture. Statistical tests had been performed to demonstrate that the relative risk reduction in the two groups was not different. The FIT 2 study had enrolled 4432 women, 1631 of whom met the WHO definition of osteoporosis based on an entry femoral neck BMD T-score ≤ – 2.5. The pooled analysis of FIT 1 and the subgroup from FIT 2 had been examined by the Medicines Control Agency (MCA) which considered the pooling valid with all included patients considered to have osteoporosis. A paragraph in the summary of product characteristics (SPC) had been approved on that basis. In the circumstances the Panel did not accept that it was unreasonable *per se* to combine the data from FIT 1 with a subgroup from FIT 2. No breach of the Code was ruled in this regard. With regard to the allegation concerning the combined population being inconsistent with the CPMP and WHO definitions of osteoporosis, the Panel noted noted Merck Sharp & Dohme's response regarding the RCP guidelines position that BMD had low sensitivity so that only half of all osteoporotic fractures occurred in women who would have osteoporosis on a T-score ≤ – 2.5 basis and it was accepted that a BMD measurement would not always be required for diagnosis. The Panel also noted Merck Sharp & Dohme's submission that the entry criteria for FIT was based on hip BMD and that many more women had osteoarthritis when other sites were taken into consideration. The MCA had accepted that the pooled patients had osteoporosis. The Panel did not accept the allegation and ruled no breach of the Code.

Procter & Gamble stated that notwithstanding the stated difference in the two populations, Merck Sharp & Dohme had chosen, years after the publication of the trial, to conduct and make claims based on a *post hoc* analysis at unplanned time points. Procter & Gamble could find no evidence that expressly confirmed a prospective plan to assess clinical vertebral fractures at twelve months or hip

fractures at eighteen months by combining results from FIT 1 with a subgroup of patients from FIT 2. Further, Merck Sharp & Dohme had indicated to Procter & Gamble that patient groups across FIT 1 and 2 were matched for comparable fracture risk prior to these analyses being undertaken. Procter & Gamble did not understand how such matching could possibly take place prospectively (prior to first patient randomisation). Finally it was alleged that Merck Sharp & Dohme had continually exacerbated the situation by not adequately disclosing the retrospective nature of the analyses (and time points). The Panel noted that the exhibition panel made no reference to whether or not the analysis was a prospective or *post hoc* analysis. Assessments in the FIT trial were to be made at 3, 6, 12, 18, 24, 30 and 36 months post randomisation for both FIT 1 and FIT 2 and at 42, 48 and 54 months post randomisation for FIT 2. The Panel considered that the time points were pre-planned. Both the data on file and a draft manuscript which had been accepted for publication stated that analysis of study endpoints in the two arms of the study and in BMD subgroups was pre-specified in the FIT data analysis plan in order to provide more precise estimates of treatment and subgroup effects and to provide greater power to explore associations among variables. The draft manuscript stated that analyses were performed separately within each subgroup (women with existing radiographic vertebral fracture and those without fractures but with femoral neck T-score < – 2.5) and were also performed for the pooled osteoporotic FIT cohort (women with femoral neck T-score < – 2.5 or an existing radiographic vertebral fracture) for the endpoint categories. The pooling of all the data from both arms of the study was pre-specified in the data analysis plan. The discussion section of the draft manuscript stated that the study had a number of strengths; *inter alia* the decision to pool the data was prespecified. It also stated that despite its large size the study had some important limitations; *inter alia* the analysis presented in the draft manuscript included only those considered to be osteoporotic solely because of the interaction between femoral neck BMD and clinical fractures in the clinical fracture arm. The authors noted that this slightly decreased the strength of the inference but considered that the strong significance and consistency of the findings overcame this limitation. The Panel considered that combining all of the data from FIT 1 with all the data from FIT 2 was a pre-planned analysis. In the Panel's view the combining of the FIT 1 data with data from 37% of FIT 2 patients did not appear to be a pre-specified analysis. It noted Merck Sharp & Dohme's submission that the analysis and time points were pre-planned. On balance the Panel did not consider that the combination of data *per se* was a breach of the Code as alleged. The Panel ruled no breach of the Code.

Procter & Gamble stated that in the first two years of FIT 1 and FIT 2, 5mg alendronate was used. This dose had a limited indication for the prevention of postmenopausal osteoporosis in the UK. The way in which Merck Sharp & Dohme portrayed the combination analyses based on the 5mg dose alone was clearly misleading as it implied an early fracture effect with alendronate 10mg which was not the case. The Panel noted that for the treatment of osteoporosis in postmenopausal women and the treatment and prevention of glucorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy with an oestrogen, the recommended dose of Fosamax was 10mg once a day. For the prevention of osteoporosis in postmenopausal women and for other patients the recommended dose was 5mg once a day. Fosamax 5mg was used in the first two years of FIT and then patients were switched to 10mg. The data in the study referred to the effect of Fosamax treatment for 3 to 4 years. Data over 36 months was presented with the reduction in risk first significant for clinical vertebral fracture (59%) by month 12 ($p < 0.001$) and for hip fracture (63%) by month 18 ($p = 0.014$). This data was included in the exhibition panel and thus was based on a dose of 5mg Fosamax which was only licensed for prevention of osteoporosis. The Panel queried whether there was any reason to suppose that the 10mg dose was less efficacious than the 5mg dose. The SPC reference to the FIT data did not mention the two doses used in the study. The Panel considered that the exhibition panel should have included more detail about the dosage and ruled that it was misleading in breach of the Code. Upon appeal by Merck Sharp & Dohme, the Appeal Board noted that alendronate 5mg was used as the dose for the first two years of FIT and then patients were switched to 10mg. The SPC reference to the FIT data did not mention the dosing schedule. The SPC stated that in all FIT patients with osteoporosis from both studies Fosamax reduced the incidence of ≥ 1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥ painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%. The Appeal Board noted comments from Merck Sharp & Dohme regarding the difficulties of whether or not to include dosing details. Such information might lead to under dosing ie prescribers using 5mg for treatment and not 10mg as recommended in the SPC for most patients. It also might lead to an expectation that the results would be improved with 10mg dose throughout. The claims at issue related to efficacy and not safety. The Appeal Board considered that taking into account all the circumstances, particularly that the SPC was silent on the issue of dose in FIT, it was not misleading to omit the dosage information. The Appeal Board ruled no breach of the Code.

Procter & Gamble stated that for one year data Merck Sharp & Dohme could only rely on clinical vertebral fractures collected as adverse events (ie via AEs such as back pain which were initially reported by the participant to his/her investigator). Clinical vertebral fractures were a subset of vertebral fractures overall. Only one third of all vertebral fractures came to clinical attention as many vertebral fractures were asymptomatic and thus went undetected (Cooper). By focusing solely on the

subset of clinical vertebral fractures (and not an overall vertebral fracture effect), Merck Sharp & Dohme was exaggerating the benefit offered by alendronate. The Panel noted that the material stated that at 12 months painful vertebral fractures were reduced by 59%. The Panel noted that before unblinding the study subgroups of clinical fractures were classified into prespecified categories: all clinical fractures, clinical vertebral fractures, non-vertebral fractures, hip fractures and wrist fractures. The reduction in risk was first significant for clinical vertebral fracture (59%) by month 12, for any clinical fracture (27%) by month 18, for non-vertebral fracture (26%) by month 24, for hip fracture (63%) by month 18 and for wrist fracture (34%) by month 30. The Panel considered that the subset data was clearly stated in the exhibition panel. The Panel noted Merck Sharp & Dohme's submission that clinical fractures were not collected as adverse events and that every clinical fracture was adjudicated by a blinded endpoint committee. The Panel did not consider that by focussing solely on the subset of clinical vertebral fractures, and not on overall vertebral fracture effect, the benefits offered by Fosamax had been exaggerated as alleged. No breach of the Code was ruled.

Procter & Gamble stated that Merck Sharp & Dohme had undertaken several different analyses on vertebral and hip fractures which yielded conflicting results. Despite these inconsistent findings, Merck Sharp & Dohme was misleading the reader having cherry picked the most favourable analyses to make claims which exaggerated the efficacy of its product. Overall the presentation of the claims and supporting data on files were not accurate, balanced, fair and objective and did not reflect the totality of evidence clearly. The claims were misleading, not based on sound statistical methodology and were exaggerated. The Panel examined the data supplied by the complainant. The Panel noted the poster, a meta-analysis by Quandt *et al* 2000, concluded that there was a consistency of effect of Fosamax in the four studies included (FIT 1, FIT 2, Karpf (1997) and Pols (1999)). The FIT studies involved a large number of patients with the study design allowing assessments of differences in fracture rate. The data were accurately reported. The Panel did not accept that the claims were misleading and exaggerated as alleged. No breach of the Code was ruled.

Procter & Gamble Pharmaceuticals UK, Limited complained about an exhibition panel for Fosamax (alendronate) which had been used by Merck Sharp & Dohme Limited at the Bone and Mineral Measurement Conference in Bath in April. Procter & Gamble stated that it was of the opinion that the claims on the exhibition panel of a 59% reduction in painful vertebral fractures at 12 months and a 63% reduction in hip fractures at 18 months in women with osteoporosis in the Fracture Intervention Trial (FIT) were in breach of Clauses 7.2 and 7.8 of the Code.

Merck Sharp & Dohme conducted FIT which had been subsequently published. The design of the trial was published in 1993 (Black) and the two arms of the trial FIT 1 (Black) and FIT 2 (Cummings) were published in 1996 and 1998 respectively.

FIT was designed to test the hypothesis that alendronate would reduce the rate of fractures in women aged 55-80 years with low hip bone mineral density (BMD) at the femoral neck. The women were assigned to one of two sub-studies. FIT 1 (vertebral fracture arm) was a study in patients with low femoral neck BMD and a pre-existing vertebral fracture confirmed by radiography prior to randomisation to alendronate or placebo. The primary end point was vertebral fractures confirmed by radiography after three years. FIT 2 (clinical fracture arm) was a study in patients with low femoral neck BMD T-score 1.6 or below. The T-score related to the number of standard deviations (SD) below the mean BMD of a young adult woman but without a pre-existing vertebral fracture prior to randomisation to alendronate or placebo. The primary end point was clinical fractures after four years.

The claims were referenced to data on file. Merck Sharp & Dohme provided in its response this data and an unpublished manuscript which had been accepted for publication. Merck Sharp & Dohme stated that the document contained information of a confidential nature and requested that it should not be forwarded to Procter & Gamble. The study had been carried out by Black *et al* (2000) to look at the fracture risk reduction with Fosamax in women with osteoporosis. The study was based on a pooled analysis of the entire population of FIT 1 and a subgroup from FIT 2 (T-score ≤ – 2.5). This amounted to 57% of the entire FIT cohort.

Procter & Gamble alleged that the claims Merck Sharp & Dohme made were false and misleading as they relied on statistical analyses and data that did not support the claimed therapeutic benefit.

1 Merck Sharp & Dohme had inappropriately pooled fracture data from subgroups of FIT

COMPLAINT

Procter & Gamble stated that despite Merck Sharp & Dohme's acknowledgement that a separate assessment of FIT 1 and FIT 2 would be made, it had subsequently and inappropriately pooled the data from these two studies to make misleading claims. A breach of Clause 7.2 was alleged.

Procter & Gamble stated that Merck Sharp & Dohme had previously acknowledged the different patients included in FIT 1 and FIT 2 by stating in the publication describing the FIT design (Black) that 'an assessment will be made separately of the effect of alendronate in two distinct populations … The possibility of stopping the Clinical Fracture Study on the basis of the observation of an early positive result in the Vertebral Deformity Study is obviated by the different populations and endpoints studied in the two trials'. Procter & Gamble was therefore surprised that despite Merck Sharp & Dohme's obvious awareness of this, it had subsequently chosen to pool data from the two studies.

Specifically, Procter & Gamble alleged that Merck Sharp & Dohme had inappropriately pooled fracture data from different subgroups of FIT. It had combined a subgroup of patients with T-scores below – 2.5 SD from FIT 2 (37% of the overall population) with the entire population from FIT 1, who had a T-score of ≤ – 1.6 SD. The populations were clearly different and such a combination analysis was methodologically flawed. Further the combined population was inconsistent with the CPMP and WHO definitions of osteoporosis (T-score ≤ – 2.5 SD).

RESPONSE

Merck Sharp & Dohme stated that separate and combined analyses of FIT 1 and FIT 2 were pre-planned at the design stages of the study. Separate analysis of the two arms of FIT did not preclude in any way combining data from them for further analysis. The combining of data from the two studies for further analysis was clinically appropriate and followed statistical best practice. Utmost care was taken to ensure that the analyses were in accordance with the supplementary information to Clause 7.2 on statistical information.

Merck Sharp & Dohme stated that there appeared to be a fundamental misunderstanding of the principles of pooling studies for combined analysis or meta-analysis. It was true to say that the patient populations in FIT 1 (the vertebral fracture arm) and FIT 2 (the clinical fracture arm) were different, in that those in FIT 1 had to have had a pre-existing vertebral fracture for entry, whereas those in FIT 2 did not (other entry criteria for the two arms were identical). This did not preclude the pooling of data from the two arms for analysis. If it did, no meta-analysis or pooled analysis could ever be performed unless all the studies included were absolutely identical in absolutely every way. This pooled analysis of FIT 1 and the subgroup from FIT 2 was submitted to the Medicines Control Agency (MCA). The MCA considered the pooling valid, all the included patients to have osteoporosis and approved a paragraph in section 5.1 of the summary of product characteristics (SPC) based on the data: 'FIT consisted of two placebo controlled studies: a three year study of 2027 patients who … In all FIT patients with osteoporosis in both studies … any painful fracture by 31% and hip fracture by 54%.'

The rationale for the pooling of the two analyses was valid from both a statistical and clinical perspective. The draft manuscript supplied had been accepted for publication:

Statistical – The appropriateness of combining the two groups from FIT for the pooled analysis was shown by demonstrating that the relative risk reduction in the two groups was not different/heterogeneous. This was done by performing appropriate statistical tests ie the Breslow-Day test. This was statistical best practice and certainly was not 'methodologically flawed' as alleged. The subgroup of patients from FIT 2 with a T-score ≤ – 2.5 was used because baseline BMD by tertiles had a significant effect on the magnitude of fracture benefit in FIT 2. On the other hand the relative risk reduction in FIT 1 did not vary with baseline BMD.

Clinical – The Royal College of Physicians (RCP) had recently published guidelines for osteoporosis. As stated in chapter 3 of those guidelines WHO actually defined osteoporosis as 'A progressive systemic disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'. The Committee for Proprietary Medicinal Products (CPMP) actually used this definition of osteoporosis in its guidelines. WHO proposed a BMD of T-score ≤ – 2.5 as a cut-off for diagnosis. However, the RCP guidelines stated that BMD had low sensitivity, so that only half of all osteoporotic fractures occurred in women who would have osteoporosis on a T-score ≤ – 2.5 basis and accepted that a BMD measurement would not always be required for diagnosis. The entry criteria for FIT was based on hip BMD. Many more women had osteoporosis when other sites were taken into consideration. The FIT 2 subgroup used in the pooled analysis was consistent with the WHO T-score cut-off. The FIT 1 arm was actually at higher risk of fracture than the FIT 2 subgroup when the placebo arms were compared so from the clinical perspective of the definition of osteoporosis by WHO the pooled analysis was appropriate.

PANEL RULING

The Panel noted that there was a difference between the two populations. Patients in FIT 1 had pre-existing vertebral fracture whereas those in FIT 2 did not. Both populations were at risk of fracture. The Panel noted that statistical tests had been performed to demonstrate that the relative risk reduction in the two groups was not different. The FIT 2 study had enrolled 4432 women, 1631 of whom met the WHO definition of osteoporosis based on an entry femoral neck BMD T-score ≤ –2.5. The Panel noted the pooled analysis of FIT 1 and the subgroup from FIT 2 had been examined by the MCA which considered the pooling valid with all the included patients considered to have osteoporosis. A paragraph in the SPC had been approved on this basis. In the circumstances the Panel did not accept that it was unreasonable *per se* to combine the data from FIT 1 with a subgroup from FIT 2. No breach of Clause 7.2 of the Code was ruled in this regard.

With regard to the allegation concerning the combined population being inconsistent with the CPMP and WHO definitions of osteoporosis, the Panel noted Procter & Gamble's submission that the FIT 1 population had a T-score of ≤ – 1.6 SD whereas the WHO proposed a BMD of T-score ≤ 2.5 as a cut off for diagnosis. The Panel also noted Merck Sharp & Dohme's response regarding the RCP guidelines position that BMD had low sensitivity so that only half of all osteoporotic fractures occurred in women who would have osteoporosis on a T-score ≤ – 2.5 basis and it was accepted that a BMD measurement would not always be required for diagnosis. The Panel also noted Merck Sharp & Dohme's submission that the entry criteria for FIT was based on hip BMD and that many more women had osteoarthritis when other sites were taken into consideration. The MCA had accepted that the pooled patients had

osteoporosis. The Panel did not accept the allegation and ruled no breach of Clause 7.2 of the Code.

2 The analyses and time points were claimed to be pre-planned when they could not be

COMPLAINT

Procter & Gamble stated that notwithstanding the stated difference in the two populations, Merck Sharp & Dohme had chosen, years after the publication of the trial, to conduct and make claims based on a post hoc analysis at unplanned time points. Procter & Gamble could find no evidence that expressly confirmed a prospective plan to assess clinical vertebral fractures at twelve months or hip fractures at eighteen months by combining results from FIT 1 with a subgroup of patients from FIT 2. Further, Merck Sharp & Dohme had indicated to Procter & Gamble that patient groups across FIT 1 and 2 were matched for comparable fracture risk prior to these analyses being undertaken. Procter & Gamble did not understand how such matching could possibly take place prospectively (prior to first patient randomisation). Finally Merck Sharp & Dohme continually exacerbated the situation by not adequately disclosing the retrospective nature of the analyses (and time points). A breach of Clause 7.2 was alleged.

RESPONSE

Merck Sharp & Dohme could not understand the alleged breach of Clause 7.2 as there were no statements in the exhibition panel relating to the pre-planned nature of the analyses. Nevertheless, the analyses and time points were pre-planned and this had been made clear in the presentations and posters of these analyses that had appeared at international osteoporosis meetings and in the manuscript provided. There were still many pre-planned analyses for FIT to be completed. The timing of their completion and presentation had nothing whatsoever to do with the timing of their conception. In the complaint there seemed to be some misunderstanding with regard to the principles of the analysis.

The data analysis plant for FIT specifically stated that data would be grouped by six-month time points. This was pre-specified. More importantly, tests for the constancy of the relative hazard over time would be performed. In all of the results, there was no interaction of the relative risk with time. The implication of this finding was that the effect of alendronate was rapid. All of the cumulative incidences reported showed a divergence as early as six months. More importantly, the claim for early effects was based on the analysis from the proportional hazards model.

Merck Sharp & Dohme submitted that it was very important to appreciate that it was pre-planned to check that the relative risk reductions were homogeneous before performing the pooled analysis as detailed in point 1 above, not, as the complainant alleged, match the fracture risk of FIT 1 and FIT 2. It was recognised at the design stage of FIT that FIT 1 patients would be at higher risk of fracture than those in FIT 2 by virtue of having a pre-existing vertebral fracture.

The Cochrane Collaboration had produced very clear guidance regarding what constituted prospective. It had nothing to do with patient randomisation and everything to do with the specifying hypotheses before trial results are known. The relevant page from the Cochrane Collaboration website was provided.

Since the analysis was prospective the last point made in this section of the complaint on disclosure was redundant.

PANEL RULING

The Panel noted that the exhibition panel at issue made no reference to whether or not the analysis was a prospective analysis or post-hoc analysis. The Panel had not seen any of the associated material presented at the exhibition. The Panel noted that the assessments in the FIT trial were to be made at 3, 6, 12, 18, 24, 30 and 36 months post randomisation for both FIT 1 and FIT 2 and at 42, 48 and 54 months post randomisation for FIT 2. The Panel considered that the time points were pre-planned.

The Panel noted the submission from Merck Sharp & Dohme and its comments at point 1 above. The Panel noted that both the data on file and the draft manuscript stated that analysis of study endpoints in the two arms of the study and in BMD subgroups was pre-specified in the FIT data analysis plan in order to provide more precise estimates of treatment and subgroup effects and to provide greater power to explore associations among variables. The draft manuscript stated that analyses were performed separately within each subgroup (women with existing radiographic vertebral fracture and those without fractures but with femoral neck T-score < – 2.5) and were also performed for the pooled osteoporotic FIT cohort (women with femoral neck T-score < – 2.5 or an existing radiographic vertebral fracture) for the endpoint categories. The pooling of all the data from both arms of the study was pre-specified in the data analysis plan.

The discussion section of the draft manuscript stated that the study had a number of strengths; *inter alia* the decision to pool the data was prespecified. It also stated that despite its large size the study had some important limitations; *inter alia* the analysis presented in the draft manuscript included only those considered to be osteoporotic solely because of the interaction between femoral neck BMD and clinical fractures in the clinical fracture arm. The authors noted that this slightly decreased the strength of the inference but considered that the strong significance and consistency of the findings overcame this limitation.

The Panel considered that combining all of the data from FIT 1 with all the data from FIT 2 was a pre-planned analysis. In the Panel's view the combining of the FIT 1 data with data from 37% of FIT 2 patients did not appear to be a pre-specified analysis. It noted Merck Sharp & Dohme's submission that the analysis and time points were pre-planned. The Panel was concerned that Merck Sharp & Dohme's response was

not sufficiently clear in this regard. The Panel also noted its ruling in point 1 above. The exhibition panel made no mention of the analysis. On balance the Panel did not consider that the combination of data per se was a breach of the Code as alleged. The Panel ruled no breach of Clause 7.2 of the Code.

3 The data on which Merck Sharp & Dohme relied as support was based on its alendronate 5mg. The alendronate summary of product characteristics clearly stated that the 5mg dose was only approved for prevention of postmenopausal osteoporosis.

COMPLAINT

Procter & Gamble stated that in the first two years of FIT 1 and FIT 2, 5mg alendronate was used. This dose had a limited indication for the prevention of postmenopausal osteoporosis in the UK. The way in which Merck Sharp & Dohme portrayed the combination analyses based on the 5mg dose alone was clearly misleading as it implied an early fracture effect with alendronate 10mg which was not the case. A breach of Clause 7.2 was alleged.

RESPONSE

Merck Sharp & Dohme stated that 5mg was indeed used as the dose for the first two years of FIT. This data had been accepted by the major regulatory bodies around the world as the basis for fracture reduction in the indication for alendronate and incorporated into the prescribing information in the relevant countries. Data from many studies suggested that 10mg had better efficacy than 5mg, and so the 10mg dose was the one licensed for treatment of osteoporosis in postmenopausal women. Alendronate 5mg was licensed for certain patients for the prevention and treatment of steroid induced osteoporosis as well as prevention of postmenopausal osteoporosis.

It was true that alendronate 5mg was used for the first two years of FIT and then patients were switched to 10mg. This was because it became apparent that 10mg was the optimal dose for increasing BMD in the treatment of osteoporosis from the phase III studies and had similar tolerability to 5mg. In the FIT data analysis plan it was clearly stated that FIT could not be used to determine if 10mg was more effective than 5mg because of the dose change at year two. However it had been shown that the greater the increase in BMD the lower the fracture risk. As stated above the FIT data had been accepted by regulatory authorities such as the MCA and the Food and Drug Administration (FDA) as evidence of fracture efficacy and included in the product prescribing information. Also the RCP guidelines quoted FIT to support a grade A recommendation for the use of alendronate to prevent vertebral and hip fractures. They made no reference to the doses of alendronate used in FIT or related reservations. The Fosamax International Trial used only the 10mg dose and found a reduction in non-vertebral fractures at one year compared with placebo (vertebral morphometry was not done in this study). It was widely accepted by regulators and clinicians that FIT provided high quality data to support the efficacy of alendronate.

PANEL RULING

The Panel noted that for the treatment of osteoporosis in post-menopausal women and the treatment and prevention of glucocorticoid-induced osteoporosis in post-menopausal women not receiving hormone replacement therapy with an oestrogen, the recommended dose of Fosamax was 10mg once a day. For the prevention of osteoporosis in post-menopausal women and for other patients the recommended dose was 5mg once a day.

The Panel noted that Fosamax 5mg was used in the first two years of FIT and then patients were switched to 10mg. The data in the study referred to the effect of Fosamax treatment for 3 to 4 years. Data over 36 months was presented with the reduction in risk first significant for clinical vertebral fracture (59%) by month 12 ($p < 0.001$) and for hip fracture (63%) by month 18 ($p = 0.014$). This data was included in the exhibition panel and thus was based on a dose of 5mg Fosamax which was only licensed for prevention of osteoporosis. The Panel queried whether there was any reason to suppose that the 10mg dose was less efficacious than the 5mg dose. It noted Merck Sharp & Dohme's submission that the greater the increase in BMD the lower the fracture rate. The FIT data had been accepted by regulatory bodies. The SPC reference to the FIT data did not mention the two doses used in the study. The Panel considered that the exhibition panel should have included more detail about the dosage. The Panel ruled that the exhibition panel was misleading in breach of Clause 7.2 of the Code.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme stated that the data on which it relied as support was based on alendronate 5mg. The Fosamax SPC clearly stated that the 5mg dose was only approved for prevention of postmenopausal osteoporosis.

In the first instance Merck Sharp & Dohme wished to highlight that the FIT data had been accepted by regulatory authorities as supporting evidence for the treatment indications for Fosamax. In addition Section 5.1 of the SPC made no mention of the two doses used in the study. Furthermore evidence would suggest that the greater the increase in bone mineral density the lower the fracture rate.

Merck Sharp & Dohme gave due consideration to the inclusion of information regarding the doses in FIT within promotional items. However, upon reflection it did not include such details for the following reasons:

1 Knowing that 5mg was used for two years of FIT, and that both 5 and 10mg tablets were available, prescribers might not use the optimal dose recommended in the SPC for **treatment** of postmenopausal osteoporosis. The price of 5 and 10mg tablets was the same.

2 Readers of the advertisement might conclude that patients were effectively underdosed with 5mg for 2 years of the study so the fracture results from FIT presented were an underestimate of efficacy with alendronate 10mg.

APPEAL BOARD RULING

The Appeal Board noted that alendronate 5mg was used as the dose for the first two years of FIT and then patients were switched to 10mg. The Appeal Board noted that the SPC reference to the FIT data did not mention the dosing schedule. Section 5.1 of the SPC stated that in all FIT patients with osteoporosis from both studies Fosamax reduced the incidence of ≥1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

The Appeal Board noted the comments from Merck Sharp and Dohme regarding the difficulties of whether or not to include dosing details. Such information might lead to under dosing ie prescribers using 5mg for treatment and not 10mg as recommended in the SPC for most patients. It also might lead to an expectation that the results would be improved with 10mg dose throughout. The claims at issue related to efficacy and not safety.

The Appeal Board considered that taking into account all the circumstances, particularly that the SPC was silent on the issue of dose in FIT, it was not misleading to omit the dosage information. The Appeal Board ruled no breach of Clause 7.2 of the Code. The appeal was successful.

4 Merck Sharp & Dohme made claims using only the subset data on painful (clinical) fractures which misled as to the effect of alendronate on overall vertebral fractures

COMPLAINT

Procter & Gamble stated that for one year data, Merck Sharp & Dohme could only rely on clinical vertebral fractures collected as adverse events (ie via AEs such as back pain which were initially reported by the participant to his/her investigator). Clinical vertebral fractures were a subset of vertebral fractures overall. Only one third of all vertebral fractures came to clinical attention as many vertebral fractures were asymptomatic and thus went undetected (Cooper). By focusing solely on the subset of clinical vertebral fractures (and not an overall vertebral fracture effect), Merck Sharp & Dohme was exaggerating the benefit offered by alendronate. A breach of Clause 7.8 was alleged.

RESPONSE

Merck Sharp & Dohme stated that the claim in the exhibition panel related to painful vertebral fractures. There were no statements with regard to those vertebral fractures that did not cause pain, or effect on morphometric (or 'overall') vertebral fractures. The information on painful fractures was a straightforward presentation of the actual data, which was certainly not exaggerated in breach of Clause 7.8. In any case, the proportion of morphometric vertebral fractures that caused symptoms was consistent with the published epidemiology.

The claim was clearly stated and there was no room for misinterpretation by the reader. It only related to painful vertebral fractures. It did not mislead as to the effect on morphometric fractures as these were not mentioned at all in the exhibition panel.

Merck Sharp & Dohme submitted that FIT was a comprehensive fracture study. The vertebral fracture arm was powered on the basis of new and worsening vertebral fractures. However, it was clearly stated in the data analysis plan that the endpoints would be as follows: new vertebral fractures (primary), clinical fractures, clinical vertebral fractures and hip fractures. Clinical vertebral fractures were a distinct endpoint from morphometric vertebral fracture. In FIT clinical vertebral fractures were not viewed as a subset of morphometric vertebral fracture. The Data and Safety Monitoring Board monitored the incidence of clinical fractures during the study. Three distinct fractures were included: hip, clinical vertebral and forearm. Morphometric vertebral fractures were not monitored during the study. Clinical fractures were not collected as adverse events. In FIT every clinical fracture was adjudicated by a blinded endpoints committee including clinical vertebral fractures. The claim that these fractures were reported only as adverse events was totally false. The endpoints committee was blinded to treatment group and to the arm of the study.

The rates for painful vertebral fractures and morphometric vertebral fractures observed in FIT were consistent with the epidemiological data, eg of the FIT 1 placebo group 15% suffered morphometric vertebral fractures whereas 5% suffered clinical vertebral fractures.

PANEL RULING

The Panel noted that the material stated that at 12 months painful vertebral fractures were reduced by 59%. The Panel noted that before unblinding the study subgroups of clinical fractures were classified into prespecified categories: all clinical fractures, clinical vertebral fractures, non-vertebral fractures, hip fractures and wrist fractures. The reduction in risk was first significant for clinical vertebral fracture (59%) by month 12, for any clinical fracture (27%) by month 18, for non-vertebral fracture (26%) by month 24, for hip fracture (63%) by month 18 and for wrist fracture (34%) by month 30.

The Panel considered that the subset data was clearly stated in the exhibition panel. The Panel noted Merck Sharp & Dohme's submission that clinical fractures were not collected as adverse events and that every clinical fracture was adjudicated by a blinded endpoint committee. The Panel did not consider that by focussing solely on the subset of clinical vertebral fractures and not on overall vertebral fracture effect the benefits offered by Fosamax had been exaggerated as alleged. No breach of Clause 7.8 of the Code was ruled.

5 Despite conflicting results from a variety of analyses, Merck Sharp & Dohme exaggerated the therapeutic benefit offered by alendronate on both vertebral and hip fractures.

COMPLAINT

Procter & Gamble stated that Merck Sharp & Dohme had undertaken several different analyses on vertebral

and hip fractures which yielded conflicting results. Despite these inconsistent findings, Merck Sharp & Dohme was misleading the reader having cherry picked the most favourable analyses to make the above claims, which exaggerated the efficacy of its product. In order to assist with the assessment of the complaint a tabulation of the availability of the one year vertebral fracture data and hip fracture data was provided.

Overall the presentation of the claims and supporting data on files were not accurate, balanced, fair and objective and did not reflect the totality of evidence clearly. The claims were misleading, not based on sound statistical methodology (breach of Clause 7.2) and were exaggerated (breach of Clause 7.8).

RESPONSE

Merck Sharp & Dohme stated that results from different studies with alendronate in postmenopausal osteoporosis were in fact quite consistent in terms of their relative risk reduction. The time points of 12 and 18 months were quite clearly referred to and there was no suggestion that this was the magnitude of the reduction at a later time point. The claim clearly referred to specific time points during FIT and the fracture reductions actually observed in osteoporotic patients at those time points.

A number of different studies were presented in a table as part of the complaint. It was unclear where the data on/including the FIT 2 subgroup with T-score < – 2.0 had been obtained from. The study by Saag *et al* was in prevention and treatment of postmenopausal osteoporosis. Protocols 035 and 037 were too small in themselves (inadequately powered) to assess the effect of alendronate on morphometric vertebral fractures over three years, so it was unclear why they had been included in the table. At one year, even in the combined analyses by Liberman *et al*, there was inadequate power to assess the effect of alendronate on morphometric vertebral fractures. This was even more true for clinical vertebral fractures which occurred more rarely than morphometric fractures. As stated in the table, vertebral morphometry was not done in FIT at one year. However the clinical vertebral fracture data was presented in the Black manuscript in Table 2 and was significant in FIT 1. As already stated above, there was a BMD interaction in FIT 2 which accounted for the finding of a significant reduction in hip fractures in the T-score < – 2.5 subgroup and not in the study overall or other subgroups. A poster presented at the European League Against Rheumatism 2000 Meeting was provided which discussed the consistency of effect of alendronate in a meta-analysis. Whilst some of the individual studies were not large enough to show a statistically significant result, the overall picture was a consistent one of reductions in hip fractures versus placebo. In terms of morphometric vertebral fractures the picture was also very consistent between studies with relative risk reductions of approximately 50% observed in a number of studies over their full duration.

In summary, Merck Sharp & Dohme believed that the data presented in the exhibition panel was accurate, balanced and represented a clear representation of the evidence available. It did not mislead and was not exaggerated in breach of Clauses 7.2 and 7.8.

PANEL RULING

The Panel examined the data supplied by the complainant. It noted the comments made by Merck Sharp & Dohme and its rulings above. The Panel noted the poster, a meta-analysis by Quandt *et al* 2000, concluded that there was a consistency of effect of Fosamax in the four studies included (FIT 1, FIT 2, Karpf (1997) and Pols (1999)). The FIT studies involved a large number of patients with the study design allowing assessments of differences in fracture rate. The data were accurately reported. The Panel did not accept that the claims were misleading and exaggerated as alleged. No breach of Clauses 7.2 and 7.8 of the Code was ruled.

Complaint received **27 July 2000**

Case completed **9 November 2000**

CASE AUTH/1061/8/00

BAYER v NAPP

Zanidip detail aid

Bayer complained about a detail aid for Zanidip (lercanidipine) produced by Napp. Bayer produced Adalat LA (nifedipine).

A bar chart appeared on page 6 beneath the heading 'Published data relating to four major calcium antagonists (pooled data)'. Data for lacidipine, nifedipine, amlodipine and felodipine was presented for headache, flushing and dizziness. However only data for lacidipine and nifedipine was presented in relation to palpitation. The lacidipine and nifedipine data came from a comparative study, Leonetti *et al* 1991. The data for amlodipine and felodipine came from review articles by Osterloh (1989) and Elvelin *et al* (1993) respectively. A second bar chart depicted the incidence of peripheral oedema for the same four calcium antagonists beneath the claim 'A high incidence of peripheral oedema may result in non-compliance and treatment withdrawal'.

Bayer stated that the first bar chart described the data as 'pooled'. This was not so. Leonetti *et al* related to a double blind comparison of lacidipine 4-6mg once daily and nifedipine SR 20-40mg twice daily, whereas Osterloh and Elvelin *et al* related to data from placebo-controlled studies from review articles on amlodipine and felodipine respectively and not the individual studies. The heading of the bar chart implied that all the data shown was derived from pooled data. The incorporation of a comparative study and placebo-controlled, pooled data within one bar chart could not be considered as accurate, balanced or objective. The bar chart also implied that palpitations only occurred in the double-blind study (Leonetti *et al*), but Osterloh and Elvelin *et al* mentioned palpitations occurring in both placebo-controlled studies and comparative studies. It was unclear why peripheral oedema had been shown in a separate bar chart to the other side-effects, as the data was sourced from the same references. By inference it related the side-effect to withdrawal rate. This was not supported by the references. Three of the medicines identified in the bar chart were administered once daily, whereas nifedipine SR was administered twice daily. It was recognised that shorter acting dihydropyridines might be associated with increased peak-to-trough plasma level variation. This had been linked to the incidence of side-effects. Once daily formulations of nifedipine were recognised to show little or no plasma level variability over 24 hours and were associated with fewer and less severe side-effects than the twice daily formulations. Bayer did not agree with Napp's view that the comparison was valid because twice daily nifedipine was more commonly prescribed than once daily. Bayer alleged that the bar charts were inaccurate and misleading.

The Panel considered that readers would assume that the reference to pooled data meant that some analysis had been done on the data, such as a meta analysis, and not simply that the data was from a number of different sources and no analysis had been done. The Panel considered that the term 'pooled data' was misleading and a breach of the Code was ruled.

Upon appeal by Napp, the Appeal Board considered that the presentation of the data together with the phrase 'pooled data' invited the reader to directly compare the data presented and implied that it was valid to do so. This was not so. The Appeal Board considered that in these circumstances the use of the phrase 'pooled data' was misleading. Not all the data had been pooled. The Appeal Board upheld the Panel's ruling of a breach of the Code.

In relation to the allegation that the incorporation of the comparative and placebo controlled data within one bar chart could not be considered as accurate, balanced or objective, the Panel considered, bearing in mind the previous ruling, that the presentation of the data in the bar chart at issue was unacceptable. A breach of the Code was ruled. Upon appeal by Napp, the Appeal Board noted its comments regarding the presentation of data in the first bar chart above. The Appeal Board upheld the Panel's ruling of a breach of the Code.

In relation to palpitations, the Panel noted that the data for lacidipine and nifedipine was referenced to Leonetti *et al*. Palpitation data for amlodipine and felodipine was not presented and the Panel noted the submission that with regard to these products and studies palpitations only occurred in one of a number of data pools making it difficult to interpret in a way that was valid. The Panel noted that the summary of product characteristics (SPC) for Istin (amlodipine) described palpitations as a rarely reported adverse event. The Plendil (felodipine) SPC stated that as with other calcium antagonists palpitations might occur. The Panel considered that the bar chart gave the impression that palpitations did not occur with amlodipine or felodipine and that was not so. There was no explanation regarding the omission of this data. A breach of the Code was ruled.

In relation to the second bar chart, the Panel's view was that it was not unreasonable to present data on peripheral oedema separately. The Panel noted the heading 'A high incidence of peripheral oedema may result in non-compliance and treatment withdrawal'. The graph depicted an incidence ranging from approximately 9% to 17%. The Panel considered that adverse events might be generally relevant to issues of compliance and withdrawal and it was not necessarily unreasonable to link the two. The Panel considered that the claim was sufficiently qualified by the use of the term 'may'. No breach of the Code was ruled.

The Panel noted that it was not necessarily unacceptable to compare twice and once daily formulations *per se*. The Panel noted Napp's submission that it had selected twice daily nifedipine as it was significantly more commonly prescribed than once daily. The Panel noted Bayer's view that there was a difference in the side-effect profile between twice daily nifedipine and once

daily nifedipine. The Panel noted that whilst the presentations and doses were clearly stated the basis of the selection of the medicines was not. The reference to 'four major calcium antagonists' (above the first graph) was not sufficient in this regard. The second graph was misleading and a breach of the Code was ruled. Upon appeal by Napp, the Appeal Board noted that twice daily nifedipine was prescribed about twice as frequently as once daily. The Appeal Board did not accept Napp's submission that the reasons for choice did not have to be detailed. The basis of the products' selection was not clear and this was misleading. The Appeal Board upheld the ruling of a breach of the Code.

On page 7, headed 'Zanidip tablets: a tolerability profile comparable with placebo*', the asterisk referred to a footnote at the bottom of the page which stated 'As reported in studies that examined the incidence of adverse events in patients being treated with Zanidip tablets 10mg od and that of control patients receiving placebo.' Beneath the subheading 'A global safety analysis of 1,128 hypertensive patients treated with Zanidip tablets 10mg od', a bar chart depicted the incidence of the most commonly reported adverse events of Zanidip 10mg od vs placebo; headache, flushing, dizziness, asthenia and reflex tachycardia. The second bar chart, headed 'Zanidip tablets: a notably low incidence of peripheral oedema', depicted the incidence of peripheral oedema. Bayer stated that the first bar chart purported to show the profile of the lowest licensed dose, 10mg, of Zanidip and compared it to placebo. In fact, this was pooled data from some 20 trials. These data included placebo and comparator controlled studies. The impression given was that this was placebo controlled data. Moreover, Bayer alleged that the scale used was far larger than necessary to demonstrate the differences shown. In fact, it would be more representative to include the actual comparators. The second bar chart on the page used the same data source as the first and was subject to the same criticisms but only featured the side-effect peripheral oedema. Again, the scale used was far larger than necessary to demonstrate the differences shown. Bayer alleged that this page was misleading in that it did not give a balanced view.

In relation to the first bar chart, the Panel considered that its previous comments regarding the use of pooled data and the comparison of placebo controlled and comparative data were relevant. The Panel noted that the subheading referred to 'A global safety analysis of 1,128 hypertensive patients'. The patient number was also stated on the graph. The Panel considered that the impression was given that the data derived from a single published study comparing Zanidip and placebo and that was not so. The Panel noted the footnote to the page heading. It was an established principle under the Code that one could not qualify a claim by reference to a footnote. The footnote was insufficient to negate the overall impression given. A breach of the Code was ruled. Upon appeal by Napp, the Appeal Board noted that the subheading 'A global safety analysis' referred to the raw data which had been collected and presented as a single tolerability summary required for the registration of Zanidip and was held on file as a single report despite being originally derived from 20 studies. Napp submitted that it had depicted this report in the same way in the bar chart ie as a global safety summary. The Appeal Board did not consider the subheading misleading as alleged and ruled no breach of the Code.

The Panel noted that the Code required clear references to be given when referring to a published study. The page in question made no reference to whether the studies were published or not. In these circumstances it was not necessary to give a reference and no breach of the Code was ruled. On balance the Panel did not consider the scale misleading as alleged and ruled no breach of the Code in that regard. In relation to the second bar chart, the Panel considered that its ruling above regarding the separation of peripheral oedema data applied here. The Panel considered that its ruling of no breach above regarding the scale of the first graph was relevant and ruled no breach of the Code.

The Panel then considered the allegation regarding the data source with reference to the second bar chart. There were differences between the two bar charts; the subheading and labelling to the second chart did not refer to a global safety analysis, the patient number was, however, stated to be 1,128. The Panel considered its ruling on the first chart was relevant here. On balance a breach of the Code was ruled. Upon appeal by Napp, the Appeal Board considered that its previous ruling also applied here and no breach of the Code was ruled.

Pages 6 and 7 faced each other and Bayer considered this presentation implied that Zanidip had a more favourable side-effect profile than competitor products largely because of the almost identical axes used in the first bar charts on each page. The effect was even more apparent with the second bar chart on each page, which had identical axes. Additionally, the juxtaposition of a single dose placebo comparison of the tolerability profile of Zanidip and the multiple dosages used in the facing bar chart was not a balanced comparison and gave a false impression of the relative tolerability profile. It led the reader to believe that the incidence of side-effects with Zanidip was much lower than the comparators on the facing page. This could not be assumed in the absence of comparative studies. Moreover, the SPC listed peripheral oedema as one of the most commonly reported side-effects in controlled clinical studies. Other commonly reported events included flushing and palpitations. Bayer's reservations regarding the relevance of once daily and twice daily formulations of nifedipine also applied to this global impression. Breaches of the Code were alleged. The Panel noted its rulings regarding pages 6 and 7. It considered that they would probably be presented as one by the representatives. The layout and data presented would invite direct comparison between the two such that a reader would assume that Zanidip on page 7 had a more favourable side-effect profile than lacidipine, nifedipine, amlodipine and felodipine on page 6. There was no direct comparative data. A breach of the Code was ruled.

Page 10 was headed 'Zanidip tablets are 18% less expensive than amlodipine' and featured two tables. The first compared the cost per 28 days of Zanidip 10mg od with amlodipine 5 and 10mg od, lacidipine 2 and 4mg od, nifedipine LA 30 and 60mg od and felodipine 5 and 10mg od. The second stated the most commonly prescribed doses of each calcium antagonist over 3 months. Page 11 featured the costs per year at therapeutic doses of Zanidip 10mg and the four other calcium antagonists of treating 25, 50, 100 and 200 patients. Bayer stated that the first table did not list the price for nifedipine LA 20mg. Bayer therefore believed this price comparison to be incomplete. The chart on page 11, which listed the costs per year, also excluded nifedipine LA 20mg. Additionally, no mention was made of the fact that doubling the dose of Zanidip, in keeping with the rest of the chart, doubled the cost per 28 days' treatment. Price comparisons should compare like with like, in this case the lowest effective dose available, or both doses, should be compared. Bayer alleged a breach of the Code. The second chart on page 10 'Zanidip tablets: doses most commonly prescribed' referred to an undefined three month period and showed the relative split of prescriptions for two doses of five calcium antagonists, including Zanidip. The source of these data was not cited and the healthcare professional had no idea as to the validity of the information or where it came from. The figures for Zanidip were highlighted. Again, there was no mention of nifedipine LA 20mg once daily. The figures for Zanidip were the only ones to add up to 100%. Bayer could only conclude that the intention behind highlighting the Zanidip figures was to imply that because, over a three month period, there was a preponderance of prescriptions for the lower dose, more patients were treated with this dose than were treated with the lower doses of the other medicines. From this it could be inferred that using Zanidip would contribute to cost minimisation in prescribing budget terms. This was not the only interpretation possible. Furthermore, there was no information on how many patients were not adequately controlled on, or intolerant of, 10mg and switched to other products. There was no consideration of the actual volume of prescriptions – the denominator was missing. The chart was therefore misleading.

The Panel noted that the heading to the first table referred to cost per 28 days at therapeutic doses. The heading to the second table referred to the doses most commonly prescribed (three months). The Panel noted that the three month period was not identified. All of the presentations mentioned in the second table appeared in the first table except Zanidip tablets 20mg od at 13.7%. The Panel noted that according to Napp the selection of medicines for the first table was based on sales. The Panel considered that therapeutic doses might not necessarily be equivalent to those most commonly prescribed. The Panel ruled that the first table on the page was misleading in breach of the Code. In relation to the second table, the Panel noted that data for certain presentations had been omitted. The Panel considered that a reader would assume that the missing data related to less commonly prescribed presentations. The Panel queried the reference to Zanidip 20mg at 13.7%. The Panel was concerned that the three month period was not identified. The Panel considered the lower table misleading in this regard and a breach of the Code was ruled.

Page 14 was headed 'Isolated systolic hypertension: long acting nitrendipine significantly reduces cardiac events' and featured a graph which depicted the percentage reduction at two year median of cardiovascular events at follow up. The facing page was headed 'Zanidip tablets: as effective as nitrendipine' and featured a graph which depicted the reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during treatment with Zanidip 10-30mg or nitrendipine 10-30mg. Bayer stated that pages 14 and 15 related Zanidip to a major outcome study using nitrendipine, a medicine not licensed in the UK. In the Zanidip study patients were titrated to dosages greater than those currently licensed in the UK. The graph showed very similar profiles of blood pressure reduction over 12 weeks' treatment for both medicines. The graph appeared beneath the heading 'Zanidip tablets: as effective as nitrendipine' and had the strapline at the bottom of the page (with the Zanidip logo) 'Treating Hypertension Saves Lives'. These two phrases and the pages facing one another implied that, because of its hypertensive efficacy over twelve weeks, Zanidip would produce the same reduction in cardiovascular events as nitrendipine did in a placebo controlled outcome study. There was no evidence to support this. Bayer alleged that the pages were misleading and unrepresentative.

The Panel considered the data on page 14 first. This showed significant reductions in total stroke incidence (42% p=0.003), non-fatal stroke (44% p=0.007) and fatal and non-fatal cardiac events (26% p=0.03). The Panel was concerned that data for nitrendipine, a product not licensed in the UK, had been included. The Panel questioned whether comparing nitrendipine with Zanidip met the requirements of the Code. Readers might be misled into assuming that nitrendipine was licensed in the UK. According to the graph on page 15 nitrendipine 10-30mg and Zanidip 10-30mg appeared to produce closely similar reductions in SBP and DBP over 12 weeks. The dose for Zanidip was 10mg od which might be increased to 20mg depending on the individual patient's response. The dose of Zanidip was clearly stated above the graph at issue, 10-30mg. The Panel noted Napp's submission that only 3% of patients received the 30mg dose. The Panel did not have the study before it but decided on balance that the graph and heading in effect promoted Zanidip at a dose that was not consistent with that in the SPC and a breach of the Code was ruled.

The Panel noted that page 15 was headed 'Zanidip tablets: as effective as nitrendipine'. Zanidip was indicated for mild to moderate hypertension. It was not licensed for the prevention or reduction of cardiac events. The Panel considered that the content and layout of pages 14 and 15 invited direct comparison between Zanidip and nitrendipine and implied that Zanidip might produce a similar

reduction in cardiovascular events. In this regard the Panel noted that pages 14 and 15 appeared within a section entitled Vs Other Antihypertensives. The Panel considered that reducing cardiac events would potentially be a feature of therapy with antihypertensives. In the Panel's view the material implied more than the reporting of a potential benefit of treatment. The Panel considered pages 14 and 15 misleading and a breach of the Code was ruled. Upon appeal by Napp, the Appeal Board considered that the juxtaposition of pages 14 and 15 invited the reader to assume that because of equivalent efficacy in a surrogate end point (blood pressure) Zanidip would also reduce cardiovascular events to the same degree as nitrendipine. In this regard the Appeal Board noted the headings to pages 14 and 15. In the Appeal Board's view a reduction in cardiac events would be a potential benefit of lowering blood pressure. The Appeal Board noted that there was no data to show that Zanidip reduced cardiovascular events and that Napp had conceded that it did not have the evidence to support such a claim. The Appeal Board noted that the bar chart on page 14 gave specific details with regard to the percentage reduction of cardiovascular events seen in the nitrendipine trial. There was no data to show that the same degree of benefit would be seen with Zanidip. The Appeal Board considered pages 14 and 15 misleading and exaggerated and upheld the Panel's ruling of a breach of the Code.

Page 17 featured, beneath a heading 'Zanidip tablets: as effective as nifedipine SR', a bar chart which depicted the reduction in SBP and DBP after four weeks' treatment with Zanidip (10mg once daily) and nifedipine SR (20mg twice daily). Bayer stated that there was no indication whether the differing effects on SBP and DBP were statistically significant or not. There was a p value quoted (<0.001) but it was not clear to what this related. As mentioned above, Bayer did not consider that it was meaningful to compare once and twice daily preparations in this way. As once daily nifedipine LA had been available for some years, a therapeutically meaningful comparison would be nifedipine LA and Zanidip. It was therefore unrepresentative and misleading to make this comparison. The Panel considered that its comments above were relevant regarding the comparison of once and twice daily medications. The Panel noted the heading wherein Zanidip was described as 'as effective as nifedipine'. The graph depicted numerical differences for SBP and DBP in favour of nifedipine. A p value (p<0.001) appeared in the bottom right-hand corner of the graph but it was not clear whether this related to DBP or to both blood pressure measurements. The Panel considered that the presentation of the data was misleading. The heading gave the impression that the data presented on the graph showed equivalent outcomes and the inclusion of a p value implied that there was a difference between the products although according to Napp the statistically significant difference was before and after treatment. A breach of the Code was ruled.

Bayer plc, Pharmaceutical Division, complained about a 20 page detail aid (ref ZA 040DA) for Zanidip (lercanidipine) produced by Napp Pharmaceuticals Limited. Zanidip was a class II calcium antagonist. The detail aid was subtitled 'Treating hypertension saves lives' and discussed Zanidip with reference to tolerability, efficacy, cost, isolated systolic hypertension, diabetes and comparison with other hypertensives. Bayer produced Adalat LA (nifedipine).

1 Tolerability – Page 6

Page 6 of the detail aid headed 'Typical calcium antagonist related adverse events' featured two bar charts; the first beneath a heading 'Published data relating to four major calcium antagonists (pooled data)' depicted the incidence of headache, flushing, dizziness and palpitation for lacidipine, nifedipine, amlodipine and felodipine and was referenced to Leonetti *et al* (1991), Osterloh (1989) and Elvelin *et al* (1993). Data for all four products was presented for headache, flushing and dizziness. However only data for lacidipine and nifedipine were presented in relation to palpitation. The key to the graph demonstrated that the lacidipine and nifedipine data came from the same reference, Leonetti *et al*. This was a comparative study. The data for amlodipine came from a review article by Osterloh. The data for felodipine came from a review article by Elvelin *et al*.

The second bar chart depicted the incidence of peripheral oedema for the same four calcium antagonists beneath the claim 'A high incidence of peripheral oedema may result in non-compliance and treatment withdrawal'. The data for Zanidip appeared opposite on page 7.

COMPLAINT

Bayer stated that the first bar chart related to published data and described it as 'pooled'. This was not the case; Leonetti *et al* related to a double blind comparison of lacidipine 4-6mg once daily and nifedipine SR 20-40mg twice daily, whereas Osterloh and Elvelin *et al* related to data from placebo controlled studies from review articles on amlodipine and felodipine respectively and not the individual studies. The heading of the bar chart implied that all the data shown was derived from pooled data. This was simply not the case.

The incorporation of a comparative study and placebo-controlled, pooled data within one bar chart could not be considered as accurate, balanced or objective. The bar chart also implied that palpitations only occurred in the double-blind study (Leonetti *et al*), however, both Osterloh and Elvelin *et al* mentioned palpitations occurring with the medicines concerned both in connection with placebo controlled studies and in unmentioned comparative studies.

In the second bar chart on the page it was unclear why the side-effect peripheral oedema had been treated separately to the other effects, as it was sourced from the same references. By inference it related the side-effect to withdrawal rate. This was not supported by the references.

Three of the medicines identified in the bar chart were administered once daily, whereas nifedipine SR was

administered twice daily. It was recognised that shorter acting dihydropyridines might be associated with increased peak-to-trough plasma level variation (alluded to in Leonetti). This had been linked to the incidence of side-effects. Once daily formulations of nifedipine were recognised to show little or no plasma level variability over 24 hours and were associated with fewer and less severe side-effects than the twice daily formulations (Kirby and Kitchin (1999) and Data on File Bayer plc). Bayer did not agree with Napp's view that the comparison was valid because twice daily nifedipine was more commonly prescribed than once daily. Comparisons should be balanced and fair – once daily formulations should be compared with once daily formulations.

Bayer alleged that the bar charts were inaccurate and misleading and in breach of Clauses 7.2 and 7.6 of the Code.

RESPONSE

Napp stated that the first point raised related to the term 'pooled'. The verb 'to pool' in the Cambridge English dictionary was defined as a 'number of people or things collected together for shared use by several people or organisations'. In the bar chart at issue Napp had 'collected together' or 'pooled' data from three studies and presented that data graphically. This was a common practice. The description of the term 'pooled data' was introduced into the title of the bar chart specifically to make the reader aware that these data had been collected together from several different sources and reinforced by annotations to those three references.

It should be noted that the numbers of patients in all groups were relatively large and there was no reason to presume that the absolute incidence of the side-effects detailed would be unrepresentative. Napp believed that the bar chart did indeed provide an accurate and balanced view of the frequency of side-effects for these four agents. The data was in no way affected by whether each study was comparative or placebo-controlled.

The data for palpitations in Osterloh and Elvelin *et al* were fragmented. In each case, palpitations only occurred in one of a number of data pools making it difficult to interpret in a way that was valid. These figures were therefore omitted due to this uncertainty and therefore risk of misrepresentation.

The reason for separating peripheral oedema from the other side-effects was that peripheral oedema was a particular problem with regard to dihydropyridine calcium antagonists. This was thought to be due to their powerful vasodilatory action, and was seen with much less frequency in other antihypertensives. The other side-effects detailed were often seen in relation to many antihypertensives.

Napp found it surprising that Bayer did not accept that the incidence and severity of side-effects of a given medicine were related to both non-compliance or withdrawal. Napp believed this to be a generally accepted phenomenon, often used as the driving force for further product development, focusing on the development of less toxic compounds. Elvelin *et al* made a point of analysing the relationship between adverse events of felodipine and withdrawal from clinical trials.

Napp disagreed with Bayer's assertion that once daily formulations should only be compared with once daily formulations. Provided that there was no ambiguity, a comparison with a twice daily formulations used for the same indication was equally valid. The bar chart was clearly labelled in this case so there was no ambiguity. Napp selected twice daily nifedipine as it was significantly more commonly prescribed in the UK than once daily nifedipine. The comparison in the bar chart was between 'major' calcium antagonists so it was appropriate to select the most commonly used form of nifedipine.

The statement detailed in the Bayer letter relating fluctuating plasma levels to side effects had not been scientifically substantiated. The Kirby and Kitchin paper cited by Bayer, the only one to be published under peer review and freely available, demonstrated a trend towards a lower side-effect profile with once daily nifedipine. However, the numbers in this study were very small and importantly not statistically significant. The other reference provided by Bayer was not freely available, and did not appear to have had peer scrutiny with regard to methodology. It could not have been considered therefore when compiling the detail aid. There was currently no published data of which Napp was aware that suggested once daily and twice daily nifedipine had statistically significant differences with regard to side-effect profile.

PANEL RULING

The Panel noted the definition of the verb 'to pool' provided by Napp. References were provided in relation to each product shown in the bar chart. The Panel considered that readers would assume that the reference to pooled data meant that some analysis had been done on the data, such as a meta analysis, and not simply that the data was from a number of different sources and no analysis had been done. The Panel considered that the term 'pooled data' was misleading and a breach of Clause 7.2 of the Code was ruled. This ruling was appealed by Napp.

The Panel then considered the allegation that the incorporation of the comparative and placebo controlled data within one bar chart could not be considered as accurate, balanced or objective. In the Panel's view, bearing in mind its ruling above, the presentation of the data in the bar chart at issue was unacceptable. A breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 7.6 was covered by this ruling. This ruling was appealed by Napp.

The Panel next considered the data for palpitations. The palpitation data for both lacidipine and nifedipine was referenced to Leonetti *et al*. Palpitation data for the other products amlodipine and felodipine was not presented. The Panel noted the submission that with regard to the other products and studies palpitations only occurred in one of a number of data pools making it difficult to interpret in a way that was valid. The Panel noted that Osterloh assessed the safety profile of amlodipine via a review of studies; a

total of 4227 patients were evaluable. Data for the incidence of palpitation was presented for one study only which compared amlodipine with diltiazem; from 39 evaluable subjects 5.1% (n=2) experienced palpitations. The study author noted that the data base was too small to allow many differences in the side-effect profile to become apparent. Elvelin *et al* assessed the tolerability and safety of felodipine; pooled data from placebo controlled dose response studies where patients were randomised to treatment and dose showed that no patients experienced palpitations causing withdrawal at 5mg (n=186) and at 10mg the figure was 0.5% (n=189). The Panel noted that the summary of product characteristics (SPC) for Istin (amlodipine) described palpitations as a rarely reported adverse event. The Plendil (felodipine) SPC stated in the undesirable effects section that as with other calcium antagonists palpitations, *inter alia*, might occur. These reactions were described as being usually transient and most likely to occur at the start of treatment or after an increase in dosage. The Panel considered that the bar chart gave the impression that palpitations did not occur with amlodipine or felodipine and that was not so. There was no explanation regarding the omission of this data. The Panel considered this was misleading and a breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 7.6 was covered by this ruling.

The Panel considered the second bar chart. In the opinion of the Panel it was not unreasonable to present data on peripheral oedema separately. The Panel noted the heading 'A high incidence of peripheral oedema may result in non-compliance and treatment withdrawal'. The graph depicted an incidence ranging from approximately 9% to 17%. The Panel considered that adverse events might be generally relevant to issues of compliance and withdrawal and it was not necessarily unreasonable to link the two. The Panel considered that the claim was sufficiently qualified by the use of the term 'may'. No breach of Clause 7.2 was ruled.

The Panel noted that it was not necessarily unacceptable to compare twice and once daily formulations *per se*; the issue was whether the comparison was fair and in accordance with the Code, particularly Clause 7.2. The Panel noted Napp's submission that it had selected twice daily nifedipine as it was significantly more commonly prescribed than once daily. The Panel noted Bayer's view that there was a difference in the side-effect profile between twice daily nifedipine and once daily nifedipine. The Panel noted that whilst the presentations and doses were clearly stated the basis of the selection of the medicines was not. The reference to 'four major calcium antagonists' above the first graph was not sufficient in this regard. The second graph was misleading and a breach of Clause 7.2 was ruled. The Panel considered the alleged breach of Clause 7.6 was covered by this ruling. This ruling was appealed by Napp.

APPEAL BY NAPP

Napp stated that the first issue related to the consideration of the word 'pooled' This definition was critical in a number of rulings that followed. In Bayer's original allegation, the suggestion was that the term 'pooled' implied meta-analysis. Napp maintained that the verb 'to pool' was a commonly used verb in the English language, which both the Oxford and Cambridge Dictionaries defined as meaning 'to collect together'. The Panel suggested that the verb would imply a statistical analysis. Despite examining many statistical textbooks, Napp had found no formal definition of the term 'to pool'; however, it was frequently used generically to imply a collection of data to form a 'data pool', which was then tabulated. Indeed, in the ruling the Panel itself used the verb with regard to the Elvelin *et al* study, where it was used in regard to data tabulations, and then proceeded to talk of data pools (ie a collection of data) in the same ruling. No meta-analysis was performed on the pooled data in the Elvelin *et al* study, and likewise none was performed on the data Napp pooled together from Elvelin *et al* and other studies referenced. It should be noted that Napp pooled the raw data from the underlying studies, not the statistical results coming out of each study, which was an important distinction. In the later situation, a metaanalysis might indeed be necessary to weight the statistics generated from many studies in an appropriate manner to arrive at statistically valid conclusions based on them. But metaanalysis or other analysis was generally unnecessary where the raw data itself was being pooled, as opposed to the statistics generated from the studies.

These points, combined with the fact that on the bar chart concerned there were no claims of p values denoting statistical analysis, would support that this term had been used simply to denote that the raw data had been collected into 'a data pool' and then had been graphically represented as seen. Indeed, the tabulations (Elvelin *et al*) where this term was used, and to which the Panel referred in its ruling, showed very similar tolerability data, presented in numerical form rather than the bar chart format Napp's was in. Napp also observed that 'pooled data' was used by other pharmaceutical companies, including Bayer, to present data in the same way. For the foregoing reasons, Napp contended that the use of 'pooled data', without some form of analysis being done on the data, was not misleading, and it appealed against the Panel's ruling of a breach of Clause 7.2.

This ruling also had a bearing on further rulings of breaches of Clause 7.2. In particular, in its judgement considering the incorporation of comparative and placebo controlled data in one bar chart, the Panel ruled this as misleading predominantly in consideration of its previous judgement on the term 'pooled data'.

Napp stated the Panel ruled a breach of Clause 7.2 because it was suggested that it was misleading that the reasons for choice of twice daily rather than once daily were not detailed. This was surprising particularly as Bayer's allegation related to a hypothesised difference in the side-effect profile of once daily versus twice daily nifedipine. Given that the recently published INSIGHT study suggested that there was an equivalent if not poorer side-effect profile with once daily nifedipine, and no therapeutic

difference between once daily and twice daily nifedipine had been demonstrated (Kirby and Kitchin), Napp maintained that the reasons for choice did not need to be detailed. To all intents and purpose, the therapies were essentially equivalent with the exception of dosage frequency. It was important to recognise that twice daily nifedipine was prescribed about twice as frequently as once daily, which was reflected in the choice of the medicine. Indeed, in this paragraph it was actually stated 'The Panel noted that it was not necessarily unacceptable to compare twice and once daily formulations *per se*'. The bar chart was clearly labelled and in Napp's view it was neither misleading nor inaccurate. Napp appealed against the Panel's ruling on this point.

APPEAL BOARD RULING

The Appeal Board considered the first bar chart. The Appeal Board noted that the lacidipine and nifedipine data were each referenced to Leonetti *et al*, a comparative study. The amlodipine and felodipine data were referenced to Osterloh and Evelin *et al* respectively; each analysed a pooled database. The Appeal Board noted that there was no commonly accepted definition of the phrase 'pooled data'; whether such a phrase was misleading would depend on the circumstances of each individual case. The Appeal Board noted that the phrase 'pooled data' would be read in conjunction with the data presented in the bar chart. The Appeal Board considered that the presentation of the data together with the phrase 'pooled data' invited the reader to directly compare the data presented and implied that it was valid to do so. This was not so. The Appeal Board considered that in these circumstances the use of the phrase 'pooled data' was misleading. Not all the data had been pooled. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted its comments regarding the presentation of data in the first bar chart above. The Appeal Board thus considered the presentation of placebo controlled and comparative data within one bar chart misleading as alleged and upheld the ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

With regard to the choice of nifedipine formulation the Appeal Board noted that twice daily nifedipine was prescribed about twice as frequently as once daily. The Appeal Board did not accept Napp's submission that the reasons for choice did not have to be detailed. The basis of the products' selection was not clear and this was misleading. The Appeal Board upheld the ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

During its consideration of this point the Appeal Board was very seriously concerned about the confusing submission from Napp regarding the difference in tolerability between once daily nifedipine and twice daily nifedipine. The Appeal Board was concerned that Napp had stated in its response to the complaint that Kirby and Kitchin had shown no statistically significant difference in side-effect profile between once daily and twice daily nifedipine. However, the paper actually stated that no statistical analysis had been done on the data relating to side-effects. The Appeal Board noted Bayer's view that it was recognised that shorter acting dihydropyridines might be associated with increased peak-to-trough plasma level variation and this had been linked to the incidence of side-effects. It also noted Bayer's submission that once daily formulations of nifedipine were recognised to show little or no plasma level variability over 24 hours and were associated with fewer and less severe side-effects than twice daily formulations. The Appeal Board noted that Napp had referred to the INSIGHT trial. This compared the effects of once daily nifedipine with co-amilozide on cardiovascular mortality and morbidity in high risk patients with hypertension. There was no data in the INSIGHT trial directly comparing the tolerability of once daily and twice daily nifedipine. The Appeal Board requested that Napp be advised of its views.

2 Tolerability – Page 7

Page 7 was headed 'Zanidip tablets: a tolerability profile comparable with placebo*'. The asterisk referred the reader to a footnote at the bottom of the page which stated 'As reported in studies that examined the incidence of adverse events in patients being treated with Zanidip tablets 10mg od and that of control patients receiving placebo.' Beneath the subheading 'A global safety analysis of 1,128 hypertensive patients treated with Zanidip tablets 10mg od', a bar chart depicted the incidence of the most commonly reported adverse events of Zanidip 10mg od vs placebo; headache, flushing, dizziness, asthenia and reflex tachycardia. The second bar chart headed 'Zanidip tablets: a notably low incidence of peripheral oedema' depicted the incidence of peripheral oedema.

COMPLAINT

Bayer stated that the first bar chart purported to show the profile of the lowest licensed dose, 10mg, of Zanidip and compared it to placebo. In fact, this was pooled data from some 20 trials. These data included placebo and comparator controlled studies. The impression given was that this was placebo controlled data. Bayer alleged that the scale used was far larger than necessary to demonstrate the differences shown. In fact, it would be more representative to include the actual comparators.

The second bar chart on the page used the same data source as the first and was subject to the same criticisms but only featured the side-effect peripheral oedema. Bayer alleged that, again, the scale used was far larger than necessary to demonstrate the differences shown.

Bayer alleged that this page was misleading in that it did not give a balanced view and was in breach of Clauses 7.2 and 7.5 of the Code.

RESPONSE

Napp stated that the wording of the two statements above the first bar chart was specifically constructed

to demonstrate that the data was collected from a number of studies, and Napp had been totally unambiguous in its methodology. The Zanidip data was the absolute incidence of the cited side-effects from these studies in the Zanidip group. The same applied for the placebo data in those trials where this group existed. The numbers that were generated were large for both groups and there was no reason to consider that either group should therefore have an unrepresentative incidence of side-effects. Napp had not at any point claimed that this was direct comparative placebo controlled data from one trial.

The reason for separating the data for oedema was the same as above and again represented the absolute frequency of the side-effect occurring from these trials in both groups. Napp had believed the data to be representative and fair. Indeed there was further evidence to corroborate these frequencies of side-effects to show both an absolute low frequency of side-effects for Zanidip and that the side-effects were reduced by substituting a once daily dihydropyridine with Zanidip, Barrios *et al* (2000) and Borghi *et al* (2000).

Napp stated that the design of the bar charts was to some degree generic. The scale had been reduced on the first bar chart on page 7 because of the low values. It was considered that the scale should not be reduced further as the small differences between placebo and Zanidip would have been amplified, in particular with regard to dizziness, asthenia and peripheral oedema. Napp therefore believed that within the constraints of including data logically in a book chapter format, the data presented was represented in such a way as to give a balanced and fair reflection of the side-effect profiles for each of the dihydropyridines concerned.

PANEL RULING

The Panel considered the first bar chart. The Panel considered that its comments at point 1 regarding the use of pooled data and the comparison of placebo controlled and comparative data were relevant. The Panel noted that the subheading referred to 'A global safety analysis of 1,128 hypertensive patients'. The patient number was also stated on the graph. The Panel considered that the subheading, in particular the word 'A' and the bar chart, gave the impression that the data derived from a single published study comparing Zanidip and placebo and that was not so. The Panel noted the footnote to the page heading. It was an established principle under the Code that one could not qualify a claim by reference to a footnote. The footnote was insufficient to negate the overall impression given. A breach of Clause 7.2 was ruled. This ruling was appealed by Napp.

The Panel noted that Clause 7.5 required clear references to be given when referring to a published study. The Panel noted that the page in question made no reference to whether the studies were published or not. In these circumstances it was not necessary to give a reference. No breach of Clause 7.5 was ruled.

The Panel noted the scale used given the data depicted. The Panel noted that the differences between Zanidip and placebo ranged from approximately 1% (headache) to less than 0.5% (dizziness). The scale on the bar chart was from 0 to 18%. The Panel noted the submission from Napp that these small differences would be amplified by reducing the scale. On balance the Panel did not consider the scale misleading as alleged and ruled no breach of Clause 7.2 of the Code in that regard.

The Panel considered the second bar chart on page 7. The Panel considered that its ruling at point 1 regarding the separation of peripheral oedema data applied here. The Panel also considered that its ruling immediately above regarding the scale of the first bar chart on page 7 was relevant here. The Panel also noted that the scale was identical to the bar chart facing on page 6 depicting peripheral oedema data for the four comparator calcium antagonists. The Panel ruled no breach of Clause 7.2 of the Code.

The Panel then considered the allegation regarding the data source with reference to the second bar chart. There were differences between the two bar charts; the subheading and labelling to the second chart did not refer to a global safety analysis, the patient number was, however, stated to be 1128. The Panel considered its ruling on the first chart on page 7 was relevant here. On balance a breach of Clause 7.2 was ruled. This ruling was appealed by Napp.

APPEAL BY NAPP

Napp stated that the first paragraph of the ruling found a breach of Clause 7.2 on the grounds that the bar chart gave a misleading impression that the data was derived from a single study comparing Zanidip with placebo. The sub-heading 'A global safety analysis of 1,128 hypertensive patients' was considered to give the impression that the data was derived from a single study, not pooled data from several studies. The aforementioned subheading 'A global …' clearly indicated that this referred to data pooled from several studies, in fact all existing studies at the time of submission. Actually the raw data was collected and presented as a single tolerability summary required for the registration of Zanidip, and was held on file as a single report, despite being originally derived from 20 studies. Napp depicted this report in the same way in the bar chart, ie as a global safety summary. The footnote to the bar chart heading simply explained that the data was collected from a number of trials, and it did not 'qualify a claim' about the tolerability of Zanidip. Napp also noted the Panel's assertion that it was an 'established principle under the Code' that claims could not be qualified by reference to a footnote. Napp did not see how something could be an established principle under the Code if it was not mentioned in the Code or the supplementary information. In any event, Napp did not use this footnote to qualify a claim, merely to explain methodology.

The Panel's rulings in point 1 regarding 'pooled data' and the comparison of placebo controlled and comparative data were recalled by the Panel when reaching the decision on this breach. Napp had already discussed the former point. With regard to the latter, the Panel's ruling did not detail why it was considered that the incorporation of comparative and placebo controlled data *per se* was misleading. The

reference here was simply made to the previous ruling again on the term 'pooled data'. Napp believed that the validity of the percentage numerical incidence of side-effects for a given medicine was related to the sample size, and would be unaffected by whether the trial was comparative or placebo controlled. It would only be relevant if the trial populations in the different groups were radically different in some way, which was not the case in these trials.

With regard to the final paragraph of the ruling, another breach of Clause 7.2 was found, based on the ruling above. For the reasons given above, Napp appealed the Panel's rulings on both of these points.

APPEAL BOARD RULING

The Appeal Board noted that the phrase 'A global safety analysis' referred to the raw data which had been collected and presented as a single tolerability summary required for the registration of Zanidip and was held on file as a single report despite being originally derived from 20 studies. Napp submitted that it had depicted this report in the same way in the bar chart ie as a global safety summary. The Appeal Board considered that the phrase 'A global safety analysis' was standard practice and did not consider it misleading as alleged and ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

The Appeal Board then considered the point regarding the data source with reference to the second bar chart and considered that its ruling above applied here; no breach of Clause 7.2 was ruled. The appeal on this point was successful.

3 Comparison between Pages 6 and 7

COMPLAINT

Pages 6 and 7 were presented as facing pages. Bayer considered this presentation to imply that Zanidip had a more favourable side-effect profile than competitor compounds. This effect was largely engendered by the almost identical axes used in the first bar charts on each page. This effect was even more apparent with the second bar chart on each page, which had identical axes. Additionally, the juxtaposition of a single dose placebo comparison of the tolerability profile of Zanidip and the multiple dosages used in the facing bar chart was not a balanced comparison and gave a false impression of the relative tolerability profile. It led the reader to believe that the incidence of side-effects with Zanidip was much lower than the comparators on the facing page. This could not be assumed in the absence of comparative studies. Moreover, the SPC for the product listed peripheral oedema as one of the most commonly reported side-effects in controlled clinical studies. Other commonly reported events included flushing and palpitations.

Bayer's reservations regarding the relevance of once daily and twice daily formulations of nifedipine also applied to this global impression.

Taken together Bayer alleged that pages 6 and 7 breached Clauses 7.2 and 7.5 of the Code.

RESPONSE

Napp pointed out that this section of the detail aid was termed 'tolerability'. It would therefore be reasonable to insert all the known tolerability data relevant to calcium channel antagonists and Zanidip. If the desired effect had been to present the Zanidip data and placebo data in direct comparison with data from the other four dihydrophyridines, they would have been presented on one chart. These data were intentionally separated in order to clearly differentiate and avoid a direct comparison.

Napp referred to its comments on the scale of the graphs and the comparison between once and twice daily nifedipine at point 2.

The SPC for Zanidip did indeed mention peripheral oedema as one of the product's more common side-effects and this was shown separately on the second graph. The statement in the SPC, however, was relative as the level of even the most common side-effects of Zanidip was low.

PANEL RULING

The Panel noted its rulings regarding pages 6 and 7. It considered that pages 6 and 7 would probably be presented as one by the representatives. The layout and data presented would invite direct comparison between the two such that the Zanidip and placebo data on page 7 would be directly compared with the data for lacidipine, nifedipine, amlodipine and felodipine on page 6. The Panel considered that a reader would assume that Zanidip on page 7 had a more favourable side-effect profile than the four calcium antagonists on page 6. There was no direct comparative data. A breach of Clause 7.2 was ruled.

4 Cost comparison

Page 10 was headed 'Zanidip tablets are 18% less expensive than amlodipine' and featured two tables; the first compared the cost per 28 days of Zanidip 10mg od with amlodipine 5 and 10mg od, lacidipine 2 and 4mg od, nifedipine LA 30 and 60mg od and felodipine 5 and 10mg od. The second table stated the most commonly prescribed doses of each calcium antagonist over 3 months. Page 11 featured the costs per year at therapeutic doses of Zanidip 10mg and the four other calcium antagonists of treating 25, 50, 100 and 200 patients.

COMPLAINT

Bayer stated that the first table on page 10 did not list the price for nifedipine LA 20mg. Bayer therefore believed this price comparison to be incomplete. The chart on page eleven, which listed the costs per year, also excluded nifedipine LA 20mg. Additionally, no mention was made of the fact that doubling the dose of Zanidip, in keeping with the rest of the chart, doubled the cost per 28 days' treatment. Price comparisons should compare like with like, in this case the lowest effective dose available, or both doses, for prescription should be compared. Bayer therefore alleged that pages 10 and 11 were in breach of Clause 7.4 of the Code.

The second chart on page 10 'Zanidip tablets doses most commonly prescribed' referred to an undefined three month period and showed the relative split of prescriptions for two doses of five dihydropyridine calcium antagonists, including Zanidip. The source of these data was not cited and the healthcare professional had no idea as to the validity of the information or where it came from. The figures for Zanidip were highlighted. Again, there was no mention of nifedipine LA 20mg once daily. The figures for Zanidip were the only ones to add up to 100%. Bayer could only conclude that the intention behind highlighting the Zanidip figures was to imply that because, over a three month period, there was a preponderance of prescriptions for the lower dose, more patients were treated with this dose than were treated with the lower doses of the other drugs. From this it could be inferred that using Zanidip would contribute to cost minimisation in prescribing budget terms. This was not the only interpretation possible. For instance, 10mg was the only dose form available and therefore patients might stay on it for longer before they were titrated up to achieve the blood pressure lowering required. Furthermore, there was no information on how many patients were not adequately controlled on, or intolerant of, 10mg and switched to other products. There was no consideration of the actual volume of prescriptions – the denominator was missing. The chart was therefore misleading and Bayer alleged a breach of Clause 7.4 of the Code.

RESPONSE

The price comparison chart at the top of page 10 showed the costs for several dihydropridines at the time of compilation of the detail aid (April 2000), according to IMS data. The doses for comparison were specifically chosen, as it was assumed the reader would be interested in clinical relevance. It could be deduced from the lower table on page 10 (also derived from IMS a commonly referred to database) that nifedipine LA 20mg accounted for 2% of nifedipine LA sales at this time. For a similar reason the 2.5mg and 20mg doses of felodipine were also omitted as these only accounted for a low proportion of sales and likewise the 20mg dose of Zanidip. Notably, the 5mg felodipine shown in the chart was cheaper than nifedipine LA 20mg. The data was accurate and, importantly for cost, clinically relevant.

Regarding the second chart on page 10, these data were derived from IMS data for the last quarter of 1999/early 2000. It was presumed that if the healthcare professional were to want to know the source of the information, the healthcare professional would ask the representative concerned and this would duly be provided, as it was to Bayer following its enquiry letter. Again the fact that nifedipine LA 20mg accounted for only 2% of total nifedipine LA sales meant it was not clinically relevant and was therefore excluded from this chart. The 20mg dosage of Zanidip was included in the table, despite its small sales volume, to be transparent over the proportion of prescriptions that accounted for this higher and thus more expensive dose.

The point that only Zanidip added up to 100% was erroneous. Napp pointed that amlodipine and lacidipine also added up to 100%. This data provided an accurate assessment for the frequency of prescriptions over this 3 month period. The interpretation of these data by Bayer were not clear. The management of hypertension was well covered by national guidelines with recommendations on review and management regarding targets regardless of therapeutic modality. The supposition that professionals would leave patients untreated because they were unwilling to increase Zanidip from 10mg per day was inaccurate and derogatory to those health professionals that managed hypertension. Consideration of volume of prescriptions and tolerability was irrelevant as it was cost, as clearly labelled, that was being addressed in this section not popularity or tolerability.

Again nifedipine LA 20mg was omitted from the chart on page 11 for the same reasons of relevance as detailed above.

Napp therefore believed that the data detailed on pages 10 and 11 was balanced, fair and representative.

PANEL RULING

The Panel noted that the heading to the first table referred to cost per 28 days at therapeutic doses. The heading to the second table referred to the doses most commonly prescribed (three months). The Panel noted that the three month period was not identified. All of the presentations mentioned in the second table appeared in the first table except Zanidip tablets 20mg od at 13.7%. The Panel noted that according to Napp the selection of medicines for the first table was based on IMS sales. The Panel considered that therapeutic doses might not necessarily be equivalent to those most commonly prescribed. The Panel noted that medicines were not necessarily prescribed at an optimum dosage. The Panel considered that the first table on the page was misleading. A breach of Clause 7.2 was ruled.

The Panel considered the second table. The Panel noted that data for certain presentations had been omitted. The Panel considered that a reader would assume that the missing data related to less commonly prescribed presentations. The Panel queried the reference to Zanidip 20mg at 13.7%. The Panel was concerned that the three month period was not identified. The Panel considered the lower table misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that Bayer had alleged a breach of Clause 7.4 which required substantiation to be provided without delay to members of the health professions. The Panel considered that Clause 7.4 was not relevant to the substance of the allegation. The matter fell within Clause 7.2 and rulings under that clause were made. In this regard the Panel noted that the substance of the response related to Clause 7.2.

5 Pages 14 and 15 Reduction in cardiovascular events

Page 14 was headed 'Isolated systolic hypertension: long acting nitrendipine significantly reduces cardiac events' and featured a bar chart which depicted the

percentage reduction at two year median of cardiovascular events at follow up.

The facing page (page 15) was headed 'Zanidip tablets: as effective as nitrendipine' and featured a graph which depicted the systolic and diastolic blood pressure reduction during treatment with Zanidip tablets 10-30mg or nitrendipine 10-30mg.

COMPLAINT

Bayer stated that pages 14 and 15 related Zanidip to a major outcome study (SYST-EUR) using nitrendipine, a medicine not licensed in the UK. Results from this study were presented on page 14. Immediately facing this was a graph presenting the results of a study, which after reading the reference, related to a randomised double-blind comparison of the efficacy of Zanidip on blood pressure lowering compared to nitrendipine. In this study patients would appear to be titrated to dosages greater than those currently licensed in the UK. Bayer alleged a breach of Clause 3 of the Code. The graph showed very similar profiles of blood pressure reduction over 12 weeks' treatment for both medicines. The graph appeared beneath the heading 'Zanidip tablets as effective as nitrendipine'; and had the following strapline at the bottom of the page (with the Zanidip logo), 'Treating Hypertension Saves Lives'. These two phrases and the pages facing one another implied that, because of its hypertensive efficacy over twelve weeks, Zanidip would produce the same reduction in cardiovascular events as nitrendipine did in a placebo controlled outcome study. There was no evidence to support this. Bayer alleged that the pages were grossly misleading and unrepresentative in breach of Clauses 7.2, 7.4 and 7.8 of the Code.

RESPONSE

Napp stated that the results displayed on page 15 (comparison between Zanidip and nitrendipine) were from an Italian study published in an international journal (Journal of Cardiovascular Pharmacology). The dosages used by the investigators were indeed up to 30mg of Zanidip. Only three out of forty patients in the study actually achieved this dose. It would be inappropriate not to report the findings of studies as they were published and Napp would not want to distort the findings of this study by falsely claiming a reduced dose of Zanidip was used for every patient. Napp was not anywhere on this page promoting the use of 30mg of Zanidip in the UK.

The strapline 'Treating hypertension saves lives' appeared on a variety of pages throughout the detail aid and was not peculiar to this page alone. In its own right, this was a widely accepted fact which was reinforced in all the national/international guidelines and was not in any way controversial and was perfectly in keeping with the content of this page.

Napp stated that the juxtaposition of the SYST-EUR trial and Zanidip comparative data was not accidental. The bar chart on page 14 showed the typical risk reduction that one might see with a dihydropyridine, in particular in this case nitrendipine, and served as an introduction. The graph on page 15 then showed that Zanidip controlled hypertension over 12 weeks as effectively as nitrendipine. Napp believed it would therefore not be unreasonable, and it was in accordance with general specialist opinion, for a healthcare professional to expect a reduction in those cerebrovascular/cardiovascular risks with similar blood pressure control. Napp had not at any point claimed that the risk reduction of Zanidip would be of the same rate as that obtained in a clinical trial with nitrendipine. It was worth noting that on the Bayer internet site the Adalat Website also referred to the results of the SYST-EUR trial and clearly implied that Adalat offered the same benefits as nitrendipine simply by virtue of being in the same class of long acting dihydropridines. Bayer was making promotional claims on the basis of the SYST-EUR trial (for which it criticised Napp) but it did not, as Napp did, show any comparative data on blood pressure control.

Napp therefore considered the data to be balanced, representative and valuable in terms of introducing the concept of successful anti-hypertensive treatment and the reduction of risk in severe cardiovascular disease.

PANEL RULING

The Panel considered the data on page 14 first. The Panel noted that nitrendipine was not licensed in the UK. It was licensed in some European countries. The Panel noted that the data depicted showed significant reductions in total stroke incidence (42% p=0.003), non-fatal stroke (44% p=0.007) and fatal and non-fatal cardiac events (26% p=0.03). During the consideration of this matter the Panel was concerned that data for nitrendipine, a product not licensed in the UK, had been included. The Panel questioned whether comparing nitrendipine with Zanidip met the requirements of Clause 7.2 of the Code. Readers might be misled into assuming that nitrendipine was licensed in the UK. The Panel noted that the footnote to page 14 stated 'Active treatment was started with nitrendipine 10-40mg daily and, if necessary, combined with or replaced by enalapril 5-20mg daily and hydrochlorothiazide 12.5-25mg daily or matching placebos'. The Panel noted its comments regarding the use of footnotes above. The Panel did not have the study at issue, Staessen *et al* (1997). It appeared that the data presented for nitrendipine might include combined treatment or patients who had been switched to other medication. The Panel noted that it did not have an allegation on these points but asked that Napp be advised of its views.

The Panel noted that according to the graph on page 15 nitrendipine 10-30mg and Zanidip 10-30mg appeared to produce closely similar reductions in systolic blood pressure and diastolic blood pressure over 12 weeks. The Panel noted that the licensed dose for Zanidip was 10mg od which might be increased to 20mg depending on the individual patient's response. The Panel noted that the dose of Zanidip was clearly stated above the graph at issue, 10-30mg. The Panel noted Napp's submission that only 3% of patients received the 30mg dose. The Panel did not have the study before it but decided on balance that the graph and heading in effect promoted Zanidip at a dose that was not consistent with that in the SPC. A breach of Clause 3.2 was ruled.

The Panel also considered that its comments above regarding the presentation of data on nitrendipine on page 14 were relevant to the data on page 15.

The Panel noted that page 15 was headed 'Zanidip tablets: as effective as nitrendipine'. The Panel noted that Zanidip was indicated for mild to moderate hypertension. It was not licensed for the prevention or reduction of cardiac events. The Panel considered that the content and layout of pages 14 and 15 invited direct comparison between Zanidip and nitrendipine and implied that Zanidip might produce a similar reduction in cardiovascular events. In this regard the Panel noted that pages 14 and 15 appeared within a section entitled Vs Other Antihypertensives. The Panel considered that reducing cardiac events would potentially be a feature of therapy with antihypertensives. In the Panel's view the material implied more than the reporting of a potential benefit of treatment. The Panel considered pages 14 and 15 misleading and breaches of Clauses 7.2 and 7.8 were ruled. This ruling was appealed by Napp.

APPEAL BY NAPP

Napp stated that the first paragraph of the Panel's ruling dealt with the bar chart displaying the results of a major hypertensive trial (the Syst-Eur trial). This was a large, respected, multi-centre, international study, which had been used by the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI), and the British Hypertension Society (BHS), as the basis for management guidelines in the US and UK respectively. It was used repeatedly by physicians throughout the world to show the benefits of the use of long acting dihydropyridine calcium antagonists and the rigorous treatment of high blood pressure, especially isolated systolic hypertension. It was a well known trial with an extremely high profile. The Panel, however, had criticised Napp for demonstrating the results of this major international trial because nitrendipine was not licensed in the UK. It was noted that the Panel did not have a copy of this study. Napp did not feel that it should be criticised for the study methodology, and it felt that it was in the public interest to highlight this important international study to continue medical education with regard to the important benefits of antihypertensive therapy. Napp did not market nitrendipine in any country and was in no way promoting its use in the UK. It was difficult to see how the Code could be breached by reporting the results of an international trial in this way, merely because the trial included a product that was not licensed in the UK. Since the guideline stated that the benefits of treatment applied to all long acting dihydropyridines, it was irrelevant in any event that nitrendipine was not marketed in the UK. Indeed, JNC VI stated 'because nitrendipine is not available in the United States, other long-acting dihydropyridine calcium channel antagonists are considered to be appropriate alternatives in these patients'.

Napp referred to the ruling concerning the juxtaposition of the bar charts and the graph. The Panel's ruling actually stated 'The Panel considered that reducing cardiac events would potentially be a feature of therapy with antihypertensives'. However, the ruling went on to state 'In the Panel's view the material implied more than a reporting of potential benefit of treatment'. The whole basis of treating hypertension was to reduce cardiovascular events. There was no other reason to treat hypertension. The Syst-Eur study was cited by the JNC VI, and BHS, which recommended the use of long acting dihydropyridines in the management of isolated systolic hypertension on the basis of this single study. It was because of this that other companies had associated their dihydropyridines with the Syst-Eur study, to demonstrate the tenet of cardiovascular protection. Napp was puzzled as to what more it could imply with regard to antihypertensive treatment with Zanidip than the fact that it reduced cardiovascular risks, as had already been accepted by the Panel as a potential feature. In addition, a breach of Clause 7.8 was ruled. Napp was unable to ascertain where an exaggerated claim was considered to exist on these two pages with regard to Zanidip. Again, Napp noted that others in the industry used this study in exactly the same way, either on Internet sites or detail aids, to promote the value of treating hypertension in order to reduce cardiovascular events with long acting dihydropyridines as recommended by the guidelines. The guidelines themselves did not qualify the benefits of treatment with long acting dihydropyridines, but stated clearly that all long acting dihydropyridines would be expected to have this benefit of reducing cardiovascular events. It was not therefore an exaggeration to suggest this effect, given the weight of specialist opinion. Napp appealed the Panel's rulings on these points.

APPEAL BOARD RULING

The Appeal Board was concerned that the nitrendipine data depicted on page 14 was referenced to a footnote which stated 'Active treatment was started with nitrendipine 10-40mg daily and, if necessary, combined with or replaced by enalapril 5-20mg daily and hydrochlorothiazide 12.5-25mg, daily or matching placebo'. Thus although treatment was started with a calcium antagonist some patients in the active treatment group would have received an ACE inhibitor and/or a diuretic instead of or in addition to their initial therapy. The antihypertensive therapy in the Syst-Eur study was thus not limited to nitrendipine.

The Appeal Board considered that the juxtaposition of pages 14 and 15 invited the reader to assume that because of equivalent efficacy in a surrogate end point (blood pressure) Zanidip would also reduce cardiovascular events to the same degree as nitrendipine. In this regard the Appeal Board noted that the heading to page 14 stated 'Isolated systolic hypertension: long-acting nitrendipine significantly reduces cardiac events' and the heading on page 15 read 'Zanidip tablets: as effective as nitrendipine'. In the Appeal Board's view a reduction in cardiac events would be a potential benefit of lowering blood pressure; the Appeal Board noted that there was no data to show that Zanidip reduced cardiovascular events and that the Napp representatives had conceded that Napp did not have the evidence to support such a claim. The Appeal Board noted that

the bar chart on page 14 gave specific details with regard to the percentage reduction of cardiovascular events seen in the Syst-Eur trial. There was no data to show that the same degree of benefit would be seen with Zanidip. The Appeal Board considered pages 14 and 15 misleading and exaggerated and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.8 of the Code. The appeal on this point was unsuccessful.

6 Page 17 Comparison with nifedipine

Page 17 featured, beneath a heading 'Zanidip tablets: as effective as nifedipine SR', a bar chart which depicted the reduction in systolic and diastolic blood pressure after four weeks' treatment with Zanidip (10mg once daily) and nifedipine SR (20mg twice daily).

COMPLAINT

Bayer stated that there was no indication whether the differing effects on systolic and diastolic blood pressure were statistically significant or not. There was a p value quoted ($p<0.001$) but it was not clear to what this related. As mentioned above in point 1, Bayer did not consider that it was meaningful to compare once and twice daily preparations in this way. As once daily nifedipine LA had been available for some years, a therapeutically meaningful comparison would be nifedipine LA and Zanidip. It was therefore unrepresentative and misleading to make this comparison and Bayer alleged a breach of Clause 7.4 of the Code.

RESPONSE

Napp stated that the p value when taken in context with the title of the bar chart and positioning (it appeared beneath the nifedipine SR column for diastolic BP change) indicated that the reduction in blood pressure before and after treatment were significant. As stated above, an unambiguous comparison between the once daily Zanidip and twice daily nifedipine was both valid and clinically relevant. This was all the more so as there was no conclusive data to show that the equivalent once daily nifedipine formulation had any advantage therapeutically over the twice daily formulation. Napp also noted that the conclusion derived from the bar chart was not questioned by Bayer.

PANEL RULING

The Panel considered that its comments above at point 1 were relevant regarding the comparison of once and twice daily medications. The Panel noted the heading wherein Zanidip was described as 'as effective as nifedipine SR '. The Panel noted that the bar chart depicted numerical differences for systolic blood pressure and diastolic blood pressure in favour of nifedipine. A p value ($p<0.001$) appeared in the bottom right-hand corner of the graph; it was not clear whether this related to diastolic blood pressure, or both diastolic and systolic measurements. The Panel noted the submission from Napp in this regard. The Panel considered that the presentation of the data was misleading. The heading gave the impression that the data presented in the bar chart showed equivalent outcomes and the inclusion of a p value implied that there was a difference between the products although according to Napp the statistically significant difference was before and after treatment. A breach of Clause 7.2 was ruled.

Complaint received **3 August 2000**

Case completed **30 November 2000**

CASE AUTH/1062/8/00

WYETH v ORGANON LABORATORIES

Promotion of Zispin

Wyeth complained about a leavepiece and a detail aid for Zispin (mirtazapine) issued by Organon Laboratories.

It was alleged that the statement on the front of the leavepiece 'Not all antidepressants are created equal – Depression with Anxiety' clearly implied that Zispin was licensed for 'depression with anxiety' but this was not so. The Panel noted that the Zispin summary of product characteristics (SPC) stated that it was indicated for the treatment of depressive illness. The depression rating scales HAMD and MADRS each referred to anxiety as a parameter of depression. The Panel considered that whilst depression and anxiety might coexist they were nonetheless distinct disorders. The SPCs of some antidepressants had an express reference to anxiety in their licensed indications. Zispin did not. The Panel considered that 'Not all antidepressants are created equal – Depression with Anxiety' gave the impression that Zispin had a specific licence for anxiety which was not the case. This impression was not negated by the content of the leavepiece. A breach of the Code was ruled. Upon appeal by Organon, the Appeal Board noted its submission that many diseases and conditions were defined by the presence of symptoms and that depression was characterised by a range of symptoms including anxiety symptoms. The Appeal Board also noted that the DSM-IV classifications did not include a disorder of 'depression with associated anxiety'. Some antidepressants were licensed for depressive illness including depression accompanied by anxiety, others were also licensed for anxiety disorders. Zispin was licensed for the treatment of depressive illness. The Appeal Board considered that the statement 'Not all antidepressants are created equal – Depression with Anxiety' gave the impression that Zispin had a specific licence for anxiety and that was not so. The claim at issue was inconsistent with the SPC. The Appeal Board upheld the Panel's ruling of a breach of the Code.

In relation to the detail aid, Wyeth alleged that a graph showing the reduction in the HAMD scores of venlafaxine and Zispin in severe depression suggested that Zispin was superior to venlafaxine though no p values were shown. In addition it was not stated that the dose of Zispin was 15-60mg daily, which was outside the licence. Wyeth alleged that Zispin was being promoted outside the terms of its marketing authorization. The Panel noted the graph was headed 'Zispin vs venlafaxine in severe depression. Reduction in 17 item HAMD score from baseline'. It had been reproduced from Guelfi *et al* (1999) which assessed the efficacy and tolerability of Zispin and venlafaxine in hospitalised, severely depressed patients with melancholia. The study concluded that both medicines were equally effective in reducing overall symptoms of depression. A statistically significant between group difference in favour of Zispin was found for the HAMD sleep disturbance factor only. The Panel considered that the graph gave the impression that there was a statistically significant between group difference in favour of Zispin with regard to reducing the overall symptoms of depression and that was not so. A breach of the Code was ruled. The Panel noted that according to its SPC treatment with Zispin should begin with 15mg daily and that 'The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45mg.' The Panel noted that the patient population in Guelfi *et al* was severely depressed. A rapid up titration schedule was used with a dose of 45mg of Zispin after the first week of treatment. The overall mean dose of Zispin was 49.5mg. Organon had submitted that after the first two weeks of the study the dose of Zispin was increased above the licensed range in a proportion of patients. The Panel considered that it was misleading to show data comparing the products when the Zispin dosage regimen was outside the licensed dose. The Panel considered that this amounted to promotion inconsistent with the SPC and a breach of the Code was ruled.

Wyeth complained about a four page leavepiece (ref: 02755C) and a detail aid (ref: 01825B/3) for Zispin (mirtazapine) issued by Organon Laboratories Limited.

COMPLAINT

Wyeth stated that after some correspondence with Organon it had been unable to resolve two issues.

1 Depression with Anxiety

The statement on the front of the leavepiece 'Not all antidepressants are created equal – Depression with Anxiety' clearly implied that Zispin was licensed for 'depression with anxiety'. This was not so and therefore the leavepiece was misleading. The Medicines Control Agency (MCA) clearly delineated between licences for 'depression' and 'depression with anxiety', with the latter requiring robust data usually based around Hamilton Anxiety rating scales. Zispin was thus being promoted for an unlicensed indication, which contravened Clause 3.2 of the Code.

2 Zispin versus veniafaxine

The detail aid included a graph on page 2 showing the reduction in the HAMD scores of venlafaxine and Zispin in severe depression suggesting that Zispin was superior to venlafaxine though no p values were shown. In addition it was not stated that the dose of Zispin was 15-60mg daily, which was outside the licence. Thus once again Zispin was being promoted outside the terms of its marketing authorization contravening Clause 3.2 of the Code.

RESPONSE

As an introduction, Organon stated that to respond properly to the complaint it believed that it was helpful to take into account the following considerations: symptoms of depression, symptoms of anxiety, depression or anxiety, efficacy measures in clinical studies, regulatory guidance for antidepressants and mode of action of Zispin.

Symptoms of depression

Organon submitted that depression was not an illness that was easy to define. It was characterised by a range of symptoms that might or might not be present in an individual patient. In typical mild, moderate or severe depressive episodes, the patient suffered from lowering of mood, reduction of energy and decrease in activity. In addition to these symptoms, and depending upon the severity of depression, one or more of a number of other symptoms might be present: sleep disturbance of any type, changes in appetite and weight, loss of confidence or self-esteem, unreasonable feelings of self-reproach or guilt, thoughts of death or suicide, difficulty concentrating, remembering things, or making decisions and change in psychomotor activity with agitation or retardation.

Similarly, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) listed among mood disorders both major depressive episode and major depressive disorder. Individuals with major depression frequently presented with a range of symptoms including irritability, brooding and anxiety.

Depression was diagnosed if a person experienced 1) persistent feelings of sadness or anxiety, or 2) loss of interest or pleasure in usual activities, in addition to five or more of the following symptoms for at least two consecutive weeks: changes in appetite that resulted in weight losses or gains not related to dieting, insomnia or oversleeping, loss of energy or increased fatigue, psychomotor agitation or retardation, feelings of worthlessness or inappropriate guilt, difficulty thinking, concentrating, or making decisions and thoughts of death or suicide or attempts at suicide.

Depression was diagnosed only if the above symptoms were not due to other conditions (eg neurological or hormonal problems) or illnesses (eg cancer, heart attack) and were not the unexpected side effects of medications or substance abuse.

Symptoms of anxiety

Organon submitted that DSM-IV also classified anxiety disorders (a group of illnesses) comprising a number of phobias and disorders including social phobia, obsessive-compulsive disorder, panic disorders and generalised anxiety disorder. Typical symptoms included: sleep disturbances, fatigue, ritualistic behaviours as a way with dealing with anxieties, muscle aches, dry mouth, jitteriness, unrealistic or excessive worry, trembling, shakiness, unrealistic fears concerning objects or situations, sweating, dizziness, racing or pounding heart, upset stomach, tension, diarrhoea and numbness/tingling of hands, feet or other body parts.

In addition, people suffering from anxiety disorders were often apprehensive and worried that something bad might happen to themselves or loved ones. They often felt impatient, irritable and easily distracted.

A similar classification system was used by ICD-10.

Depression or anxiety?

Organon stated that a recurrent problem was the distinction between anxiety states and depressive syndromes. The two were represented by overlapping clusters of symptoms, but it was important to distinguish them in the differential diagnosis since they might differ in their prognosis and their response to particular forms of treatment.

Distinct from these two major classifications was a newly defined disorder, mixed anxiety-depressive disorder (MAD) where patients could not be diagnosed as having either a mood or an anxiety disorder but showed symptoms of both.

DSM-IV did not classify a disorder known as 'depression with anxiety'.

These classifications were almost exactly replicated in ICD-10 Classification of Mental and Behavioural Disorders. There was no classification of 'depression with anxiety'.

Efficacy measures in clinical studies

Organon stated that the Hamilton Depression Rating Scale (HAMD) was currently the most widely-used, validated scale for patient selection and follow-up in clinical studies of treatments for depression. It covered most symptoms that were associated with depression. Although variants of the scale were used, the scale was based on the evaluation of 21 items or symptoms. Another validated depression rating scale was the Montgomery Asberg Depression Rating Scale (MADRS).

Included in both of these scales were parameters such as anxiety, insomnia and tension, confirming that anxiety and insomnia were two of the many symptoms of depression.

For the avoidance of doubt, anxiety could be a symptom of depression, and patients could not be diagnosed as having both depression and an anxiety disorder.

Regulatory guidance for antidepressants

Organon was not aware of any published guidance from the MCA or the Committee on Safety of Medicines (CSM) that there should be a separate indication 'depression with anxiety'. Some authorized products (including venlafaxine) had an indication including the wording 'depression including anxiety'. This indeed reflected the strapline used in Organon's leavepiece that 'Not all antidepressants are created equal' since some antidepressants (because of their mode of action) were not effective in relieving the symptoms of anxiety in depressed patients.

Organon noted that the approval of specific wording in the summary of product characteristics (SPC) for a product did not necessarily imply a distinct indication.

Guidance from the Committee for Proprietary Medicinal Products (CPMP) advised use of DSM or ICD-10 for classification of depression, and the use of HAMD and/or MADRS rating scales in clinical studies. Section 3.2 of the CPMP guideline advised that 'Actions of medicinal products on particular somatic or psychological symptoms associated with the depressive illness, such as anxiety, … should also be determined.' Organon did of course comply with this guideline in the development of mirtazapine.

No mention was made in the guideline of a separate indication 'depression with anxiety'.

A concept paper on revision of the CPMP Guidance Note had recently been published, however there was no further guidance on the subject of the current complaint.

Mode of action of Zispin

Organon stated that in the depressed patient, levels of norepinephrine (NE) and/or serotonin (5-HT) were thought to be reduced. While most available antidepressants were thought to effect serotonin and/or norepinephrine, their pharmacological actions varied. A common pharmacological characteristic was that the increased serotonin was free to interact with a variety of post-synaptic receptors which might result in the following serotonergic side effects: 5-HT_2 = sexual dysfunction, anxiety, agitation, and insomnia and 5-HT_3 = gastrointestinal side effects such as nausea or vomiting.

Zispin was the first noradrenergic and specific serotonergic antidepressant. As with some earlier antidepressants, the pharmacological action of Zispin enhanced the release of both norepinephrine and serotonin.

In addition to its effect on increasing levels of both NE and 5-HT, the action of Zispin blocked two of the post-synaptic 5-HT receptors, 5-HT_2 and 5-HT_3.

Zispin was receptor-specific. By blocking the 5-HT_2 and 5-HT_3 post-synaptic serotonin receptors Zispin relieved depression effectively, including improvement in two of the most disruptive symptoms of depression – anxiety and loss of sleep – within the first week of therapy; full antidepressant effects might take several weeks.

In clinical trials, Zispin demonstrated superiority over placebo in certain factors of the Hamilton Depression Rating Scale, including anxiety/somatization factor, and sleep disturbance factor. The efficacy of Zispin as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with Zispin from a dose range of 5mg up to 35mg/day. Overall, these studies demonstrated Zispin to be superior to placebo on the following measures: 21-Item Hamilton Depression Rating Scale (HAMD) total score and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of Zispin over placebo was also found for certain factors of the HAMD, including anxiety/somatization factor and sleep disturbance factor. The mean Zispin dose for patients who completed these four studies ranged from 21 to 32mg/day. A fifth study of similar design utilised a higher dose (up to 50mg) per day and also showed effectiveness.

Depression with Anxiety leavepiece

The leavepiece was used by Organon's sales force in a transparent manner, by simple progression through the points illustrated.

There was plentiful evidence from the medical literature that some antidepressants had an effect on anxiety symptoms of depression, but that not all antidepressants did. Indeed some antidepressants were reported as having side-effects such as agitation. Thus the strapline 'Not all antidepressants are created equal…' was a statement of fact.

The subsequent wording in the leavepiece was chosen carefully to state 'Depression with anxiety', rather than 'Depression and anxiety' in order to avoid confusion among the target audience, and to emphasise that Organon's claim related to depressed patients (with symptoms of anxiety as part of the depressed condition).

A major property of Zispin, derived from its mode of action, and confirmed in clinical studies using the HAMD rating scale, was its effectiveness in improving anxiety symptoms of depression; as explained above, this was due to its blockade of 5-HT_2 receptors. Some other studies had further confirmed the efficacy of Zispin in treating symptoms of anxiety using the Hamilton Anxiety Rating Scale (HAMA) as also shown in the leavepiece (graph of results of meta analysis with Zispin, citalopram and paroxetine).

Equally, another major property of Zispin, derived from its mode of action, and confirmed in clinical studies using the HAMD rating scale, was its effectiveness in improving sleep, one of the symptoms of depression. Organon was not aware that 'Depression with improvement in sleep' would be regarded as a distinct clinical indication.

It was apparent from above that there was no classification of a mood disorder 'depression with anxiety'. It did not seem to Organon that separate indications should be developed for each of the symptoms of depression as indeed the disorder was typified by a range of symptoms which in fact differed from patient to patient.

The approved indication for Zispin was 'Treatment of depressive illness.'

Organon submitted that its claim was clear; Zispin was used to treat depression, and in those patients who also complained of anxiety symptoms, the validated HAMD anxiety/somatization factor demonstrated a statistically different improvement for example versus paroxetine. Therefore Organon's claim was that, when treating depressed patients with Zispin, anxiety symptoms of their depression might improve. Organon therefore denied a breach of Clause 3.2 of the Code.

Zispin versus venlafaxine

Superiority to venlafaxine

Organon stated that the graph in the detail aid showed the reduction in the HAMD scores and was identical to the graph in the original poster as presented by the investigators (Guelfi *et al* 1999). Organon had made no adjustments to the scale axes. The graph was presented in compliance with the supplementary information to Clause 7.6 of the Code. The graph was headed by the strapline 'In all types of patients', with the subheading 'Zispin versus venlafaxine in severe depression'.

There were no statistically significant differences between Zispin and venlafaxine, therefore no p-values were given. The graph presented the full reductions

on HAMD scores over the full duration of the study of both drugs.

The title of the graph did not suggest superiority for Zispin, and Organon did not agree that the graph suggested that there was superiority of Zispin over venlafaxine. When using the sales aid Organon's representatives were instructed that this study demonstrated the efficacy of Zispin in severely depressed patients. They did not claim any advantage over venlafaxine.

Organon did not regard its presentation of the data misleading in any way and denied a breach of Clause 3.2 of the Code.

Promotion of dose outside the terms of the marketing authorization

Patients in the Guelfi study were hospitalised, severely depressed patients with melancholic features, a patient group for which the investigators regarded the option of high doses of Zispin and venlafaxine appropriate. Patients with a diagnosis of anxiety disorders (DSM-IV) were excluded.

The study protocol allowed a rapid titration-up schedule for both drugs, starting with 15mg daily of Zispin. The dosage of Zispin used in at least the first two weeks of the study was up to 45mg.

Therefore use of the study and the data up to week two was valid, and could not be considered to be outside the terms of the marketing authorisation. Organon considered that modification of the graph to exclude the data beyond week two could be deemed to be a misrepresentation of the study. The findings at two weeks were in agreement with other clinical studies with Zispin showing its rapid onset of action. As stated in the SPC, 'Zispin begins to exert its effect in general after 1-2 weeks of treatment.'

A small number of patients, who were all severely depressed, received a higher dosage than 45mg. Although dosages exceeding 45mg had been used and studied, especially in this patient population, Organon had sufficient data to suggest there were not safety concerns with regard to the 60mg dose. Dose linearity had been studied and confirmed up to 80mg.

Organon denied a breach of Clause 3.2 of the Code.

PANEL RULING

Pages two and three of the leavepiece were headed 'Zispin. A unique action with anxiolytic benefits'. Page two discussed anxiety symptoms and stated that 'Zispin provided early and effective relief of anxiety symptoms, reducing the need for polypharmacy.' Treatment options for anxiety in depression were discussed. It was mentioned that the side effects of treatment with an SSRI exacerbated anxiety symptoms. Page 3 featured an illustration of Zispin's mode of action above two comparative graphs; one depicting the reduction from baseline in anxiety/somatization factor of Zispin and paroxetine, the second depicting the remission rates on HAMD of Zispin, paroxetine and citalopram.

The Panel noted that the Zispin SPC stated that it was indicated for the treatment of depressive illness. The Panel noted the submission that depression was not an illness that was easy to define. It was characterised by a range of symptoms that might or might not be present in an individual patient. The Panel noted the depression rating scales HAMD and MADRS each referred to anxiety as a parameter of depression. The Panel noted that there was a specific scale for assessing anxiety, the Hamilton Anxiety Rating Scale. The Panel considered that whilst depression and anxiety might coexist they were nonetheless distinct disorders. The Panel noted that the SPCs of some antidepressants had an express reference to anxiety in their licensed indications. Zispin did not. The Panel noted the difficulties in defining depression. The Panel considered that the statement on the front of the leavepiece 'Not all antidepressants are created equal. Depression with anxiety' gave the impression that Zispin had a specific licence for anxiety and that was not so. This impression was not negated by the content of the leavepiece. A breach of Clause 3.2 was ruled. This ruling was appealed by Organon.

The Panel then considered the graph at issue in the detail aid. The Panel noted the graph was headed 'Zispin vs venlafaxine in severe depression. Reduction in 17 item HAMD score from baseline'. The graph was referenced to data presented at the 12th ECNP meeting (1999). The graph indicated a difference in favour of Zispin at all timepoints (8 weeks). No p value was provided. It was thus not possible to assess the significance of the difference. The Panel noted that the graph was reproduced from Guelfi *et al* (1999) which assessed the efficacy and tolerability of Zispin and venlafaxine in hospitalised, severely depressed patients with melancholia. The study concluded that both medicines were equally effective in reducing overall symptoms of depression as shown by a clinically relevant reduction in group mean 17 HAMD scores at the end of the treatment period. The between group difference was 2.5 points on the HAMD scale. A statistically significant between group difference in favour of Zispin was found for the HAMD sleep disturbance factor only. The Panel considered that the graph gave the impression that there was a statistically significant between group difference in favour of Zispin with regard to reducing the overall symptoms of depression and that was not so. The Panel noted that Wyeth had referred to Clause 3.2 in its complaint. The Panel considered that the matter was more appropriately dealt with under Clause 7.2 and a breach of Clause 7.2 of the Code was ruled. This ruling was not appealed.

The Panel noted that according to its SPC treatment with Zispin should begin with 15mg daily. 'The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45mg.' The Panel noted that the patient population in Guelfi *et al* was severely depressed. A rapid up titration schedule was used with a dose of 45mg of Zispin after the first week of treatment. The overall mean dose of Zispin was 49.5mg. The Panel noted Organon's submission that after the first two weeks of the study the dose of Zispin was increased above the licensed range in a proportion of patients. The Panel considered that it was misleading to show data comparing the products when the Zispin dosage regimen was outside the

licensed dose. The Panel considered that this amounted to promotion inconsistent with the SPC and a breach of Clause 3.2 of the Code was ruled. This ruling was not appealed.

APPEAL BY ORGANON LABORATORIES

Organon stated that it did not agree with the Panel's ruling that the leavepiece was in breach of Clause 3.2 of the Code with regard to 'Depression with anxiety'. Organon's initial submission discussed extensively the difficulty of diagnosing mental disorders. For completeness the information submitted to the Panel with regard to symptoms of depression, symptoms of anxiety, the differential diagnosis of the two conditions, efficacy measures in clinical studies, mode of action of Zispin and its efficacy in clinical trials was repeated in the appeal. Organon added that Zispin had an exceptional safety profile in overdose which was an important consideration in depressed patients, especially those with significant anxiety symptoms. Therefore both the pharmacological profile, and the clinical data on Zispin, confirmed its effect on depression, including the anxiety symptoms of depression.

Organon noted that the Panel had accepted that depression was not an illness that was easy to define, and that it was characterised by a range of symptoms that might or might not be present in an individual patient.

Organon referred to the Panel's view that 'the depression rating scales HAMD and MADRS each referred to anxiety as a parameter of depression' and 'The Panel noted that there was a specific scale for assessing anxiety, the Hamilton Anxiety Rating Scale'. Organon stated that the implications of this observation by the Panel were not clear. The HAMA scale could indeed be used as an additional scale to evaluate the effect of antidepressants on anxiety symptoms of depression, and studies with mirtazapine were available. Nevertheless use of the HAMA scale did not imply that this scale must be used to evaluate efficacy in the treatment of depression.

With regard to the view that 'The Panel considered that whilst depression and anxiety may co-exist they were nonetheless distinct disorders', Organon submitted that this was indeed an incorrect interpretation of the classification systems. As discussed, the clinical conditions could only co-exist in mixed anxiety-depressive disorder, a new and rare classification. The Panel had confused the fact that it was the symptoms of anxiety and the symptoms of depression that could co-exist, not the conditions themselves. It was not at all clear from the wording used by the Panel that it had clearly distinguished that anxiety could be, and was usually, a symptom of depression rather than a co-existing condition.

With regard to the view that 'The Panel noted that the SPCs of some antidepressants had an express reference to anxiety in their licensed indications' Organon submitted that there would appear to be an implied assumption that the wording in an SPC was sufficient to define a new or distinct clinical disorder. It was clear that patients could not be diagnosed with a condition 'depression with anxiety' or 'depression associated with anxiety' or 'depression accompanied by anxiety' since these disorders did not exist as separate clinical entities. It was equally certain that these formulations of words were not intended to describe patients who were diagnosed as having mixed anxiety depression. It was interesting to ponder what type of patients would be prescribed such medications. Organon could be certain that the intention was that they were diagnosed as having depression.

Organon repeated that 'depression associated with anxiety' was not a distinct clinical indication recognised in the field of psychiatry. It was not described in the pre-eminent classifications systems for mental disorders, DSM-IV and ICD-10. It was accepted that depression and anxiety were distinct disorders. It was accepted that over 80% of depressed patients displayed symptoms of anxiety.

It was also relevant to consider if the wording 'depression accompanied by anxiety' was intended to include the same meaning as 'anxiety associated with depression'. Traditional logic would suggest that the former described a depressive disorder where symptoms of anxiety might be present, ie 90% of all depressed patients. The latter could then be deduced as being an anxiety disorder where symptoms of depression could be present. It was interesting, and indicative of confusion, that both forms of wording were used in the same advertisement for Efexor XL, an advertisement that announced what Wyeth appeared to believe was a new indication for its product.

Claims in the leavepiece

Organon pointed out that the approved indication for Zispin was 'Treatment of depressive illness.' Based upon the well-established fact that almost 90% of depressed patients complained of anxiety symptoms, the leavepiece identified a number of claims for Zispin.

'Zispin – A unique action with anxiolytic benefits'. This wording introduced the pharmacological profile of the medicine. The leavepiece explained the mechanism of action of Zispin that accounted for early relief of anxiety symptoms.

'Zispin provides early and effective relief of anxiety symptoms'. This wording conveyed the benefit of this effect by reducing the need for polypharmacy.

Instructions for use of the leavepiece

The instructions provided to Organon's sales force for use with this leavepiece were as follows:

> 'Zispin vs paroxetine on anxiety symptoms.
>
> Besides improving sleep (due to 5-HT_2 blockade) Zispin also treats anxiety symptoms effectively (again due to 5-HT_2 blockade). This is clearly demonstrated when (in the study vs paroxetine) the anxiety/somatization factor in the HAMD (items 4, 9, 12-15) is analysed separately. On this parameter, Zispin is significantly more effective than paroxetine in treating anxiety symptoms in depression. This

is also clearly demonstrated using the HAMA scale.

'This means that, when taking Zispin, patients will benefit from rapid relief of anxiety symptoms which will assist patient compliance.'

Three things are important to realise in this respect.

1) Anxiety is an important symptom of depression, which is experienced by approximately 80% of depressed patients.

2) The above mentioned (sub) analysis thus looks at how effective Zispin is compared to paroxetine in treating anxiety symptoms associated with depression and not at anxiety disorders (eg panic disorder).

3) Because paroxetine has a licence to treat an anxiety disorder (obsessive-compulsive disorder) and Zispin has not, doctors sometimes prescribe paroxetine when they see a depressed patient in which anxiety symptoms are predominant. In fact they confuse anxiety as a symptom of depression with an anxiety disorder.'

Organon submitted that it was clear from these instructions that Organon consistently referred to the effectiveness of Zispin in treating anxiety symptoms of depression and the effectiveness of Zispin was compared with paroxetine in treating anxiety symptoms associated with depression and not anxiety disorders.

Claims versus indications

Organon stated that claims for medicines were allowed under the conditions of Clause 7 of the Code. Claims were commonly based upon the clinical properties, or lack of them of the medicine. Such claims would generally be based upon the effects of the medicine upon the disease in question. Clearly a simplistic claim would be that an antihypertensive agent reduced blood pressure. Associated with this main claim, there might well be further claims such as that for Adalat LA 'Proven to reduce morbidity and mortality'.

In the case of Zispin, and as a consequence of its pharmacological profile, a number of claims were possible. Many of these claims arose from the measurement of the effectiveness of Zispin in the treatment of depression. Use of the HAMD or MADRS rating scales provided a measure of the efficacy of Zispin in treating major depression. This measure of effectiveness in depression, using rating scales, was in fact an amalgam, providing a complex profile of how Zispin performed over a range of symptoms associated with depression.

Analysis of the clinical data for Zispin illustrated, for example, that it was effective in treating the symptom insomnia as a result of its pharmacological properties. This allowed Organon to make the claim that 'Zispin improves sleep', or 'Zispin is effective in treating depression with associated insomnia'. This claim was based on evidence from efficacy studies. Zispin's effect on sleep was an intrinsic and inextricable part of its measured efficacy in depression.

Other examples could be given, however the case in point related to use of such a claim in relation to anxiety symptoms of depression.

A major property of Zispin, derived from its mode of action, and confirmed in clinical studies using the HAMD rating scale, was its effectiveness in improving anxiety symptoms of depression. This effect derived from the blockade of 5-HT_2 receptors. Another study had further confirmed the efficacy of Zispin in treating symptoms of anxiety using the Hamilton Anxiety Rating Scale (HAMA) as also shown in the leavepiece. Zispin's effect on anxiety was an intrinsic and inextricable part of its measured efficacy in depression.

Overall conclusion

Organon's conclusion was that it was fully entitled to make claims on the clinical profile of its medicine when, as in this case, it had promoted the medicine in its licensed indication; shown it to be effective using internationally accepted criteria; made claims based on the evidence from efficacy studies.

Organon was not aware of any published guidance from the MCA or the CSM that there should be a separate indication along the lines of 'depression with anxiety'. Some authorised products (including venlafaxine) had an indication including the wording 'depression including anxiety'. Organon noted that the approval of specific wording in the SPC for a product did not necessarily imply a distinct indication. The difficulty of defining terminology in psychiatric disorders had led to the extremely complex classification systems in ICD-10 and DSM-IV. Organon re-emphasised that neither of the classification systems, which included a large number of categories of mental illness, included the wording chosen in the indications section of a number of UK marketed products.

Organon's marketing claim was clear; Zispin was used to treat depression, and in those patients who also complained of anxiety symptoms, the validated HAMD anxiety/somatization factor demonstrated a statistically different improvement. Therefore Organon's claim was that, when treating depressed patients with Zispin, anxiety symptoms of their depression might improve.

Organon therefore denied a breach of Clause 3.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted the submission that many diseases and conditions were defined by the presence of symptoms and that depression was characterised by a range of symptoms including anxiety symptoms. The Appeal Board also noted that the DSM-IV classifications did not include a disorder of 'depression with associated anxiety'. The Appeal Board noted that the indications sections in the SPCs for antidepressants varied; some were licensed for depressive illness including depression accompanied by anxiety, others were also licensed for anxiety

disorders. Zispin was licensed for the treatment of depressive illness. The Appeal Board considered that the statement on the front of the leavepiece 'Not all antidepressants are created equal – Depression with anxiety' gave the impression that Zispin had a specific licence for anxiety and that was not so. The claim at issue was inconsistent with the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2 of the Code. The appeal was unsuccessful.

During its consideration of this case the Appeal Board was concerned that a claim that Zispin had 'a unique action with anxiolytic benefits' was misleading. The claim implied that the unique action led to anxiolytic benefits and this was not so as according to the representatives the unique action related to its pharmacological effects. The Appeal Board was also concerned that the description of potential outcomes of treatment with an SSRI as 'SSRI side effects (e.g. activation, agitation, sleep disturbances) exacerbate anxiety symptoms' gave the impression that these transient effects were permanent and that was misleading. The Appeal Board asked that its concerns be drawn to the company's attention.

Complaint received **4 August 2000**

Case completed **6 November 2000**

CASE AUTH/1063/8/00

GLAXO WELLCOME v 3M HEALTH CARE

Communications about Qvar to health authorities and a journal advertisement

Glaxo Wellcome complained about a letter sent by 3M Health Care to regional health authority chief executives, chairmen, directors of public health, prescribing advisers and finance directors. The letter discussed changing patients to Qvar and the associated savings. Glaxo Wellcome also complained about a 'switch model' for changing patients to 3M Health Care's CFC-free beclomethasone diproprionate (BDP) inhaler, Qvar, and a journal advertisement.

Glaxo Wellcome alleged that the letter was inaccurate and misleading. It was not possible for the majority of patients prescribed Flixotide to switch to Qvar. More than half the patients currently prescribed Flixotide were either children under 12 (Qvar was not licensed for this age group) or were on dosages equal or greater than 1000mcg/day for which there was no directly corresponding Qvar dosage.

The Panel was concerned that the letter did not make it clear that the calculation was based on switching all patients. This was not possible as Qvar could not be used in patients under the age of 12 or requiring more than 800mcg/day, as stated in a footnote to the letter. No account was taken of the costs of switching although patients on CFC corticosteroids would have to be switched to CFC-free products due to the phasing out of CFC-containing products. The Panel considered that the letter was misleading as insufficient detail had been given about the calculation of the estimated cost savings. A breach of the Code was ruled.

Similar allegations were made about the switch model document which the Panel considered was in effect promotional material. The switch model was based on medicine acquisition costs alone. The Panel considered that the use of the model to promote switching patients to Qvar was misleading given the failure to include any detail about the potential costs of transition or the reasons why the costs of the transition were not relevant. A breach of the Code was ruled.

Glaxo Wellcome alleged that a claim in the advertisement 'In symptomatic patients, Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone [Flixotide] (1000mcg/day) …' was misleading. It was based on the per protocol population. Glaxo Wellcome referred to the high withdrawal rate in the study and its view was that it could be more appropriate and representative to use the intention-to-treat (ITT) population. The study concluded that '[Qvar] 800mcg/day provided at least the same efficacy as 1000mcg/day [Flixotide] in patients with moderate-to-severe symptomatic asthma'. Glaxo Wellcome alleged that the claim lacked a sound statistical basis and was a misleading representation of the clinical significance of the findings.

The Panel did not consider that the claim was a fair reflection of the data. Given the purpose of the study and the equivalence demonstrated by the ITT results, it was not appropriate to use the differences in the per-protocol analysis as a basis for a claim of superiority for Qvar over fluticasone. A breach of the Code was ruled.

Glaxo Wellcome alleged that a claim in the advertisement '… and it can also save you up to 66% of the cost of an equivalent fluticasone propionate prescription' was ambiguous, unfair and misleading. The claim followed another claim which referred to doses of Qvar (800mcg/day) and HFA-fluticasone (1000mcg/day). Glaxo Wellcome stated that it was reasonable to assume that the comparison referred to these doses. This was not so as the figure of 66% had been obtained by the selection of the most expensive Flixotide device/dose combination with which to achieve a dose of 400mcg/day comparing this with the cheapest method of achieving this dosage with Qvar. The Panel considered that the claim was misleading. It was not based on the doses given in the advertisement in the first part of the sentence. No details of the inhalers were provided. The difference in cost of fluticasone compared with Qvar varied from 12% to 71%. A breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about a letter sent by 3M Health Care Limited to the primary care director at an NHS regional office, a 'switch model' and a journal advertisement (ref: 0200/QV/001/018).

A Letter entitled 'We will have to decide what we can't fund' and the switch model

Glaxo Wellcome stated that it had serious concerns about a letter to the primary care director at a NHS executive regional office and a model of cost savings if patients taking inhaled corticosteroids were switched to 3M Health Care's CFC-free beclomethasone dipropionate (BDP) inhaler (Qvar).

3M Health Care stated that the letter in question was sent to regional health authorities for the attention of chief executives, chairmen, directors of public health, prescribing advisers and finance directors. It gave information concerning potential cost savings in the prescription of inhaled corticosteroids. Glaxo Wellcome also raised concerns about the validity of the switch model on which the information was based.

1 Statement 'We will have to decide what we can't fund'

COMPLAINT

Glaxo Wellcome stated that in a previous case, Case AUTH/1015/4/00, it was stated that a radio interview was misleading in the claims regarding cost savings. It was ruled that 'the costs of the switch had not been taken into account. For example the time taken to explain the switch and to demonstrate the new device to patients. The data was based on substituting Qvar for all inhaled corticosteroid preparations'. Glaxo Wellcome considered that the same calculations had been used to provide the cost comparisons in this document.

Glaxo Wellcome also pointed out that for a majority of the patients currently prescribed Flixotide, it was not possible to make a direct switch to Qvar. More than half of the patients currently prescribed Flixotide were either children below the age at which Qvar was licensed or were on dosages equal to or greater than 1000mcg/day for which there was no directly corresponding dosage with Qvar. Therefore, these patients would not be able to switch to Qvar within the terms of its current licence.

In light of the above, Glaxo Wellcome alleged that the letter was inaccurate and misleading and in breach of Clause 7.2 of the Code.

RESPONSE

3M Health Care noted that the complainant referred to Case AUTH/1015/4/00. That case referred to a discussion of the overall findings of the modelling of potential cost savings with specific reference to the estimate of savings of interest to the regional broadcaster requesting the interview. The salient point was that the interview was considered misleading. However, no ruling of a breach of the Code was made on the switch model itself.

3M Health Care confirmed that the estimated cost savings referred to in this letter were derived from the switch model. In its view Glaxo Wellcome had selectively quoted from Case AUTH/1015/4/00.

In its letter to the primary care director 3M Health Care clearly stated in reference 3 the dosage and age restrictions that had been assumed, and very clearly stated in the final paragraph that the savings quoted were estimates. 3M Health Care then gave the recipient the opportunity to go into more detail with 3M Health Care. The clearly labelled upper dose limit of Qvar was 800mcg per day. No claim was made for comparative efficacy against fluticasone products available in the UK at the time the letter was sent that was not in accordance with the summary of product characteristics (SPC) which suggested a 1:1 equivalence ratio on a microgram for microgram basis.

3M Health Care therefore believed that its letter gave a fair description of its product's place within asthma treatment, considered the assumption inherent in Qvar's current lack of approval in children and its upper dose limit and denied that the letter was misleading or inaccurate.

PANEL RULING

The Panel noted that the previous case, AUTH/1015/4/00 concerned radio broadcasts by 3M Health Care about asthma inhalers. The complaint from Glaxo Wellcome referred to promotion to the public, the use of the word 'new' and a misleading reference to the increases in the costs of inhalers. The Panel had not considered a complaint about the study itself; 3M Health Care stated that it had launched a press release initiative following findings from the switch model study. The Panel ruled, *inter alia*, that the interview was misleading as the qualifications in the study had not been given. It had been stated in the interview that a total of over £50 million could have been saved but the basis of the data had not been explained ie the data was based on a switch of all patients. No mention had been made in the interview regarding the treatment of costs that might arise from such a switch nor that the data was based on substituting Qvar for all inhaled corticosteroid preparations.

Turning to the present case, the Panel examined the details of the switch model provided by 3M Health Care. The aim was to identify the cost savings that accrued to primary care groups (PCGs) if Qvar was used instead of other formulations of inhaled corticosteroids. The Panel noted that the switch model assessed the cost of switching all patients on inhaled corticosteroids to Qvar. The report noted that the model was not an unrealistic one for developing simplistic arguments for the modification of resource allocation at the population level over the prescribing period. The authors referred to the model's obvious limitations. The report noted that it should be clearly understood that Qvar was only licensed in the 12 years and over age group and had an upper dose limit of 800mcg/day (equivalent to 2000mcg/day of CFC-containing beclomethasone dipropionate). Some patients could not or would not use a metered dose

inhaler and as Qvar contained a small quantity of ethanol it might not be acceptable to some religious groups.

The Panel noted that the letter included a calculation of the potential savings for the relevant region which were then used to calculate the number of practice nurses that could be employed for one year, the number of patients with Alzheimer's disease that could be treated for one year and the number of patients with high cholesterol that could be treated for one year with statins.

The statement in the letter 'Switching to the CFC-free beclomethasone Qvar at recommended doses …' was referenced to a footnote that 'Qvar was not currently licensed for patients under 12 and the maximum recommended dose was 800mcg a day'. The Panel noted that it was a well established principle under the Code that material could not be qualified by the use of footnotes. The letter concluded that the calculations were estimates of what the potential savings could be.

The letter advocated switching patients on inhaled corticosteroid preparations to Qvar. The Panel was concerned as the letter did not make it clear that the calculation was based on switching all patients. It was not possible to switch children under 12 to Qvar nor would Qvar be suitable for patients requiring more than 800mcg/day. There was no account taken of the costs of switching although the Panel noted that patients on CFC corticosteroids would have to be switched to CFC-free corticosteroids due to the phasing out of CFC-containing products. The Panel considered that the letter was misleading as insufficient detail had been provided about the calculation of the estimated cost savings. A breach of Clause 7.2 of the Code was ruled.

2 Switch model

COMPLAINT

Glaxo Wellcome stated that this was a model of cost savings if patients taking inhaled corticosteroids were switched to Qvar. This model had been circulated by fax by 3M Health Care.

For the same reasons as stated in the complaint in A1 above, Glaxo Wellcome regarded the claims relating to the cost advantages of switching to Qvar to be misleading and in breach of Clause 7.2 of the Code.

As 3M Health Care had refused to consider withdrawing these materials in spite of the previous ruling on the same claims used elsewhere, Glaxo Wellcome asked the Authority to consider requesting that steps should be taken by 3M Health Care to withdraw these materials from health authorities and other health professionals to whom they had been circulated.

RESPONSE

3M Health Care stated that the complaint seemed to be based on a facsimile copy of the letter sent to a primary care director at a NHS executive office. To 3M Health Care's knowledge all planned recipients of this mailing received letters not facsimiles. Only one facsimile was sent out after this mailing, in specific response to a request for this from the region's prescribing advisor.

This project was a medicine acquisition budget impact analysis. The aim of the switch model was to identify potential savings in medicine acquisition costs that might accrue if Qvar was used instead of other formulations of inhaled corticosteroids. The analysis was conducted from the perspective of a budget holder for prescription medicines. The analysis was conducted to assess the cost impact of medicine changes on these prescription budgets. This was identified in the letters.

3M Health Care provided copies of the internal paper which described the switch model methodology. The papers provided covered the background, project aims, data sources, scenarios, Qvar switch factors (the basic 'equivalence' ratios for the inhaled steroids and delivery systems from which 3M Health Care calculated costs in the model) and the model itself. The listings in the report that pertained to each primary care group or region for which model projections were calculated had not been provided as these were simply numeric tables based on the model and were not considered germane to the case. Prescribing information for Qvar was included.

In the final paragraph of the data sources section, 3M Health Care again clearly acknowledged the limitations and assumptions inherent in the model including the lower age limit and upper dose limit of Qvar use, and the fact that some patients could not or would not use pressurised metered dose inhalers. 3M Health Care's analysis was not designed to assess the impact of prescribing Qvar on total direct or indirect healthcare expenditure. Therefore, no allowance was made in the switch model for costs beyond medicine acquisition costs, such as a healthcare professional's time to explain the reasons behind the mandated switch to CFC-free aerosols, nor the time required to teach the use of a new inhaler device. If it were to conduct an analysis of the effect of switching to Qvar on total healthcare expenditure, 3M Healthcare believed that these types of costs might be cost neutral as they might be equally distributed between groups for the following reasons.

i) The majority of patients were using the standard 'press and breathe' metered dose inhaler (MDI) and could be switched to a Qvar press and breathe inhaler used in the same way. No inhaler technique teaching was required. In both the Global Initiative on Asthma (GINA) Guidelines and the British Guidelines on Asthma Management (Thorax 1997:52:Suppl) best practice included a check of inhaler technique as part of regular follow-up. The majority of primary care physicians claimed fees for chronic care of asthma under the Red Book also indicating that regular follow up was being carried out in practice. Thus teaching the use of a new inhaler was not a specific cost of switching.

ii) Patients unable to properly use the standard MDI would be transferred to another system (usually a breath actuated device) as part of normal care. The minority of patients in 3M Health Care's model who

would transfer from the standard MDI to the 3M breach actuated device did not therefore represent an additional cost of switch within this model.

iii) The transition to CFC-free inhalers (a Government Policy under DETR September 1999) had already happened in the case of salbutamol, and would happen in the next few years with inhaled steroids.

Given that the switch model was purely a medicines acquisition budget impact analysis, the costs of explaining transition were not germane. Since 3M Health Care had clearly stated this perspective in its communications, it did not believe that its analysis or subsequent communications pertaining to the analysis were inaccurate or misleading. Indeed, 3M Health Care contended that its medicines acquisition budget impact model was comprehensive, robust and would stand scrutiny.

Finally the switch model was only able to identify a prescription for inhaled steroids, not the number of steroid inhalers on each prescription. The model thus assumed that only one inhaler was provided per prescription. It was very reasonable to assume that on a number of prescriptions two or possibly three steroid inhalers would be provided. Thus the model projections might well be a significant underestimate of potential savings.

To conclude 3M Health Care submitted that the switch model used in calculating potential savings had its limitations clearly discussed in the text. The limitations on inclusion of fixed costs associated with the physical switch had been considered, as had the likely underestimate inherent in the model. 3M Health Care therefore believed that the model and its letter were eminently fair and balanced, and were not in breach of Clause 7.2 of the Code. For these reasons, 3M Health Care did not accept the suggestion from Glaxo Wellcome that either the letters or the switch model should be withdrawn.

PANEL RULING

The Panel noted that Glaxo Wellcome had supplied only 3 pages of the switch model document. 3M Health Care had supplied a document consisting of 14 pages. The document supplied by 3M Health Care included prescribing information and the reference 0499/QV/022/004.

The Panel considered that the document giving details of the switch model was in effect a piece of promotional material. The Panel noted that the document gave full details of the basis of the calculations. No mention was made of the costs of switching patients to Qvar. The Panel noted that patients would have to be switched to CFC-free inhaled corticosteroids due to the phasing out of CFC-containing products. Nevertheless there was no mention of these transition costs. The view of 3M Health Care was that the costs of explaining transition were not germane. The Panel noted that the Qvar summary of product characteristics (SPC) stated that patients should be instructed in the proper use of their inhaler and advised that Qvar may have a different taste and feel than a CFC inhaler. The Panel noted that the switch model was based on medicine acquisition costs alone. The Panel considered that the use of the model to promote switching patients to Qvar was misleading given the failure to include any detail about the potential costs of transition or the reasons why the costs of transition were not relevant. A breach of Clause 7.2 of the Code was ruled.

B Journal advertisement ref: 0200/QV/001/018

The advertisement stated that 'In symptomatic patients, Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone (1000mcg/day) and it can also save you up to 66% of the cost of an equivalent fluticasone prescription'.

3M Health Care stated that the advertisement had appeared in Pulse and General Practitioner at various times in May and June. No use had been made of it in journals since that time.

1 Claim 'In symptomatic patients, Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone (1000mcg/day) …'

COMPLAINT

Glaxo Wellcome stated that this claim had been derived from study BRON-1267 which was an open-label, equivalence study designed to compare inhaled Qvar 800mcg/day with inhaled Flixotide 1000mcg/day over a period of eight weeks.

The claim clearly implied that in several clinical outcomes, Qvar 800mcg/day was significantly more effective than Flixotide 1000mcg/day.

In Glaxo Wellcome's initial letter to 3M Health Care it noted that the study used in support of this claim was set up as an equivalence study. The results of all of the outcome measures in the intention-to-treat (ITT) population confirmed the equivalence of the two treatment groups at endpoint (with the exception of eosinophil count and eosinophil cationic protein). In only one clinical parameter was there a difference, the mean change from baseline in days free from all asthma symptoms at week 3, but this difference was not maintained at week 8. Therefore, on the basis of these results, there was no consistent evidence that Qvar 800mcg/day could significantly improve clinical outcomes over Flixotide 1000mcg/day.

A difference was claimed in terms of morning peak expiratory flow rate (AM PEF) for the per-protocol population after 8 weeks. However, following a review of the study methodology, Glaxo Wellcome was concerned as to the validity of the statistical analysis conducted on the per-protocol population and expressed these concerns to 3M Health Care. That company's response stated that the null hypothesis, that the mean change from baseline in AM PEF at the end of the study for patients on Qvar 800mcg/day was unequal to that of Flixotide 1000mcg/day, could not be rejected in the per-protocol analysis, and therefore the two treatments were not equivalent. The reason for this was that the 90% confidence interval (CI) for the difference between the two treatment means, stated by 3M Health Care to be 2.66L/min, 31.10L/min, did not fall wholly within the protocol-defined equivalence limit of ± 25L/min.

This logic appeared to derive from analysis of bioequivalence data, in which the whole of the 90% CI must lie within 80 to 125% of the mean value for the index product for bioequivalence to be proven statistically. However, it was inappropriate to extrapolate this argument to the clinical situation.

Glaxo Wellcome stated that for the two products to be clinically non-equivalent, the 90% CI for the mean difference in AM PEF must lie wholly outside the predefined clinically relevant range (defined as ±25L/min in the study). If part of the 90% CI lay within this range, as it did in the study (in fact most of it did), there was a >5% chance that the true difference lay within this range and the possibility that Flixotide and Qvar were equivalent could not be excluded. Thus, the confidence interval showed the results to be inconclusive, particularly since the ITT population showed clinical equivalence for this endpoint. Therefore, 3M Health Care's response had not altered Glaxo Wellcome's view that the claim lacked a sound statistical basis.

Glaxo Wellcome also believed that the claim was misleading as to the clinical significance of the study findings. The pre-defined criterion for equivalence in the study was ±25L/min, a difference greater than this being indicative of a significant treatment difference, both statistically and clinically. The mean treatment difference for the ITT sample was 12L/min and for the per-protocol sample was 14L/min. Neither of these treatment differences was greater than 25L/min (or indeed the 15L/min commonly accepted as a clinically relevant difference). Therefore they could not be deemed clinically significant, even if they were statistically so (and as Glaxo Wellcome had discussed, it did not believe there was a valid statistically significant difference between the two groups).

In addition, Glaxo Wellcome had concerns about the number of protocol violators from both groups, who would have been excluded from the per-protocol population, particularly since there was a higher number of withdrawals from the Qvar group than the Flixotide group (43 compared with 34). This could have biased the analysis in favour of Qvar.

Overall, Glaxo Wellcome believed that to base a claim of superiority on the per-protocol population was misleading and an unfair representation of the findings of the study, as it was based only on non-protocol violators and therefore only applicable to patients without these major violations. Bearing in mind the high withdrawal rate, Glaxo Wellcome considered that it would be more appropriate and representative to use the ITT population.

Even taking the per-protocol result into account, the overall results of the study suggested that the two treatments were equivalent, and the claim of significant improvement in clinical outcomes was exaggerated and misleading. Indeed, the authors concluded only that '[Qvar] 800mcg/day provided at least the same efficacy as 1000mcg/day [Flixotide] in patients with moderate-to-severe symptomatic asthma' and therefore the claim should be amended to reflect the clinical data in a more balanced and accurate way.

Glaxo Wellcome alleged that the claim was in breach of Clause 7.2 of the Code as it lacked a sound statistical basis and was a misleading representation of the clinical significance of the findings.

RESPONSE

3M Health Care stated that Glaxo Wellcome had suggested that the difference seen between Qvar and fluticasone in the per-protocol analysis of change from baseline morning peak expired flow lacked a sound statistical basis. Glaxo Wellcome further questioned the significance of overall changes and rates of change of a symptom (percentage of days free from asthma symptoms).

i) The per-protocol analysis of change from baseline peak expired flow, lacks a sound statistical basis.

3M Health Care stated that the claim was referenced to data on file BRON-1267 and the data in Wettengel R *et al* 2000, a poster recently presented at the American Thoracic Society meeting in Toronto.

The study was designed with the null hypothesis that the mean change from baseline in AM PEF at the end of the study for patients on Qvar 800mcg/day was unequal by more than +/-25L/min to that of fluticasone 1000mcg/day. The rejection of this hypothesis would imply equivalence of the two active treatments (ie if a 90% CI constructed for the mean difference between the two treatments was completely contained within an interval of +/-25L/min). Primary analyses were performed on the intent-to-treat (ITT) study population while supportive analyses of the primary efficacy parameter were performed on a per-protocol population (subjects with no major protocol violation).

3M Health Care stated that the per-protocol population data was also analysed to reject the null hypotheses and show equivalence between the two active treatments. It did not however confirm equivalence for the primary efficacy parameter (AM PEF) as the mean change from baseline in AM PEF at week 8 was significantly greater in the Qvar group (n=58) than the fluticasone group (n=63). Statistical analysis of the difference between the mean values showed that the results were not equivalent (90% CI; 2.66,31.10), with superiority for Qvar as the CI was not contained within the defined equivalence limit of +/- 25L/min.

With regard to clinical significance as opposed to statistical significance, 3M Health Care disagreed that the difference was not clinically significant. The study used this equivalence limit as significant statistically and clinically for the population in this study. The null hypothesis that the mean change from baseline in AM PEF at the end of the study for patients on Qvar 800mcg/day was unequal to that of fluticasone 1000mcg/day could not be rejected on the per-protocol analysis. This was well above the minimum accepted difference of 15L/min. Indeed, had the study stipulated that the 90% CI constructed for the mean difference between the two treatments be contained within +/- 15L/min as the limit equivalence, then even the intention-to-treat population analysis would have found the two treatment arms to be non-

equivalent in favour of Qvar. The difference in the mean change (SE) from baseline in AM PEF at the week 8 visit for the ITT population was 29.59 (5.19) L/min for Qvar and 17.13 (5.45) L/min for fluticasone; a difference of 12.46 L/min (90% CI; -0.02, 24.91).

With regard to the usage of the per-protocol analysis, this analysis excluded all patients with major protocol violations and therefore, for assessment of statistical equivalence, was a more rigorous analysis. A claim based on this analysis would therefore have a sound statistical basis and abided by Clause 7.2 of the Code.

ii) A significant difference in change from baseline in percentage of asthma free days is not a significant clinical outcome as the difference is not seen at the end of the study.

3M Health Care stated that the data from study 1267-BRON and the Wettengel poster showed the symptomatic improvements in the study. The time points shown represented early improvements in symptoms (at week 3 of treatment) and at the end of the study. The histograms of the symptom improvements showed significant improvements from baseline for both products in most of the symptoms. In 'Daily Asthma Symptoms' at week 3 this 'conglomerate' measure also showed a significant difference between the products. Over the full 8 week study period an increasing effect was seen. This could only be interpreted as a clear indication that treatment with Qvar produced the desire clinical improvement in symptoms at an earlier time point than fluticasone and that after a longer period of treatment both products continued to have an effect which at its peak was similar. 3M Health Care believed that an improvement in patient symptoms, as early as possible, was clinically important in asthma therapy. A significant difference between two products in such a measure, during a period when a change (increase in dose) of treatment was effected to regain asthma control, constituted a significant improvement in a clinical outcome. Again, in the data presented in the Wettengel poster, markers of inflammation (both blood eosinophils and eosinophilic cationic protein levels) were significantly reduced with Qvar compared with fluticasone. Such markers were hard to put into clinical context but in view of the results seen in improved lung function and symptom parameters 3M Health Care believed that they added further weight to its claim.

In conclusion 3M Health Care could not agree that the statistical basis behind the claim was unsound, misleading or a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the BRON-1267 study (data on file and poster) had the primary objective to demonstrate clinical equivalence regarding efficacy and safety of Qvar 800mcg daily and fluticasone 1000mcg daily in symptomatic patients.

Two hundred patients were enrolled. The primary efficacy parameter was morning peak respiratory flow (AM PEF) measurement. The secondary efficacy variables were PM PEF, daily variation of PEF, asthma symptoms, sleep disturbance scores and use of short acting beta-agonist medication. The primary analysis tested the null hypothesis that the mean change from baseline in AM PEF of Qvar was unequal by more than +/-25L/min to that of fluticasone. The study stated that the rejection of this hypothesis implied equivalence of the two active treatments. For the comparison a 90% confidence interval for the mean difference between the two treatments was constructed. The mean change from baseline in the Qvar patients was considered equivalent to the mean change from baseline of the fluticasone patients if this 90% confidence interval was completely contained within an interval of ± 25L/min. The results for the ITT population showed an equivalent mean change from baseline at week 8 in AM PEF for Qvar of 29.59L/min and for fluticasone of 17.13L/min and equivalence was concluded. This was not confirmed by the per protocol analysis where the mean change in baseline was 34.84L/min for Qvar compared to 20.63L/min for fluticasone. The confidence interval of Qvar – fluticasone was outside the stated ± 25L/min. Seventy-nine (39.5% of the randomized population) presented major protocol deviations. The main reason for exclusion from the per protocol population was bad compliance. The study (data on file) concluded that a total daily dose of Qvar was found to be at least equivalent to a daily dose of 1000mcg of fluticasone concerning lung function parameters and symptom control. The per protocol population could show significantly better AM PEF values in favour of Qvar. The poster concluded that Qvar provided at least the same efficacy as fluticasone in patients with moderate to severe asthma.

The Panel noted that the study referred to a difference between the products at week 3 in relation to the mean change from baseline in percentage of days free from all daytime asthma symptoms which was reported as being significantly greater in the Qvar group than in the fluticasone group ($p = 0.03$). There was no statistically significant difference in this parameter at week 8.

The Panel did not consider that the claim was a fair reflection of the data. The Panel considered given the purpose of the study and the equivalence demonstrated by the ITT results, it was not appropriate to use the differences in the per protocol analysis as a basis for a claim of superiority of Qvar over fluticasone. The claim was misleading and a breach of Clause 7.2 of the Code was ruled.

2 Claim '… and it can also save you up to 66% of the cost of an equivalent fluticasone propionate prescription.'

COMPLAINT

Glaxo Wellcome stated that in its initial letter to 3M Health Care it asked for clarification of the calculation carried out to arrive at the figure of 66%. Since it directly followed a claim relating to a clinical study in which doses of 800mcg/day Qvar and 1000mcg/day Flixotide both via MDI were used, it was reasonable to assume that it referred to these doses delivered by these devices.

On this basis, 28 days' treatment with Flixotide Evohaler (a CFC-free MDI) 250mcg 2 puffs bd would cost £36.29, while 28 days' treatment with 100mcg Qvar 4 puffs bd would cost £19.27, a difference of 47%. Even when the cheapest 28-day cost for Qvar (£17.63: 50mcg 8 puffs bd) was compared with the most costly Flixotide option (£42.67: 125mcg 4 puffs bd), the difference was only 58%.

However, Glaxo Wellcome was informed by 3M Health Care that the quoted cost difference of 66% was based on a comparison between 400mcg/day of Qvar delivered via a 50mcg MDI and 400mcg/day of Flixotide delivered via the 50mcg Accuhaler. As this was not apparent from the advertisement, and the claim appeared to relate the figure of 66% with dosages other than those used for the calculation, Glaxo Wellcome maintained that the claim was misleading.

Since 3M Health Care had selected a dosage of 400mcg/day, Glaxo Wellcome believed that a more balanced comparison would be based on 28 days' cost of Flixotide 50mcg Evohaler (a CFC-free MDI) and of 3M Health Care's Qvar 50mcg MDI. This comparison gave monthly costs of £10.92 and £8.81, respectively, a difference of just 19%.

Further, Glaxo Wellcome questioned 3M Health Care's choice of the particular strength of Flixotide Accuhaler selected for the cost comparison. Flixotide Accuhaler 50 was commonly used to deliver a dosage of 100mcg/day (50mcg bd). If a healthcare professional chose to prescribe 400mcg/day Flixotide using the Accuhaler, it was more likely that he or she would select the 100mcg Accuhaler, which would cost £17.92 for 28 days' treatment, much lower than the £25.61 quoted by 3M Health Care in its response to Glaxo Wellcome's letter.

Thus, 3M Health Care had obtained the figure of 66% by selection of the most expensive Flixotide (Accuhaler) device/dose combination with which to achieve a dosage of 400mcg/day, and comparing this with the cheapest method of achieving this dosage with Qvar.

Glaxo Wellcome therefore believed that these claims were ambiguous, unfair and misleading, and in breach of Clause 7.2 of the Code.

RESPONSE

3M Health Care stated that Glaxo Wellcome alleged that the claim was ambiguous, unfair and misleading. It also erroneously suggested that the price comparison was based on the clinical trial data discussed in B1 above. The price comparisons were based on the Qvar switch factors presented as part of the switch model and were based on the Qvar SPC.

In making comparisons of the costs of Qvar therapy with other commonly used inhaled steroids 3M Health Care was acutely conscious of the wide variations in the costs of a steroid depending on its dose form and delivery system. It therefore took the precaution of clearly stating that the savings were 'up to 66%' to indicate this variation to the reader. 3M Health Care chose to compare the dose of 400mcg daily of Qvar and fluticasone since this was in the middle of the dose range. A clinical study (Fairfax and Spelman AJRCCM 1999) had shown the Qvar and CFC fluticasone products to be statistically and clinically equivalent at this dose. This dose was most logically achieved by using Qvar 100mcg (2 puffs twice daily). However, there was no CFC fluticasone comparator at the 100mcg strength.

Options open to the prescriber included use of Qvar in a breath actuated device (Qvar Autohaler 50mcg per puff – 8 puffs daily) or fluticasone in a breath operated device (Flixotide Accuhaler 50mcg – 8 puffs daily) or CFC fluticasone 50mcg – 8 puffs daily. 3M Health Care's calculation of the cost of 28 day's treatment, based on the fluticasone Accuhaler 50mcg option, presented the best comparative match of inhaler devices. The complainant suggested 3M Health Care could have more fairly compared the Flixotide Evohaler 50mcg product. 3M Health Care would point out that this product was not licensed in the UK at the time of publication of the advertisement. However, 3M Health Care acknowledged the principle that Glaxo Wellcome was proposing. Had 3M Health Care wished to be ambiguous and unfair, it could have chosen to compare Qvar Autohaler 50mcg with Flixotide Diskhaler 50mcg again ensuring that both devices were matched, as both were breath actuated. In this case 3M Health Care could have suggested that there would have been savings in favour of Qvar of up to 71% (excluding the cost of the Diskhaler device). To demonstrate the range of prices from which 3M Health Care could have chosen, prices, cost per dose, cost per day and percentage comparative prices of Qvar and the fluticasone product range based on MIMS March 2000 were provided. 3M Health Care believed that a fair comparison must be made to best inform the health care professional and that its use of the phrase 'up to 66%' was entirely within the Code. 3M Health Care noted the omission of the words 'up to' throughout the Glaxo Wellcome complaint, other than in the subtitle.

In conclusion, 3M Health Care did not agree that the claims in the advertisement of significantly improved clinical outcome or savings of up to 66% compared with fluticasone were misleading, ambiguous or unfair.

PANEL RULING

The Panel noted that Glaxo Wellcome had referred to the cost of Flixotide Evohaler 50mcg inhaler and that 3M Health Care had pointed out that this was not licensed in the UK at the time of the advertisement. The Panel also noted that the cost calculation was not based on the doses referred to in the study at point B1 and given in the advertisement in the first part of the sentence. The 66% difference in cost was from a comparison of Flixotide Accuhaler 50mcg (8 puffs daily) and Qvar 100mcg (4 puffs daily) giving a daily dose of 400mcg. The cost of Flixotide Accuhaler for 28 days was given in the chart as £91.47 whereas Qvar was given as £31.20.

The Panel considered that the claim was misleading. It was not based on the doses referred to in the first part of the sentence. No details of the inhalers were provided. There was a difference in the cost of Qvar

inhalers depending on the dose per puff, 50mcg or 100mcg. There was a difference in cost of Flixotide depending on both the dose per puff, 50mcg or 100mcg, and on the presentation, be it an Accuhaler, a Diskhaler or an MDI. The difference in cost of fluticasone compared with Qvar varied from 12% to 71%. A breach of Clause 7.2 of the Code was ruled.

Complaint received	**8 August 2000**
Case completed	**3 November 2000**

CASE AUTH/1066/8/00 *NO BREACH OF THE CODE*

BRISTOL-MYERS SQUIBB v GLAXO WELLCOME

Combivir leavepiece

Bristol-Myers Squibb complained about a leavepiece for Combivir (lamivudine (3TC)/zidovudine (AZT)) issued by Glaxo Wellcome. Bristol-Myers Squibb produced Zerit (stavudine (d4T)). The complaint concerned a page headed 'Less strongly implicated in the onset of lipodystrophy' followed by 'The weight of evidence from over 3,000 patients in nine independent studies worldwide suggests that backbone combinations including AZT are less strongly implicated in the onset of lipodystrophy than combinations including d4T'. Bristol-Myers Squibb stated that the headline claim in the material referred to AZT and the piece was promoting Combivir. Clearly, any claim relating to the implication of a product with lipodystrophy must take account of all constituents and could not be based on only one, in this instance zidovudine. This was therefore misleading. Bristol-Myers Squibb had two concerns, firstly, only one of the studies listed in the table was published in a peer reviewed journal and secondly, none of the studies were randomised-controlled trials. The only randomised trial that was conducted involving 407 patients showed that there was no difference in the incidence of lipodystrophy in an AZT based regimen compared to a d4T-containing regimen. In addition, in the summary for one of the studies, no mention was made of the fact that 3TC treatment was also significantly associated with development of lipodystrophy and buffalo hump. In the largest study involving 1077 subjects, there was a significant association of duration of 3TC and d4T therapy with lipodystrophy but again there was no mention of the 3TC association in the table in the leavepiece. It was therefore clear that the other constituent of Combivir, 3TC, was also associated with lipodystrophy. It was therefore misleading to only compare the association of one of the components, in this instance AZT. It was alleged that the headline claim, core message and summary of relevant findings, were misleading, disparaging of d4T and unsubstantiable on the basis of current evidence.

The Panel noted with regard to the data referenced in the leavepiece that an association between lipodystrophy and d4T was at least suggested in eight of the references and unconfirmed in one, Mercie. Comparisons were made between d4T and AZT in five studies. The only randomised controlled trial (Dale *et al*) showed no difference in lipodystrophy between d4T and AZT. The other studies were observational studies and showed more lipodystrophy with d4T than with AZT. The Panel noted that this was an area of emerging clinical or scientific opinion which had not been resolved in favour of one generally accepted viewpoint. In this regard the Panel noted that the study by Carr *et al* stated that 'The association of lipoatrophy with current [d4T] therapy and the apparent weak protection effect of [AZT] should be interpreted with caution'. Molina *et al* stated that 'Whether the use of NRTI is associated with an increased risk of a lipodystrophy syndrome remains controversial'. The Panel considered that the bold heading 'Less strongly implicated in the onset of lipodystrophy' and the claim 'The weight of evidence from over 3000 patients in nine independent studies worldwide suggests that backbone combinations including AZT are less strongly implicated in the onset of lipodystrophy than combinations including d4T' were misleading. The product being promoted, Combivir, was a combination of AZT and 3TC. 3TC therapy had been associated with the development of lipodystrophy and buffalo hump. The Panel considered that overall the page was misleading, not capable of substantiation and disparaging of d4T. Breaches of the Code were ruled.

Upon appeal by Glaxo Wellcome, the Appeal Board noted that most of the studies cited in the leavepiece were not randomized controlled trials and their results had not been published in peer reviewed journals. The Appeal Board noted, however, that HIV had such a rapidly expanding knowledge base that abstracts were an acceptable form of communicating clinical results very quickly. Such data might not be sufficiently robust to support major claims in other therapy areas. The Appeal Board noted that a randomized controlled trial by Molina *et al* had not been cited in the leavepiece in support of the claim that combinations including AZT were less strongly implicated in the onset of lipodystrophy than combinations including d4T. The results of this study, which showed a significant difference (p=0.02) in favour of an AZT/3TC combination compared with d4T/ddI, were available in March 2000 when the leavepiece was prepared. Two other available studies supportive of the claim had also not been included in the leavepiece. The Appeal Board noted that the study by Dale *et al* had been included despite the fact that its results did not support the claim at issue. The Appeal Board noted an analysis of the relative risk of lipodystrophy taken from the eleven trials which had been available in March 2000. The results were presented as hazard ratio plots of the incidence of d4T

containing regimens causing lipodystrophy compared with that of AZT regimens; the results overall showed a consistently greater risk for d4T containing regimens over AZT regimens. In the Appeal Board's view this style of presentation and analysis of the available data more clearly supported the claim at issue than the way in which the data had been set out in the leavepiece. The Appeal Board considered that at the time that the leavepiece had been prepared the available data was sufficient to support the claim. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a leavepiece (ref: 20210963) for Combivir (lamivudine (3TC)/zidovudine (AZT)) issued by Glaxo Wellcome UK Limited. Bristol-Myers Squibb produced Zerit (stavudine (d4T)).

The complaint concerned a page headed 'Less strongly implicated in the onset of lipodystrophy' followed by 'The weight of evidence from over 3,000 patients in nine independent studies worldwide suggests that backbone combinations including AZT are less strongly implicated in the onset of lipodystrophy than combinations including d4T'. An adjacent table summarised the relevant findings from nine different studies.

COMPLAINT

Bristol-Myers Squibb complained about the claim 'Less strongly implicated in the onset of lipodystrophy'. Bristol-Myers Squibb stated that the headline claim in the material referred to AZT and the piece was promoting Combivir. Clearly, any claim relating to the implication of a product with lipodystrophy must take account of all constituents and could not be based on only one, in this instance zidovudine. This was therefore misleading and in breach of Clause 7.2 of the Code.

Bristol-Myers Squibb had two concerns, firstly, only one of the studies listed in the table was published in a peer reviewed journal and secondly, none of the studies were randomised-controlled trials. The only randomised trial that was conducted involving 407 patients showed that there was no difference in the incidence of lipodystrophy in an AZT based regimen compared to a d4T-containing regimen. In addition, in the summary for one of the studies, no mention was made of the fact that 3TC treatment was also significantly associated with development of lipodystrophy and buffalo hump. In the largest study involving 1077 subjects, there was a significant association of duration of 3TC and d4T therapy with lipodystrophy but again there was no mention of the 3TC association in the table in the leavepiece. It was therefore clear that the other constituent of Combivir, 3TC, was also associated with lipodystrophy. It was therefore misleading to only compare the association of one of the components, in this instance AZT.

It was clear from the above that the headline claim, core message and summary of relevant findings, were misleading, disparaging to d4T and unsubstantiable on the basis of current evidence and were therefore in breach of Clauses 7.2, 7.3, 7.7 and 8.1 of the Code.

In intercompany correspondence a letter from Bristol-Myers Squibb referred to the fact that most of the references cited in support of the claim were only abstracts, Glaxo Wellcome had responded with:

1 a summary of a number of other articles in further support of its claims;

2 statements that the British HIV Association (BHIVA) guidelines could be based on abstracts up to 3 years old.

Bristol-Myers Squibb's reply to these points was as follows:

1 Duration of treatment with antiretrovirals was widely accepted to be associated with lipodystrophy. AZT was the first antiretroviral to be used and hence subjects in trials were likely to have been on this medicine longer than on d4T. In addition prior exposure to treatment with AZT was believed, theoretically, to be associated with later development of lipodystrophy. The patients in most of the studies cited by Glaxo Wellcome would have been previously treated with AZT although this information was not provided in the majority of cases. This made drawing any conclusions particularly difficult and unreliable. In addition Bristol-Myers Squibb was still concerned as to the quality of this data for the reasons stated below:

a) One of the 'additional' peer reviewed published articles by Saint-Marc was already quoted on the original leavepiece and was therefore not new. It was concluded from this study that there was a higher incidence of lipodystrophy in the d4T arm than the AZT arm. The inference being made did not take account of the fact that 63% of subjects in the d4T group had been previously exposed to AZT. In addition Bristol-Myers Squibb drew attention to an independent review of this study which severely criticised this paper.

b) The second published article mentioned in Glaxo Wellcome's response was initially also quoted in the original leavepiece but was then in abstract form. This study was again a non-randomised cohort study with no mention being made of prior AZT exposure in the majority of patients.

c) It was quoted that the ALBI study was the most impressive new study in support of Glaxo Wellcome's claim. Firstly, in this study data was only available from 83 out of the 151 subjects with no explanation. Secondly, although it was concluded that patients treated with d4T/ddI reported lipodystrophy twice as frequently as those on AZT/3TC, the difference in prevalence did not reach statistical significance.

d) From the study by Goujard it was claimed that 646 patients were studied when in fact only 149 of these were included in the analysis. It was widely accepted that protease inhibitors were strongly associated with lipodystrophy. In this study only 23% of the study population had had no prior exposure to this group of medicines. Again no mention was made of prior AZT exposure. In addition the patients in the d4T arm had been on anti-retroviral therapy for a longer time than in the AZT arm and this could have skewed the results.

e) From the HOPS (HN outpatients study) study, which was again non-randomised and cross sectional, prior AZT exposure was again not mentioned. Also the conclusion did not take into account that d4T on its own was not associated with lipodystrophy but there had to be other predisposing factors present as well. The numbers quoted by Glaxo Wellcome were again misleading with only 197 patients and not 548 being included in the analysis.

f) From the paper by Bernasconi the patient numbers were again misrepresented with only 585 out of the 1379 patients being involved in the analysis. This was again a cross sectional study with no mention of prior AZT exposure.

2 Quality of publications used to support independent and impartial BHIVA guidelines might differ from that required to support a promotional claim.

The Code stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. Bristol-Myers Squibb therefore maintained its position that based on the balance of evidence, the headline claim, core message and summary of relevant finds were misleading, disparaging to d4T and unsubstantiable on the basis of current evidence and were therefore in clear breach of Clauses 7.2, 7.3, 7.7 and 8.1 of the Code.

In support of its concerns, Bristol-Myers Squibb also drew attention to a review of the lipodystrophy literature which a medical statistician had carried out on its behalf. The review highlighted the inaccuracies of the conclusions that were being drawn on the basis of the evidence in the literature.

RESPONSE

Glaxo Wellcome stated that the item was a leavepiece used in discussions with health professionals about the efficacy and tolerability of Combivir. It was designed to be left with the doctor to read in his/her own time and it was made available on promotional stands.

The complaint related to the claim 'Less strongly implicated in the onset of lipodystrophy'. In the leavepiece this claim was qualified by the statement that 'The weight of evidence … suggests that backbone regimens including AZT are less strongly implicated in the onset of lipodystrophy than combinations containing d4T.' Lipodystrophy referred to a syndrome of peripheral fat wasting, often combined with central fat gain.

Glaxo Wellcome firmly believed that the claim was a fair and balanced assessment of the most up-to-date data and it therefore did not agree that the leavepiece was in breach of the Code.

With regard to the view that much of the data supporting the claim had not appeared in peer reviewed journals, Glaxo Wellcome submitted that the HIV therapy area was particularly dynamic and prescribing decisions were frequently made based on non-peer reviewed data. The BHIVA recognised this and supported part of its guidelines with studies which had only appeared in abstract form. The BHIVA had taken a decision to cite studies which had only appeared in abstract form in the three years prior to the publication of its guidelines. The studies cited in the leavepiece were in keeping with this policy.

In the review commissioned by Bristol-Myers Squibb the concerns about non-peer reviewed data were expressed yet the point was made that 'very recent work can usually only be available as abstracts, and this may need to be taken into account.'

Glaxo Wellcome agreed that a peer review of data was ideal and it would not draw conclusions based on a small number of non-peer reviewed studies. Glaxo Wellcome's claim was actually based on the conclusions of a large number of independent studies, the vast majority of which supported the claim, ie that backbone regimens including AZT were less strongly implicated in the onset of lipodystrophy than combinations containing d4T. Glaxo Wellcome believed it would be unethical and inappropriate to ignore these important data until such time as they were published.

With regard to the concern that none of the studies supporting the strapline were randomised, controlled trials, Glaxo Wellcome submitted that it did not disagree with the medical statistician's statement that the 'ideal is to have the information from randomised trials'. The statistician recognised that these trials were 'not a good way to assess the risk of rare adverse events' and he stated that 'Ideally, therefore, we would like data from a cohort of newly diagnosed HIV patients some of whom have not received Protease Inhibitors (PIs) and/or Nucleoside Reverse Transcriptase Inhibitors (NRTIs)'.

Glaxo Wellcome recognised that there were not many randomised, controlled clinical trials investigating lipodystrophy but it was impressed by the number of independent cohort studies which supported the claim made in the leavepiece. More data was becoming available and Glaxo Wellcome provided new data, not included in the leavepiece, which supported the claim. The new data included a randomised, controlled clinical trial and prospective cohort studies.

With regard to Bristol-Myers Squibb's complaint that the study by Dale *et al*, quoted in the leavepiece, showed no difference in the incidence in lipodystrophy in patients treated with regimens including d4T or AZT, Glaxo Wellcome submitted that this study was deliberately included in order to present a fair balance of evidence. The results of this study were not consistent with the vast majority of research and Glaxo Wellcome believed that despite the result, the weight of evidence strongly suggested that backbone regimens including AZT were less implicated in the onset of lipodystrophy than combinations containing d4T.

With regard to the concern that the claim referred to AZT and not Combivir, Glaxo Wellcome submitted that the data highlighted in the leavepiece and the new data outlined below suggested that combinations containing d4T had a greater association with lipodystrophy than combinations containing AZT.

Since Combivir contained AZT, Glaxo Wellcome considered these data to be relevant. Furthermore, data from a randomised, controlled trial (see below) demonstrated that the combination of AZT/3TC was associated with less lipodystrophy than the combination of d4T/ddI (didanosine, Bristol-Myers Squibb's product, Videx).

With regard to the concern that no mention was made of 3TC related lipodystrophy in the study by Carr *et al*, Glaxo Wellcome submitted that in the study by Carr *et al* the association of d4T therapy with lipodystrophy and the association of 3TC with buffalo hump was significant. The association of 3TC with lipodystrophy was also significant in the study by Ward *et al*. Despite the results of these two studies the weight of evidence still supported the claim in the leavepiece that combinations containing d4T had a greater association with lipodystrophy than combinations containing AZT. Data outlined below supported this statement by providing data on the combination of AZT with 3TC (the same combination as Combivir).

In the study by Molina *et al* (a randomised controlled clinical trial) the combination of 3TC/AZT was associated with significantly less lipodystrophy than d4T/ddI. In a peer reviewed study by Saint-Marc *et al* no association was seen between 3TC and lipodystrophy. In the study by Bernasconi *et al* multi-variate analysis revealed that AZT/3TC conferred significant protection with respect to fat loss.

With regard to concern that factors such as duration of antiretroviral therapy, co-administration of PIs etc might bias the results of the supporting studies, Glaxo Wellcome did not suggest that d4T alone caused lipodystrophy. This was known to be a multifactorial syndrome and the leavepiece only emphasised that there were differences in the contribution d4T and AZT made to this syndrome.

Bristol-Myers Squibb commented that many people treated with d4T in the cohort studies might have been pre-treated with other NRTIs (particularly AZT) and this might have impacted on the development of lipodystrophy. This was a valid point and was why in many studies a rigorous multivariate analysis had been conducted to control for such confounding factors (Carmena *et al*, Saint-Marc *et al*, Mauss *et al*, Mallal *et al*). Many of these analyses identified both time on NRTIs and d4T therapy as risk factors and showed that even when one controlled for the former, the latter was still highly significant. In addition, the studies by Mauss *et al* and Molina *et al* were conducted in therapy naïve patients.

Glaxo Wellcome referred to the supporting data. There had been two recent publications in peer review journals which supported the claim made in the leavepiece.

Mallal *et al* reported a longitudinal cohort study of 277 patients which was peer reviewed. The use of d4T was associated with a 265% increase in fat wasting compared with AZT. The difference in fat wasting was highly significant ($p<0.0001$). This study was criticised by Bristol-Myers Squibb because it was not a randomised study and did not mention prior AZT use in patients. Most of the patients in the cohort were on therapy prior to entry although no patients were treated with a protease inhibitor. It was stated that this calculation took prior exposure to these medicines into account.

Saint Marc *et al* reported a study (referenced in the leavepiece) in which 43 HIV patients were treated with therapy including either d4T or AZT. This group reported a significantly higher incidence of fat wasting in the d4T group (63%) relative to the AZT group (19%). These patients were a subset of the LIPCO study in AIDS which had also now been reported by Saint-Marc *et al*. This report included a multi-variate analysis which adjusted for time on anti-retroviral therapy and time on current therapy. The analysis concluded that d4T was significantly more correlated with lipodystrophy than AZT ($p=0.0068$). The use of 3TC in this study was not significantly associated with lipodystrophy.

The following data had been presented in abstracts and posters at major international conferences. It included data which had emerged since the leavepiece was produced.

The most impressive new data probably came from the ALBI study by Molina *et al*. This was a randomised, controlled trial and 120 patients had been included in an interim analysis. These patients were previously untreated and were randomly assigned treatment with d4T/ddI, AZT/3TC or d4T/ddI alternating with AZT/3TC. Lipodystrophy was reported in d4T/ddI patients more than twice as often as patients treated with AZT/3TC. Some of the differences had not reached statistical significance in the abstract of this study at the 7th Conference on Retroviruses and Opportunistic Infections (as noted by Bristol-Myers Squibb). By the time this study was presented at the meeting, however, data was available on more patients and the difference was statistically significant.

At the same conference Goujard *et al* presented a cross sectional study of 646 patients of which 149 were naïve to treatment with a protease inhibitor and were included in an assessment of lipodystrophy. The results of this study were that the incidence of lipodystrophy in regimens including d4T was 54.9% while the incidence in AZT treated patients was 30.2% ($p=0.003$). Glaxo Wellcome did not understand why Bristol-Myers Squibb raised the concern about the incidence of protease inhibitor naïve patients in this cohort as this was the very group of patients being studied. All 149 patients were therefore selected on the basis of being naïve to treatment with a PI. Bristol-Myers Squibb had also raised the concern that d4T patients had a longer exposure to d4T than AZT but this difference was non-significant. Glaxo Wellcome believed that the conclusion that d4T was associated with significantly more lipodystrophy than AZT was valid.

Lichtenstein *et al* reported on the HOPS (HIV outpatients study) at the XIII International AIDS Conference 2000. In 548 patients 18% had moderate to severe fat redistribution The authors reported that lipodystrophy was associated with the use of d4T ($p=0.0001$). Bristol-Myers Squibb complained that Glaxo Wellcome had misrepresented the numbers in

this study but Glaxo Wellcome was clear that only 18% of the full cohort (197 patients) had lipodystrophy and it was these patients who were studied. It would be misleading not to quote the full size of the cohort. Glaxo Wellcome did not disagree with Bristol-Myers Squibb when it stated that many factors contributed to lipodystrophy. This study, which included a multi-variate analysis, did indicate that d4T was independently associated with lipodystrophy.

At the same conference Mauss *et al* reported on 212 patients who were followed for 36 months in a prospective cohort study of therapy naïve patients. A significant association was found between d4T treatment and the development of lipodystrophy.

Bernasconi *et al* presented data from a cohort of 1379 patients. The results of a multi-variate analysis showed that 585 patients developed lipodystrophy and the combination of d4T/ddI was significantly associated with a risk of lipodystrophy. The multi-variate analysis revealed that AZT/3TC conferred significant protection with respect to fat loss. Again Glaxo Wellcome was puzzled as to why Bristol-Myers Squibb complained that it misrepresented the data. The whole cohort was included in the multi-variate analysis.

Carmena *et al* reported a prospective cohort study at the XIII International AIDS conference. Of 232 patients included in the study 35% were treated with d4T and 37% with AZT. Of all the patients treated with triple antiretroviral therapy, 20 out of 119 patients treated with d4T presented lipodystrophy compared to 4 out of 113 patients treated with AZT, relative risk 3.14 (p=0.0009).

Two studies supporting the claim in the original leavepiece had not been mentioned by Bristol-Myers Squibb in its letters of complaint to either the Authority or Glaxo Wellcome. Glaxo Wellcome assumed that Bristol-Myers Squibb had no specific concern about the conclusions of these studies but it summarised the results for information.

Galli *et al* reported a longitudinal study of 188 subjects. This was a prospective study excluding those patients treated with a protease inhibitor or an NRTI for more than a week prior to study entry. Any patients with fat redistribution at study entry were also excluded. Over the follow up the incidence of developing lipodystrophy in patients treated with AZT/3TC was 9.7% and the incidence in patients treated with d4T/ddI was 27.1%.

Polo *et al* reported data on 156 patients treated with triple combination regimens of 2 NRTIs and a PI between January 1997 and May 1999. The incidence of lipodystrophy reported in patients treated with AZT/3TC/PI was 4.2% (2/46) compared with 89.4% (17/19) in those treated with d4T/ddI/PI (p<0.001).

Glaxo Wellcome stated that the statistical report, commissioned by Bristol-Myers Squibb, made interesting reading and raised a number of issues, many of which were addressed above. It was, however, an incomplete analysis of the issue since it only focused on four papers, two of which were on the same cohort of patients and were primarily studies of PIs. The review also ignored data presented as abstracts 'partly … because there are so many of these'. This report, which was completed in December 1999, was now out of date.

In summary, Glaxo Wellcome was assured that the claim in the leavepiece was well supported by the above data and was not misleading or disparaging of d4T. Glaxo Wellcome, therefore, did not consider that the leavepiece was in breach of the Code and it hoped that the above information addressed adequately the concerns raised by Bristol-Myers Squibb.

PANEL RULING

The Panel considered that this was a difficult case. The leavepiece had to be assessed on the data available when it was used (March 2000). Glaxo Welcome had given brief details of nine studies in the leavepiece; eight abstracts and one full paper. The Panel noted Glaxo Wellcome's submission that publication of abstracts was inevitable in an area such as HIV which was particularly dynamic. Most of the studies were observational ie a group of patients receiving treatment for HIV were studied to assess the presence or absence of lipodystrophy. In only two studies Dale *et al* (1999) and Molina *et al* (2000) were patients randomised to the treatments groups. Several of the studies provided by Glaxo Wellcome but not referenced in the leavepiece were prospective cohort studies ie groups of patients receiving different treatment regimens were identified and then observed over a period of time to assess lipodystrophy.

The Panel noted that in most of the studies there was little or no information about previous treatment. Bristol-Myers Squibb argued that duration of treatment with antiretrovirals including zidovudine (AZT) was a factor associated with lipodystrophy and failure to take this into account might confound study findings. This also applied to treatment with PIs. The Panel noted that PIs were associated with lipodystrophy and metabolic effects. According to the British National Formulary (BNF September 2000) the Medicines Control Agency had advised that combination antiretroviral therapy, including regimens containing a PI, was associated with redistribution of body fat in some patients.

The Panel noted that Glaxo Wellcome acknowledged that lipodystrophy was a multi-factorial syndrome but submitted that several studies (Carmena *et al*, Saint-Marc *et al*, Mauss *et al* and Mallal *et al*) involved multivariate analysis to control for confounding factors.

The Panel noted that the area was rapidly developing. With regard to the data referenced in the leavepiece the Panel noted that an association between lipodystrophy and d4T was at least suggested in eight of the references and unconfirmed in one, Mercie. Comparisons were made between d4T and AZT in five studies. The only randomised controlled trial (Dale) showed no difference in lipodystrophy between d4T and AZT. The other studies were observational studies and showed more lipodystrophy with d4T than with AZT.

The Panel noted that this was an area of emerging clinical or scientific opinion which had not been

resolved in favour of one generally accepted viewpoint. In this regard the Panel noted that the study by Carr (2000) stated that 'The association of lipoatrophy with current [d4T] therapy and the apparent weak protection effect of [AZT] should be interpreted with caution'. The preamble to Molina (2000) stated that 'Whether the use of NRTI is associated with an increased risk of a lipodystrophy syndrome remains controversial'.

The Panel considered that the bold heading 'Less strongly implicated in the onset of lipodystrophy' and the claim 'The weight of evidence from over 3000 patients in nine independent studies worldwide suggests that backbone combinations including AZT are less strongly implicated in the onset of lipodystrophy than combinations including d4T' were misleading. The area was one of emerging clinical opinion. The product being promoted, Combivir, was a combination of AZT and 3TC. 3TC therapy had been associated with the development of lipodystrophy and buffalo hump. The Panel considered that overall the page was misleading, not capable of substantiation and disparaging of d4T. Breaches of Clauses 7.2, 7.3 and 8.1 of the Code were ruled. The Panel considered that the alleged breach of Clause 7.7 was covered by its rulings.

APPEAL BY GLAXO WELLCOME

Glaxo Wellcome stated that lipodystrophy was recognised as an important issue in the HIV therapy area and was a problem which clinicians dealt with on a daily basis. The term described a syndrome of peripheral fat wasting and central fat accumulation and was often accompanied by metabolic changes such as hypertriglyceridaemia, hypercholesterolaemia and insulin resistance. The very obvious physical changes which could occur might lead to stigmatisation of HIV positive patients and this could have a devastating impact on a patient wishing to live a fully functional, normal life without others knowing his/her HIV status. Concern about these physical changes could lead to poor adherence with therapy and this in turn could lead to failure of therapy with related morbidity and mortality. In addition, there was the theoretical risk of long term cardiovascular disease (related to the metabolic abnormalities) to consider.

Highly active antiretroviral therapy (HAART) consisted of at least three antiretroviral drugs in a daily regimen. In most cases this would consist of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a third NRTI. A link between PIs and lipodystrophy was well established but more recently a link between NRTIs and lipodystrophy had also been established.

Since NRTIs were present in almost all regimens, the association of this group with lipodystrophy was particularly significant. NRTIs formed the 'backbone' of most regimens and, unlike PIs, it was impractical to avoid this class of medicine in most stages of treatment. Prescribing decisions would therefore be influenced by the relative potential of each NRTI to cause lipodystrophy.

Glaxo Wellcome had considered presenting lipodystrophy data in promotional materials for some time prior to the leavepiece being produced. It recognised that the issue was an emerging one, but it considered that by March 2000 there was enough data to support a statement that 'the weight of evidence' supported the claim. Glaxo Wellcome therefore thought it appropriate at that time to summarise the evidence in the leavepiece.

Summary and overview of complaint

Bristol-Myers Squibb complained directly to Glaxo Wellcome in July 2000 about the Combivir leavepiece. Glaxo Wellcome responded but Bristol-Myers Squibb considered that a number of issues could not be resolved.

Glaxo Wellcome listed aspects of Bristol-Myers Squibb's complaint and gave its response as follows:

- *The claim, which referred to AZT containing regimens, appeared in a Combivir (a combination of AZT with 3TC) leavepiece*

Since Combivir was an AZT containing regimen, the claim was appropriate in a Combivir leavepiece. In addition, data demonstrated that an AZT/3TC combination caused less lipodystrophy than a d4T containing regimen.

- *Non-peer reviewed studies were used to support the claim*

HIV was a particularly dynamic area and even guidelines were supported by non-peer reviewed studies (including the British HIV Association Guidelines). Although many studies supporting the claim were not peer reviewed, a very strong trend supporting the claim had emerged from a series of independent studies.

- *Cohort studies were used to support the claim*

Most of the supporting cohort studies were prospectively designed to assess lipodystrophy, included objective measures and involved multivariate analyses. The results of these well designed cohort studies were fairly consistent.

- *3TC was associated with lipodystrophy*

When 3TC was used in combination with AZT, this regimen had been shown to be less implicated in causing lipodystrophy than a d4T containing regimen.

- *Patient numbers quoted in inter-company correspondence were misleading*

Glaxo Wellcome explained why the numbers quoted in correspondence were correct.

Glaxo Wellcome listed aspects of the Panel's ruling and gave its reasons for appealing as follows:

- *The leavepiece had to be assessed on the data that was available when it was produced.*

Although Glaxo Wellcome accepted that data available after March 2000 could not be considered by the Panel, it did think that data not referenced in the leavepiece, but available before March 2000, were relevant. Importantly a randomised, controlled clinical trial (the ALBI study by Molina *et al*) met this

criteria and this study provided key data to help resolve this issue.

- *The only randomised, controlled trial referenced in the leavepiece (Dale et al) did not support the claim.*

On closer inspection of the study by Dale, serious concerns were raised about the methodology. Since this key study supporting the complaint was inadequately designed to address the issue, the weight of evidence shifted even further to support the claim.

- *Most of the studies referenced in the leavepiece did not provide information about time on treatment*

Time on treatment was addressed in many studies. The ALBI study recruited treatment naïve patients and most of the cohort studies took time on treatment into account.

- *PIs were also associated with lipodystrophy and could be a confounding factor*

Some of the supporting studies recruited treatment naïve patients and the methodology meant that patients were never treated with a PI during their period of assessment. Other studies, with multivariate analysis, would control for PI treatment. There was therefore good data available which took the potential confounding factor of a PI into account.

- *This was an emerging area which had not been resolved*

Representative data which both supported and disputed the claim were presented in the leavepiece and therefore this emerging issue was treated transparently and appropriately.

- *3TC, which was also contained in Combivir, was associated with lipodystrophy*

The ALBI study and three cohort studies showed that when 3TC was used in combination with AZT, less lipodystrophy occurred than with d4T containing regimens.

Glaxo Wellcome stated that lipodystrophy had a major impact on the treatment of HIV positive patients and the company considered there was enough evidence available in March 2000 to allow for appropriate discussion of this important issue in promotional material. Glaxo Wellcome explained in more detail why it addressed this issue in the way it did and outlined below why it considered that it had addressed the issue in a manner compliant with the Code.

Glaxo Wellcome quoted from the Panel's ruling and gave its comments as follows:

1 The leavepiece had to be assessed on the data that was available when it was produced

The leavepiece was not intended to provide an exhaustive review of all the relevant data. The referenced studies were selected on the basis that they were representative of the data. Some important studies, which could further support the claim, were omitted.

Although Glaxo Wellcome understood that the Panel could not assess data presented after March 2000, Glaxo Wellcome did think that data available before March 2000, but not referenced in the leavepiece, were relevant. The ALBI randomised, controlled study and the Goujard cohort study met this criteria and were discussed below.

2 The only randomised, controlled trial referenced in the leavepiece (Dale *et al*) did not support the claim

Glaxo Wellcome had asked an independent expert, a consultant in HIV medicine from an internationally respected centre, to assess the data as it existed in March 2000 and provide an opinion on whether the evidence supported the claim that 'The weight of evidence … suggests that backbone combinations including AZT are less strongly implicated in the onset of lipodystrophy than combinations containing d4T'. The expert's review of the data and criticism of certain study designs significantly altered the balance of the evidence.

All nine studies referenced in the leavepiece were reviewed in the expert's report. These consisted of one randomised, controlled study, one case control study and seven cohort studies. The following key points were discussed.

- The report raised serious issues about the methodology of the randomised controlled clinical trial (Dale *et al*). These concerns focused mainly on the fact that the trial was not initially designed to look at lipodystrophy and employed a post hoc, non-objective method of assessment. It was concluded that this study was inadequately designed to assess lipodystrophy.
- Most of the cohort studies employed multivariate analyses which controlled for various factors including time on therapy and time since diagnosis. The majority also had well-defined and objective measures of lipodystrophy. These studies therefore provided relatively robust data.
- Four cohort studies made direct comparisons of d4T with AZT and supported the claim. A further two cohort studies and one case control study reported that there was an association of d4T with lipodystrophy.
- Two studies did not support the claim. Of these, the conclusions by Dale *et al* were discredited (see above). Concern could also be raised about the number of patients in the study by Mercie.

In addition to the studies referenced in the leavepiece, the ALBI study (Molina *et al*) had been reviewed. This was reported at the 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 29 January – 2 February 2000. Although not referenced in the leavepiece, this study provided data which was available at the time the leavepiece was produced and was therefore of relevance to this case. Cohort studies by Goujard *et al* and Gervasconi *et al* had also been presented prior to March 2000.

- The ALBI study was a randomised, controlled, clinical trial which prospectively set out to measure lipodystrophy using objective measures. The incidence of lipodystrophy in d4T/ddl

patients was more than twice that of patients treated with AZT/3TC and this difference was significant (p=0.02). This trial was assessed to provide strong and robust data which supported the claim.

- The additional new data (Goujard *et al*) included a cohort study which supported the claim that AZT was less implicated in causing lipodystrophy than d4T.
- Gervasconi also reported that in a cohort of 306 women, 32 developed fat redistribution. In this group d4T significantly correlated with fat redistribution and the risk was significantly lower in patients taking combinations including AZT (OR 0.3; 95% CI 0.1 – 0.7). Duration of treatment in this cohort was not well described.

In summary, at the time the leavepiece was produced, one randomised, controlled, clinical trial, eight cohort studies and one case control study supported the claim. Two studies reported contradictory results but there was concern with the methodology of the key study (Dale *et al*) and how well equipped this study was to address the issue. Glaxo Wellcome submitted that the conclusion of the independent expert's report supported its assessment of the lipodystrophy data and drew the same conclusions, ie that backbone regimens including AZT were less strongly implicated in the onset of lipodystrophy than combinations containing d4T.

3 Most of the studies referenced in the report did not provide information about time on treatment

Time on treatment was a factor which could contribute to the development of lipodystrophy. This had been recognised by many investigators and as a result many trials were designed with a methodology which took this confounding factor into account.

- The two, randomised, controlled clinical trials (Dale *et al* and the ALBI study by Molina *et al*) addressed this potential problem by recruiting therapy naïve patients in the study arms (although the Dale study had been discredited). This design removed the confounding factor of time on therapy as groups of patients being compared had been treated for the same length of time within the study.
- Many cohort studies involved multivariate analyses (Saint-Marc *et al*, Mallal *et al*, Ward *et al*, Galli *et al*) and therefore accounted for this confounding factor in the statistical report.

4 PIs were also associated with lipodystrophy and could be a confounding factor

Treatment with a PI was recognised as a factor which could contribute to lipodystrophy. Many of the studies took this confounding factor into account.

- The ALBI study involved patients treated with NRTIs only.
- The cohort studies by St Marc *et al*, Mercie *et al*, Goujard *et al* and Galli *et al* recruited patients who were not treated with PIs.
- Multivariate analyses were used in many cohort studies and would account for PI use.

5 This was an emerging area which had not been resolved

HIV itself was an emerging therapy and clinicians working within the speciality analysed data with the knowledge that it was constantly being updated. Good promotional material could be of great value to health professionals by providing information on emerging issues in an educational and transparent manner.

In referring to lipodystrophy, Glaxo Wellcome was careful to present a fair and balanced overview of the data and included studies in the table which did not support the claim. It considered that by raising the issue in a carefully considered and transparent way it adhered to the spirit of the Code.

6 3TC, which was also contained in Combivir, was associated with lipodystrophy

The Panel noted that 3TC therapy was associated with lipodystrophy and buffalo hump. Since the claim was made in a Combivir leavepiece it was judged misleading to make the above claim.

Glaxo Wellcome submitted that this ruling did not take into account the specific and carefully considered wording of the claim. All NRTI drugs had the potential to cause lipodystrophy and this was now recognised by practising clinicians. The claim did not state that AZT or 3TC were not associated with lipodystrophy, but stated that an AZT containing regimen was associated with less lipodystrophy than a d4T containing regimen.

Although 3TC was associated with lipodystrophy in two studies it should be noted that this association was not found in the remaining nine studies. Importantly, studies outlined in the summary by the independent expert demonstrated that the combination of AZT and 3TC (as contained in Combivir) was associated with less lipodystrophy than d4T containing regimens. Some of the most robust data, from the ALBI study, actually demonstrated that the combination contained in Combivir (AZT/3TC) was less implicated in lipodystrophy than a d4T containing regimen. The studies by Polo and Galli drew the same conclusion. In addition, Saint-Marc presented his findings from the LIPOCO study (subsequently published in AIDS) at the 3rd International Conference on Nutrition and HIV infection in Cannes on 22 April 1999. In this presentation he reported that there was an increased risk of lipodystrophy with d4T compared to AZT therapy, but no correlation was seen with 3TC.

In summary, Glaxo Wellcome believed that the evidence supported the claim that an AZT containing regimen was less implicated than a d4T containing regimen when AZT was given in combination with 3TC (as in Combivir).

In addition to the above Glaxo Wellcome wished to raise the following issues.

7 Quotes supporting the Panel's judgement and context

Glaxo Wellcome believed that quotations needed to be placed in context. Carr, for example, was quoted as stating that 'The association of lipoatrophy with current (d4T) therapy and the apparent weak protection effect of (AZT) should be interpreted with caution'. Glaxo Wellcome agreed with Carr's caution in interpreting the results of his single case control study in isolation. It could not be assumed he would come to the same conclusion if he had assessed all the data available in March 2000.

Glaxo Wellcome considered that undue weight had been placed on the report commissioned by Bristol-Myers Squibb. The report raised some interesting issues but only focused on four papers, two of which were on the same cohort of patients and were primarily studies of PIs. The report also ignored important studies presented as abstracts, 'partly … because there are so many of these.' It should also be noted that this report was written in December 1999 and therefore did not make reference to some key data.

8 Errors in the original complaint were not addressed

Bristol-Myers Squibb stated that misleading patient numbers had been quoted in inter-company correspondence by Glaxo Wellcome. Glaxo Wellcome did not believe that it was misleading in the numbers quoted and wished to refer the Appeal Board back to its original response.

HIV was a complex area and Glaxo Wellcome hoped that its appeal explained why it was justified in making this important claim.

APPEAL BOARD RULING

The Appeal Board noted that most of the studies cited in the leavepiece were not randomized controlled trials and their results had not been published in peer reviewed journals. The Appeal Board noted, however, that HIV had such a rapidly expanding knowledge base that abstracts were an acceptable form of communicating clinical results very quickly. Such data might not be sufficiently robust to support major claims in other therapy areas.

The Appeal Board noted that a randomised controlled trial by Molina *et al* had not been cited in the leavepiece in support of the claim that combinations including AZT were less strongly implicated in the onset of lipodystrophy than combinations including d4T. The results of this study, which showed a significant difference (p=0.02) in favour of an AZT/3TC combination compared with d4T/ddI, had been reported at a conference in January/February 2000 and so were available in March 2000 when the leavepiece was prepared. Other available studies supportive of the claim had also not been included in the leavepiece ie Boufassa *et al* and Mallolas *et al*. The Appeal Board noted that the study by Dale *et al* had been included despite the fact that its results did not support the claim at issue.

The Appeal Board noted that the representatives from Glaxo Wellcome presented an analysis of the relative risk of lipodystrophy taken from the eleven trials which had been available in March 2000. The results were presented as hazard ratio plots of the incidence of d4T containing regimens causing lipodystrophy compared with that of AZT regimens; the results overall showed a consistently greater risk for d4T containing regimens over AZT regimens. In the Appeal Board's view this style of presentation and analysis of the available data more clearly supported the claim at issue than the way in which the data had been set out in the leavepiece. The Appeal Board considered that at the time that the leavepiece had been prepared the available data was sufficient to support the claim. No breaches of Clauses 7.2, 7.3 and 8.1 were ruled. The appeal was successful.

Complaint received **18 August 2000**

Case completed **9 November 2000**

NOVARTIS v FUJISAWA

Prograf journal advertisement

Novartis complained about a journal advertisement for Prograf (tacrolimus) issued by Fujisawa. Novartis stated that it cited two studies carried out in liver transplant patients, both of which used doses of tacrolimus considerably in excess of the licensed dose as given in the summary of product characteristics (SPC). Pichlmayr *et al* (1997) used an initial IV dose of 0.075mg/kg bd = 0.15mg/kg/day x 3 days. This dose was reduced to 0.06mg/kg/day later in the course of the study. Initial oral dose following IV, 0.3mg/kg/day. In contrast the SPC for Prograf stated that '… intravenous tacrolimus therapy should be initiated at … 0.01 to 0.05mg/kg [per 24 hours] for liver transplants …' and 'oral tacrolimus should commence at 0.10 – 0.20mg/kg/day for liver transplantation'. Wiesner *et al* (1998) used an initial IV dose of 0.15mg/kg/day in 48 of 263 patients on tacrolimus, then 0.1mg/kg/day in the remainder. The initial oral dose was 0.3mg/kg/day. Again, these doses were outside those given in the SPC. Novartis alleged that the use of these two studies to promote Prograf was in breach of the Code which required that promotion must not be inconsistent with the SPC.

The Panel noted that the Prograf SPC stated that 'The dosage recommendations given below for oral and intravenous administration are intended to act as a guideline. Prograf doses should be adjusted according to individual patient requirements. Only initial dosing is recommended and therefore therapy should be based on clinical judgement aided by measurement of tacrolimus concentrations in blood'. A subsection which referred to the primary immunosuppression dose level for adults in kidney and liver transplantation stated that 'Oral tacrolimus therapy should commence at 0.10-0.20mg/kg per day for liver transplantation and at 0.15-0.30mg/kg per day for kidney transplantation administered as two divided doses. … If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion at 0.01 to 0.05mg/kg for liver transplants and 0.05 to 0.1mg/kg for kidney transplants'. The SPC also stated that 'The dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability in each patient individually'. The latter section did not refer to any specific dose.

The Panel noted that transplantation was a highly specialised and complex area. Various pharmacokinetic and pharmacodynamic factors needed to be taken into account when administering Prograf which would influence the dosage regimen. Transplant specialists would be aware of these clinically important factors. The dosage recommendations in the SPC related to initial dosage rather than maintenance. The introductory sentence stated that dosage recommendations were intended to act as a guideline and referred to adjustment of dose according to individual requirements. In opinion of the Panel the introductory sentence would necessarily relate to initial dosing. There were no maintenance dosage recommendations. According to the SPC the indicated dosing was flexible. No breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about an advertisement for Prograf (tacrolimus) issued by Fujisawa Limited which had been published in The Lancet on 20 May, 2000.

COMPLAINT

Novartis stated that during the consideration of another case, Case AUTH/1030/6/00, it had become apparent that the advertisement constituted a clear breach of Clause 3.2 of the Code.

The advertisement cited two studies carried out in liver transplant patients, both of which used doses of tacrolimus considerably in excess of the licensed dose as given in the summary of product characteristics (SPC). Pichlmayr *et al* (1997) used an initial IV dose of 0.075mg/kg bd = 0.15mg/kg/day x 3 days. This dose was reduced to 0.06 mg/kg/day later in the course of the study. The initial oral dose following IV therapy was 0.3mg/kg/day. In contrast the SPC for Prograf stated that '… intravenous tacrolimus therapy should be initiated at …0.01 to 0.05mg/kg [per 24 hours] for liver transplants …' and 'oral tacrolimus should commence at 0.10-0.20 mg/kg/day for liver transplantation'. Wiesner (1998) used an initial IV dose 0.15mg/kg/day in 48 of 263 patients on tacrolimus, then 0.1mg/kg/day in the remainder. The initial oral dose was 0.3mg/kg/day. Again, these doses were outside those given in the SPC.

Novartis alleged that the use of these two studies to promote Prograf was in breach of Clause 3.2 which 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 summary of product characteristics or data sheet'.

RESPONSE

Fujisawa did not agree with the allegations and disputed that the studies Pichlmayr *et al* (1997) and Wiesner *et al* (1998) used doses of tacrolimus outside the licensed doses given in the SPC. The doses used in the cited studies were well in line with the recommendations and guidelines outlined in the Prograf SPC and therefore Fujisawa disputed that there was any breach of Clause 3.2 of the Code.

Background information on immunosuppression in transplantation

The use of immunosuppression in the field of organ transplantation was a highly specialised and complex area. Medicines like Prograf (tacrolimus) or Sandimmun (cyclosporin) were usually used with others making up tacrolimus-based or cyclosporin-based immunosuppressive regimens. In order to achieve optimal outcome, the regimens were individualised on a patient by patient basis. The

following factors needed to be taken into consideration in order to optimise an immunosuppressive regimen:

Pharmacokinetic: Inter- and intra-patient variability in pharmacokinetic parameters, change in clearance with time post-transplant. Influence of the patient's clinical condition on the pharmacokinetics. For example, the inter-patient variability in oral bioavailability was high, and, therefore, the oral dose (mg/kg) was a poor predictor of systemic exposure, and therefore doses needed to be individualised to achieve a target systemic exposure (monitoring blood levels).

Clinical status of the patient, both prior to transplantation and post-transplantation: Factors such as, pre-existing renal impairment in patients undergoing liver transplantation, post-transplant liver impairment, immunological risks prior to transplant etc influenced both the initial as well as the maintenance dose. For example, in the event of post-transplant liver impairment, a lower dose (mg/kg) of tacrolimus would be used.

Concomitant medication: Potential for pharmacodynamic and pharmacokinetic interaction.

The transplant specialists were very familiar with the above factors and took these into consideration when deciding on the initial as well as the maintenance dose to be used in the individual patient.

It was well accepted in the area of clinical transplantation that the initial dosing (ie based on mg/kg) of Prograf or cyclosporin were only recommendations and were intended to act as a guideline. In transplantation, physicians were at liberty to choose a dose of tacrolimus or cyclosporin outside of the recommended guidelines if clinically justified. Subsequent doses of these agents were then adjusted based on the individual patient's clinical condition aided by monitoring blood levels of the respective drugs.

Doses of Prograf were adjusted in the event of adverse effects of drug/s (suspicion of drug toxicity), blood levels being below or above the therapeutic range, drug interactions, side-effects, rejection and the clinical status of the patient. For example, in section 4.2 of the SPC under Administration with Other Therapies: 'Prograf is normally given with other immunosuppressive agents'; and under Compromised Patients: Patients with liver impairment: 'A dose reduction might be necessary in patients with pre- and/or post operative impairment.

Section 4.5 listed a whole host of interactions with other medications taken in transplantation. All of these factors were clinically important factors that needed to be taken into consideration in the transplant patient.

A close examination of the Prograf SPC in detail would confirm that numerous statements were made in virtually every section of the SPC on the need and importance of adjusting the dosages (initial or maintenance dose) due to these and a number of other clinically important factors.

Hence in transplantation, immunosuppressive therapy with either Prograf or cyclosporin was based on monitoring of blood levels and took into consideration the overall clinical condition of the patient.

The studies in question

The concern expressed by Novartis related to the following two publications:
Pichlmayr *et al*, 1997: This was the European multi-centre liver study.
Wiesner *et al*, 1998: This was the US multi-centre liver study.

It was worth noting that the protocols of the above studies were approved by the respective health authorities of the countries where the studies were performed (including the MCA in the case of the UK). In addition the studies were also approved by the independent review boards (ethics committees) of the respective institutions. As stated in the study protocols, Prograf was compared with the best Sandimmun-based regimen at the participating centre (each of the centres had nearly 10 years of experience in using Sandimmun). This was to ensure the control group would provide the highest success rate at the institution.

Both of these studies were undertaken in the period of 1990-1992 and the protocols of the studies were based on the initial experience from the phase II studies and the experience from the University of Pittsburgh, USA, where Prograf was originally developed.

Prograf was licensed in the UK and US in 1994 and as was the case in the field of transplantation, the immunosuppressive regimens continued to evolve and the learning curve continued, including the time after approval of the medicines. For example, Sandimmun was launched in 1983 and its UK data sheet in 1990/91 stated that a dose of 14.0-17.5mg/kg/day was recommended. In contrast, this dose was subsequently reduced to 10-15mg/kg/day. Similarly, when Prograf was launched in the US in 1994, its recommended dose in liver transplantation was 0.3mg/kg/day. In contrast, the current recommended initial dose for Prograf in the US was one third to half this amount (0.1-0.15mg/kg/day). Thus confirming that as clinical experience had been gained over the last decade, lower doses and blood levels were targeted. This had been possible due to more understanding of the medicine's profile and the development of combination therapy with other immunosuppressive agents.

One other point of note was that in all subsequent studies (and in current clinical practice) tacrolimus dosing was initiated by the oral route. The use of IV Prograf was very rare and was only used when the clinical condition of the patient did not permit oral dosing. For example, the SPC stated: 'If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated'. Likewise in the paediatric dosing section, it stated: 'If the dose cannot be taken orally, an initial intravenous daily dose of … should be administered'.

The licence for Prograf in liver transplantation was granted in Europe and the US based on these two studies. Therefore, Fujisawa pointed out that the doses and dosing regimen mentioned in the Prograf

SPC were based on the actual doses and dosing regimen used and the data generated from these two studies.

Although the protocol in the studies recommended higher initial dosing level, however, this did not imply that these were the actual doses employed in these studies. The actual dosing (as determined by the clinical condition of the patient and the blood levels) was considerably lower both for Prograf and cyclosporin.

Fujisawa referred to actual dosing in the Pichlmayr *et al* 1997 study. Fujisawa submitted that a confidential report showed that the doses were in line with the recommended range in the SPC. Similarly Fujisawa referred to the actual dosing in the Wiesner *et al* 1998 study. An internal confidential report showed that the mean doses of Prograf (and those of Sandimmun) were wide ranging (as in all transplantation studies) and the mean doses were well within the range specified in the Prograf SPC.

Fujisawa stated that as pointed out above, the dosing of Prograf was not only based on the initial recommended dose in mg/kg/day, but the wording of the SPC was such that the dosing was based on a composite of integral factors such as blood levels and the clinical condition of the patient. In the published paper by Wiesner *et al* 1998 a graph showed the blood concentrations for Prograf from day 0 to 5 years. The results showed that the blood concentrations were wide ranging, however, the mean blood levels shown in the graph were reflective of the blood levels recommended in the SPC to aid dose adjustment.

This publication also showed that daily mean and median oral doses as well as the blood levels decreased with time for both the drugs.

Clause 3.2 of the Code stated that: 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics …'. Fujisawa pointed out that the doses of Prograf used in the studies were in line with the particulars listed in the Prograf SPC as outlined below.

In section 4.2 of the Prograf SPC.

Posology and Method of Administration, under 'General considerations' it was clearly stated that:

'The dosage recommendations given for oral and intravenous administration are intended to act as a guideline. Prograf doses should be adjusted according to individual patient requirements'. 'Only initial dosing is recommended and therefore therapy should be based on clinical judgement aided by measurement of tacrolimus concentrations in blood'.

In the same section of the SPC, the actual wording of the heading for the dosing was given as: 'Dosage Level Recommendations' and the subheading was given as: 'Initial dose level recommendation'.

Furthermore, additional statements to these facts were made further down in the same section and other sections of the SPC, informing the prescribing physician that the doses were intended to act as guidelines only, and that the doses should be individualised on a patient basis by taking into account their clinical condition and aided by monitoring blood levels of tacrolimus.

Fujisawa was somewhat surprised as to why Novartis had made this complaint in this respect, since by its own admission in its appeal letter of 1 August (letter relating to the same advertisement, Case AUTH/1030/6/00), it admitted and acknowledged that: 'Unlike the SPC for Prograf, there is no statement in the Sandimmun SPC which indicates that the dosage recommendations provided are intended to act as guidelines only…'. Furthermore, Novartis' letter admitted: 'It should be noted that whilst the Prograf SPC does make provision for dosages to be 'guidelines'…'.

Based on these recommendations and the particulars listed in the Prograf SPC, Fujisawa was confident that the Panel would agree that the studies in question did not breach Clause 3.2 of the Code.

In addition, it had to be pointed out that in its ruling relating to the same advertisement (in Case AUTH/1030/6/00), the Panel noted that 'Clinicians using the various medicines would be experts in their field. Clinicians might use doses outside the licensed recommendations'. In section 4.4 of the Prograf SPC, this fact was confirmed: '[Prograf] should only be prescribed, and changes in immunosuppression therapy should only be initiated, by physicians experienced in immunosuppressive therapy and management of transplant patients. The physician responsible for maintenance therapy should have complete information requisite for the follow-up patient. Prograf therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources'.

In concluding, it could be said that the main interpretation which could be drawn from the SPC for Prograf was that the initial dosing was only a recommendation to act as a guideline. Doses of Prograf were adjusted for each patient by monitoring tacrolimus blood levels (to be within the specified therapeutic range) and based upon the clinical condition of the patient.

Fujisawa respectfully asked the Panel to consult and seek advice from some of the transplant physicians on this issue and Fujisawa was confident that they would also support its case.

PANEL RULING

The Panel noted section 4.2 of the Prograf SPC headed 'Posology and Method Of Administration'. The first subsection headed 'General Considerations' stated that 'The dosage recommendations given below for oral and intravenous administration are intended to act as a guideline. Prograf doses should be adjusted according to individual patient requirements. Only initial dosing is recommended and therefore therapy should be based on clinical judgement aided by measurement of tacrolimus concentrations in blood'. A further subsection headed 'Dosage Level Recommendations. Initial dose level recommendation' referred to the primary immunosuppression dose levels for adults in kidney and liver transplantation

and stated that 'Oral tacrolimus therapy should commence at 0.10-0.20mg/kg per day for liver transplantation and at 0.15-0.30mg/kg per day for kidney transplantation administered as two divided doses. …If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion at 0.01 to 0.05mg/kg for liver transplants and 0.05 to 0.1mg/kg for kidney transplants'. The subsection headed 'Maintenance Therapy Dose Levels' stated that 'The dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability in each patient individually'. The Panel noted that the latter section did not refer to any specific dose.

The Panel noted the dosages used in Pichlmayr *et al* 1997) and Wiesner (1998) and the companies' submissions in this regard.

The Panel noted that transplantation was a highly specialised and complex area. Various pharmacokinetic and pharmacodynamic factors needed to be taken into account when administering Prograf which would influence the dosage regimen. Transplant specialists would be aware of these clinically important factors.

The Panel noted that the dosage recommendations in the SPC related to initial dosage rather than maintenance. The introductory sentence stated that dosage recommendations were intended to act as a guideline and referred to adjustment of dose according to individual requirements. In the opinion of the Panel the introductory sentence would necessarily relate to initial dosing. There were no maintenance dosage recommendations. According to the SPC the indicated dosing was flexible. No breach of Clause 3.2 was ruled.

Complaint received **30 August 2000**

Case completed **25 October 2000**

CASE AUTH/1070/9/00

MERCK SHARP & DOHME v ALCON

Promotion of Azopt

Merck Sharp & Dohme complained that by promoting Azopt (brinzolamide) for twice daily use Alcon had over simplified the licensed indication for the product. A leaflet and a journal advertisement were provided in which 'Twice daily' was included in the product logo. Merck Sharp & Dohme noted that the summary of product characteristics (SPC) stated 'the dose is one drop of Azopt in the conjunctival sac of the affected eye(s) twice daily' which was qualified by the statement 'Some patients may have a better response with one drop three times a day'.

The Panel noted that in the materials at issue the only mention of the fact that some patients might have a better response with one drop three times a day was in the prescribing information. The Panel considered that the materials were inconsistent with the particulars listed in the SPC as they gave the impression that the only dose was twice daily. A breach of the Code was ruled. This was appealed by Alcon. The Appeal Board noted that clinical data showed that the mean reductions in intraocular pressure with Azopt twice daily vs three times daily were clinically and statistically equivalent. New patients on Azopt would receive a twice daily dose and if this was not effective they would receive another treatment. Azopt was often added to twice daily therapy; to avoid confusion and assist patient compliance it was unlikely to be used three times a day. The number of patients who would receive a three times daily dose was small. The Appeal Board considered that in the circumstances it was not unreasonable to refer to the dosage of Azopt as twice daily. No breach of the Code was ruled.

Merck Sharp & Dohme complained about a graph in the leaflet which showed the results of a study comparing twice daily Azopt with its product, dorzolamide (Trusopt), used three times daily. It was alleged that omission of the data relating to the use of Azopt three times daily further promoted twice daily Azopt as the only dose.

The Panel noted that the study from which the graph was taken showed that the responses to Azopt twice daily and three times daily were clinically and statistically equivalent to each other and to Trusopt three times daily. Azopt was licensed for twice daily use and the graph was clearly labelled. The Panel did not accept that the omission of the Azopt three times daily data meant that the graph on its own *per se* further promoted the twice daily dose rather than the licensed indication as alleged. No breach of the Code was ruled.

Merck Sharp & Dohme alleged that the presentation of data in the leaflet claiming that 81.3% of patients reported no ocular discomfort with Azopt vs 17% with dorzolamide was misleading and did not reflect available evidence for the incidence of all ocular adverse events.

The Panel noted that ocular discomfort was not defined in the main body of the leaflet; it was defined in the prescribing information as transient burning or stinging upon instillation. Other ocular effects were mentioned in the SPC. The data shown in the leaflet had been taken from only one study and while other studies were also in favour of Azopt with regard to ocular discomfort (burning and stinging) the differences were not as marked. The

Panel considered that it was misleading to refer to ocular discomfort without defining the term; it might be taken to mean a whole range of ocular side effects and not just stinging and burning. The Panel considered that the data was not a fair reflection of all the available evidence. Breaches of the Code were ruled.

Merck Sharp & Dohme stated that the promotional materials inferred improved compliance with Azopt. The European Public Assessment Report (EPAR) stated that compliance was never directly assessed in the clinical trials. Merck Sharp & Dohme believed compliance was, therefore, an inferred benefit based on unbalanced or misleading information as outlined above.

The Panel noted that the claim 'New Azopt for comfort, compliance and control' appeared in the journal advertisement. The words 'comfort, compliance, control' appeared in the leaflet. The leaflet also contained a general statement relating compliance to ocular comfort. Alcon had no data on compliance with Azopt although the company submitted that compliance in patients with glaucoma was improved when frequency of dosing and side effects were reduced. The Panel considered that there was no data to support the claim that Azopt improved compliance. A breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about the promotion of Azopt (brinzolamide) by Alcon Laboratories (UK) Limited, the items at issue being a leaflet (ref AZ:DA/M:0300(MCA)) and a single page journal advertisement (unreferenced).

1 Reference to dosage as 'twice-daily' Azopt

Both the leaflet and the journal advertisement included the brand name in logo style immediately beneath the words 'New' and 'twice daily' which were included as part of the logo.

COMPLAINT

Merck Sharp & Dohme referred to the summary of product characteristics (SPC) dosage statement that 'the dose is one drop of AZOPT in the conjunctival sac of the affected eye(s) twice daily', this statement was clearly qualified by the statement 'Some patients may have a better response with one drop three times a day'.

Thus, 'twice-daily' Azopt was an over simplification of the licensed indication. This was not a question of whether bid dosing or tid dosing was more effective. Rather, the statement 'twice-daily' Azopt, without further clarification, simply failed to acknowledge the clinically significant number of treatment non-responders (approximately 10%) to the twice daily dosing schedule compared with the tid regimen. Merck Sharp & Dohme believed that to advertise Azopt only as 'twice-daily' without this clarification displayed clearly and prominently in conjunction with the statement amounted to a breach of Clauses 3.2 and 7.2 of the Code.

That some patients might require Azopt three times a day to achieve an adequate clinical response was clearly an issue that was highlighted within the European Public Assessment Report (EPAR) of the application to the European Medicines Evaluation Agency where the following statements were made with regard to dosage:

> '… it could be argued the TID regimen should be the preferred one. The arguments in favour of a TID regimen are the following: with regard to the compliance, the statement made by the applicant is weak as compliance was never assessed in the file. Although the IOP differences are inferior to 1mmHg and thus, without clinical significance the overall number of controlled patients is always higher with the TID regimen rather than the BID regimen. This is of clinical significance and demonstrated in the file. Moreover in the 18-month study IOP was not measured at the late afternoon point, and thus due to the inter-individual variation in nycthemeral IOP, there is no confirmation of the nycthemeral control beyond a 3-month duration.
>
> Therefore the following wording has been included in section 4.2 of the SPC:
>
> 'When used as monotherapy or adjunctive therapy, the usual dose is one drop of Azopt eye drops in the conjunctival sac of the affected eye(s) twice daily. Some patients may have a better response with one drop three times a day.''

Merck Sharp & Dohme alleged that it was misleading to ignore the fact that for some patients, tid dosing might be necessary to attain adequate intraocular pressure (IOP) control. Although the tid dosage statement was in the prescribing information, Merck Sharp & Dohme believed that this was insufficient and should be clearly and prominently acknowledged whenever twice-daily dosing was mentioned in promotional material.

RESPONSE

Alcon did not accept that the twice-daily statements in its detail aid and advertisement were misleading or an over-simplification and in breach of Clauses 7.2 and 7.6 of the Code. This was supported by the Introduction to the 'Scientific Discussion' of the EPAR, the second paragraph stated 'When used as monotherapy or adjunctive therapy, the dose is one drop of Azopt in the conjunctival sac of the affected eye(s) BID'. This statement was not qualified in any way. Similarly, the Abstract at the front of the EPAR stated 'These studies showed that Azopt can be usually used BID, but that some patients may have a better response with one drop TID. Both dosage regimens were shown to be effective'.

If the authors of the EPAR thought it appropriate when summarising or writing an introduction about Azopt to refer to the dose as 'BID' or 'usually used BID', Alcon did not think it was inappropriate for it to do the same in its promotional items and advertisement for Azopt.

Alcon did not ignore the fact that some patients might have a better response with one drop three times a day because this was clearly stated in the prescribing information.

Alcon referred to Merck Sharp & Dohme's letter which quoted from parts of the discussion about the dosage regime in the EPAR comparing bid to tid therapy and said that the paper supported Merck Sharp & Dohme's view. However, in the same section of the EPAR it stated 'The superior efficacy of the TID regimen, if it exists, would be about 1mmHg, which has no clinical significance. The long term trial does not find differences in IOP between both regimens and only one of the two 3-month trials suggests a difference of the above-mentioned magnitude'. It was Alcon's position that most patients were adequately controlled with the bid dosage, which also facilitated compliance. The European licensing authorities obviously concurred with this view because Alcon had received approval for the twice-daily dosage, if they did not agree they would have insisted that the dose was three times a day for all patients. Merck Sharp & Dohme had also pointed out that approximately 90% of patients were controlled on the twice-daily dosage, which was considered clinically acceptable and within the normal response rate for most anti-glaucoma treatments.

PANEL RULING

The Panel noted that Azopt was indicated to decrease elevated IOP in ocular hypertension and open angle glaucoma as monotherapy in patients unresponsive to beta blockers or in patients in whom beta blockers were contra-indicated or as an adjunctive therapy to beta blockers. The SPC section headed 'Posology and Method of Administration' stated that when used as monotherapy or adjunctive therapy the dose was one drop of Azopt twice daily Some patients might have a better response with one drop three times a day.

The Panel noted that the materials in question referred to twice daily dosing. The only mention of the fact that some patients might have a better response rate with one drop three times a day was in the dosage section of the prescribing information on each item.

The Panel considered that the leaflet and the journal advertisement were inconsistent with the particulars listed in the SPC as they gave the overall impression that the only dose of the product was twice daily. This was not so. There would be some patients on a dose of three times daily and this had not been mentioned in the main body of the text. The Panel considered that the material in question was misleading and a breach of Clause 7.2 of the Code was ruled. The Panel considered that the allegation of a breach of Clause 3.2 was covered by this ruling.

APPEAL BY ALCON

Alcon referred to Merck Sharp & Dohme's complaint which stated 'twice daily Azopt, without further clarification, simply failed to acknowledge the clinically significant number of treatment non-responders (approximately 10%) to the twice daily dosage schedule compared with the tid regime'.

Alcon submitted that the twice daily versus three times daily dosage of Azopt was not clinically significant in the treatment of glaucoma as stated by Silver *et al* (1998) and March *et al* (2000). A letter from a UK glaucoma specialist also supported this, his review of the literature found that the optimal intraocular pressure lowering schedule of brinzolamide 1% was twice daily.

The 10% non-responder figure mentioned by Merck Sharp & Dohme was not an absolute figure either and had been taken from the two Azopt primary therapy studies, Silver *et al* and Sall *et al* 2000. The total number of patients on these two trials was 1035. The responder analysis data (intraocular pressure (IOP) reduction of ≥ 5mmHg or a controlled pressure of ≤ 21mmHg) gave the mean percentage of patients responding to bid Azopt at 60.3% and tid Azopt at 65.8%. The percentage difference between these two groups was 10%, based on the IOP reduction criteria described above. The difference was not considered clinically relevant in the treatment of glaucoma as there was often a considerable variability between patients to the pressure lowering effects of medication.

New patients treated with Azopt would be expected to start with a twice daily dosage, if the response was marginal perhaps tid dosage could be an option. However, evidence Alcon had from consultant ophthalmologists would suggest that if the twice daily dosage did not adequately control IOP, they would not switch to a tid dosage. This had been further supported by a letter from a consultant ophthalmologist, and Alcon's medical advisor, in which he stated that using a tid dosage would give an insignificant incremental lowering of IOP and a switch to an alternative therapy would be in order.

Alcon did not consider the twice daily dosage to be misleading as it would be the dosage patients were started on, a switch to tid dosing might not give adequate IOP control if patients did not respond to bid dosage. Pressure control was optimal in this disease that could possibly lead to loss of vision. The European Glaucoma Society treatment guidelines 1998 stated, 'the goal of glaucoma treatment is to maintain the patient quality of life at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. The quality of life is closely linked with visual function. The treatment side effects, the dosing schedule and the constant worry about losing eye-sight are all detrimental to the quality of life. In order to preserve visual function, current therapy is to lower the IOP'.

Alcon submitted that the prescribing information was clear, and it was clearly indicated on the brochure where the prescribing information could be found. For a clinician to obtain full details of a medicine ie dosage, side effects, interactions, toxicity, etc, it was good clinical practice and their professional responsibility to be familiar with the SPC or prescribing information of the product. The SPC and prescribing information of Azopt clearly stated that the dosage was twice daily. They did expand further by saying that some patients might have a better response with a tid dosage.

Alcon provided two letters from consultant ophthalmologists. Alcon's medical advisor had outlined his reasoning and justification of the twice-daily dosage, and the glaucoma specialist, who had no financial interest in Alcon or an advisory role, had

clearly stated his opinion of the bid and tid dosage regimes of Azopt.

APPEAL BOARD RULING

The Appeal Board noted the submission that mean intraocular pressure reductions with Azopt bid versus tid were clinically and statistically equivalent (Silver *et al* and March *et al*).

The Appeal Board noted the submission from Alcon that new patients on Azopt would receive bid dosage and that if this was not effective a clinician would switch to another treatment, pharmacological or surgical. Azopt was often used adjunctive to bid therapy and so to avoid confusion and to assist patient compliance clinicians were unlikely to use it three times a day. The Appeal Board noted that the number of patients who would receive the tid dose was small. The Appeal Board noted Alcon's submission regarding the 10% non-responder figure mentioned by Merck Sharp & Dohme. The Appeal Board considered that taking all the circumstances into account it was not unreasonable to refer to the dosage of Azopt as twice daily. No breach of Clause 7.2 was ruled. The appeal was thus successful.

2 Graph in the leaflet headed 'Azopt bid monotherapy is as effective as dorzolamide 2% tid'

The graph at issue was referenced to data on file. It showed a three month comparison of Azopt bid monotherapy with Merck Sharp & Dohme's product dorzolamide 2% tid (Trusopt) with regard to mean reduction in intraocular pressure. It stated that there was no statistically significant difference between dorzolamide 2% tid and Azopt 1% bid.

COMPLAINT

Merck Sharp & Dohme alleged that following the arguments outlined in point 1 above, it believed that the graph shown in this promotional item, by the deliberate omission of the Azopt tid arm of the study, further promoted 'twice-daily' Azopt rather than the licensed indication (in which the need for tid dosing in some patients was clearly identified) and was therefore misleading. This was alleged to be in breach of Clauses 7.2 and 7.6 of the Code.

RESPONSE

As Alcon did not agree with the argument in point 1, it did not think that this graph was misleading or that it was in breach of Clauses 7.2 or 7.6 of the Code. The graph showed the usual dose of Azopt which was one drop twice a day when used as monotherapy and compared it to the usual dose of dorzolamide used likewise. This study had been published and in the conclusion it stated that the IOP reductions after bid and tid dosing with Azopt were both clinically and statistically equivalent to each other.

PANEL RULING

The Panel noted that the comparison shown was between Azopt bid and dorzolamide tid. The study Silver *et al* (1998) investigated the IOP lowering efficacy and safety of Azopt administered two and three times daily, dorzolamide 2% administered three times daily and timolol 0.5% administered twice daily in patients with open angle glaucoma. The results of the study demonstrated that the IOP reductions after bid and tid dosing with Azopt were both clinically and statistically equivalent to each other and to dorzolamide 2% tid.

The Panel noted that Azopt was licensed for twice daily use. In the Panel's view it was reasonable to include data comparing Azopt bid with dorzolamide tid without necessarily having to refer to Azopt tid. The graph was clearly labelled. The Panel noted its ruling in point 1 above which related to the items in general. In effect the context of the graph had been ruled in breach in point 1 above [this ruling was overturned upon appeal by Alcon]. The Panel did not accept that the omission of the brinzolamide tid arm of the study meant that the graph on its own *per se* further promoted 'twice daily' dose rather than the licensed indication as alleged. The product was licensed for twice daily use. The Panel ruled no breach of Clauses 7.2 and 7.6 of the Code.

3 Reference to ocular tolerability

The leaflet included a bar chart comparing the percentage of patients with no ocular discomfort referenced to a study by Silver *et al* (2000). The figures in the bar chart were 81.3% for Azopt (n = 48) and 17% for dorzolamide 2% (n = 47). Beneath the bar chart was the claim '… 'brinzolamide 1% was significantly more comfortable than dorzolamide 2% when instilled in the eye.'' A p value of $p<0.001$ was given beneath the bar chart.

Above the bar chart it was stated that the results were from two multicentre comfort studies.

COMPLAINT

Merck Sharp & Dohme alleged that the presentation of the data claiming 81.3% of patients reported no ocular discomfort with Azopt versus 17% with Trusopt (that was 18.7% vs 83% patients respectively presented with ocular discomfort) was misleading and did not reflect available evidence for the incidence of all ocular adverse events with either compound previously reported in other clinical trials.

In the first place, the incidence of burning and stinging reported in these clinical trials (which used three-times daily Azopt and not twice-daily dosing) as assessed by the incidence of responses on an ocular discomfort scale, was unusually high compared with those previously reported in other larger multicentre trials (eg 2.0-3.0% and 10.7-16.4% incidence of burning and stinging on instillation of Azopt and Trusopt respectively). It was important to recognise that questionnaire data, which was collected by direct questions, was not the same as spontaneous, unprompted reports of an adverse experience, which were the preferred method of measuring effect, and might explain the differences between these results and those previously reported in other clinical trials. As such, the leaflet was inconsistent with previously reported incidence of burning and stinging with

either compound and therefore misleading when presented without further clarification for this discrepancy. A breach of Clauses 7.2 and 7.7 of the Code was alleged.

In addition, although ocular discomfort was defined a priori to be based on burning and stinging alone, the authors recognised that there were other symptoms of ocular discomfort which could contribute to patient compliance and had reported their incidence as well. For example, the incidence of blurred vision in the referenced study was significantly higher in the Azopt group than in the dorzolamide group, occurring in 25% vs 3.7% respectively. Further, foreign body sensation occurred in 6.5% vs 4.7% of the patients treated with brinzolamide and dorzolamide respectively. Further, it had been reported that the demise of another IOP lowering agent, pilocarpine, was in part due to it causing blurred vision. Merck Sharp & Dohme alleged that the omission of the incidence of these other ocular effects was unbalanced, unfair, and misleading in breach of Clauses 7.2 and 7.7.

RESPONSE

Alcon stated that the EPAR, Table 5, divided the clinical trials into efficacy studies and comfort studies. When discussing comfort in the leaflet, it was thought appropriate to refer to the two double blind randomised studies in patients referred to in this table. These studies had been published in Silver *et al* (2000) which was the reference given in the leaflet. It clearly stated in the title of the graph that these were 'Results from Two Multicentre Comfort Studies', ie not the incidence of ocular adverse events from efficacy clinical trials. It was not misleading because the same criteria had been applied to both products.

The summary of this study stated 'the findings obtained from the two separate studies independently confirmed that brinzolamide 1.0% ophthalmic suspension is well-tolerated and that its ocular tolerability represents a clinically significant improvement over the topical carbonic anhydrase inhibitor dorzolamide. Such findings suggest that a well-tolerated formulation may contribute to improved patient acceptance and compliance with long-term therapy'.

The statement 'brinzolamide 1% was significantly more comfortable than dorzolamide 2% when instilled in the eye' was a direct quote from the reference and could be corroborated by other publications.

It was correct in that Alcon had chosen to discuss burning and stinging in relation to ocular discomfort because that was how ocular discomfort was defined and evaluated in these studies. It was true there were other adverse events, but Alcon was not obliged to discuss all adverse events when it had defined ocular comfort as burning and stinging. A full listing of all undesirable effects was given in the abbreviated prescribing information where it stated that 'In clinical studies the most frequently reported treatment related adverse events and local symptoms were …temporary blurred vision upon instillation, lasting for a few seconds to a few minutes'. This was an expected consequence of the delivery system, ie a slightly viscous suspension, and could not be equated to the blurred vision associated with pilocarpine which was a pharmacological effect of the drug acting on the ciliary muscle which could lead to ciliary spasm and blurring of vision.

For the reasons stated above, Alcon did not believe that the data presented on ocular comfort was unbalanced, unfair or misleading.

PANEL RULING

The Panel noted that ocular discomfort was not defined in the main body of the leaflet. In the ocular effects section of the prescribing information ocular discomfort was defined as transient burning or stinging upon instillation. Other ocular effects such as blurred vision and foreign body sensation (common) and ocular pain (uncommon) were also mentioned in the SPC. The studies used as a reference in the leaflet defined ocular discomfort as burning and stinging. Both studies independently showed that administration of Azopt tid resulted in a statistically significant ($p = 0.0001$) lower ocular discomfort (burning/stinging) score than administration of dorzolamide 2% tid after one week. Each study independently found that a significantly ($p < 0.001$) greater percentage of patients experienced no ocular discomfort with Azopt compared to dorzolamide. The results of the study showed a significantly higher incidence of transient blurred vision in the brinzolamide group compared to the dorzolamide group This finding was in contrast to the results obtained in two large multicentre studies.

The Panel noted that the results given in the leaflet were from one of the two studies. The results for the other study was 71.2% patients with no ocular discomfort for Azopt and 19.6% for dorzolamide. The leaflet did not state that the data was from tid dosing of Azopt. The data from the clinical trials showed differences between the products in favour of Azopt in relation to ocular discomfort but the differences were not as marked as those shown in the leaflet. The Panel noted that the claim beneath the bar chart referred simply to brinzolamide 1% being '… more comfortable than dorzolamide 2% …'.

The Panel considered that it was misleading to refer to ocular discomfort without defining what was meant by the term. It might be taken to mean the whole range of ocular side effects and not just burning and stinging. The claim beneath the bar chart referring merely to 'comfortable' would in the Panel's view add to the confusion as to what was meant. The Panel also considered that the data was not a fair reflection of all of the available evidence. The Panel ruled breaches of Clauses 7.2 and 7.7 of the Code.

4 Inference of improved compliance with Azopt

COMPLAINT

Merck Sharp & Dohme stated that through careful construction, improved compliance with Azopt was inferred. On one level, the promotional items appeared to suggest that improved ocular comfort, as defined by a lower incidence of burning or stinging,

improved ocular tolerability and therefore compliance. However the argument that the improvement in burning or stinging sensation alone led to improved patient compliance appeared to be flawed and unbalanced. As indicated in point 3 above, whilst it was clear that improvements in burning and stinging were important, it was unlikely to be the only aspect of ocular tolerability which might improve ocular comfort and, indirectly, patient compliance. In addition it had been reported that patient compliance to use eye drops was not significantly influenced by side effects.

On another level, one could also argue, based on information presented in the material at issue, that compliance might be improved with twice-daily dosing Azopt, as compared with three times daily dorzolamide. Again, based on arguments presented in point 1 above, this could not be supported since some patients would require tid dosing Azopt to achieve adequate IOP lowering.

Clearly, as stated within the EPAR, compliance was never directly assessed in the clinical trials. Thus Merck Sharp & Dohme believed that compliance was, therefore, an inferred benefit based on unbalanced and misleading information and was in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Alcon said that it did not directly claim that Azopt improved compliance; it only stated that 'Compliance can be an important factor to consider in controlling IOP' and that 'Eye drops should, therefore, be comfortable for glaucoma patients to apply'.

However, it was well established that compliance in patients with glaucoma was improved when the frequency of dosing and side effects were reduced.

Although some published papers did suggest that Azopt's well-tolerated formulation might contribute to improved patient compliance (see point 3 above), Alcon did not make this claim.

PANEL RULING

The Panel noted that the claim 'New Azopt for comfort, compliance and control' appeared in the advertisement. A similar claim was made on the leaflet which had the words 'comfort, compliance, control' at the bottom of one of the pages. The leaflet also stated on two separate pages 'Compliance can be an important factor to consider in controlling IOP. Eye drops should therefore be comfortable for glaucoma patients to apply'.

The Panel noted that compliance was never directly assessed in the clinical trials. Alcon had no data on compliance with Azopt although the company submitted that compliance in patients with glaucoma was improved when the frequency of dosing and side effects were reduced.

The Panel considered that the materials were claiming that Azopt improved compliance and there was no data to support this. The Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

Complaint received **1 September 2000**

Case completed **2 January 2001**

ANONYMOUS v INNOVEX and NOVO NORDISK

Role of nurse field force

An anonymous complaint was received about the activities of a Novo Nordisk field force for nurses. It was alleged that the nurses formed relationships with GPs and practice nurses in order to obtain names and addresses from diabetic patients' notes. Novo Nordisk would then mailshot those patients with messages about diabetes and Novo Nordisk's medicines. A breach of Clause 2 was alleged.

The matter also concerned Innovex which was establishing the Diabetes Nurse Advisers for Novo Nordisk. Innovex had only provided the service to Novo Nordisk. The Director therefore decided that there was no *prima facie* case for Innovex to answer under the Code.

With regard to Novo Nordisk, the Panel noted the arrangements for the Diabetes Nurse Advisers. They were to work in secondary care although some of the documentation also referred to primary care work. The Panel noted that there was no evidence that nurse advisers were obtaining patient details from GPs and practice nurses for Novo Nordisk mailing purposes. The Panel noted that patients would be written to about the availability and use of a pen device, the proforma letter was to be signed by the consultant and the patient was offered an appointment with the Diabetes Support Nurse. The issue of data protection and patient confidentiality was covered in the documents provided. The instructions to the nurse advisers stressed the importance of patient confidentiality. The Panel ruled that there had been no breach of the Code.

COMPLAINT

An anonymous complaint was received. The complainant referred to a colleague (a nurse specialising in diabetes) who went for an interview at Innovex for a contract position with Novo Nordisk. She was told by Innovex that Novo Nordisk had a field force of nurses to 'form relationships' with GPs and practice nurses in order to gain access to the notes of diabetic patients and get their names and addresses. Novo Nordisk would then 'mail shot those patients with appropriate messages about diabetes and (?) [sic] their POM products'.

The complainant was appalled. The colleague was so alarmed at this activity that she naturally declined to take her interest in the position further. If this was true it was a major breach of patient confidentiality on the part of the GP and one of the most cynical breaches of Clause 2 of the Code the complainant had ever encountered. The complainant was surprised that a reputable company like Innovex should be complicit with such shady dealings.

It had previously been decided that anonymous complaints should be accepted and dealt with in the usual way. The complaint was accordingly taken up with both Innovex (UK) Limited and Novo Nordisk Pharmaceuticals Ltd, though it was not clear in the circumstances as to the extent to which the Code applied to the former company.

When writing to the companies, the Authority asked them to bear in mind Clauses 9.1 and 18 of the Code, as well as Clause 2 which had been referred to in the complaint.

Case AUTH/1071/9/00

RESPONSE FROM INNOVEX

Innovex stated that notwithstanding Clause 15 of the Code, it operated a policy of full accountability for the actions of all employees in relation to the Code. This was particularly so in relation to the activities of its nurse advisers where Innovex had to ensure that it was operating not only within the Code, but also within UKCC and GMC codes of professional conduct. A detailed response was received from Innovex.

Case AUTH/1072/9/00

RESPONSE FROM NOVO NORDISK

Novo Nordisk stated that it was concerned by the anonymity of the complaint, especially in view of the serious inaccuracies contained within it. Novo Nordisk also considered that it had an unfortunate clinical disrespect for those diabetes nurse specialists who worked as advisers for Innovex.

The background to these nurse advisers was recognition that under-funding in secondary care had led to waiting lists for people to be converted to insulin from oral hypoglycaemic agents. In addition, the Government's decision to reimburse insulin pens and needles earlier this year meant that patients who previously had been using syringes now had a new treatment option but with further impact in terms of time and resources on the diabetes care team. As a service to diabetes care, Novo Nordisk decided to fund a limited number of nurse advisers in diabetes who would work partly on duties assigned by the lead consultant in the unit (perhaps to reduce waiting lists) and partly on device conversion clinics. It was important to state that there was no agreed stipulation either verbally or in writing about which insulin patients would be prescribed or which insulin delivery devices they would use.

The complainant alleged that their colleague was told at an interview that Novo Nordisk was using these nurses to gain access to confidential information about patients with diabetes so that Novo Nordisk could mail those patients directly. Novo Nordisk's Diabetes Nurse Advisers only ever worked in secondary care and as would be seen in the Honorary Contract under point 3, only anonymized data aggregated over a large patient population would be available such that it would not be possible to distinguish a particular hospital. It was also not a

condition of the agreement that the hospital had to release such data if it felt disinclined to do so. Like the complainant, Novo Nordisk too would be appalled at any company attempting to gain access to patients in this way. Novo Nordisk could confirm that no mailings originating from Novo Nordisk were planned in connection with this activity and no mailing would be possible from any data received.

Novo Nordisk was clearly therefore not in breach of Clause 2 of the Code. It would be noted from the activity flow sheet that patient mailings generated by the hospital clinic would occur inviting patients to attend a pen conversion clinic and that these mailings would not be seen by Novo Nordisk and were sent to patients regardless of which insulin they were currently using.

The Authority had raised potential breaches of Clause 9.1 and Clause 18. With regard to Clause 9.1, Novo Nordisk failed to see how this professional arrangement between a diabetes nurse specialist employed by Innovex and the diabetes unit could possible amount to sponsorship likely to cause offence. With regard to Clause 18, it was important to note that provision of medical services which would enhance patient care was specifically covered in the supplementary information to Clause 18.1. It would be seen from reading the contracts and job descriptions that there was no attempt to link the nurse with the prescription of any particular product or device which was a key differentiator from previous activities of other companies which had been well covered in Code of Practice Reviews.

Novo Nordisk trusted it had provided enough explanation and background material for it to be concluded that this program was carefully designed to be compliant with all relevant codes, and that no breaches of Clause 2, Clause 9.1 or Clause 18 of the Code had occurred.

Cases AUTH/1071/9/00 and AUTH/1072/9/00

PANEL RULING

The Panel noted that the pharmaceutical company responsible for the activities was Novo Nordisk. Innovex had provided a service to Novo Nordisk. The Director therefore decided that there was no *prima facie* case to answer under the Code in relation to Innovex.

The Panel noted that the allegation referred to the nurse advisers forming relationship with GPs and practice nurses in order to gain access to diabetic patients' addresses for mailing information about diabetes and prescription only medicines. The Panel noted that this was denied by Novo Nordisk which stated that its diabetes practice nurses only ever worked in secondary care ie in hospital clinics. The Panel queried whether this was so. The briefing document to Novo Nordisk sales specialists (attachment 4) referred to the fact that at the request of the consultant the nurse advisers would provide support for broader aspects of care of patients within the individual units. These roles would vary across various locations but would be clinical in nature. One of the examples given was providing educational support to NHS staff within the Trust or primary care settings. The Panel also noted that a slide presentation 'The role of the diabetes specialist nurse' stated that the nurse was based in primary and/or secondary care.

The Panel noted that there was no evidence that nurse advisers were obtaining patient details from GPs and practice nurses for Novo Nordisk mailing purposes. The Panel noted that patients would be written to about the availability and use of a pen device, the proforma letter was to be signed by the consultant and the patient was offered an appointment with the Diabetes Support Nurse. The issue of data protection and patient confidentiality was covered in the documents provided. The Honorary Contract for the Temporary Secondment of Innovex Nurse Adviser in secondary care discussed patient and practice confidentiality and data management and stated *inter alia* that the nurse adviser was required to protect all personal information concerning named patients to which they might have access during their work with the hospital and maintain patient confidentiality. Named patient information would not be removed from the hospital and hospitals would have all data made anonymous by the allocation of an appropriate code held at that hospital. The sponsoring company might have access to anonymous aggregated data in order to gain a large population for analysis; similar information appeared in a letter (Appendix 2 of the Honorary Contract) to be signed by a hospital whereby it gave permission to access patient information. The Panel noted that the letter also stated that 'no named patient information will be removed from your hospital at any time without your explicit permission'. The instructions to the nurse advisers stressed the importance of patient confidentiality. The Panel did not consider that there was a breach of the Code as alleged and no breach of Clauses 2, 9.1 and 18.1 was ruled.

Complaint received	**4 September 2000**
Cases completed	**27 September 2000**

CASE AUTH/1073/9/00

CONSULTANT PHYSICIAN v NOVO NORDISK

Invitation to participate in workshop

A consultant physician complained about an invitation which he had received from a health authority medical adviser to participate in one of two evening workshops for general practitioners on the management of type 2 diabetes which would review the use of repaglinide (Novo Nordisk's product NovoNorm). The complainant said that he had been offered an honorarium to participate and was uneasy about this as only repaglinide was to be discussed. He would have been more comfortable if the health authority had invited other companies as well or if Novo Nordisk had been running the meeting itself.

The Panel noted that Novo Nordisk had been asked to support a meeting where the relevance of NovoNorm was to be discussed. The product had been given a limited prescribing status on the regional drug formulary which was coming up for review. The health authority medical adviser decided to consult widely with interested parties. The invitation came from the medical adviser. He had received administrative help from Novo Nordisk in the initial drafting but the final text was his own and it was sent by his department. As the meeting was initiated by the health authority, Novo Nordisk had not intended offering an honorarium and the invitation did not refer to one. The company could not explain why the complainant thought he would be offered a fee. The costs of the meeting were to be met by Novo Nordisk. The Panel considered that the arrangements for the meeting were not unacceptable. It was reasonable for a company to sponsor a meeting on one of its products. The anticipated costs did not appear to be unreasonable. No payment was to be made to either speakers or attendees. The Panel therefore ruled no breach of the Code in those respects.

The invitation stated that the author had invited Novo Nordisk to become involved in the initiative but it failed to declare that the meeting was sponsored by it. A breach of the Code was ruled. Novo Nordisk had sponsored the meeting and had been involved in the preparation of the letter and the Panel considered that the letter in effect promoted NovoNorm and this meant that it should have included prescribing information. The Panel also considered that the activity might be seen as disguised promotion. Bearing in mind its comments about the letter and that the company had failed to declare its sponsorship, the Panel considered that the company had not maintained a high standard and a breach of the Code was also ruled in that regard.

A consultant physician complained about a letter which he had received from the medical adviser to a health authority inviting him to participate in one of two evening workshops to be held for general practitioners on the management of type 2 diabetes. The letter stated that it was hoped that this would provide the complainant with the opportunity to share his views on treatment options and gain the views of general practitioners who were already using repaglinide (NovoNorm – Novo Nordisk Pharmaceuticals Ltd's product). A number of GPs were particularly interested in this product which appeared to offer an alternative towards good glycaemic control. Use of repaglinide could be initiated at the present time only by regional or local specialists but this was shortly coming up for review. The letter went on to say that Novo Nordisk had been invited to become involved in the initiative and had proposed that its medical affairs manager present the most up-to-date clinical data. One or two GPs would be invited to present interesting case studies involving the use of repaglinide. The workshops would commence at 7pm for two hours followed by dinner.

COMPLAINT

The complainant said that he had been offered an honorarium to participate in the meeting. He felt uneasy that Novo Nordisk was promoting the meeting and would be seen to do so jointly with the health authority and he wondered whether it complied with the Code. The complainant would be comfortable for Novo Nordisk to be sponsoring a meeting, for the health authority, in which the treatment of type 2 diabetes was discussed, rather than just Novo Nordisk's product. It could easily appear that the health authority specifically endorsed the product. Had the other interested companies had a chance to promote the same type of meetings with the health authority? The complainant would also have been comfortable with Novo Nordisk running the meeting and inviting speakers from a variety of backgrounds including the health authority.

The complainant stated that he had on many occasions spoken at meetings sponsored by pharmaceutical companies and had always insisted that he was free to give his unbiased opinion on any product and it had always been clear that the meeting was a 'drug company meeting'.

The complainant had also in the past been left feeling uneasy by Novo Nordisk, for example once attending what he took to be an educational activity, with paid board and lodging, but also receiving £600!

When writing to Novo Nordisk the Authority drew attention to Clauses 2, 9.1, 18 and 19 of the Code.

RESPONSE

Novo Nordisk stated that the complainant had concerns regarding a potential bias where a meeting run by a health authority was being supported by Novo Nordisk with a Novo Nordisk product (repaglinide). It was also alleged that the speakers at the meeting had been offered an honorarium to take part.

The background to this meeting was that the medical adviser to the health authority approached Novo Nordisk to support a meeting where the relevance of repaglinide could be discussed amongst clinicians in secondary and primary care. Repaglinide had been given a limited prescribing status on the regional drug formulary which meant that it could only be prescribed by regional or local specialists in diabetes care. This decision was coming up for review and

Novo Nordisk understood that the medical adviser decided to consult widely with interested parties. He decided to organise two meetings, one on each side of the region, which would allow both secondary and primary care input to the decision making process. Contact with the medical adviser was initially made via a contract primary care sales representative who saw him on a routine call while he was working as a GP locum. The medical adviser had an interest in diabetes and was keen to meet with the Novo Nordisk local sales team. A meeting took place between the medical adviser, Novo Nordisk's primary care representative and Novo Nordisk's regional NHS liaison manager where his idea was discussed.

Novo Nordisk was happy to support these meetings. The cost of the meetings would be £250 for room hire and £25 per head for the meal. The invitees were all four of the consultant diabetologists (non-paediatric) in the region and the meeting was open to all general practitioners; there was no planned selection bias. The invitation to the consultants was sent by the medical adviser. He received administrative help from Novo Nordisk in the initial drafting of the letter but the final text was his own and was sent by his department The invitations for primary care had not yet been designed. Novo Nordisk had no idea how many GPs were likely to attend. One consultant had declined the invitation, one had accepted and a third had accepted provided his on-call could be covered; Novo Nordisk awaited the decision of the fourth consultant. No PGEA accreditation had been applied for since this would be unlikely to be given in view of the focus of the meeting on one particular agent.

Since this meeting was initiated by the health authority Novo Nordisk had not intended offering an honorarium to the speakers and it would confirm that no consultant or GP had been offered any money to take part, which would have been inappropriate as the complainant implied. Novo Nordisk could not explain why the complainant thought he would receive a fee but the local sales team was confident that the subject had not even been discussed. It may have been that he felt the meeting was driven by Novo Nordisk where, of course, an honorarium would normally have been paid.

The attendees from Novo Nordisk were likely to be the medical affairs manager (speaker), the primary and secondary care representatives and the NHS liaison manager (four in total). The second meeting would be exactly the same format but invitations would go to GPs on that side of the region.

In summary, therefore, these meetings were initiated by the medical adviser for the health authority and not by Novo Nordisk which was nevertheless happy to support the meetings. The focus around repaglinide was specifically designed to aid the health authority in its review of the compound. No speakers' fees had been discussed and none would be paid. No one would be paid to attend the meetings which were open to all GPs in the respective areas and would be attended by all the consultant diabetologists working with the adult population in the area (both meetings). The health authority medical adviser should be contacted for further information (Novo Nordisk had not made contact with him and he was to its knowledge unaware of the complaint).

It appeared that there had been some misunderstanding of the nature of these meetings by the complainant and Novo Nordisk failed to see how it had breached any of Clauses 2, 9.1, 18 and 19 of the Code by agreeing to support these meetings.

PANEL RULING

The Panel noted that Novo Nordisk had been asked to support a meeting where the relevance of NovoNorm was to be discussed. The product had been given a limited prescribing status on the regional drug formulary which was coming up for review. The health authority medical adviser decided to consult widely with interested parties. Initial contact was made by a Novo Nordisk primary care sales representative who visited the medical adviser while he was working as a GP locum.

The Panel noted that the invitation to the consultants was sent by the medical adviser who received help with the initial drafting but the final text was his own and was sent by his department. The Panel noted the submission that as the meeting was initiated by the health authority Novo Nordisk had not intended offering an honorarium to the speakers. The invitation did not refer to an honorarium. The company could not explain why the complainant thought he would be offered a fee. On the information before the Panel it appeared that no one would be paid to attend the meeting.

The Panel noted that the costs of the meetings were to be met by Novo Nordisk. The company would be paying £250 room hire and £25 per head for the meal.

The Panel considered that the arrangements for the meeting were not unacceptable; it was reasonable for a company to sponsor a meeting on one of its products. The anticipated costs did not appear to be unreasonable. No payment was to be made to either speakers or to attendees. The Panel therefore ruled no breach of Clauses 18.1 and 19.1 of the Code.

The Panel noted that the letter inviting consultants to attend stated that the author had invited Novo Nordisk to become involved in the initiative but failed to declare that the meeting was sponsored by Novo Nordisk. The Panel therefore ruled a breach of Clause 19.3 of the Code.

The Panel noted that Novo Nordisk had sponsored the meeting and been involved in the preparation of the letter. The Panel considered that the letter in effect promoted NovoNorm. This meant that it should have included prescribing information. The Panel also considered that the activity might be seen as disguised promotion. Bearing in mind its comments about the letter and that the company had failed to declare its sponsorship, the Panel considered that the company had not maintained a high standard and a breach of Clause 9.1 of the Code was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

Complaint received **7 September 2000**

Case completed **3 November 2000**

CASES AUTH/1074/9/00 and 1075/9/00

MERCK SHARP & DOHME v PROCTER & GAMBLE and AVENTIS PHARMA

Promotion of Actonel

Merck Sharp & Dohme alleged that promotional materials for Actonel (risedronate) used claims that were in breach of the Code, citing a double page journal advertisement as an example. Actonel was co-promoted by Procter & Gamble and Aventis Pharma.

The advertisement was headed 'In established postmenopausal osteoporosis and postmenopausal women taking oral corticosteroids: New Actonel. Proven to significantly reduce vertebral fractures – in just 1 year'. Text discussed the progression of the disease and claimed 'New Actonel answers the need for rapid protection from vertebral fracture in postmenopausal women with established osteoporosis, because it significantly reduces the risk of new vertebral fractures by up to 74%* within just one year'. The asterisk referred the reader to a footnote in small type which stated 'At least two pre-existing vertebral fractures'. The claim was referenced to Roux *et al* (1999). Merck Sharp & Dohme stated that the 74% reduction was in a subgroup of patients with at least two pre-existing fractures from one study. Reductions at one year in a similar high risk group were less than this in a parallel study (65%), and in both studies as a whole (65 and 61%). Merck Sharp & Dohme alleged that the claim did not reflect the body of evidence and was misleading and an exaggerated claim. The claim 'cherry picked' data and misled as to the true efficacy of the product. The claim quoted data for new vertebral fractures from a high risk subgroup in a single study and was not a fair reflection of all the evidence.

The Panel noted that according to its summary of product characteristics (SPC) Actonel was indicated for the treatment of established postmenopausal osteoporosis: to reduce the risk of vertebral fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5mg/day prednisone or equivalent. Roux *et al*, an abstract entitled 'Risedronate rapidly reduces vertebral fracture risk in postmenopausal women with established osteoporosis', was a prospective analysis of two studies; Reginster *et al* (2000) and Harris *et al* (1999). Reginster *et al* concluded that Actonel reduced the incidence of vertebral fractures in women with two or more prevalent fractures; reducing the risk of vertebral fractures by 61% over 12 months and 49% over 3 years. In Harris *et al* a significant reduction of 65% in vertebral fracture risk was seen in the first year of treatment and 41% over three years. The Panel noted that 80% of patients in the Actonel 5mg group had prevalent vertebral fractures at baseline; a mean of 2.5 per patient. The one year data from these studies were analysed in Roux *et al* which presented 5mg year one effect data on new vertebral fracture incidence for Harris *et al* and Reginster *et al* and pooled data for the intention-to-treat population at 65%, 61% and 62% respectively, and the high risk group at 74%, 65% and 68%. The authors concluded that the antifracture effect was rapid with significant reductions in the risk of new vertebral fractures occurring in the first year of treatment. The Panel noted the companies' submission that analysis at the one year time point was prospectively planned for both studies. The Panel noted the comparison of relative risk reductions at one year provided by the respondent companies which indicated a consistent overlap in confidence intervals across the studies and their populations. The Panel considered, however, that the claim at issue gave the impression that the risk of new vertebral fractures would be reduced by 74% within one year in all postmenopausal women with established osteoporosis. This was not so. This magnitude of risk reduction was only seen in a high risk sub-group in the study by Harris *et al*. The Panel noted that the 74% was followed by an asterisk which referred the reader to a footnote in small type in the bottom left hand corner that stated 'At least two pre-existing vertebral fractures'. It was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. The Panel considered that the claim gave a misleading impression and did not reflect the body of evidence and was exaggerated. Breaches of the Code were ruled.

The claim 'Protection that's fast and lasts' appeared as a prominent strapline in the bottom right-hand corner of the advertisement and in the final paragraph of text 'And because Actonel has also been proven to sustain vertebral fracture risk reduction over three years in postmenopausal women with established osteoporosis, your patients can expect protection that's fast and lasts.' Merck Sharp & Dohme stated that the claim was used in the context of fracture reduction at one year being sustained throughout a three year period. The numerical reduction at one year was quoted. Whilst the reduction at three years was not statistically different to the reduction at one year, it was much smaller. Merck Sharp & Dohme alleged that this claim, without qualification, clearly implied that the magnitude of the reduction at year one was sustained at year three and was misleading and exaggerated. This claim was related to the speed of the fracture reduction with risedronate and its duration. It stated in the text above the most prominent appearance of this claim 'And because Actonel has also been proven to sustain vertebral fracture risk reduction over 3 years in postmenopausal women with established osteoporosis, you can expect protection that's fast and lasts' immediately following the claim 'Reduces the risk of new vertebral fractures by up to 74%* within just one year'. Merck Sharp & Dohme believed this clearly implied that the risk reduction of 74% was maintained over three years. However, the relative risk reduction (RRR) in this subgroup in

Reginster *et al* and Harris *et al* combined at three years was 47%. The FDA approved label provided the most easily appreciated summary of the relevant data for the two studies overall. The reductions in fracture risk were much less than 74% with RRRs for new vertebral fractures 41% in Harris *et al* and 49% in Reginster *et al*, RRRs for new worsening fractures (the primary endpoint) were 33% and 46%.

The Panel noted that Harris *et al* and Reginster *et al* were each three year studies and each demonstrated that Actonel showed statistically significant reductions in vertebral fracture risk over one and three years. The Panel noted the submission that whilst the reduction at three years was not statistically different to the reduction at one year it was smaller. The three year data was referred to in the Actonel SPC which stated that Actonel 5mg daily for 3 years reduced the risk of new vertebral fractures in post menopausal women with osteoporosis relative to the control group which was treated with calcium and vitamin D. In Reginster *et al* and Harris *et al* the incidence of new vertebral fractures was 29% and 16.3% in control patients and 18.1% and 11.3% in risedronate treated patients respectively. The sentence at issue formed the final paragraph of text and was immediately preceded by the paragraph referring to the 74% reduction within just one year. The Panel noted its ruling above regarding the claim. The Panel considered that use of the word 'and', which began the sentence at issue would lead a reader to link the two paragraphs. The sentence at issue referred to Actonel being 'proven to sustain vertebral fracture risk reduction over three years …'. The Panel considered that the juxtaposing of the claims would give readers the impression that the 74% risk reduction was sustained over three years and this was not so. Breaches of the Code were ruled.

Merck Sharp & Dohme Limited alleged that a number of materials promoting Actonel (risedronate) used claims that were in breach of the Code and submitted a double page journal advertisement as an example (ref A1345). Actonel was co-promoted by Procter & Gamble Pharmaceuticals UK, Limited and Aventis Pharma Ltd. In a joint response they refuted the allegations that the specified claims breached the Code.

1 Claim 'Reduces the risk of new vertebral fractures by up to 74%* within just one year'

The advertisement was headed 'In established postmenopausal osteoporosis and postmenopausal women taking oral corticosteroids: New Actonel. Proven to significantly reduce vertebral fractures – in just 1 year'. Text discussed the progression of the disease and claimed 'New Actonel answers the need for rapid protection from vertebral fracture in postmenopausal women with established osteoporosis, because it significantly reduces the risk of new vertebral fractures by up to 74%* within just one year'. The asterisk referred the reader to a footnote in small type in the bottom left hand corner which stated 'At least two pre-existing vertebral fractures'. The claim was referenced to Roux *et al* (1999).

COMPLAINT

Merck Sharp & Dohme stated that the 74% reduction was in a subgroup of patients with at least two pre-existing fractures from one study. Reductions at one year in a similar high risk group were less than this in a parallel study (65%), and in both studies as a whole (65 and 61%). Merck Sharp & Dohme believed the claim did not reflect the body of evidence and was misleading in breach of Clause 7.2 of the Code and constituted an exaggerated claim in breach of Clause 7.8.

Merck Sharp & Dohme believed the claim 'cherry picked' data and misled as to the true efficacy of the product. The claim quoted data for new vertebral fractures from a high risk subgroup in a single study and was not a fair reflection of all the evidence. Whilst the nature of the subgroup was referred to in a footnote, it was not particularly prominent at the foot of the facing page.

Fracture efficacy of risedronate was studied in two studies of similar design (the Multinational Vertebral Efficacy with Risedronate Therapy (VERT) Study Group (Reginster *et al* 2000) and the North American VERT Study Group (Harris *et al* 1999)). The relative risk quoted was from Harris *et al*. The relative risk reduction (RRR) for the similar subgroup in Reginster *et al* was 65% (Roux *et al* 1999). The overall results for the two studies were reproduced in the FDA approved label (Actonel US prescribing information). The RRR for new vertebral fractures in each study was less than 74% at one year; 65% in the North American study and 61% in the multinational study. However, the primary endpoint of the two studies was new and worsening vertebral fractures at three years. The RRR for such fractures at one year in each study was far less than 74% at 49% in Harris *et al* and 50% in Reginster *et al*.

RESPONSE

Procter & Gamble and Aventis Pharma stated that the 74% reduction came from a clinically important subgroup of women with two or more vertebral fractures at baseline. Vertebral fracture risk reduction in this group was a prospectively planned endpoint in the companies' pivotal studies, and the data was from a published reference. The claim was clearly qualified by the words 'up to'; in addition, the footnote described the specific population in which the results were obtained. The companies did not believe that the use of data that were in line with the summary of product characteristics (SPC) from a correctly referenced, prospectively planned analysis was misleading for the audience concerned.

Two major pivotal studies evaluated the effect of Actonel on vertebral fracture risk; a multinational study (Reginster *et al* 2000) in 1226 postmenopausal women with at least two prevalent vertebral fractures at baseline, and a North American study (Harris *et al* 1999), which included 2458 postmenopausal women with at least one prevalent vertebral fracture at baseline. Similar significant reductions in the risk of vertebral fracture were observed over one year in each study (61% and 65% respectively).

Recent data showed that one in five postmenopausal women with established osteoporosis fractured again

within one year of sustaining an incident vertebral fracture (Lindsay *et al* 2000). These data were prompting growing awareness amongst physicians of the need for rapid intervention in osteoporosis.

The discussion of results from different patient populations was clearly of clinical importance. In each study, a prospectively planned analysis of women at higher risk of fracture (with two or more vertebral fractures at baseline) demonstrated reductions of 65% and 74% respectively. These similar reductions were qualified by the words 'up to'. This was a population in which physicians commonly used bisphosphonates once fractures had come to clinical attention. Importantly, analysis at the one year time point was prospectively planned for both studies (Reginster, Harris). The Roux *et al* (1999) abstract clearly showed a statistically significant reduction in the risk of new vertebral fractures in the prospectively planned pooled analysis as well (Roux 1 year abstract). The consistency of the ability of Actonel to significantly reduce the risk of vertebral fractures over one year in different patient populations had been summarised by Eastell *et al* (2000). Whether considering new fractures or new and worsening fractures, risk reductions obtained after only one year of treatment were significant.

Procter & Gamble and Aventis submitted that it was admissible in advertising to present results from any prospectively planned endpoint which was covered by the SPC and supported by robust data. The SPC (section 5.1) summarised the results of these pivotal studies as follows:

'Actonel 5mg given daily for 3 years reduced the risk of new vertebral fractures in postmenopausal women with osteoporosis…. The effect of treatment was seen as early as the end of the first year of treatment'.

The claim relating to this effect after the first year of treatment was clearly qualified by the words 'up to 74%' (emphasis added); the footnote described the specific population in which the results were obtained. In addition, the claim was clearly referenced to published data.

Further, the companies did not believe that the use of the 74% risk reduction figure was exaggerated or misleading. A comparison of relative risk reductions observed at one year in the companies' pivotal vertebral fracture studies showed a consistent overlap in confidence intervals. A table was provided. This suggested a consistent effect across these studies and populations. Given that these results were consistent, they were clearly and adequately described by the expression 'up to 74%'.

PANEL RULING

The Panel noted that according to its SPC Actonel was indicated for the treatment of established postmenopausal osteoporosis: to reduce the risk of vertebral fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5mg/day prednisone or equivalent.

The Panel noted that Roux *et al* (1999), an abstract entitled 'Risedronate rapidly reduces vertebral fracture risk in postmenopausal women with established osteoporosis', was a prospective analysis of two studies; Reginster *et al* (2000) and Harris *et al* (1999). Reginster *et al* assessed the efficacy and safety of risendronate in the prevention of vertebral fractures in postmenopausal women with established osteoporosis over 3 years. Ambulatory women up to 85 years old and at least five years postmenopausal were eligible if they had at least two radiographically confirmed vertebral fractures. The study concluded that Actonel reduced the incidence of vertebral fractures in women with two or more prevalent fractures; reducing the risk of vertebral fractures by 61% over 12 months and 49% over 3 years. Harris *et al* (1999) assessed the safety and efficacy of Actonel to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis who had two or more radiographically identified vertebral fractures or one vertebral fracture and low lumber spine bone mineral density. A significant reduction of 65% in vertebral fracture risk ($p<0.001$) was seen in the first year of treatment and 41% over three years. The Panel noted that 80% of patients in the Actonel 5mg group had prevalent vertebral fractures at baseline; a mean of 2.5 per patient. The one year data from these studies were analysed in Roux (1999) which presented 5mg year 1 effect data on new vertebral fracture incidence for Harris and Reginster and pooled data for the intention-to-treat population (ITT) at 65%, 61% and 62% respectively, and the high risk group at 74%, 65% and 68%. Each reduction was statistically significant versus control ($p<0.001$). The high risk group was defined as ≥ 2 prevalent fractures. The authors concluded that the antifracture effect was rapid with significant reductions in the risk of new vertebral fractures occurring in the first year of treatment. Detail about the statistical methodology was not provided. The Panel noted the companies' submission that analysis at the one year time point was prospectively planned for both studies.

The high risk data mentioned in Roux (1999) did not appear to be clearly presented in the studies. The Panel noted the different patient populations and primary end points. Not all patients in Harris had two pre-existing vertebral fractures.

The Panel also noted the comparison of relative risk reductions at one year provided by the respondent companies which indicated a consistent overlap in confidence intervals across the studies and their populations. The Panel considered, however, that the claim at issue gave the impression that the risk of new vertebral fractures would be reduced by 74% within one year in all postmenopausal women with established osteoporosis. This was not so. This magnitude of risk reduction was only seen in a high risk sub-group in the study by Harris *et al*. The Panel noted that the 74% was followed by an asterisk which referred the reader to a footnote in small type in the bottom left hand corner that stated 'At least two pre-existing vertebral fractures'. It was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. The Panel considered that the claim gave a misleading

impression and did not reflect the body of evidence. It was also exaggerated. Breaches of Clauses 7.2 and 7.8 of the Code were ruled.

2 Claim 'Protection that's fast – and lasts'

This claim appeared as a prominent strapline in the bottom right-hand corner of the advertisement and in the final paragraph of text 'And because Actonel has also been proven to sustain vertebral fracture risk reduction over three years in postmenopausal women with established osteoporosis, your patients can expect protection that's fast and lasts.'

COMPLAINT

Merck Sharp & Dohme stated that the claim was used in the context of fracture reduction at one year being sustained throughout a three year period. The numerical reduction at one year was quoted. Whilst the reduction at three years was not statistically different to the reduction at one year, it was much smaller. Merck Sharp & Dohme believed this claim, without qualification, clearly implied that the magnitude of the reduction at year one was sustained at year three, and was misleading and exaggerated in breach of Clauses 7.2 and 7.8 of the Code.

This claim was related to the speed of the fracture reduction with risedronate and its duration. It stated in the text above the most prominent appearance of this claim 'And because Actonel has also been proven to sustain vertebral fracture risk reduction over 3 years in postmenopausal women with established osteoporosis, you can expect protection that's fast and lasts' immediately following the claim 'Reduces the risk of new vertebral fractures by up to 74%* within just one year'. Merck Sharp & Dohme believed this clearly implied that the risk reduction of 74% was maintained over three years. However, the RRR in this subgroup in Reginster *et al* and Harris *et al* combined at three years was 47%. Again the FDA approved label provided the most easily appreciated summary of the relevant data for the two studies overall. The reductions in fracture risk were much less than 74% with RRRs for new vertebral fractures 41% in Harris *et al* and 49% in Reginster *et al*, RRRs for new worsening fractures (the primary endpoint) were 33% and 46%.

RESPONSE

Procter & Gamble and Aventis stated that the advertisement did not link the 74% risk reduction observed over one year with any results over three years. Health professionals needed to know whether the initial effects of a product were transitory or sustained, and three year data were now required for regulatory approval of osteoporosis treatments. Over both one and three years, Actonel had demonstrated consistent and significant reductions in vertebral fracture risk in established postmenopausal osteoporosis.

As the wording of the advertisement did not link the 74% reduction observed over one year with any results over three years, the companies therefore refuted the allegation that the advertisement implied that a 74% reduction in vertebral fracture risk was maintained over three years. The companies did not agree with Merck Sharp & Dohme's interpretation of the text from which it quoted two sentences out of context. The text in question was reproduced for clarity:

'New Actonel… significantly reduces the risk of new vertebral fractures by up to 74%* within just one year [reference to Roux, 1999].

And because Actonel has also been proven to sustain vertebral fracture risk reduction over three years in postmenopausal women with established vertebral osteoporosis [reference to Harris and Reginster], your patients can expect protection that's fast and lasts.'

The one and three year claims were clearly separated in three ways: firstly they were presented in two separate paragraphs; secondly the use of the word 'also' in the second paragraph made a distinction between the study results quoted here and the study results quoted in the paragraph above; and finally each claim was referenced to different publications. There was therefore no implication that the relative risk reduction of 74% applied to the three year time period.

In the context of prescribing medicines for osteoporosis, health professionals needed to know whether the initial effects of a product were transitory or sustained. The standard regulatory requirement for authorisation of an osteoporosis treatment was now three year data. The Note for Guidance on Involutional Osteoporosis issued by the Committee for Proprietary Medicinal Products in 1999 stated that 'serial X-rays [should be] performed once a year… to assess vertebral fractures' and data from 'at least three years is usually appropriate'. In chronic conditions like osteoporosis, it was particularly relevant for prescribing physicians to know if initial effects were maintained over time. Of significance was the fact that the ability of Actonel to demonstrate a reduction in vertebral fractures within one year and over three years was recognised as clinically relevant as this initial effect maintained over time was expressly referred to in section 5.1 of the SPC.

It was important to note that over both one and three years, Actonel showed consistent and significant reductions in vertebral risk in established postmenopausal osteoporosis.

Once again, Merck Sharp & Dohme appeared to be commercially mischievous by quoting many data points irrelevant to the specific claims alleged in breach of the Code. Procter & Gamble and Aventis could not understand why Merck Sharp & Dohme had chosen to quote the FDA-approved US prescribing information when the relevant data were summarised in the MCA approved SPC. The claims in question were supported by the data summarised in the SPC relevant to the country in which the claims were being made.

In summary, Procter & Gamble and Aventis therefore believed that the data used were representative of the body of evidence available, and were not misleading as to the true efficacy. They therefore refuted Merck Sharp & Dohme's allegation of breaches of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that Harris and Reginster were each three year studies and each demonstrated that Actonel showed statistically significant reductions in vertebral fracture risk over one and three years. The Panel noted the submission that whilst the reduction at three years was not statistically different to the reduction at one year it was smaller. The Panel noted that the three year data was referred to in the Actonel SPC. This stated that Actonel 5mg daily for 3 years reduced the risk of new vertebral fractures in post menopausal women with osteoporosis relative to the control group which was treated with calcium and vitamin D. In the multinational and North American studies the incidence of new vertebral fractures was 29% and 16.3% in control patients and 18.1% and 11.3% in risedronate treated patients respectively.

The Panel noted that the sentence at issue formed the final paragraph of text and was immediately preceded by the paragraph referring to the 74% reduction within just one year. The Panel noted its ruling regarding this claim made in point 1 above. The Panel considered that use of the word 'and', which began the sentence at issue would lead a reader to link the two paragraphs. The sentence at issue referred to Actonel being 'proven to sustain vertebral fracture risk reduction over three years …'. No details of the three year data were given. The Panel considered that the juxtaposing of the claims would give readers the impression that the 74% risk reduction was sustained over three years and this was not so. Breaches of Clauses 7.2 and 7.8 of the Code were ruled.

Complaint received **21 September 2000**

Case completed **22 November 2000**

CASE AUTH/1076/9/00 *NO BREACH OF THE CODE*

MEDIA/DIRECTOR v AVENTIS PHARMA

BMJ article about Taxotere advertisement

An article by a general practitioner in the BMJ criticised an advertisement issued by Aventis Pharma for Taxotere (docetaxel), a medicine used in the treatment of advanced breast cancer. The advertisement in question featured a photographic pastiche of a picture by Eugène Delacroix, 'Liberty Leading the People'. The central character of the picture was a woman, the bodice of her dress having been torn/pulled down to reveal her breasts. The article acknowledged that the advertisement was both innovative and striking but questioned whether or not the image of a bare breasted woman had been used as a shock tactic to attract attention. Did the fact that the advertisement had been placed in leading medical journals, was for a treatment for breast cancer and was based on a famous painting, excuse the use of a partially naked woman? Overall the author expressed surprise that such an image had been used and implied that it did not seem appropriate.

In accordance with established practice whereby published criticisms of the promotional activities of pharmaceutical companies are treated as complaints under the Code of Practice, the matter was taken up by the Director.

The Panel considered that the imagery used in the Taxotere advertisement was powerful. It had some relevance to the therapeutic area. Whilst noting the views expressed in the article and follow up correspondence, the Panel did not consider that the advertisement failed to meet the requirements of the Code and no breach was ruled. The advertisement would not cause offence to the majority of the audience.

An article in the BMJ of 2 September, written by a general practitioner, criticised an advertisement for Taxotere (docetaxel), a medicine used in the treatment of advanced breast cancer. The advertisement in question featured a photographic pastiche of a picture by Eugène Delacroix, 'Liberty Leading the People'. The central character of the picture was a woman, the bodice of her dress having been torn/pulled down to reveal her breasts.

In accordance with established practice whereby published criticisms of the promotional activities of pharmaceutical companies are treated as complaints under the Code of Practice, the matter was taken up by the Director with Aventis Pharma Ltd, attention being drawn to Clause 9.1 of the Code.

COMPLAINT

The author acknowledged that the Taxotere advertisement was both innovative and striking but questioned whether or not the image of a bare breasted woman had been used as a shock tactic to attract attention. Did the fact that the advertisement had been placed in leading medical journals, was for a treatment for breast cancer and was based on a famous painting, excuse the use of a partially naked woman? Overall the author expressed surprise that such an image had been used and implied that it did not seem appropriate.

RESPONSE

Aventis Pharma noted that in his article the author had questioned the appropriateness of the visual image used in the advertisement for Taxotere. The image in question was a pastiche of the painting 'Liberty Leading the People', painted by Eugène Delacroix in 1830. The company also noted that after receiving a letter from the Authority informing him

that the article was to be taken up as a complaint under the Code, the author contacted the company to reassure it that his intention when writing the article was not to complain about the advertisement for Taxotere *per se*, but to provoke a wider debate on the issues of pharmaceutical advertising.

Aventis stated that it was extremely proud of its product Taxotere and the clear benefits that it could bring to patients and was equally proud of its current advertisement for the medicine. It took great care and paid particular attention to the suitability of the image it had used when it developed the advertisement. The company strongly believed that it had acted in a proper manner to safeguard the sensibilities of all parties who would reasonably be expected to view the advertisement and the company did not consider that the image used represented a breach of either the letter or the spirit of the Code.

Aventis stated that the BMJ had used a part of its web-site to enable readers of the article to vote on two questions that were posed, namely:

1 *Should the BMJ have published this advertisement, featuring a woman with bare breasts?*

2 *Should Delacroix have painted this picture, featuring a woman with bare breasts?*

A copy of the results of the votes received by the BMJ, downloaded from the BMJ web site on 14 September, was provided. Aventis stated that while the methodology used by the BMJ was open to question, and bias could not be ruled out, the data clearly showed that more than 70% of respondents were in favour of the BMJ publishing the advertisement. The data suggested that women were less supportive than men about the issue (69.9% vs 72.8%). However, it would be unwise to read too much into this numerical difference without conducting additional more rigorous research.

Aventis also provided copies of the thirty-six electronic letters received by the BMJ on the subject. A simple, qualitative analysis of these letters showed that 4 (11%) people thought that the advertisement might have transgressed modesty, 19 (53%) questioned what the fuss was about and 13 (36%) wrote to make some other point. So if the last type of response was excluded, 83% of people who took the trouble to write were supportive and questioned what the fuss was about.

Aventis considered that one letter in particular, from a female NHS consultant, not only captured the spirit of what the company was trying to achieve but also expressed what the company considered it had achieved with its advertisement:

'The use of this particular image, as part of an acknowledged work of art is very clever. These breasts are not selling sex. The woman portrayed is not even aware that they are uncovered. She is beautiful, healthy and powerful, a leader of the people who are responding to her rallying cry. She has a job to do and her mind is fully taken up with the task. She has to remain in health to carry out the task. Can a woman object to such a positive portrayal?'

Aventis stated that the company had a very clear responsibility to doctors and, as a consequence, the patients that they served, to ensure that the relevant facts about the treatment of advanced breast cancer were known. The company considered its advertisement had achieved this difficult task and that it had not transgressed either the written or unwritten boundaries of what was acceptable for the industry or society at large.

PANEL RULING

The Panel noted the requirements of Clause 9.1 of the Code that materials and activities must recognise the special nature of medicines and the professional standing of the audience and must not be likely to cause offence. High standards had to be maintained. The supplementary information stated that the display of naked or partially naked people for the purpose of attracting attention or the use of sexual imagery for the purpose of attracting attention was unacceptable.

The Panel considered that the imagery used in the Taxotere advertisement was powerful. It had some relevance to the therapeutic area. Whilst noting the views expressed in the article and in the follow up correspondence, the Panel did not consider that the advertisement failed to meet the requirements of Clause 9.1 and its supplementary information. The advertisement would not cause offence to the majority of the audience. No breach of Clause 9.1 of the Code was ruled.

Proceedings commenced 13 September 2000

Case completed 7 November 2000

CASE AUTH/1077/9/00

SMITHKLINE BEECHAM v FERRING

Distribution of CD ROM on 'Inflammatory Bowel Disease'

SmithKline Beecham complained about a CD ROM entitled 'Inflammatory Bowel Disease', with the sub-title 'Pathophysiology, diagnosis and treatment of Crohn's disease and ulcerative colitis' which was described as a multimedia patients' guide to Crohn's disease and ulcerative colitis. The CD case included the Ferring Pharmaceuticals logo and referred to support given by Ferring Pharmaceuticals Germany and Denmark and Schering-Plough/Centocor, USA. SmithKline Beecham stated that the CD ROM was distributed in the UK by Ferring in the promotion of Pentasa (mesalazine). Ferring had denied that it was its intention to supply the item directly to patients.

SmithKline Beecham alleged that the CD ROM promoted the use of Pentasa in the treatment of Crohn's disease for which Ferring did not have a UK licence. A statement regarding the mode of administration of a number of branded products was incorrect as it was stated that these medicines should be taken one hour before meals to allow for an even dissolution. Such a requirement did not appear in the Asacol prescribing information. The brand name for SmithKline Beecham's mesalazine preparation, Asacol, was used repeatedly without its prior consent.

The Panel considered that the CD ROM was not promotional *per se*. Ferring had no influence over the content etc although Ferring in Germany and Denmark had sponsored the item.

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

The Panel noted that Ferring had made the CD ROM available from a promotional stand at a hospital meeting. Copies had been given to gastroenterologists by direct request or been provided at medical meetings. Representatives had offered a copy to departments during the course of an interview.

The Panel considered that Ferring had not sufficiently distanced the provision of the CD ROM from its promotional activities. Making the CD ROM available at the company stand at medical meetings meant that it was being used for a promotional purpose and was therefore within the scope of the Code.

The Panel noted that in the UK Pentasa was indicated for the treatment of mild to moderate exacerbations of ulcerative colitis and for the maintenance of remission of ulcerative colitis. The Panel noted that the CD ROM referred to the use of Pentasa in the treatment of an unlicensed indication, Crohn's disease. The Panel therefore ruled a breach of the Code.

The Panel considered that the reference to the use of Asacol one hour before meals to allow for even dissolution was misleading as alleged. Such a requirement did not appear in the Asacol summary of product characteristics. The Panel ruled a breach of the Code. The Panel did not accept that the reference was disparaging as alleged and ruled no breach of the Code in this regard. The Panel also ruled a breach of the Code in relation to the use of SmithKline Beecham's brand name Asacol without prior permission.

The Panel noted that the CD ROM had not been supplied by Ferring directly to patients. The Panel considered that the CD ROM was not an advertisement to the general public for Pentasa and no breach was ruled. Ferring had commented that some doctors had used the material with patients. The Panel noted that the ruling that the CD ROM was misleading meant that material provided to patients failed to meet the requirements of the Code in this regard and a breach was ruled.

The Panel did not accept that the matter warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

SmithKline Beecham Pharmaceuticals UK complained about a CD ROM entitled 'Inflammatory Bowel Disease', with the sub-title 'Pathophysiology, diagnosis and treatment of Crohn's disease and ulcerative colitis'. The CD ROM was described as a multimedia patients' guide to Crohn's disease and ulcerative colitis. Over 250 images and illustrations, animations, sound recordings and video clips were included. The overall running time was 30 minutes. The CD case included the Ferring Pharmaceuticals logo. It also referred to support given by Ferring Pharmaceuticals Germany and Denmark and Schering-Plough/Centocor, USA.

SmithKline Beecham stated that the CD ROM was distributed by Ferring Pharmaceuticals Ltd in the promotion of Pentasa (mesalazine). SmithKline Beecham supplied mesalazine as its product Asacol.

COMPLAINT

SmithKline Beecham alleged that the CD ROM breached a number of clauses of the Code.

Clause 3

The item promoted the use of Pentasa in the treatment of Crohn's disease for which Ferring did not have a UK licence.

Clauses 7.2 and 8.1

The item made incorrect and differentiating claims with regard to the distribution of mesalazine released from various preparations, including Asacol, within

the GI tract. A statement was also made regarding the mode of administration of a number of branded products, including Asacol, which was also incorrect as it was stated that these medicines should be taken one hour before meals to allow for an even dissolution. Such a requirement did not appear in the Asacol prescribing information.

Clause 7.10

The brand name for SmithKline Beecham's mesalazine preparation, Asacol, was used repeatedly without its prior consent.

Clauses 20.1 and 20.2

Although Ferring denied that it was its intention to supply this item directly to patients, the following statement appeared on the reverse side of the CD ROM: ''Inflammatory Bowel Disease' is a multimedia patients' guide to Crohn's disease and ulcerative colitis'.

SmithKline Beecham supplied a copy of the main menu from which the treatment module could be accessed and stated that it should be noted that this module could be accessed from most of the other sections of the CD ROM.

SmithKline Beecham understood that the item was made available in large numbers to doctors at a one day hospital meeting organised by a professor for consultant physicians. The CD ROM was running on the computer on the Ferring stand. Copies were on the stand alongside for anyone to take.

SmithKline Beecham had taken up these issues with Ferring but was dissatisfied by its response. Copies of the correspondence were provided. As the Authority would be aware, in recent months SmithKline Beecham had made a number of complaints regarding Ferring's promotional activities. SmithKline Beecham believed that the current breaches of the Code were by far the most serious to date and brought discredit upon the pharmaceutical industry and as such were in breach of Clause 2.

RESPONSE

Ferring stated that its first reaction was one of disappointment and frustration that SmithKline Beecham should have considered it appropriate to raise this matter with the Authority after Ferring believed that it had been resolved to SmithKline Beecham's satisfaction by Ferring's written agreement to stop distributing the CD ROM.

Ferring stated that a professor had originally created the CD ROM as an educational aid for patients, in the German language, independently of Ferring, and subsequently an English version was prepared to enable its wider international use. Educational grants from Ferring companies in Germany and Denmark, together with additional grants from Schering-Plough/ Centocor, USA, were used to help in programming the CD ROM and to evaluate its use in clinical practice. Ferring at no time had editorial control or influence over the contents of the CD ROM.

Ferring had contacted the professor and asked him to confirm the basis on which the CD ROM was conceived and produced. Ferring had also asked him to comment on the point raised by SmithKline Beecham concerning the administration advice given for pH dependent mesalazine products and it was clear from his reply that the professor held very strong academic views, which were well argued and entirely reasonable. Copies of these replies were provided.

The CD ROM remained commercially available from the publishers and could be freely purchased from Springer. It was listed on the Springer website.

The CD ROM contained a very large amount of educational material concerning many aspects of inflammatory bowel disease and its symptoms, diagnostic methodology and a section that described all currently available treatments including medication and surgery. Other information was also included, such as the physiology of the gastrointestinal tract and some details of support groups in a number of countries worldwide. The CD ROM was well balanced and expressed the impartial views of the authors. It would be seen that no branding and no promotional messages for Pentasa appeared on the CD ROM or its packaging. Indeed, all the products available to treat inflammatory bowel diseases in Europe and the USA were dealt with in an even handed manner and no preference was given to Pentasa over Asacol, or any of the other products described.

A paper copy of the information on the CD ROM showed that it comprised a total of over 300 screens in 12 sections, of which one included treatments for inflammatory bowel diseases. Mesalazine was mentioned, either generically or by brand, on a total of only 22 screens, split between ulcerative colitis and Crohn's disease, each with 11 similar screens, including 6 screens in each section showing the release profile for each brand. The paper copy clearly demonstrated that the educational content of the CD ROM was extremely extensive and that the information concerning treatment with mesalazine was neither excessive nor unreasonable.

Ferring purchased copies of the CD ROM only direct from the publishers and the Ferring logo was printed on the back cover of these copies, as allowed under Clause 18.1. Copies of the CD ROM were provided to gastroenterologists as an educational aid, for use in their medical practice. The doctor might choose to run through parts of the CD ROM with some patients to help them understand certain aspects of their condition and its treatment. However, this would only be at the discretion of the doctor and could not be construed as promotional activity by Ferring directed at patients. In fact, the greatest use for the CD ROM in gastroenterology units seemed to have been as an introduction and training aid for nurses and junior doctors. Ferring considered that the provision of the CD ROM in this manner was no different to providing a medical book with educational value.

To put the distribution of this CD ROM in perspective, over the period from March 1999 to July 2000, approximately 1,150 were given to gastroenterologists either by direct request, or at closed meetings such as the one referred to by

SmithKline Beecham. Ferring estimated that there were between 1,600 and 1,800 gastroenterology consultants and senior registrars currently practising in the UK. Current estimates of the patient population suggested that there were up to 140,000 patients receiving treatment for Crohn's disease or ulcerative colitis in the UK, so it was clear that the scale of use of this CD ROM did not support an allegation of widespread distribution to patients.

There were approximately 360 gastroenterology units in the UK and so on average three copies of the CD ROM had been provided to each centre . This was in line with Ferring's experience that one copy resided in the gastroenterology department, one in the colorectal surgery department and one in the endoscopy unit.

Ferring stated that the CD ROM was not offered in any written promotional material. Health professionals were only made aware of the CD ROM at symposia and meetings or during the course of a visit from one of the representatives.

The CD ROM had been placed on the Ferring stand together with copies of a Pentasa dose card, Glypressin product information, proceedings from a meeting in Dublin and reprints of Pentasa and Glypressin publications.

The response to the allegations was as follows.

Clause 3

It was alleged that the item promoted the use of Pentasa in the treatment of Crohn's disease for which Ferring did not have a UK licence.

As the CD ROM was not a promotional item, there was no basis for this complaint.

Pentasa was licensed in many countries for the treatment of Crohn's disease and in the UK it was also widely used by many doctors to treat this condition. This educational CD ROM recognised the widespread use of Pentasa in Crohn's disease in clinical practice throughout the world and, therefore, it was entirely justifiable that the authors chose to include information on Crohn's disease and its treatment on the CD ROM. The information on the CD ROM was well balanced, unbiased and certainly carried no promotional message in favour of any single product.

Clauses 7.2 and 8.1

It was alleged that the item made incorrect and differentiating claims with regard to the distribution of mesalazine released from various preparations, including Asacol, within the GI tract. A statement was also made regarding the mode of administration of a number of branded products, including Asacol, which was also incorrect as it was stated that these medicines should be taken one hour before meals to allow for an even dissolution. Such requirements did not appear in the Asacol prescribing information leaflet.

As previously stated, the CD ROM was not a promotional item and Ferring was not involved in commissioning it, nor did it have any editorial input or control over the contents and so there was no basis for these complaints.

The responses from the professor confirmed that the contents of the CD ROM represented the position in Germany and his own academic opinion.

Clause 7.10

It was alleged that the brand name for SmithKline Beecham's mesalazine preparation, Asacol, was used repeatedly without prior consent.

As previously stated, the CD ROM was not a promotional item and Ferring was not involved in commissioning it, nor did it have any editorial input or control over the contents and so there was no basis for this complaint.

Clauses 20.1 and 20.2

Although Ferring denied that it was its intention to supply this item directly to patients, the following statement appeared on the reverse side of the CD ROM: ''Inflammatory Bowel Disease' is a multimedia patients' guide to Crohn's disease and ulcerative colitis'

Ferring had not distributed the CD ROM directly to patients. As described earlier, the CD ROM was independently created as an educational guide for patients by the authors and was freely available to purchase. Ferring had no control or influence over the contents and merely purchased copies of the CD ROM from the publisher and provided a limited number of them, either at medical meetings or in response to requests from gastroenterologists for use in their medical practice.

The complaint raised by SmithKline Beecham regarding the provision of this CD ROM could only have any basis if the CD ROM was classified as a promotional item for which Ferring would take responsibility for the contents. Ferring had shown above that the CD ROM was independently produced and that Ferring had no influence concerning the contents. The CD ROM should therefore be considered as it was intended – that was, an educational aid, which had been provided in reasonable quantities to gastroenterology units. The CD ROM was not branded with the name of any product, but did bear a small Ferring logo. This activity was entirely consistent with Clause 18.1, which did not prevent the provision of educational goods and services which enhanced patient care or benefited the NHS.

Ferring provided detailed comments from the original creator of the CD ROM.

The content of the CD ROM was free from the influence of pharmaceutical manufacturers and solely represented the academic opinion of the involved experts. Therefore, the CD ROM had been published by de Gruyter (Germany) and Springer (international edition). To the professor's knowledge, Ferring (but also some other pharmaceutical companies (in low numbers)) had bought the CD ROM from the publisher as one would buy a book for distribution. Of course, everybody could purchase the CD ROM.

PANEL RULING

The Panel noted Ferring's submission that the CD ROM was not a promotional item and therefore there was no basis for the complaint.

The Panel noted that grants from Ferring in Germany and Denmark together with grants from Schering-Plough/Centocor in the US were used to help in programming the CD ROM, to evaluate its use in clinical practice and to update the concepts and contents. Ferring at no time had editorial control or influence over the contents of the CD ROM.

The Panel noted the submission that the item was no different to a medical textbook and that the distribution of the CD ROM was in accordance with the supplementary information to Clause 18 of the Code. Activities and materials to enhance patient care or benefit the NHS were permitted. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply administer or buy any medicine. The Panel considered that the CD ROM was not promotional *per se*. Ferring had no influence over the content etc although Ferring in Germany and Denmark had sponsored the item.

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

The Panel noted that Ferring had made the CD ROM available from the company stand at a hospital meeting. Copies had been given to gastroenterologists by direct request or been provided at medical meetings. It had been provided on a promotional stand and representatives offered a copy to departments during the course of an interview.

The Panel considered that Ferring had not sufficiently distanced the provision of the CD ROM from its promotional activities. Making the CD ROM available at the company stand at medical meetings meant that it was being used for a promotional purpose and was therefore within the scope of the Code.

The Panel noted that in the UK Pentasa was indicated for the treatment of mild to moderate exacerbations of ulcerative colitis and for the maintenance of remission of ulcerative colitis. The Panel noted that the CD ROM referred to the use of Pentasa in the treatment of an unlicensed indication, Crohn's disease. The Panel therefore ruled a breach of Clause 3.2 of the Code.

The reference to the use of Asacol one hour before meals to allow for even dissolution was misleading as alleged. Such a requirement did not appear in the Asacol summary of product characteristics. The Panel ruled a breach of Clause 7.2 of the Code. The Panel did not accept that the reference was disparaging as alleged and ruled no breach of Clause 8.1 of the Code. The Panel also ruled that the use of SmithKline Beecham's brand name Asacol without prior permission was a breach of Clause 7.10 of the Code.

The Panel did not make a ruling on the allegation that incorrect and differentiating claims were made regarding the distribution of mesalazine released from various preparations including Asacol as insufficient detail had been given.

The Panel noted that the CD ROM had not been supplied by Ferring directly to patients. The Panel considered that the CD ROM was not an advertisement to the general public for Pentasa and no breach of Clause 20.1 was ruled. Ferring had commented that some doctors had used the material with patients. The Panel noted that its ruling of a breach of Clause 7.2 meant that the CD ROM had failed to meet the requirements of Clause 20.2 and a breach of that clause was ruled.

The Panel did not accept that the matter warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

Complaint received **13 September 2000**

Case completed **4 December 2000**

CASE AUTH/1078/9/00

GENERAL PRACTITIONER v ALLEN & HANBURYS

'Dear Doctor' letter and reply paid card about the Accuhaler and the 'turbo-inhaler'

A general practitioner complained about a 'Dear Doctor' letter and reply paid card which he had received from Allen & Hanburys. The letter, headed 'A is for Accurate', concerned the choice between the Accuhaler (Allen & Hanburys) and the 'turbo-inhaler'. The reply paid card bore three questions and offered an 'In-Check Dial' to the first one hundred replies with correct answers. The letter stated that 'The In-Check Dial provides a means of assessing a patients [sic] ability to use certain inhaler devices effectively'. The complainant alleged that the information in the mailing was misleading and did not contribute to an evidence-based treatment approach for asthmatic patients.

The complainant had a number of concerns. The mailing suggested throughout that inhaled drug delivery and efficacy (and therefore asthma control) was simply an outcome of inspiratory flow rate. This was not the case, as was well known from many studies on lung deposition, which was the accepted standard of inhaler performance. It quoted only one study to support its assertions (Malton *et al* 1996). This was an in-house Glaxo Wellcome *in-vitro* study which in isolation was clearly of limited value to clinical practice. Unnecessary asides within the study text (eg 'Presence of lactose [in the Accuhaler] also minimises the risk of overdosage since the patient knows that a dose has been inhaled by tasting the lactose deposited on the back of the throat') were unreferenced opinion. Sections of the mailing text were belied by published clinical evidence. For instance 'This [consistency of dose across flow rates] may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'. There were numerous clinical trials showing effectiveness of Turbohalers in acute asthma and children as young as pre-school. The mailing alone might have little impact, but it was being used as part of a wider campaign by Allen & Hanburys' representatives using the 'In-Check' device to suggest the superiority of one device against the other. No lung deposition data or clinical evidence was being offered to support this. The complainant was repeatedly asked by asthma nurses at workshops about this issue, which was clearly being given a high profile. By ignoring a much wider body of clinical research the complainant believed a narrow and inaccurate picture was being painted. There was considerable published clinical evidence on the efficacy of the Turbohaler device.

The reply card further misled by asking 'To guarantee over 89% of drug delivery, what flow rate would you require: Via an Accuhaler? Via a turbo-inhaler?'. Again, this set out to deliberately confuse inspiratory flow rate with drug delivery. The two were simply not the same. Inspiratory flow rate was only one of a number of factors influencing drug delivery, and ultimately asthma control. Studies had demonstrated the efficacy of the Turbohaler and directly compared the Turbohaler with the Accuhaler in terms of the most important outcome measure – that of disease control.

The Panel noted that the letter began by stating 'Once you have made the decision to prescribe a dry powder – let's make the choice easy'. It then detailed the results of Malton *et al*, an *in vitro* comparison of the drug delivery characteristics of Allen & Hanburys' Ventolin Accuhaler and AstraZeneca's Bricanyl Turbohaler, which demonstrated that at inspiratory flow rates of 30, 60 and 90 litres/minute the Turbohaler delivered between 54% and 99% of the stated dose whilst over the same range of flow rates the Accuhaler consistently delivered over 89%. The authors concluded that the dose consistency seen with the Accuhaler was clinically relevant and the reduction in dose delivery from the Turbohaler seen at 30 litres/minute might have clinical implications. The presentation of the results in the letter was followed by the statement 'This means that the patient, and you, can be confident that they are receiving a consistent dose of medication when they use their Accuhaler'. In the Panel's view the results from an *in vitro* study were clearly being linked to a clinical benefit. The letter implied that at inspiratory flow rates of less than 90 litres/minute the Turbohaler would be less efficacious than the Accuhaler. The Panel considered that in the clinical situation the respirable dose was not just dependent upon inspiratory flow rate but also the powder formulation as well as patient training and compliance. The letter made no mention of these other variables nor did it state that inspiratory flow rate was just one of a number of important issues in determining clinical outcome. By 'making the choice easy' it appeared that inspiratory flow rate was the only parameter that needed to be considered when choosing a dry powder inhaler. The Panel considered that the letter, by implying clinical benefit from the results of an *in vitro* study of only one parameter that was important in determining the respirable dose, was misleading. A breach of the Code was ruled. The Panel noted that it was a principle under the Code that promotional material referred to the clinical situation unless it was clearly stated otherwise. The study by Malton *et al* was an *in vitro* investigation although this point had not been stated in the 'Dear Doctor' letter. The Panel considered that the letter was misleading in this respect and ruled a breach of the Code.

The letter stated that the consistency of doses delivered by the Accuhaler '… may be important in children and patients whose asthma is deteriorating, who may have low respiratory rates'. In the Panel's view this implied that, in contrast, given the bar chart which showed variable doses delivered from the Bricanyl Turbohaler, the Turbohaler might not be efficacious in children and patients with acute asthma. This was not so. A study by Pedersen *et al* noted that 'Virtually all children ≥ 6 years were able to generate an inspiratory flow rate of 30L/min indicating that they would all be able to benefit optimally from Turbohaler treatment'. The Panel noted that Bricanyl Turbohaler was indicated for use in children. With regard to adults presenting with

acute asthma, Glaxo Wellcome cited in its response a paper by Brown *et al* which showed that 50% of such patients might not be able to achieve an inspiratory flow of 60 litres/minute through a Turbohaler, and that 9% might not be able to achieve an inspiratory flow of 40 litres/minute. The Panel noted, however, that the authors of the paper stated that 98% of patients in the study (n=99) generated inspiratory flow through an empty Turbohaler which would allow a therapeutically active amount of a bronchodilator to be delivered to the airways. The Panel noted that the Bricanyl Turbohaler was effective even at low inspiratory flow rates such as those present during an acute asthmatic attack. In the Panel's view the 'Dear Doctor' letter cast doubt upon the efficacy of the Bricanyl Turbohaler in children and those presenting with acute asthma. This was misleading and a breach of the Code was ruled.

The 'Dear Doctor' letter was accompanied by a reply paid card which offered the reader a chance to win an 'In-Check Dial'. The letter explained that this device provided a means of assessing a patient's ability to use certain inhalers effectively. The representatives' briefing material regarding the 'In-Check Dial' referred to a range of other devices for comparison using the 'In-Check' device and also prominently referred to patient compliance and individual patients' needs. The briefing material stated that the 'In-Check' device could help doctors identify the most suitable inhaler for a particular patient. The Panel did not consider that the material encouraged the device to be used to suggest the superiority of one inhaler against another. No breach of the Code was ruled in that regard. In order to win an 'In-Check Dial' respondents had to answer three questions. The second question stated 'To guarantee over 89% of drug delivery, what flow rate would you require?' The answer was to be obtained from the results of the Malton *et al* study as set out in the 'Dear Doctor' letter. Again the Panel considered that a link was being implied between an *in vitro* pharmaceutical measurement and clinical outcome. This was misleading. The Panel considered that its first ruling of a breach of the Code covered this point.

A general practitioner complained about a 'Dear Doctor' letter (ref HM5537-Alp/May 2000) and reply paid card (ref HM5538-Alp/May 2000) which he had received from Allen & Hanburys Limited. The letter, headed 'A is for Accurate', concerned the choice between the Accuhaler (Allen & Hanburys) and the 'turbo-inhaler'. The reply paid card bore three questions and offered an 'In-Check Dial' to the first one hundred replies with correct answers. The letter stated that 'The In-Check Dial provides a means of assessing a patients [sic] ability to use certain inhaler devices effectively'. The complainant stated that the letter had been accompanied by a representative campaign using the 'In-Check Dial' and purporting to show the superiority of the Accuhaler against the Turbohaler (AstraZeneca).

COMPLAINT

The complainant said that he believed the information in the mailing was misleading and did not contribute to an evidence-based treatment approach for asthmatic patients. The complainant had the following concerns about this mailing;

1 The mailing suggested throughout that inhaled drug delivery and efficacy (and therefore asthma control) was simply an outcome of inspiratory flow rate. This was not the case, as was well known from many studies on lung deposition, which was the accepted standard of inhaler performance.

2 The mailing quoted only one study to support its assertions (Malton *et al* 1996). This was an in-house Glaxo Wellcome, *in-vitro* study, which in isolation was clearly of limited value to clinical practice.

Unnecessary asides within the study text (eg 'Presence of lactose [in the Accuhaler] also minimises the risk of overdosage since the patient knows that a dose has been inhaled by tasting the lactose deposited on the back of the throat') were unreferenced opinion.

3 Sections of the mailing text were belied by published clinical evidence. For instance 'This [consistency of dose across flow rates] may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'. There were numerous clinical trials showing effectiveness of Turbohalers in acute asthma and children as young as pre-school.

4 This mailing alone might have little impact, but it was being used as part of a wider campaign by Allen & Hanburys' representatives using the 'In-Check' device to suggest the superiority of one device against the other. No lung deposition data or clinical evidence was being offered to support this. The complainant was repeatedly asked by asthma nurses at workshops about this issue, which was clearly being given a high profile. By ignoring a much wider body of clinical research the complainant believed a narrow and inaccurate picture was being painted. There was considerable published clinical evidence on the efficacy of the Turbohaler device.

5 The reply card further misled by asking 'To guarantee over 89% of drug delivery, what flow rate would you require: Via an Accuhaler? Via a turbo-inhaler?'. Again, this set out to deliberately confuse inspiratory flow rate with drug delivery. The two were simply not the same. Inspiratory flow rate was only one of a number of factors influencing drug delivery, and ultimately asthma control. Studies had demonstrated the efficacy of the Turbohaler (see above) and directly compared the Turbohaler with the Accuhaler in terms of the most important outcome measure – that of disease control.

In the previous week information had been published showing that up to 42% of asthmatics (1.4 million people) suffered daily restriction due to asthma symptoms, despite the advances in treatment and delivery of care in the last few years. It seemed to the complainant that this mailing did nothing to address the fundamental issues of treatment and compliance, but rather was liable to seriously mislead those practitioners who did not have a wider knowledge of the evidence base. The complainant accepted that pharmaceutical companies must presumably promote their own products over those of their rivals, but surely in a manner that stood up to scrutiny; if done

in such a frankly cavalier way then the losers were the patients whose quality of life healthcare professionals were supposed to be improving.

RESPONSE

Glaxo Wellcome responded to the complainant's concerns as follows:

1 'The mailing suggested throughout that inhaled drug delivery and efficacy (and therefore asthma control) was simply an outcome of inspiratory flow rate'

Glaxo Wellcome refuted this complaint, in that nowhere in the mailing did it suggest that inhaled drug delivery and efficacy were simply outcomes of inspiratory flow.

However, it had been accepted and understood for many years that the effort a patient put into inspiring through a dry powder inhaler device might affect the dose of medicine that was delivered, and that this in turn might affect clinical outcome.

Dry powder inhalers used energy, generated within the device during inhalation, to promote dispersion and de-aggregation of the powder, thus producing particles of respirable size (between 2 and 5 microns). The level of energy generated inside each dry powder inhaler, from a set inhalation rate, was dependent on the resistance in the device. As inspiratory effort was proportional to inspiratory flow rate multiplied by the device resistance, it was easier to generate a given inspiratory flow through a device with low internal resistance than through one with high internal resistance. Richards and Saunders (1993) showed that to achieve a flow of 60 litres/minute through the Turbohaler, three times the inspiratory effort was needed compared with the Diskhaler.

Everard *et al* (1996) evaluating the Turbohaler stated 'inspiratory flow and the flow profile should be considered when assessing any dry powder inhaler'. An Astra study (Olsson and Asking 1994) stated 'The flow rate attained by a patient depends on the effort expended and on the air flow resistance of the device. A comparison between powder inhalers should therefore take their air flow resistances into account'.

Andersen and Hansen (1993) found that the majority of patients preferred to inhale from a device with a lower internal resistance than from a device with a high resistance.

It was thus generally accepted that internal resistance and inspiratory flow rate were important aspects of dry powder inhalers and should be considered in device selection.

It had been shown in many studies that drug delivery from the Turbohaler was flow dependent.

Newman *et al* (1991) and Borgstrom *et al* (1994) had shown that the deposition from a Turbohaler varied considerably with different flow rates (9.1-16.8%, 14.8-27.7%). Both concluded that inspiratory flow had an important effect on lung deposition. Meakin *et al* (1995) reported that drug delivery from the Turbohaler was variable by +/- 50%, and that the fine particle fraction fell three-fold at low flow rates; and also varied through the life of the device and different environmental conditions. Ross and Schultz (1996) found that the fine particle fraction of terbutaline from the Turbohaler fell by over 60% at low flow rates.

An Astra study (Persson *et al* 1997) found when the standard instruction of 'inspire deeply' was given, less than 50% of asthma patients could achieve the recommended inspiratory flow of 60 litres/minute through the Turbohaler. The authors commented that 'Furthermore, it has been shown that a reduction of inspiratory flow from 60 litres/minute to about 30-40 litres/minute lowers the lung deposition by approximately 50%'.

Glaxo Wellcome stated that AstraZeneca was aware of the issue of optimal inspiratory flow rate and its relevance to clinical effect. Following the publication of this last study, it amended the instructions in the patient information leaflet enclosed with the Turbohaler from 'breathe in deeply' to 'breath in as deeply and as hard as you can'. Furthermore, an AstraZeneca study protocol evaluating efficacy of the Turbohaler required that patients should be able to inhale through the Turbohaler at 60 litres/minute, recognising the importance of this optimal inspiratory flow for effective use of the Turbohaler.

An Astra paediatric study (Bisgaard *et al* 1994) found an age dependent increase in ability to use the Turbohaler with considerable scatter across age groups, and concluded that the dose delivered could not be predicted in young children. It had also been shown that the maximal inspiratory flow rates generated by young asthmatic children might be insufficient for effective operation of high resistance dry powder inhalers.

Studies evaluating the Accuhaler, and studies comparing the Accuhaler with the Turbohaler, had shown that the Accuhaler delivered a consistent fine particle fraction at a range of flow rates between 30 and 90 litres/minute, whereas with the Turbohaler drug delivery was flow dependent across this range.

These and other studies evaluating the effect of varying flow rates on drug delivery through dry powder inhalers, had led to consensus that lower flow rates through the Turbohaler reduced drug delivery and drug deposition significantly, and that deposition through the Accuhaler was not affected by varying flow rates between 30-90 litres/minute.

Glaxo Wellcome submitted that the clinical relevance of these findings was shown by further studies. Hirsch *et al* (1997) evaluated the effectiveness of bronchodilatation with terbutaline delivered through the Turbohaler in 118 children with asthma. They found significant differences in bronchodilatation, which correlated with inspiratory flow. The authors concluded that when using the Turbohaler for bronchodilatation, the effectiveness of terbutaline depended upon the degree of inspiratory capacity. This could lead to impaired bronchodilatory effect in subgroups of young asthmatics with low inspiratory flow. Borgstrom *et al* (1996) assessed the lung deposition and bronchodilating effect of terbutaline through the Turbohaler, and found that reduced deposition was associated with reduced bronchodilating effect. In contrast Nielsen *et al* (1998)

evaluated the clinical effect of the Accuhaler at low and high flow rates. They concluded, 'consistent *in vitro* fine particle dosing from the Diskus (Accuhaler) inhaler translates into consistent clinical effect at low and high flow rates in children'.

Glaxo Wellcome considered that there was sufficient evidence to support a connection between inspiratory flow rate, drug deposition and clinical effect with respect to dry powder inhalers.

2 The complainant stated that only one study was referenced

Only one study was referenced, as the bar chart was taken from a particular study.

However, as Glaxo Wellcome had stated in response to the complainant's first point, there was a great deal of evidence to show dose consistency from the Accuhaler/Diskus over a range of inspiratory flow rates between 30 and 90 litres/minutes, and dose variability with Turbohaler across a range of flow rates from 30-90 litres/minutes.

Glaxo Wellcome did not consider that the complainant's comment regarding extracts from the referenced study text discussing lactose was relevant, as no reference whatsoever was made within the mailing to the presence or absence of lactose in devices.

3 The complainant stated that, sections of the mailing text were belied by clinical evidence. For instance 'This (consistency of dose across flow rates) may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'

Glaxo Wellcome did not consider that the importance of consistency of dose across flow rates in children and patients, whose asthma was deteriorating, was belied by clinical evidence.

Pedersen *et al* (1990) evaluated the influence of inspiratory flow resistance on the effect of a Turbohaler. They concluded that the effect was found to be reduced at inhalations slower that 28 litres/minute. They found that 26% of children under six years and 60% of children with acute wheeze could not generate this flow.

The authors considered that young children might gain less benefit from the Turbohaler because they could not generate sufficiently high inspiratory flow rates, especially during episodes of acute bronchoconstriction, and that this might also be true for a few older children during episodes of acute wheeze.

De Boeck *et al* (1999) evaluated the ability of children with asthma to use a Turbohaler. They found that 73% of the children studied were unable to achieve an inspiratory flow greater than 60 litres/minute, and 15% could not achieve 40 litres/minutes.

Amirav and Newhouse (2000) found that 30% of the children experienced in the use of the Turbohaler could not achieve 60 litres/minute. Children inexperienced in the use of the device performed even less well. The age above which the optimum peak inspiratory flow could be achieved was 3.5 years for the Accuhaler and 6 years for the Turbohaler. The authors commented that 'Diskus (Accuhaler) usage can be attempted at a younger age than the Turbohaler', and stated that 'it is important to measure peak inspiratory flow in any child who uses a dry powder inhaler or in whom dry powder inhaler use is contemplated, and that this can be easily performed with the In-Check Dial device'.

A study had shown that 50% of adults presenting with acute severe asthma might not be able to achieve an inspiratory flow of 60 litres/minute through the Turbohaler, and that 9% might not be able to achieve an inspiratory flow of 40 litres/minute [Brown *et al* 1995].

Nsour *et al* (1999) evaluated the ability of patients with COPD to use the Turbohaler. They found that 87% could not achieve an inspiratory flow over 60 litres/minute and 31% could not achieve over 40 litres/minute. The authors commented that 'The In-Check [sic] measurement highlights the potential of this simple meter as an aid to decide which DPI to prescribe'.

4 The complainant stated that the mailing was being used as part of a wider campaign using the 'In-Check Dial'

Glaxo Wellcome stated that the mailing was sent to 15,000 general practitioners in the UK. It considered that it was reasonable to compare its devices with those of its competitors using balanced evidence. Glaxo Wellcome did not at any time cast doubt on the efficacy of the Turbohaler, but showed a difference in the delivery characteristics of dry powder inhalers. It sought to ensure that the ability of patients to use particular devices was checked (as advised in the British Thoracic Society guidelines on device selection and the National Asthma and Respiratory Training Centre device selection recommendations) when patients with asthma were reviewed. This was made clear in the representatives' 'In-Check Dial' briefing document, which was provided. From this document, it could be seen that the emphasis was on the importance of checking inhaler device technique, as a part of rounded asthma management, when patients were reviewed.

There was an increasing interest in inspiratory flow as greater understanding of the importance of this aspect of drug delivery had developed. Measurements of inspiratory flow were increasingly forming a part of respiratory studies, and many presentations at national and international meetings highlighted inspiratory flow as an important measurement of lung function. In discussing this aspect of inhaler technique and device selection, Glaxo Wellcome was reflecting the growing interest in inspiratory flow resistance.

5 The complainant stated that the question 'To guarantee over 89% of drug delivery, which flow rate would you require: Via an Accuhaler? Via a turbo-inhaler?' did not reflect available evidence

Glaxo Wellcome considered that the question posed in the quiz reflected the available evidence. As stated

earlier it was generally accepted that inspiratory flow was an important factor influencing drug delivery.

The complainant further stated that the mailing did nothing to address the fundamental issues of treatment and compliance

The complainant quoted a study showing that up to 42% of asthmatics suffered daily restriction from their asthma. Glaxo Wellcome accepted that it had not covered the burden of asthma in this mailing. The mailing was only intended to address differences between inhaler devices.

As a company Glaxo Wellcome had worked hard with health professionals over the past twenty years to increase awareness of asthma, and improve its management. Other mailings and studies initiated by Glaxo Wellcome had covered this aspect of asthma. Glaxo Wellcome did not consider that it had in any way attempted to mislead practitioners as to the fundamental issues of the morbidity and burden of asthma.

The flow rates and ranges for optimum drug delivery described on the 'In-Check Dial' were made following consultation by Clement Clarke International with the various pharmaceutical companies whose products were represented on the device. These inspiratory flow rates were 30-90 litres/minute for the Accuhaler and 60-90 litres/minute for the Turbohaler. Glaxo Wellcome had been informed by Clement Clarke International that all the calibrations on the device had been independently validated as accurate.

In summary Glaxo Wellcome considered that its mailing was reasonable and an accurate reflection of the evidence on the subject of inspiratory flow, its relevance to clinical practice and the general interest in this subject.

PANEL RULING

The Panel noted that the 'Dear Doctor' letter began by stating 'Once you have made the decision to prescribe a dry powder inhaler – let's make the choice easy'. The letter then detailed the results of a study by Malton *et al* which was an *in vitro* comparison of the drug delivery characteristics of Allen & Hanburys' Ventolin Accuhaler and AstraZeneca's Bricanyl Turbohaler. The study demonstrated that at inspiratory flow rates of 30, 60 and 90 litres/minute the Turbohaler delivered between 54% and 99% of the stated dose whilst over the same range of flow rates the Accuhaler consistently delivered over 89%. The authors concluded that the dose consistency seen with the Accuhaler was clinically relevant and the reduction in dose delivery from the Turbohaler seen at 30 litres/minute might have clinical implications.

The results of the Malton study were shown in a bar chart in the letter. The presentation of the results was followed by the statement 'This means that the patient, and you, can be confident that they are receiving a consistent dose of medication when they use their Accuhaler'. In the Panel's view the results from an *in vitro* study were clearly being linked to a clinical benefit. The Panel considered that the letter implied that at inspiratory flow rates of less than 90 litres/minute the Turbohaler would be less efficacious than the Accuhaler. The Panel considered, however, that in the clinical situation the respirable dose was not just dependent upon inspiratory flow rate but also the powder formulation as well as patient training and compliance. The letter made no mention of these other variables nor did it state that inspiratory flow rate was just one of a number of important issues in determining clinical outcome. By 'making the choice easy' it appeared that inspiratory flow rate was the only parameter that needed to be considered when choosing a dry powder inhaler. The Panel considered that the letter, by implying clinical benefit from the results of an *in vitro* study of only one parameter that was important in determining the respirable dose, was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that it was a principle under the Code that promotional material referred to the clinical situation unless it was clearly stated otherwise. The study by Malton *et al* was an *in vitro* investigation although this point had not been stated in the 'Dear Doctor' letter. The Panel considered that the letter was misleading in this respect and ruled a breach of Clause 7.2 of the Code.

The Panel noted that the letter stated that the consistency of doses delivered by the Accuhaler '… may be important in children and patients whose asthma is deteriorating, who may have low respiratory rates'. In the Panel's view this implied that, in contrast, given the bar chart which showed variable doses delivered from the Bricanyl Turbohaler, the Turbohaler might not be efficacious in children and patients with acute asthma. This was not so. A study by Pedersen *et al* noted that 'Virtually all children ≥ 6 years were able to generate an inspiratory flow rate of 30L/min indicating that they would all be able to benefit optimally from Turbohaler treatment'. The Panel noted that Bricanyl Turbohaler was indicated for use in children (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). With regard to adults presenting with acute asthma, Glaxo Wellcome cited in its response a paper by Brown *et al* which showed that 50% of such patients might not be able to achieve an inspiratory flow of 60 litres/minute through a Turbohaler, and that 9% might not be able to achieve an inspiratory flow of 40 litres/minute. The Panel noted, however, that the authors of the paper stated that 98% of patients in the study (n=99) generated inspiratory flow through an empty Turbohaler which would allow a therapeutically active amount of a bronchodilator to be delivered to the airways. The Panel noted that the Bricanyl Turbohaler was effective even at low inspiratory flow rates such as those present during an acute asthmatic attack (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). In the Panel's view the 'Dear Doctor' letter cast doubt upon the efficacy of the Bricanyl Turbohaler in children and those presenting with acute asthma. The Panel considered that the letter was misleading in this respect and a breach of Clause 7.2 was ruled.

The 'Dear Doctor' letter was accompanied by a reply paid card which offered the reader a chance to win an 'In-Check Dial'. The letter explained that this device provided a means of assessing a patient's ability to

use certain inhalers effectively. The representatives' briefing material regarding the 'In-Check Dial' referred to a range of other devices for comparison using the 'In-Check' device and also prominently referred to patient compliance and individual patients' needs. The briefing material stated that the 'In-Check' device could help doctors identify the most suitable inhaler for a particular patient. The Panel did not consider that the material encouraged the device to be used to suggest the superiority of one inhaler against another. No breach of the Code was ruled in that regard.

In order to win an 'In-Check Dial' respondents had to answer three questions. The second question stated 'To guarantee over 89% of drug delivery, what flow rate would you require?' The answer was to be obtained from the results of the Malton *et al* study as set out in the 'Dear Doctor' letter. Again the Panel considered that a link was being implied between an *in vitro* pharmaceutical measurement and clinical outcome; this was misleading. The Panel considered that its first ruling of a breach of Clause 7.2 of the Code covered this point.

Complaint received	**14 September 2000**
Case completed	**28 November 2000**

CASE AUTH/1079/9/00

NOVO NORDISK v AVENTIS PHARMA

Advertisement in Balance for OptiPen Pro

Novo Nordisk stated that in the light of the Appeal Board's ruling regarding the advertising of insulin delivery devices to the general public (Case AUTH/1018/4/00) it wished to complain about an advertisement issued by Aventis Pharma for OptiPen Pro which appeared in a patient magazine. Novo Nordisk considered that the OptiPen Pro could only be used with Aventis insulins. It was alleged that the advertisement constituted an advertisement to the public for a prescription only medicine (POM).

The Panel noted that Case AUTH/1018/4/00 had involved a mailing to the public about NovoPen 3 sent by Novo Nordisk. The Panel noted that the Code applied to the promotion of medicines and not the promotion of devices *per se*. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of that medicine and the matter would be covered by the Code. The NovoPen 3 device was such that it could only be used with Novo Nordisk insulins. Promotion of NovoPen 3 thus constituted promotion of Novo Nordisk insulins and was thus within the scope of the Code.

The Panel considered that the mailing in Case AUTH/1018/4/00 constituted an advertisement to the public for a POM. It would encourage patients to ask their doctors to prescribe NovoPen 3 and in effect a Novo Nordisk insulin cartridge. Breaches of the Code were ruled which were upheld on appeal by Novo Nordisk.

Turning to the case before it the Panel noted that OptiPen Pro was for use with cartridges of the Insuman range of insulins marketed by Aventis. The relevant summaries of product characteristics stated that the cartridges had been developed for use in the OptiPen. The insulins were POMs. MIMS (November 2000) stated that OptiPen Pro 1 was a reusable insulin pen for use with 3ml cartridges of the Insuman insulins and that Lilly's Humalog and Humulin insulin cartridges could be used in a BD Pen Ultra or Lilly's own Humapen.

In the Panel's view promotion of OptiPen Pro constituted promotion of Aventis insulin cartridges and was thus within the scope of the Code. The Panel noted the submission that insulin cartridges from Lilly would fit into the OptiPen Pro but did not consider that this would represent normal practice. Use of the Lilly cartridges required more insulin to prime the OptiPen Pro and some 20 units of insulin would remain unused. Use of non-Aventis cartridges was therefore not ideal.

The Panel considered that the advertisement, by promoting the OptiPen Pro, constituted promotion of Aventis' insulins to the public and ruled a breach of the Code.

Novo Nordisk Pharmaceuticals Ltd complained about an advertisement issued by Aventis Pharma Ltd for the insulin pen device OptiPen Pro. The advertisement appeared in Balance, the patient magazine issued by the charity Diabetese UK (formerly the British Diabetic Association).

COMPLAINT

Novo Nordisk stated that in light of the Appeal Board's ruling regarding the advertising of insulin delivery devices to the general public (Case AUTH/1018/4/00) it wished to complain about the advertisement for OptiPen Pro (ref INS 005 03 00) which had appeared in Balance. Novo Nordisk considered that the OptiPen Pro could only be used with Aventis insulins and had a letter from Aventis outlining that Aventis had no evidence that other manufacturers' insulin could be used in OptiPen Pro. This contradicted the reply that Novo Nordisk had had from Aventis that OptiPen Pro could be used with the insulins of Eli Lilly and Company Limited. Novo Nordisk stated that it was led to believe that the insulin cartridges from Aventis and from Lilly had identical diameters but that the thickness of the rubber bung differed between the two; it was not at all clear if indeed the insulins were interchangeable or whether any evidence existed for this.

Novo Nordisk stated that while it considered that this sort of advertising should be allowed, it also had a right to compete in a market place where all complaints were treated equally and since Aventis had refused to withdraw its advertising Novo Nordisk had no option but to refer the matter to the Authority. A breach of Clause 20.1 of the Code was alleged.

RESPONSE

Aventis Pharma stated that it did not agree that the advertisement was in breach of Clause 20.1 of the Code and considered that this case was different from Case AUTH/1018/4/00 for the following reasons:

The complaint was based on the contention that OptiPen Pro could only be used with Aventis insulins. Evidence existed to the contrary. Firstly, Aventis stated that Lilly cartridges fitted the OptiPen Pro. The external dimensions of the Lilly cartridges were very similar to those of Aventis and could be inserted without any problems into the OptiPen Pro. The length of the rubber piston in Lilly cartridges was, however, about 3mm shorter. As a result of this, more insulin was needed to prime the pen prior to use and to ensure that the first drops appeared at the tip of the needle. Thereafter, the pen should deliver as expected and serious overdosage was, in any case, ruled out. Use of the OptiPen Pro with Lilly cartridges would leave approximately 20 insulin units unused, representing some wastage of the product. Secondly, Aventis was aware that Lilly cartridges were being used in the OptiPen Pro both by health professionals and patients.

With respect to the communications from Aventis on this subject, the company wished to re-iterate that the cartridges had been designed and extensively tested specifically for use with Aventis insulins. However, other insulins could be used in it although the company had, in its possession, limited data to support its use in such circumstances.

Aventis stated that the advertisement was intended for those with an interest in diabetes and merely introduced a new delivery device. It was not targeted and did not in anyway link the OptiPen to an Aventis insulin either by similarity of name or offer of future communications.

Aventis stated that based on the above, it considered that the Appeal Board's ruling in Case AUTH/1018/4/00 did not apply. The OptiPen Pro could be used with another manufacturer's insulin and therefore the advertisement did not breach Clause 20.1 of the Code.

PANEL RULING

The Panel noted that in Case AUTH/1018/4/00 it was alleged that a mailing to the general public about NovoPen 3, an insulin injection device, constituted indirect advertising to patients of specific brands of insulin because the device was designed such that it could only be used with Novo Nordisk human insulins. The mailing had been sent by Novo Nordisk. If they wanted more information recipients of the mailing could request a patient video about the NovoPen 3 device.

In Case AUTH/1018/4/00 the Panel noted that the Code applied to the promotion of medicines and not the promotion of devices *per se*. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine and the matter would be covered by the Code. The Panel noted that no other manufacturer's insulin cartridges could be used in the NovoPen system. Promotion of the NovoPen 3 system therefore constituted promotion of Novo Nordisk insulin cartridges and was thus within the scope of the Code.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2, *inter alia*, required that statements must not be made for the purpose of encouraging members of the public to ask their doctors for a specific medicine.

The Panel considered that the mailing and the video in Case AUTH/1018/4/00 constituted an advertisement to the public for a prescription only medicine. The mailing would encourage patients to ask their doctors to prescribe the NovoPen 3 and in effect a Novo Nordisk insulin cartridge. Breaches of Clauses 20.1 and 20.2 were ruled which were upheld upon appeal by Novo Nordisk.

The Panel considered that there were similarities between Case AUTH/1018/4/00 and the case now before it, Case AUTH/1079/9/00.

Turning to the case now before it the Panel noted that OptiPen Pro was for use with cartridges of Insuman insulins which were marketed by Aventis. The summaries of product characteristics for Insuman Basal, Insuman Comb 15, 25, 50 and Insuman Rapid stated that the cartridge presentation of the products had been developed for use in the OptiPen. The insulins were prescription only medicines. MIMS (November 2000) stated that OptiPen Pro 1 was a reusable insulin pen for use with 3ml cartridges of Insuman Basal, Insuman Comb and Insuman Rapid insulins. Lilly's Humalog and Humulin insulin cartridges could be used in a BD Pen Ultra or Lilly's own Humapen (MIMS November 2000).

In the Panel's view promotion of OptiPen Pro constituted promotion of Aventis insulin cartridges and was thus within the scope of the Code. The Panel noted the submission that insulin cartridges from Lilly would fit into the OptiPen Pro but did not consider that this would represent normal practice. In this regard the Panel noted that use of Lilly cartridges required more insulin to prime the OptiPen Pro and that some 20 units of insulin would remain unused. Use of non-Aventis cartridges was therefore not ideal.

The Panel noted that the advertisement in Balance was headed 'Introducing the New OptiPen Pro'. Eight bullet points listed favourable features of the device such as 'A highly sophisticated injection pen that's simple and easy to use', 'Designed for confident handling' and 'Discreet and elegant'. Readers were told that if they wanted more information on OptiPen Pro they should ask their doctor or diabetes nurse specialist.

The Panel considered that the advertisement in Balance by promoting the OptiPen Pro constituted promotion of Aventis' insulins to the general public and ruled a breach of Clause 20.1.

Complaint received 22 September 2000

Case completed 4 December 2000

CASE AUTH/1080/9/00

WYETH v ASTRAZENECA

Promotion of Nexium

Wyeth alleged that the promotion of Nexium by AstraZeneca to GPs was misleading with regard to the licensed indication in that statements in a mailer and an advertisement linked 'on-demand use' to 'maintenance dosing'. Wyeth stated that conventional maintenance in the summary of product characteristics (SPC) referred to long-term management of patients with healed oesophagitis while the on-demand use was for symptomatic treatment of GORD in patients without oesophagitis and should not be interpreted as a maintenance dose. Wyeth stated that doctors might get the misleading impression that patients on a conventional dose of a proton pump inhibitor (PPI) to prevent relapse of erosive reflux oesophagitis could be safely changed to Nexium on-demand. Wyeth stated that the advertisement was misleading because there were no statements, as in the SPC, that initial symptom control was a pre-requisite to on-demand dosing, that patients remaining symptomatic should be further investigated or that there were implications of the on-demand dosing with regard to interactions with other medicines. Wyeth also alleged that the statement 'The first and only PPI licensed for on-demand use' gave the misleading impression that Nexium could be given on-demand for all indications. Wyeth further alleged that the statement in the mailer that 'Nexium offers value for money' was also misleading as it implied that substantial savings could be made by prescribing Nexium for all GORD maintenance patients whereas only patients requiring symptomatic treatment of GORD without oesophagitis were covered by the on-demand licence. The depiction of potential savings exaggerated the potential number of patients taking Nexium on-demand.

The Panel did not consider that it was misleading *per se* to describe the on-demand use of Nexium as a maintenance dose. In the Panel's view on-demand dosing represented maintenance dosing for those patients who needed symptomatic treatment of GORD without oesophagitis and in whom initial symptom control had been achieved. The Panel did not consider that the use of the term maintenance would mislead doctors into thinking that other patients could be switched to on-demand Nexium therapy. No breach of the Code was ruled. The Panel also did not consider that it was misleading to have omitted reference to initial symptom control and the possible need for further investigation if symptoms could not be controlled. In the Panel's view both situations represented normal clinical practice. Similarly the Panel did not consider that omission of information relating to the implications of on-demand therapy with regard to interactions with other medicines would lead doctors to assume that Nexium had a similar interaction profile to omeprazole. No breach of the Code was ruled.

The Panel noted that the mailer referred to the use of Nexium in both reflux oesophagitis and GORD without oesophagitis. Beneath the statement 'The first and only PPI licensed for on-demand use' it was explained that 'Following initial symptom control, this new approach potentially reduces maintenance dosing by up to two-thirds'. Although these statements appeared immediately next to a section discussing GORD without oesophagitis the Panel did not consider that, in a piece discussing two indications, it had been made clear which patients were appropriate for on-demand Nexium. A breach of the Code was ruled. The Panel considered that it was clear that 'Nexium offers value for money' related only to the annual on-demand treatment of one patient with GORD without oesophagitis. There was no attempt to exaggerate the potential number of patients who might be suitable for on-demand therapy. No breach of the Code was ruled.

Wyeth alleged that the claim 'High acid suppression enables Nexium to be used on-demand, potentially reducing maintenance costs and dosing by up to two-thirds in patients with GORD (without oesophagitis)' was misleading as the substantiating references only provided 5 day data. It would be more appropriate to use day 1, 2 or 3 acid suppression data to reflect the inferred on-demand dosage regimen of once every three days.

The Panel noted that, as opposed to taking one tablet every three days, patients taking Nexium on-demand generally took a tablet each day for a few days followed by a variable number of days with no medication. The claim in question made no reference to the period in which acid suppression had been measured and given the way patients took Nexium on-demand the Panel considered 5 day data was applicable. No breach of the Code was ruled.

Wyeth alleged that '001' in the claim 'Powerful Stuff 001', which appeared in two advertisements and a mailer, implied that Nexium was the number one PPI which was unsubstantiable and an implied superlative. The Panel considered that the use of '001' was ambiguous; some readers would think that it referred to Nexium and not to the poem printed on the page. Breaches of the Code were ruled.

Wyeth alleged that the phrase 'The Nexium evolution' was misleading as it was omeprazole which had evolved. In addition the statement

'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole' was unsubstantiated and exaggerated as the studies cited in support had used a higher dose of Nexium compared to omeprazole. It was also misleading as Nexium was unproven in some of the indications for which omeprazole had a licence. Wyeth stated that in the graphical depiction of reflux healing data the initial, misleading impression was that the comparison with omeprazole was at equivalent doses as the header statement omitted the actual doses.

The Panel noted that Nexium had been shown to provide more effective acid control than other PPIs and that on-demand dosing for certain patients was a novel regimen for PPIs. The Panel did not consider the phrase 'The Nexium evolution' was misleading. No breach of the Code was ruled. The Panel considered that the studies cited in support of the statement 'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole' had demonstrated that Nexium had advantages over omeprazole. The Panel did not consider that the claim was misleading, unsubstantiated or exaggerated. No breach of the Code was ruled. With regard to the depiction of the healing study the Panel noted that although the heading did not state the dose of Nexium and omeprazole used the subheading clearly did. No breach of the Code was ruled.

Wyeth alleged that the statement 'Nexium 40mg maintains intragastric pH above 4 significantly longer in each 24 hours than all other PPIs at healing doses' was misleading as the lansoprazole comparison was only made on day 5. The Panel noted that two of the studies cited in support of the statement had only measured 24 hour intragastric pH on day 5 of each dosing period. The Panel considered that to cite these studies in support of a claim relating to each 24 hours was misleading. A breach of the Code was ruled.

Wyeth alleged that the use of the word effectively in relation to symptom control was misleading and exaggerated as the referenced data stated the end-points were patients' 'unwillingness to continue' due to 'inadequate symptom control'. The Panel noted that while 10% of patients in the cited study did not achieve adequate symptom control with Nexium on-demand the majority of patients did, and so in this group treatment was effective. No breach of the Code was ruled.

Wyeth alleged that the stated monthly cost of Nexium on-demand therapy was misleading as it did not take into account the need for one month's continuous treatment to resolve symptoms nor did it allow for only 90% of patients having adequate symptom control. Wyeth also alleged that a cost comparison chart of PPIs was misleading as it showed a price range rather than specific prices thereby depicting Nexium in a disproportionately good light compared to the other PPIs as it hid the cost of Nexium taken daily. Also it was misleading to make no clear distinction between prices relating to SPC dosage recommendations compared with Nexium on-demand, as the two categories were distinctly different. Wyeth also stated that the reference to 'all dosage regimens' and the reproduction of the recommendation by the National Institute for Clinical Excellence (NICE) that 'The least expensive PPI should be used' [sic] inferred that Nexium was licensed for the same indications as all of the other PPIs.

The Panel noted that the monthly cost of Nexium appeared on a page discussing on-demand therapy and was one third of the cost of a pack of 28 tablets. The Panel did not consider that in a discussion of on-demand therapy it was necessary to detail the cost of the first month of daily therapy. No breach of the Code was ruled.

The Panel noted that the cost comparison chart was headed 'Price comparison of Nexium and other PPIs for all dosage regimens'. Beneath the chart was the guidance from NICE that 'The least expensive appropriate PPI should be used [Wyeth had omitted the word 'appropriate' from its complaint]. The Panel did not consider that the chart inferred that Nexium was licensed for all the same indications as all of the other PPIs. In addition the Panel considered that the NICE guidance suggested that in some situations not all PPIs would be appropriate. The Panel did not consider that the cost comparison was misleading or that it promoted Nexium beyond the terms of its licence. No breach of the Code was ruled.

Wyeth alleged that overall the Nexium campaign was in breach of Clause 2 of the Code. The Panel did not consider that the materials warranted such a ruling which was used as a sign of particular censure.

Wyeth complained about the promotion of Nexium (esomeprazole) by AstraZeneca. Wyeth marketed Zoton (lansoprazole).

1 Misleading interpretation of licensed indication

Nexium was licensed for, *inter alia*, 'long-term management of patients with healed oesophagitis to prevent relapse' and 'symptomatic treatment of gastro oesophageal reflux disease (GORD)'. The dosage regimen for the first indication was given as '20mg once daily'. For the symptomatic treatment of GORD the dosage given was '20mg once daily in patients without oesophagitis. If symptom control had not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 20mg once daily when needed' (ref Nexium summary of product characteristics (SPC)).

COMPLAINT

Wyeth noted that a GP mailer (ref NEX MLR 6949a) contained the statement 'The first and only PPI [protein pump inhibitor] licensed for on-demand use. Following initial symptom control, this new approach potentially reduces maintenance dosing by up to two-thirds'. In addition two advertisements which had appeared in the GP press (ref NEX AD 7040 and NEX AD 7034b) contained the statement 'High acid suppression enables Nexium to be used on-demand,

potentially reducing maintenance costs and dosing by up to two-thirds in patients with GORD (without oesophagitis)'.

Wyeth stated that common to both statements was the grossly misleading interpretation of the Nexium on-demand indication as being a maintenance dose. Conventional maintenance was covered in the SPC under 'long-term management of patients with healed oesophagitis to prevent relapse 20mg once daily'. In contrast, the on-demand regimen was stated in the SPC as being for 'symptomatic treatment of gastroesophageal reflux disease (GORD) 20mg once daily in patients without oesophagitis' and consequently should not be interpreted as a licensed maintenance dose.

Wyeth stated that this misinterpretation was both misleading and unsubstantiable, as well as being outside the marketing authorization, and was therefore in breach of Clauses 7.2, 7.3 and 3.2 respectively.

Wyeth stated that reference to on-demand as maintenance dosing was also potentially a serious efficacy issue. Clinicians might easily gain the erroneous impression that patients on a conventional maintenance dose of a PPI to prevent relapse of erosive reflux oesophagitis could safely be changed to an on-demand Nexium regimen. This was potentially seriously misleading and as such in breach of Clause 7.2. In addition Wyeth stated that in the advertisements it was potentially seriously misleading to omit any reference to the need for initial symptom control, as this was clearly a prerequisite as stated in the SPC.

Wyeth also alleged that in both the advertisements and the mailer it was misleading to omit any mention that patients remaining symptomatic following initial symptom control should be further investigated, as again this was clearly referred to in the SPC. It was also misleading to omit any reference to the implications of an on-demand therapy to interact with other pharmaceuticals as stated in the SPC under special warnings and special precautions (Section 4.4). This potentially had major safety implications as doctors would presume that Nexium had a similar interaction profile to omeprazole.

Wyeth stated that omission of the above three points in the scenario of on-demand dosing was not only potentially seriously misleading, but also inconsistent with the particulars listed in the SPC. Breaches of Clauses 7.2 and 3.2 were alleged.

Wyeth alleged that the statement in the mailer 'The first and only PPI licensed for on-demand use' was grossly misleading as it gave the initial impression that it was licensed for on-demand use in all indications, as there was not an obvious qualification of the specific indication. Again, Wyeth alleged that this was misleading and inconsistent with the on-demand dosing particulars listed in the SPC and was therefore in breach of Clauses 7.2 and 3.2 respectively.

Finally Wyeth alleged that the statement 'Nexium offers value for money' in the mailer was also misleading as the initial impression was that substantial savings could be made by prescribing Nexium for all GORD maintenance patients. Strictly, the potential savings could only be made in patients requiring symptomatic treatment of GORD without oesophagitis on an on-demand basis (ie not maintenance), as distinct from long-term management of patients with healed oesophagitis to prevent relapse at a licensed dose of 20mg daily (conventional maintenance). This depiction was misleading in terms of exaggerating the potential number of patients taking Nexium on-demand and consequently the potential savings. It was therefore in breach of Clause 7.2.

RESPONSE

AstraZeneca stated that it did not accept the contention that the statements regarding the on-demand usage of Nexium were a misleading interpretation and representation of the approved indication. The use of on-demand Nexium 20mg once daily in patients with gastro oesophageal reflux disease (GORD) without oesophagitis was a licensed dosage regimen which would be readily understood by clinicians to be the maintenance phase of treatment of this condition. Indeed, it was pertinent to note that neither the SPC for Zoton nor Nexium used the word maintenance, rather the use of the phrase long-term management. Thus, on-demand therapy was clearly a form of maintenance dosing.

AstraZeneca did not consider there had been any breach of Clauses 3.2, 7.2 or 7.3.

AstraZeneca stated that it was clear in both pieces that the on-demand dosage regimen was only indicated for patients with GORD without oesophagitis (as per the Nexium SPC). There was no reason why clinicians would confuse this with the prevention of relapse of erosive reflux oesophagitis (RO).

As there were no published data reporting the use of Nexium on-demand in erosive oesophagitis, the promotional materials for Nexium made a clear distinction between reflux oesophagitis and GORD without oesophagitis. It was explicit in all materials that when on-demand was discussed it was made clear that it only applied to GORD without oesophagitis, as per the Nexium licence. As it would be totally inappropriate, no reference was made in the materials to the switching of RO patients to Nexium on-demand.

AstraZeneca, therefore, disagreed that clinicians were likely to get the erroneous impression that on-demand treatment was suitable for patients with reflux oesophagitis and denied any breach of Clause 7.2.

With regard to the advertisement, AstraZeneca considered that the suggestion that it was necessary to refer to initial symptom control in each reference to on-demand therapy was without basis. The need to make reference to initial symptom control clearly depended upon the context and the company considered that this had been fully accounted for in the preparation of its materials. Similarly, reference to the need to further investigate patients who remained symptomatic despite four weeks of initial therapy depended entirely upon context, and had been fully taken into account in the materials.

AstraZeneca noted that in the advertisements the claims were clearly referenced to the Nexium SPC. It was a principle of all current PPI therapy (as per the respective SPCs) that the management of GORD required an initial 4-8 week period of initial symptom control/healing before switching to a maintenance dose thereafter. Since PPIs had been extensively used as a class for the last 11 years it did not seem necessary to spell out the requirement for this initial phase of treatment. The same comment applied to the need for further investigation.

AstraZeneca considered the specific reference to on-demand and the potential for interactions to be erroneous; the necessary precautions and warnings, as stated in the SPC, were included within the prescribing information in accordance with normal promotional practice. On this basis the company did not consider that the on-demand use of Nexium should be a specific cause of concern regarding the interaction profile of Nexium.

AstraZeneca noted that interactions were an issue for many highly prescribed medications, including PPIs such as omeprazole and lansoprazole, and prescribers would be expected as a matter of course to check for potential interactions at the time of prescribing. In the 'Notice to Applicants – A Guideline on the Summary of Product Characteristics – December 1999' it was stated that 'other medicines which should be specifically avoided for concomitant use' or '…where there are strong theoretical reasons for not using the combination…' should be stated in Section 4.3 (Contraindications). The Nexium SPC only mentioned interactions in Sections 4.4 (Special warnings and special precautions for use) and 4.5 (Interactions…). AstraZeneca also noted that the SPC for Zoton mentioned that '… caution should be exercised when preparations such as phenytoin, theophylline and warfarin are taken concomitantly with Zoton'. All of these interactions would have potentially serious clinical outcomes and yet Wyeth had not considered it necessary to highlight these in its promotional materials.

Finally, AstraZeneca stated that there was no reason why doctors should assume that Nexium had a similar interaction profile to omeprazole; Nexium had a black triangle indicating that it was considered sufficiently novel to merit enhanced reporting of adverse events.

On this basis, AstraZeneca did not consider the representation of on-demand dosing within its promotional materials to be misleading and in breach of Clauses 3.2 and 7.2.

AstraZeneca submitted that the claim 'Nexium is the first and only PPI licensed for on-demand use' was a statement of fact. The company disagreed that this was grossly misleading as it clearly did not give the impression that Nexium was licensed for on-demand use in all indications. It was highly unlikely that physicians would gain the impression that on-demand use would be suitable for *H. pylori* eradication. The company denied any breach of Clauses 3.2 and 7.2.

AstraZeneca contended that the statement 'Nexium offers value for money' did not *per se* express or imply cost savings. Within the mailer in question, immediately beneath this 'value for money' headline was the qualification that maintenance (as discussed above) treatment costs for patients with GORD (without oesophagitis) were potentially reduced by up to two-thirds. Thus, the company did not accept the allegation that the initial impression was that savings could be made by prescribing Nexium for all GORD maintenance patients.

Furthermore, the company did not consider the depiction in the mailer exaggerated the potential number of patients taking Nexium on-demand and consequently the potential savings. It was clear from the graphical data presented that Nexium did offer value for money in this group of GORD patients without oesophagitis, based on clinical trial data. Since the majority of patients with GORD would be on a long-term maintenance regimen, it seemed appropriate to compare direct costs for this group of patients. There was no attempt to exaggerate the potential numbers of patients taking Nexium on-demand or the potential savings as the data presented was based on the cost of treating one patient over one calendar year. AstraZeneca considered that it clearly stated this by the use of the phrase '…[costs]… are potentially reduced by up to two-thirds' at the top of this piece of promotional material.

On this basis, the company did not accept that this claim and its representation were in breach of Clause 7.2.

PANEL RULING

The Panel noted that the claims at issue referred to the on-demand use of Nexium potentially reducing maintenance dosing and costs. The Panel did not consider that it was misleading *per se* to describe the on-demand use of Nexium as a maintenance dose. Nexium 20mg was licensed for the symptomatic treatment of GORD without oesophagitis. Once symptoms had resolved, subsequent symptom control could be achieved by using an on-demand regimen when needed. In the Panel's view this on-demand therapy represented maintenance dosing for that particular group of patients. The Panel did not consider that the term maintenance applied exclusively to the long-term management of patients with healed oesophagitis to prevent relapse. The Panel thus did not consider that the use of the term maintenance would mislead clinicians into thinking that they could safely change patients from a conventional maintenance dose of a PPI to prevent relapse of erosive oesophagitis to an on-demand Nexium regimen. No breaches of Clauses 7.2, 7.3 and 3.2 were ruled in this regard.

The Panel noted that patients with symptomatic GORD without oesophagitis should receive Nexium 20mg daily for up to four weeks to achieve initial symptom control. If symptom control was not achieved after four weeks the patient should be investigated further. Once symptoms had resolved the patient could be prescribed Nexium 20mg to be taken on-demand. Section 4.4 of the Nexium SPC stated that patients on on-demand treatment should be instructed to contact their doctor if their symptoms changed in character. When prescribing Nexium for

on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole, should be considered. The Panel considered that it was not misleading to have omitted reference to initial symptom control and the possible need for further investigation if symptoms could not be controlled in the main copy. In the Panel's view both situations represented normal clinical practice. Similarly the Panel did not consider that the omission of information relating to the implications of on-demand therapy with regard to interactions with other medicines would lead doctors to assume that Nexium had a similar interaction profile to omeprazole. No breaches of Clauses 7.2 and 3.2 were ruled.

The Panel noted that the mailer (ref NEX MLR 6949a) referred to the use of Nexium in both reflux oesophagitis and GORD without oesophagitis. One section of mailer referred to Nexium as 'The first and only PPI licensed for on-demand use'. Beneath this claim was the explanation that 'Following initial symptom control, this new approach potentially reduces maintenance dosing by up to two-thirds'. The Panel noted that this section of the mailer appeared immediately next to a section discussing GORD without oesophagitis. Despite the juxtaposition of the two sections, however, the Panel did not consider that, in a piece discussing two indications, it had been made clear that the on-demand use of Nexium was only appropriate in those patients with GORD without oesophagitis. The Panel considered that while this was misleading it did not amount to promotion of Nexium outside the terms of its licence. The Panel thus ruled a breach of Clause 7.2 and no breach of Clause 3.2.

The same mailer also contained a comparison of the annual costs of treating one patient with GORD (without oesophagitis) with either omeprazole 20mg or 10mg daily or Nexium 20mg on-demand. The annual cost of Nexium on-demand therapy was less than one half that of omeprazole 10mg and only one third of the cost of using omeprazole 20mg. The Panel considered that it was clear that the claim 'Nexium offers value for money' related only to the annual on-demand treatment of one patient with GORD without oesophagitis. There was no attempt to exaggerate the potential number of such patients who might be suitable for on-demand therapy. No breach of Clause 7.2 was ruled.

2 Claim 'High acid suppression enables Nexium to be used on-demand, potentially reducing maintenance costs and dosing by up to two-thirds in patients with GORD (without oesophagitis)'.

This claim appeared in two GP advertisements (ref NEX AD 7040 and NEX AD 7034b) and 'High acid suppression' was referenced to Lind *et al* 2000 and Rohss *et al* 2000.

COMPLAINT

Wyeth stated that the 'high acid suppression' references (Lind *et al* and Rohss *et al*) only provided day 5 data. Also, in this context the SPC stated that acid suppression increased over the first five days. Consequently, in this context of on-demand therapy, where it was suggested that patients take Nexium on average once every three days (potential two-thirds savings), it was misleading to reference day 5 data. It would be more appropriate to use day 1, 2 or 3 acid suppression data to reflect the inferred on-demand dosage regimen of once every three days.

Wyeth alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

AstraZeneca submitted that the claim was a valid claim and was the premise for the on-demand licence being granted for Nexium. Moreover clinically patients did experience symptoms related to acid reflux and high acid suppression enabled symptom relief.

AstraZeneca stated that its clinical trial data clearly showed that GORD patients without oesophagitis took a dose of Nexium on average on one-third of the days to effectively control their symptoms, rather than once every three days as incorrectly stated by Wyeth. This was statistically significant compared to placebo. The difference could, therefore, be assumed to be due to high acid suppression. Although the study by Lind *et al* looked at day 5 data only, the study by Rohss *et al* also looked at day 1 and this showed that the mean percentage of time with intragastric pH>4 was significantly higher with Nexium 40mg compared to omeprazole 40mg at both days 1 and 5. There was no scientific reason to expect that on any of the intervening days the situation would be any different.

AstraZeneca considered that the promotional materials for Nexium on-demand were quite explicit in stating that patients took a tablet on a third of the days because, as also stated in the materials, the majority of patients took a tablet on three or less consecutive days. In other words, patients frequently tended to take a few days of therapy followed by a variable number of days on which they did not take a tablet.

The company did not accept the allegation that the claim was misleading and in breach of Clause 7.2.

PANEL RULING

The Panel noted that Lind *et al* was a double-blind crossover study to compare the acid inhibitory effects of esomeprazole (20mg or 40mg od) and omeprazole (20mg od) in patients with GORD. Patients were treated for five days and at the end of each five day dosing period 24-hour intragastric pH was measured. The results showed that both doses of esomeprazole maintained intragastric pH > 4 for significantly longer than omeprazole. Twenty four hour median intragastric pH was significantly higher with both doses of esomeprazole than with omeprazole.

The Panel noted that the Rohss *et al* citation in the advertisement referred to a scientific poster; the Rohss *et al* reference provided to the Panel was an abstract printed in Gastroenterology. The abstract reported a study similar in design to that by Lind *et al* except that the subjects were healthy volunteers and they

received either esomeprazole 40mg or lansoprazole 30mg daily for five days. The results showed that at the end of each five day dosing period esomeprazole maintained intragastric pH > 4 for longer than lansoprazole and produced a significantly higher 24-hour median pH. The Panel was not provided with any data from Rohss *et al* detailing day 1.

The Panel noted that on-demand therapy could not be initiated in patients with symptomatic GORD without oesophagitis until initial symptom control had been achieved.

The Panel noted AstraZeneca's submission that patients taking Nexium on-demand generally took a tablet each day for a few days followed by a variable number of days with no medication. Although patients therefore took tablets for one third of the available days they did not take them for one day in every three. The Panel noted that the claim in question made no reference to the period in which acid suppression had been measured. Given the way in which patients took Nexium on-demand the Panel considered that day 5 data was applicable. Both studies demonstrated that esomeprazole provided more effective acid control than omeprazole (Lind *et al*) or lansoprazole (Rohss *et al*). The Panel thus did not consider that the claim was misleading and no breach of Clause 7.2 was ruled.

3 Claim 'Powerful Stuff 001'

This claim appeared in two GP advertisements (ref NEX AD 7040 and NEX AD 7032b) and in the GP mailer (ref NEX MLR 9649a).

COMPLAINT

Wyeth stated that the ambiguous '001' part of the statement initially appeared to be ambiguous, but on closer consideration implied that Nexium was the number one PPI. This was obviously unsubstantiable, and therefore in this context an implied superlative. Breaches of Clauses 7.2, 7.3 and 7.8 were alleged.

RESPONSE

AstraZeneca stated that the '001' adjacent to 'Powerful Stuff' referred to the number of the poem printed on the page and the first in the series of advertisements. The use of two zeros was deliberately chosen to avoid any accusations of implying that Nexium was number one. There was nothing to indicate in any of the content of the materials that Nexium was claimed to be number one.

AstraZeneca stated that as it was its intention that subsequent advertisements in this series would feature different poems and carry sequentially higher numbers i.e. '002' , '003' etc., it did not consider this to be an implied superlative and denied any breach of Clauses 7.2, 7.3 and 7.8.

PANEL RULING

The Panel considered that the use of '001' was ambiguous. It was not unreasonable to assume that some readers would think that the '001' referred to Nexium, the subject of the advertisement, and not the poem by William Blake. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

4 Claims 'The Nexium evolution' 'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole'

These claims appeared on the front cover of a leavepiece distributed by the sales representatives (ref NEX LVP 6890). The leavepiece also contained a graph depicting data from Kahrilas *et al*.

COMPLAINT

Wyeth alleged that the phrase 'The Nexium evolution' was misleading, in breach of Clause 7.2, as it was actually omeprazole (Losec) which had evolved.

Wyeth stated that the statement that 'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole' was totally unsubstantiated by the Kahrilas and Lind data comparisons and was consequently exaggerated in this context as the differences were more related to the higher dose of Nexium compared to omeprazole, rather than to properties of the single isomer. Also it was misleading, as in not being currently licensed for acid related dyspepsia and treatment/prophylaxis of NSAID-associated ulcers/symptoms, Nexium was as yet unproven in these major indications for which omeprazole was currently licensed. Consequently in this important context of licensed indications, Nexium could not be said to be 'beyond the standard set by omeprazole'. Wyeth alleged that the statement was therefore in breach of Clauses 7.3, 7.8 and 7.2. Wyeth stated that in the graphical depiction of the reflux healing data from Kahrilas *et al*, the initial impression was that the comparison was at equivalent doses, in that the header statement omitted the actual dosages. Wyeth alleged that this depiction was therefore misleading and consequently in breach of Clause 7.2.

RESPONSE

AstraZeneca stated that the reference to 'The Nexium evolution', was not misleading as alleged. 'evolution' was defined in Stedman's Medical Dictionary as 'a continuing process of change from one state, condition, or form to another'. Nexium represented a change from previous PPI therapy, such as omeprazole. It was the first PPI developed as a single optical isomer, for example, and the on-demand regimen in GORD without oesophagitis could also be perceived as a significant change from previous therapy with PPIs. It was therefore, reasonable to describe this as the 'Nexium evolution'. AstraZeneca did not consider this to be a breach of Clause 7.2.

AstraZeneca stated that the claim 'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole' within the leavepiece in question was not specifically referenced to Lind or Kahrilas, as alleged by Wyeth. However, in addressing Wyeth's concerns AstraZeneca made the following points:

The assertion that the Lind and Kahrilas data comparisons were exaggerated due to the higher doses of Nexium was untrue. The Kahrilas study compared 40mg Nexium with 20mg omeprazole in the healing of reflux oesophagitis.

In early studies, Nexium 40mg once daily was found to be the most effective dose for the treatment/healing of GORD and, consequently, it was this dose that was carried forward into the Nexium clinical programme. Omeprazole 20mg was selected as the comparator in the clinical trials because it was considered a current 'gold standard' and the licensed dose for the treatment of GORD and reflux oesophagitis. Omeprazole 40mg daily was reserved for the treatment of patients with reflux oesophagitis refractory to other therapy and would, therefore, not have been an appropriate comparator with Nexium 40mg.

The study by Lind *et al* investigating acid suppression in GORD patients, also showed that Nexium 20mg was more effective than omeprazole 20mg. In addition, Rohss *et al*, showed that Nexium 40mg was more effective than omeprazole 40mg in acid suppression. The data therefore supported the claim that PPI therapy had advanced beyond the standard set by omeprazole.

With regard to comment concerning the licensed indications AstraZeneca noted that nowhere in the promotional materials for Nexium did it suggest that the product had the same licensed indications as omeprazole. The company, therefore, considered that this claim was substantiated by the data and was not in breach of Clauses 7.2, 7.3 and 7.8.

AstraZeneca noted that a subheading to the graphical presentation of the Kahrilas data clearly stated 'Nexium 40mg od vs. omeprazole 20mg od'. The issue of which doses were appropriate for comparison was discussed above and the doses depicted were the licensed doses for healing for both medicines. The company did not consider the depiction was misleading and in breach of Clause 7.2.

PANEL RULING

The Panel noted that Lind *et al* and Rohss *et al* had shown that Nexium provided more effective acid control than other PPIs (see point 2 above). In addition the on-demand dosing regimen for the maintenance of patients with GORD, without oesophagitis, was a novel regimen for PPIs. The Panel thus did not consider that the phrase 'The Nexium evolution' was misleading. No breach of Clause 7.2 was ruled.

The Panel noted that the leavepiece in question (ref NEX LVP 6890) discussed the intragastric acid suppression observed with Nexium, the use of the product to heal reflux oesophagitis and its use in combination with antibiotic therapy to eradicate *H.pylori*, heal *H.pylori*-associated duodenal ulcers and the prevention of relapse of peptic ulcers in patients with *H.pylori*-associated ulcer disease. The Panel noted that the Lind data (see point 2 above) demonstrated that Nexium provided more effective acid control than omeprazole. The data by Kahrilas *et al* showed that Nexium 40mg was superior to omeprazole 20mg in the healing of erosive oesophagitis; Nexium also provided greater heartburn resolution. The Panel noted that Nexium 40mg and omeprazole 20mg were both licensed as healing doses.

The Panel considered that the studies by Lind *et al* and Kahrilas *et al* both demonstrated that Nexium had advantages over omeprazole. The Panel therefore did not consider the claim that 'AstraZeneca has advanced PPI therapy beyond the standard set by omeprazole' was misleading, unsubstantiable or exaggerated. No breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

The Panel noted that although the header above the graphs depicting the results from the Kahrilas study did not state the doses of Nexium or omeprazole used, the subheading and the graphs themselves clearly gave this data. The depiction of the data was thus considered not to be misleading and the Panel ruled no breach of Clause 7.2.

5 Claim 'Nexium 40mg maintains intragastric pH above 4 significantly longer in each 24 hours than all other PPIs at healing doses'

This claim appeared in a GP mailer (ref NEX MLR 6949a).

COMPLAINT

Wyeth alleged that this statement was entirely misleading in stating '…in each 24 hours ….' as it inferred that there were significant pH differences on days 1, 2, 3, 4 and 5. However, the data showed that the lansoprazole comparison was only made on day 5. A breach of Clause 7.2 was alleged.

RESPONSE

AstraZeneca stated that the inclusion of the statement 'in each 24 hours' was not misleading as alleged, but was an important statement to be included as an accurate representation of the gastric acid suppression data.

AstraZeneca explained that presentations of data on the maintenance of intragastric pH above the threshold levels of pH 3 or 4 were usually expressed as either a percentage of time or as a cumulative duration. In both instances it was absolutely critical that the observation period was clearly expressed; without reference to the observation period the data would be absolutely meaningless. Thus, 'in each 24 hours' referred to the dosing interval which was also the duration of the observation period and was a reference to the fact that the advantage for Nexium was observed within a 24 hour period. Furthermore the company considered that the headline claim was substantiated by the fact that the differences for the PPIs cited were statistically significant at all the time points studies.

AstraZeneca did not consider that this was a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim in question appeared as a headline and was referenced to four studies including Lind *et al* and Rohss *et al*. Beneath the headline, data from the four studies was given. Lind *et al* and Rohss *et al*, however, only measured 24 hour intragastric pH on day 5 of each dosing period (see point 2 above). The Panel considered, therefore that to cite these studies in support of a claim relating to each 24 hours was misleading as alleged. A breach of Clause 7.2 was ruled.

6 Claims for 'effective' control of symptoms

COMPLAINT

Wyeth noted that in a GP mailer (ref NEX MLR 6949a) and in a leavepiece (ref NEX LVP 6892) stab points correctly stated that patients achieved adequate symptom control. In contrast, other stab points incorrectly stated that symptoms were effectively controlled. In relation to the referenced data, Talley *et al*, which stated the end-points as patients' 'unwillingness to continue' due to 'inadequate symptom control', the use of the word effectively was obviously exaggerated and misleading.

Wyeth noted that the word effectively also misleadingly appeared as an exaggerated claim in the press release (ref NEX 6982).

Wyeth alleged that the use of the word effectively in relation to symptom control was in breach of Clauses 7.2 and 7.8.

RESPONSE

AstraZeneca stated that when a treatment provided a level of symptom control which was statistically significantly superior to that provided by placebo it was normally accepted terminology to consider that that treatment was effective. The statement that symptoms were effectively controlled implied nothing more than that the treatment was effective in providing a level of control greater than placebo.

The primary end point in both the on-demand studies by Talley *et al* was in fact 'unwillingness to continue for any reason' (inadequate symptom control was a secondary endpoint). The results showed significant differences in favour of Nexium over placebo for both endpoints. Indeed, over 90% of patients were willing to continue with their treatment, in a study where symptoms were the main reason for being enrolled into the study. A 90% response rate could not be considered to be anything less than 'effectively controlled'.

AstraZeneca considered that it was justifiable to use the term 'effectively controlled', that it was neither an exaggerated or misleading claim and was not in breach of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that it had not been supplied with a copy of the data from Talley *et al*. The data had, however, been used to support claims that over a six month period approximately 90% of patients with GORD (without oesophagitis) had adequate symptom control taking on-demand Nexium 20mg once daily and that such patients took Nexium on-demand to effectively control their symptoms. The Panel noted that while 10% of patients did not achieve adequate symptom control with Nexium on-demand the majority of patients did, and so in this group treatment was effective. The Panel thus did not consider the use of the word 'effectively' in relation to symptom control to be misleading or exaggerated as alleged. No breaches of Clauses 7.2 and 7.8 were ruled.

7 Claims '£6.17 per month in patients with GORD (without oesophagitis)' 'Nexium – value for money' and cost comparison chart

The claims appeared in a leavepiece (ref NEX LVP 6892). 'Nexium – value for money' appeared above a price comparison chart of Nexium and other PPIs for all dosage regimens. The bar representing the cost of 28 days of therapy with Nexium was labelled '20mg od on-demand – 40mg od' and ranged from approximately £6 to £29.

COMPLAINT

Wyeth stated that the bold statement '£6.17 per month in patients with GORD (without oesophagitis)' was grossly misleading in that it was incorrect as it was insufficiently qualified. It did not take into account the need for an initial month of continuous treatment with Nexium 20mg to resolve symptoms, nor did it allow for only 90% of patients having adequate symptom control as stated in the second stab point. Wyeth alleged a breach of Clause 7.2.

Wyeth also alleged that the price comparison chart was misleading in the following respects: It showed a price range rather than specific prices for the products, thereby depicting Nexium in a disproportionately good light compared with other PPIs, not least as it hid the Nexium 20mg once daily price. It was also misleading not to make a clear distinction on the chart between the prices relating to the SPC dosage recommendations compared with the Nexium on demand clinical trial programme, as the two categories were significantly different. A breach of Clause 7.2 was alleged.

Wyeth stated that the reference to 'all dosage regimens' and the recommendation by the National Institute for Clinical Excellence (NICE) that 'The least expensive PPI should be used' [sic] inferred that Nexium was licensed for the same indications as all the other PPIs shown on the cost comparison chart, not least as in the same context the NICE reference was unbalanced as it omitted the NICE associated qualifying paragraph which stated that a PPI should only be used in line with its licensed indications.

Wyeth alleged that the page was consequently not only severely misleading but also promoting outside the marketing authorization and was therefore in breach of Clauses 7.2 and 3.2.

RESPONSE

AstraZeneca stated that as the majority of patients with GORD without oesophagitis would be on long-term maintenance therapy it was inappropriate to attempt to build into the equation an unknown minority of patients on an initial 4 week treatment course. The only sensible presentation was that for patients in whom symptom control had already been achieved. The two trials that investigated Nexium on-demand therapy were analysed on an Intention to Treat (ITT) basis and the finding that patients only took Nexium on one third of days was also an ITT analysis.

The company did not consider this representation to be in breach of Clause 7.2.

With regard to the cost comparison AstraZeneca noted that the chart was clearly titled that it was a comparison of Nexium and other PPIs 'for all dosage regimens'. Thus, it was entirely appropriate that the comparison should be made on the dosage regimens specified within the individual SPCs. There was no intention to hide the 20mg daily dose; the Nexium bar clearly showed the likely minimum monthly cost (GORD patients without oesophagitis based on the average seen in clinical trials) and the maximum cost (RO patients on healing course of treatment).

The subheader clearly stated that potential costs were based on relevant SPCs and the Nexium clinical trial programme. There was no intention to mislead; indeed a number of GORD patients without oesophagitis might need to take Nexium less than one third of days, thus reducing potential costs even further. The company noted, however, that it had chosen not to depict this since it was considered only fair to represent the mean ie one third of days.

AstraZeneca did not consider that the cost comparison was in breach of Clause 7.2.

AstraZeneca noted that the quoted statement from NICE actually stated 'the least expensive appropriate PPI should be used'. This was important, as absolute cost minimisation was not necessarily a sole determinant in choice of PPI without considering other factors such as efficacy, safety profile and licensed indications. The company was not advocating the use of Nexium outside of the terms of its licensing authorization. AstraZeneca did not consider this to be in breach of Clauses 7.2 and 3.2.

PANEL RULING

The Panel noted that the statement '£6.17 per month in patients with GORD (without oesophagitis)' appeared on a page discussing Nexium on-demand therapy. The Panel noted that £6.17 was one third of the cost of a pack of 28 tablets of Nexium 20mg and thus accounted for patients only taking the tablets on one third of days. The Panel did not consider that in a discussion of on-demand therapy it was necessary to detail the cost of the first month of symptom control ie Nexium 20mg once every day. As long-term therapy of GORD without oesophagitis progressed the cost of the first month's treatment would become a smaller and smaller percentage of the whole cost. The Panel did not consider that the statement was misleading and no breach of Clause 7.2 was ruled.

The Panel noted that the cost comparison chart was headed 'Price comparison of Nexium and other PPIs for all dosage regimens'. Beneath the chart was the guidance from NICE that 'The least expensive appropriate PPI should be used' [Wyeth omitted the word 'appropriate' from its complaint]. The Panel did not consider that the cost comparison inferred that Nexium was licensed for all of the same indications as all of the other PPIs. (In this regard it was noted that the subsequent page in the leavepiece clearly set out Nexium's therapeutic indications and recommended dosages). In addition the Panel considered that the NICE guidance below the chart suggested that in the some situations not all PPIs would be appropriate. The Panel thus did not consider that the cost comparison was misleading or that it promoted Nexium beyond the terms of its licence. No breaches of Clauses 3.2 and 7.2 were ruled.

8 Alleged breach of Clause 2

COMPLAINT

Wyeth stated that it was obviously most concerned about the extensive and potentially serious amount of misinformation contained throughout the Nexium promotional campaign as outlined above and also the press confusion. In light of the level and degree of misinformation, the company alleged a breach of Clause 2.

RESPONSE

AstraZeneca stated that with regard to the comment that there had been confusion in the press regarding the on-demand indication for Nexium, the medical press release (ref NEX 6982) stated that Nexium was the only medicine in its class licensed for on-demand use. This press release then clearly stated that doctors could advise patients with symptomatic GORD without oesophagitis to take a daily dose of Nexium (20mg od) only when required to control their recurrent symptoms. In addition, at the bottom of each page of the press release it was clearly stated that the prescribing information for Nexium could be found on the back of the first page of the document.

PANEL RULING

The Panel did not consider that the Nexium promotional materials warranted a ruling of a breach of Clause 2 of the Code which was used a sign of particular censure and was reserved for such circumstances.

Complaint received **25 September 2000**

Case completed **29 November 2000**

CONSULTANT PHYSICIAN v PFIZER

Radio advertisement

A consultant physician complained about a radio advertisement which advised men suffering from impotence to seek medical advice. His concern was that the advertisement was 'supported by an educational grant from Pfizer'. Viagra was not mentioned by name but given its position in the field the complainant wondered whether this was in effect a form of advertisement to the general public of a product available only on prescription and available on the NHS only in specific conditions. The complainant had not had the opportunity to hear the advertisement again to concentrate on precisely what was said and he assumed that this might constitute a sufficiently indirect form of advertising to stay within the guidelines. However, he did feel some disquiet over it.

The Panel examined the transcripts for the two versions of the radio advertisement. The advertisement entitled 'Excuses' referred to impotence often being a symptom of other health problems like heart disease, high blood pressure or diabetes and that effective treatments were available. Listeners were advised to call a number for further information. The advertisement entitled 'Don't put off today …' referred to the embarrassment of impotence and recommended that the listener should call the helpline or talk to his doctor. The telephone helpline referred to erectile dysfunction and some of the causes of the condition and stated that family doctors were now able to treat the majority of cases with a range of treatment options. Callers could be connected to a trained counsellor at the Impotence Association or they could ask for an information pack. The information pack consisted of a booklet 'Understanding Men's Health' which on the front cover referred to the Impotence Association and to the fact that the booklet was supported by an educational grant from Pfizer. The booklet went into more detail about the subject and discussed treatment in general terms. The booklet referred to the availability of treatments on the NHS or privately and recommended sufferers to discuss their condition with their GP.

The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine and no breach of the Code was ruled in that regard. The Panel noted that one of the requirements of the Code was that statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. None of the materials provided mentioned specific medicines. Treatments were referred to in a general sense. No products were named. The Panel considered that the materials would increase public awareness of impotence and encourage people to discuss the matter with their general practitioner. This was not necessarily unacceptable. From the information provided men were not being encouraged to ask their doctors for a specific medicine. The Panel noted that there were a number of different treatments available, including Pfizer's product, Viagra. Not all of the treatments were medicines. The Panel, while acknowledging that there was a fine distinction between education and promotion, did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of the Code was ruled.

A consultant physician complained about a radio advertisement which he had heard on 13 September on Radio Clyde 2.

COMPLAINT

The complainant said that the advertisement advised men suffering from impotence to seek medical advice. His concern was that the advertisement was 'supported by an educational grant from Pfizer'. Viagra was not mentioned by name but given its position in the field the complainant wondered whether this was in effect a form of advertisement to the general public of a product available only on prescription and available on the NHS only in specific conditions. The complainant had not had the opportunity to hear the advertisement again to concentrate on precisely what was said and he assumed that this might constitute a sufficiently indirect form of advertising to stay within the guidelines. However, he did feel some disquiet over it and he would be grateful to the Authority for checking the position.

When writing to Pfizer Limited, the Authority drew attention to Clauses 20.1 and 20.2 of the Code.

RESPONSE

Pfizer stated that the radio advertisement would have been one of two versions, both of which were broadcast on Radio Clyde 2 on the date referred to. Since Pfizer could not determine from the complaint precisely which one it was, it provided copies of the scripts for each of them.

The radio advertisements formed part of the 'Understanding Impotence' disease awareness/health education programme led by the Impotence Association and the Men's Health Forum, supported by an educational grant from Pfizer ('the programme'). The programme was initiated in the print media on 2 September 1999 and re-launched on National Impotence Day, 14 February 2000, and from that date these radio advertisements had been broadcast on numerous local and national radio stations nationwide. Full details were provided.

In addition to media advertising, the programme consisted of surgery posters and leaflets and an information booklet which was provided upon request to sufferers who either called the helpline referred to in the radio advertisements, completed a coupon or requested it via the accompanying Internet website. If they wished, callers could be connected via the helpline directly to a trained counsellor at the Impotence Association. Shortly before the programme was originally launched in 1999, doctors were informed about it in a mailing and to date over 7000 healthcare professionals had requested and received the information booklet. This was the only complaint

of which Pfizer was aware. A copy of the helpline script and a copy of the information booklet 'Understanding Men's Health' were provided.

By way of background, the Impotence Association was a charitable body which was the only UK patient support group for sufferers of impotence (properly termed erectile dysfunction or ED). The Men's Health Forum was a group which campaigned on men's health issues and comprised over 50 organisations including charities, medical/professional bodies and patient groups. The aim of the programme was to raise awareness of ED and encourage sufferers to seek the advice of their family doctor, rather than suffering alone in silence, assuming mistakenly that nothing could be done.

ED was a distressing condition primarily caused by an underlying chronic disease, for example cardiovascular disease. It was also a common condition, affecting at least 10% and as many as 52% of men aged 40 to 70. ED was in itself a serious disorder which could have a profound impact on a patient's psychological, functional and social health, their partner and the family unit. There was evidence associating ED with depression, loss of self-esteem, increased anxiety or tension with sexual partners and feelings of fear and inadequacy with regard to sexual relationships. The negative effect that this could have on relationships was demonstrated by a RELATE survey of 3,693 men seen by their counsellors (1992-1994) in which one in four men were suffering from ED.

Historically, impotence had been something of a taboo subject. It was believed that currently only a small proportion of sufferers sought medical advice about their condition: one study found that approximately 30% of men aged 40 to 70 had ED, and yet less than 1% of affected men sought professional treatment. Another reported that only about 10% of patients with sexual concerns were sufficiently confident to ask their GP for advice.

The programme aimed to dispel the numerous myths which surrounded ED and to provide both the encouragement and the information which patients needed in order to approach their doctor and discuss this extremely sensitive subject. It was well known that men visited their doctors less often and more reluctantly than women, and often failed to do so until late in the progression of a medical problem (a recent media campaign to raise awareness of testicular cancer highlighted this concern in one important disease area). Given the embarrassment and reluctance many men understandably felt about ED, all the parties supporting the programme believed that it was very important to encourage them to seek medical advice from their doctor, not only so that they might discuss their impotence and the treatment options that might be available for this distressing problem, but also because ED was often the first sign of a still more serious underlying condition, such as cardiovascular disease, high blood pressure, diabetes or depression. When a patient with ED presented to his doctor, the doctor would first seek to establish the underlying cause of the problem. This, therefore, created an opportunity to diagnose and treat such a disease or condition which had previously gone undetected. As mentioned in one of the radio advertisements and explained more fully in some of the other materials comprised in the programme, ED was in fact caused by other physical conditions in the majority of sufferers.

With regard to Clauses 20.1 and 20.2 of the Code, neither the radio advertisements, nor any of the materials forming part of the programme described above, mentioned any particular form of treatment or specific product. Treatments were only mentioned in the general and collective sense (eg 'there are treatments available') in order to encourage sufferers to seek medical advice, by dispelling the popular myth that nothing could be done for them and that there was therefore no point in coming forward. No more information or detail about possible treatments was provided.

In fact, a range of effective treatments was available for ED, comprising both prescription medicines and other forms of treatment. These included intracavernosal prostaglandin (alprostadil) injection (Caverject, Viridal Duo), transurethral alprostadil application (MUSE), Pfizer's oral treatment sildenafil citrate (Viagra), vacuum constriction devices, surgical intervention/penile prostheses, and psychosexual and couple therapy/counselling. The most appropriate treatment would depend on the particular condition and circumstances of the individual patient, as determined by his doctor's clinical judgement. Most men with ED could be successfully treated with one or other of these forms of therapy; treatment efficacy rates were in the region of 50-90% depending on the type of patient and the cause of their ED, and the particular treatment used.

For these reasons, Pfizer firmly believed that no medicine was being advertised in the radio advertising complained of (or any other part of the programme) in breach of Clause 20.1. Furthermore, no statement was made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine in breach of Clause 20.2. Rather, the aim throughout the programme was to encourage them to discuss their condition as a whole with their doctor, so that its causes and effects might be examined, and in suitable cases treatment options explored, as determined by the doctor. The brief information provided in the radio advertisements, whilst intended to be encouraging, was presented in a balanced and factual manner without raising unfounded hopes of successful treatment or misleading as to safety in any way.

With regard to the complainant's concern about Pfizer's company name being mentioned at the end of the advertisement, this point was in fact originally raised by the Radio Advertising Clearance Centre (RACC) when it reviewed the radio advertising before its launch in February. Its concern was similar to that of the complainant. On 4 February, Pfizer consulted the Director of the Authority since the company name had been included not for the purposes of advertising but in the interests of transparency, so that listeners would be aware of Pfizer's sponsorship of the programme, in line with Clause 9.9 of the Code. The Director confirmed to Pfizer her view that the reference to Pfizer's sponsorship did not of itself

constitute an advertisement of any particular medicine and that to leave it out of the advertisement might result in Pfizer infringing Clause 9.9 of the Code. Pfizer informed the RACC of this and offered to omit the company name at its request, in return for that request being put in writing in order to provide a defence to any future complaint under the Code. The RACC, however, was satisfied with Pfizer's response and the advice of the Authority and therefore permitted the radio advertising to proceed as originally scripted. Pfizer continued to believe that the reference to the company's sponsorship was necessary under the Code and did not constitute any breach of it, but the reference could easily be removed if required by any ruling of the Authority or other regulatory body.

The programme was similar in many ways to Pharmacia & Upjohn's public health campaign on bladder problems, which was the subject of Case AUTH/911/8/99. The complaint in that case was that the campaign was a disguised advertisement for Pharmacia & Upjohn's product Detrusitol. Like ED, the subject of bladder problems was an embarrassing one and the aim of the campaign was to break the taboo so that sufferers would be better informed both regarding their conditions and of the fact that treatment and care options were available for them. Like the programme, the Pharmacia & Upjohn campaign was endorsed by patient support and healthcare professional groups and referred to Pharmacia & Upjohn's sponsorship on the materials. It did not mention any specific treatment or medicines and Detrusitol was one of a number of possible treatment options for bladder problems. The Panel found that the campaign did not encourage patients to ask their doctors for a specific Pharmacia & Upjohn product and that it therefore complied with the Code. Pfizer believed that its programme complied with the Code on the same basis, for the reasons set out above.

PANEL RULING

The Panel examined the transcripts for both radio advertisements. The advertisement entitled 'Excuses' referred to impotence often being a symptom of other health problems like heart disease, high blood pressure or diabetes and that effective treatments were available. Listeners were advised to call a number for further information.

The advertisement entitled 'Don't put off today …' referred to the embarrassment of impotence and recommended that the listener should call the helpline or talk to his doctor.

The telephone helpline referred to erectile dysfunction and some of the causes of the condition. The helpline stated that family doctors were now able to treat the majority of cases with a range of treatment options. Callers could be connected to a trained counsellor at the Impotence Association or they could ask for an information pack.

The information pack consisted of a booklet 'Understanding Men's Health' which on the front cover referred to the Impotence Association and to the fact that the booklet was supported by an educational grant from Pfizer. The booklet went into more detail about the subject and discussed treatment in general terms. The booklet referred to the availability of treatments on the NHS or privately and recommended sufferers to discuss their condition with their GP.

The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine and no breach of Clause 20.1 of the Code was ruled.

The Panel noted that one of the requirements of Clause 20.2 of the Code was that statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel noted that none of the materials provided mentioned specific medicines. Treatments were referred to in a general sense. No products were named. The Panel considered that the materials would increase public awareness of impotence and encourage people to discuss the matter with their general practitioner. This was not necessarily unacceptable. From the information provided men were not being encouraged to ask their doctors for a specific medicine. The Panel noted that there were a number of different treatments available including Pfizer's product, Viagra. Not all of the treatments were medicines.

The Panel, while acknowledging that there was a fine distinction between education and promotion, did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of Clause 20.2 of the Code was ruled.

Complaint received **2 October 2000**

Case completed **22 November 2000**

PHARMACEUTICAL ADVISER v JANSSEN-CILAG

Risperdal poster

The pharmaceutical adviser to a primary care group complained about a double sided poster issued by Janssen-Cilag which promoted the new 0.5mg Risperdal (risperidone) tablet. The poster was sent to specialist and primary care staff including pharmacists. The heading on one side of the poster stated 'From Psychotic to Cool, Calm and Collected', the first three words being over-printed with the same words slightly offset. Beneath were the claims 'Risperdal is effective in aggressive, agitated elderly patients' and 'Risperdal comes in a highly flexible range of presentations for the elderly'. The claims were followed by a visual of the tablet and liquid formulations. The complainant stated that risperidone was advertised as effective in aggressive, agitated elderly patients, implying a wide licence that would encompass many diagnoses. Risperidone only had a product licence for psychoses. Although the word psychotic appeared at the head of the poster, it was certainly not clear that risperidone had only a limited licence.

The Panel noted that according to its summary of product characteristics Risperdal was indicated for the 'treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.' The Panel considered that the general thrust of the poster was treatment of elderly patients; symptoms of aggression and agitation were mentioned. The Panel noted that the heading referred to psychoses. The design of the poster was such that the reader's eye was drawn to the central visual and the preceding claims. The Panel considered that whilst the claims did not refer to psychoses in the elderly they would be read in light of the heading. The Panel considered that the poster was not misleading as alleged. No breach of the Code was ruled.

The pharmaceutical adviser to a primary care group complained about a double sided poster (ref 605385A) issued by Janssen-Cilag Ltd which promoted the new 0.5mg Risperdal (risperidone) tablet. The heading on one side of the poster stated 'From Psychotic to Cool, Calm and Collected', the first three words being over-printed with the same words slightly offset. Beneath were the claims 'Risperdal is effective in aggressive, agitated elderly patients' and 'Risperdal comes in a highly flexible range of presentations for the elderly'. The claims were followed by a visual of the tablet and liquid formulations.

The poster was part of a mailing campaign highlighting the recent availability of a 0.5mg tablet which was sent to both specialist and primary care staff including pharmacists.

COMPLAINT

The complainant stated that risperidone was advertised as effective in aggressive, agitated elderly patients, implying a wide licence that would encompass many diagnoses. Risperidone only had a product licence for psychoses. Although the word psychotic appeared at the head of the poster, it was certainly not clear that risperidone had only a limited licence. The complainant alleged that the poster was in breach of the Code.

When writing to Janssen-Cilag, the Authority drew attention to Clauses 3.2 and 7.2 of the Code.

RESPONSE

Janssen-Cilag stated that at the top of the poster was the strapline: 'From Psychotic to Cool, Calm and Collected'. The strapline was a prominent part of the piece being in a larger font size than the other text and stylised and emboldened to draw the reader's attention. The statement itself clearly denoted the movement from a psychotic condition (diagnosis invariably required prominent positive and/or negative psychotic symptoms) to a non-psychotic state (symptoms controlled and/or absent) and was therefore completely consistent with the stated summary of product characteristics (SPC) indication for risperidone.

Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

This strapline was a common feature of Janssen-Cilag's overall campaign which predominantly targeted primary care and was tailored towards that audience. Janssen-Cilag also wished to point out that the complainant accepted that Janssen-Cilag's product licence included psychosis.

The subsequent and secondary claim regarding aggressive, agitated elderly patients which was at the heart of the complaint, had to be seen in the context of the overarching statement regarding psychosis as described above (it was immediately adjacent to that strapline). Market research with primary care staff strongly suggested that general practitioners identified well with this terminology when allied to descriptions of symptomatology ie it was relevant to its intended audience. In the SPC hostility or aggression was clearly identified as a positive symptom and Janssen-Cilag would assert that agitation was a very common sequelae of a psychotic state such that it would frequently accompany such a condition especially in the elderly. Thus the claim that

Risperdal was effective in aggressive, agitated elderly patients within the context of psychosis was both accurate and legitimate. Janssen-Cilag had specifically chosen to highlight hostility (and agitation) here in the context of a psychotic illness as this often posed the most difficult management problems in primary care and was thus of particular relevance to the intended audience.

Janssen-Cilag therefore did not accept that there had been a breach of Clause 3.2 or Clause 7.2 of the Code.

PANEL RULING

The Panel noted that according to its SPC Risperdal was indicated for the 'treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.'

The Panel considered that the general thrust of the poster was treatment of elderly patients; symptoms of aggression and agitation were mentioned. The Panel noted that the heading referred to psychoses. The Panel noted that the design of the poster was such that the reader's eye was drawn to the central visual and the preceding claims. The Panel considered that whilst the claims did not refer to psychoses in the elderly they would be read in light of the heading. The Panel considered that the poster was not misleading as alleged. No breach of Clauses 3.2 and 7.2 was ruled.

Complaint received	**4 October 2000**
Case completed	**17 November 2000**

CASE AUTH/1084/10/00

SERVIER LABORATORIES v SMITHKLINE BEECHAM

Promotion of Avandia

Servier Laboratories complained about a leavepiece and a journal advertisement for Avandia (rosiglitazone), issued by SmithKline Beecham, alleging that they were not consistent with its summary of product characteristics (SPC) as the overall impression did not reflect the precise and limited indications.

The SPC stated that the product was '…indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

- **in combination with metformin only in obese patients**
- **in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated'.**

In Servier's view, the omission of the word 'only' in the prescribing information on three occasions and the use of semicolons rather than subclauses meant that the impression given was not consistent with the original, specific statement in the SPC which restricted the categories of patients in which Avandia might be used.

Servier also pointed out that the Avandia SPC stated that 'Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes' whereas the Avandia prescribing information stated: 'Initiation by an experienced physician'. Again Servier did not consider that this was consistent with the specific statement in the SPC.

The Panel did not consider that the prescribing information was inconsistent with the SPC. There was no real difference as to whether the product was indicated 'only in oral combination' or in 'oral combination'. No other use of the product was mentioned. The Panel had similar views with regard to 'only in obese patients' and 'in obese patients' and 'only in patients who show intolerance to metformin' and 'in patients who show intolerance to metformin'. No breach of the Code was ruled. The Panel considered that the reference to an experienced physician was adequate. It would be interpreted by the majority as being a physician with relevant experience. The Panel ruled no breach of the Code.

Servier alleged that the leavepiece as a whole was inconsistent with the SPC as the overall impression did not reflect the precise and limited therapeutic indications or the requirement that treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

In this regard Servier referred to the claims 'I think control of type 2 diabetes will reach new heights' and 'Avandia is easy to prescribe and easy to take'. Servier stated that SmithKline Beecham justified this on the basis that Avandia did not require a complicated dose titration regimen, that it could be taken independently of food and that there was a once daily option. While this was accurate, Servier alleged that the overall impression of this statement in this context went beyond these practical issues and again, did not fully reflect the specifics of the SPC.

Servier stated that the leavepiece failed to make any mention of the requirement that Avandia was indicated only if glycaemic control was insufficient despite maximal tolerated doses of either metformin or a sulphonylurea. SmithKline Beecham had offered to include an asterisked comment in relation

to maximal tolerated doses but Servier did not accept that a footnote could adequately correct the overall impression of a flow chart which was headed 'Avandia is easy to prescribe and easy to take' and described when to use Avandia.

The claim 'I think control of type 2 diabetes will reach new heights' also appeared in the advertisement.

The Panel considered that the leavepiece was misleading as to the indications for the product. Insufficient detail had been given. The only mention of maximal tolerated doses was in the prescribing information. In the Panel's view this should have been stated in the flow chart. A breach of the Code was ruled.

The Panel considered that the journal advertisement failed to make it clear that the product was indicated for use as add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the advertisement was that Avandia could be used in any patient with type 2 diabetes. The Panel considered that this was misleading and a breach of the Code was ruled.

Servier Laboratories Limited complained about the promotion of Avandia (rosiglitazone) by SmithKline Beecham Pharmaceuticals UK. The promotional items at issue were a leavepiece (ref 07/00: AVLP00095) and a journal advertisement (ref 07/00: AVAD00053a). The leavepiece was left with general practitioners by sales representatives. The advertisement had appeared in GP and Pulse.

COMPLAINT

Servier alleged that the promotion of Avandia was not consistent with its summary of product characteristics (SPC) and hence was in breach of Clause 3.2 of the Code. Servier based its complaint on the overall impression created by the promotional materials. This impression did not reflect the very precise and limited therapeutic indications or the requirement that treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes. Servier considered this of considerable significance as the restrictions on the product licence appeared to be related to concerns about possible long term safety issues.

Avandia prescribing information

Servier pointed out that the Avandia SPC stated:

'4.1 Therapeutic indications

Rosiglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.'

The Avandia prescribing information stated:

'Indications Oral combination treatment of Type 2 diabetes in patients with insufficient glycaemic control despite maximal tolerated dose of either metformin or a sulphonylurea; with metformin in obese patients; with a sulphonylurea in patients who show intolerance to or are contraindicated for metformin.'

In Servier's view, the omission of the word 'only' on three occasions and the use of semicolons rather than subclauses meant that the impression of the prescribing information was not consistent with the original, very specific statement in the SPC which clearly restricted the categories of patients in which Avandia might be used. Servier noted that SmithKline Beecham had offered to change the first semicolon to a colon but not to include 'only' in relation to any phrase.

The Avandia SPC further stated:

'4.2 Posology and method of administration

Treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.'

The Avandia prescribing information stated:

'Posology and administration Initiation by an experienced physician.'

Again Servier did not consider that the impression of this was consistent with the very specific statement in the SPC. Servier noted that SmithKline Beecham had offered to change the prescribing information to 'Posology and administration Initiation by a physician experienced in type 2 diabetes' but again, had not offered to include the word 'only'.

Avandia leavepiece

Servier alleged that the piece as a whole was inconsistent with the SPC as the overall impression did not reflect the very precise and limited therapeutic indications or the requirement that treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes.

This impression was contributed to by the claims 'I think control of type 2 diabetes will reach new heights' and 'Avandia is easy to prescribe and easy to take'. Servier stated that SmithKline Beecham justified this on the basis that Avandia did not require a complicated dose titration regimen, that it could be taken independently of food and that there was a once daily option. While this was accurate, Servier alleged that the overall impression went beyond these practical issues and again, did not fully reflect the specifics of the SPC.

Servier stated that the leavepiece failed to make any mention of the requirement that Avandia was indicated only if glycaemic control was insufficient despite **maximal tolerated** doses of either metformin or a sulphonylurea. SmithKline Beecham had offered to include an asterisked comment in relation to maximal tolerated doses but Servier did not accept that a footnote could adequately correct the overall impression of a flow chart on page three of the leaflet. The flow chart was headed 'Avandia is easy to prescribe and easy to take' and described when to use Avandia.

Avandia advertisement

This again included the claim 'I think control of type 2 diabetes will reach new heights'.

Servier concluded that the overall impression was to present Avandia, not as a product to be prescribed only by physicians experienced in type 2 diabetes and only for clearly restricted patient groups, but as a product which could be used much more widely and easily. Servier therefore alleged the promotion to be inconsistent with the SPC and in breach of Clause 3.2 of the Code.

RESPONSE

SmithKline Beecham submitted that the promotion of Avandia was consistent with its SPC and therefore denied a breach of Clause 3.2 of the Code. The company failed to see the relevance of hypothesised long term safety concerns outlined in Servier's complaint. This was an issue quite separate from whether Avandia promotion was consistent with its SPC.

Avandia prescribing information

SmithKline Beecham had abbreviated the SPC whilst ensuring that all the relevant information required for prescribing Avandia was stated. It believed the prescribing information did not mislead the prescriber.

The prescribing information was exact and complete in that Avandia was indicated in oral combination treatment. This was not misleading. By omitting the word only, it did not imply that Avandia could be used for any other indication.

The prescribing information was exact and complete in that 'with metformin in obese patients', meant exactly what it said. Adding the word 'only' did not more clearly define the statement. The statement as it stood did not imply any other indication.

The prescribing information was exact and complete in that 'with a sulphonylurea in patients who show intolerance to or are contraindicated for metformin', clearly reflected the SPC. There was no implication that any other indication was implied. Adding the word 'only' did not clarify the meaning of the statement further.

SmithKline Beecham agreed with Servier that there should be some sort of pause between the subgroups in the licensed indications. SmithKline Beecham's prescribing information used the semicolon, which was described in The Collins English Dictionary as 'used to indicate a pause between a comma and a full stop'. Grammatically it was therefore correct English to use semicolon in preference to a comma or full stop. This was a perfectly legitimate means to distinguish between the subgroups in the prescribing information. However in the interests of co-operation, SmithKline Beecham had agreed to alter its prescribing information and had begun the process of doing so to include a colon in place of a semicolon.

SmithKline Beecham maintained that the statement that treatment should be initiated by an experienced physician was not misleading. Avandia was a type 2 diabetes medication and as such it was not necessary to substantiate the definition of 'experienced'. There was no implication that any other physician should instigate Avandia treatment. In the interests of co-operation though, SmithKline Beecham had agreed to alter its prescribing information and had begun the process of doing so to 'Treatment should be initiated by a physician experienced in type 2 diabetes'. Adding the word 'only' did not add further definition to the meaning of the statement.

While SmithKline Beecham accepted that Servier's complaint gave it the opportunity to provide further clarification, it did not accept that in its current format the prescribing information was in breach of Clause 3.2 of the Code.

Avandia leavepiece

This leavepiece was left with general practitioners following a discussion with a SmithKline Beecham medical representative regarding type 2 diabetes and Avandia.

SmithKline Beecham disagreed with Servier's surmise that Avandia had 'very precise and limited' indications. Avandia had licensed indications that resulted in prescribing opportunities for a large number of type 2 diabetes patients at some stage in their progressive disease process. 76% of type 2 diabetes patients on oral hypoglycaemics were obese and therefore more likely to be prescribed metformin, as a recommended first line therapy. When these patients became uncontrolled on maximal monotherapy, they could be considered for Avandia within its licensed indication. Research had shown that 35% of patients allocated to metformin as an add on therapy to a sulphonylurea refused the additional therapy. Avandia could also be considered for those patients when glycaemic control was not achieved on maximal doses of a sulphonylurea. It was widely accepted that 50% of type 2 diabetics were uncontrolled despite maximal monotherapy within 3 years following diagnosis and 75% within 9 years.

Avandia did therefore not have 'very precise and limited' indications. Having set this in context, the promotional material was not inconsistent with the SPC.

Taking each of Servier's points in turn:

'I think control of type 2 diabetes will reach new heights'

Type 2 diabetes was characterised by a progressive rise in blood glucose as a result of increasing insulin resistance and deteriorating beta cell function. Avandia was the only currently available therapy that both reduced insulin resistance and improved beta cell function. These effects were sustained for up to two years. As a result Avandia provided improved and sustained glucose control in combination therapy. This was a treatment goal which physicians treating type 2 diabetes aspired to and something that existing add on therapies had been unable to provide. The statement 'I think control of type 2 diabetes will reach new heights' was an aspirational one in keeping with the novel mode of action and clinicians' expectations. The statement was placed in close proximity to a diagrammatic representation of a head and was obviously attributable to it.

'Avandia is easy to prescribe'

This statement was valid as Avandia did not require a complicated dose titration regimen, could be taken independently of food and was available as a once daily dose. This contrasted with other oral hypoglycaemics, which required bd or even tds daily dosing and had to be taken at specific times in relation to food. Therefore in terms of writing initial and repeat prescriptions Avandia was in practice easy to prescribe. By virtue of its metabolic pathway through cytochrome 2C8, Avandia had a low potential to interact with concomitant medication. As a result, the doctor could be reassured regarding potential interactions with a patient's other medication.

Servier had itself stated that this claim was accurate, so this claim could not be in dispute.

Flow chart

The flow chart was designed as a simple visual aid for prescribers to follow a stepwise process for management of patients who might be suitable for treatment with Avandia. If one was to enter all the SPC details in a flow chart, then the use of the chart as a simple visual aid was completely negated. SmithKline Beecham anticipated that prescribers would still refer to the prescribing information which clearly stated Avandia should be used in patients with insufficient glycaemic control despite maximal tolerated doses of either a sulphonylurea or metformin.

While SmithKline Beecham accepted that Servier's complaint gave it the opportunity to provide further clarification, it did not accept that in its current format the flow chart was in breach of Clause 3.2 of the Code.

Avandia advertisement

This advertisement appeared in the medical press, specifically published in GP and Pulse, which would have been read by general practitioners who were experienced in managing their own type 2 diabetes clinics in primary care.

'I think control of type 2 diabetes will reach new heights'

SmithKline Beecham referred to its comments above on this point.

PANEL RULING

The Panel did not consider that the prescribing information was inconsistent with the SPC as alleged. In the Panel's view there was no real difference as to whether the product was indicated 'only in oral combination' or in 'oral combination'. No other use of the product was mentioned. The Panel had similar views with regard to 'only in obese patients' and 'in obese patients' and 'only in patients who show intolerance to metformin' and 'in patients who show intolerance to metformin'. No other types of patient were mentioned. The omission of the word 'only' in the prescribing information did not mean that Avandia was being promoted contrary to the requirements of Clause 3.2. No breach of Clause 3.2 was ruled.

The Panel did not consider that the instruction in the prescribing information that 'initiation by an experienced physician' was inconsistent with the SPC which stated that 'treatment should only be initiated by a physician experienced in the treatment of type 2 diabetes'. The Panel noted that the prescribing information was supposed to be a succinct summary of various information given in the SPC. On balance the Panel considered that the reference to an experienced physician was adequate. It would be interpreted by the majority as being a physician with relevant experience. The Panel ruled no breach of Clause 3.2 of the Code.

With regard to the leavepiece, the Panel noted that the flow chart which detailed when to use Avandia did not state that the product was indicated in oral combination in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea: in combination with metformin only in obese patients and in combination with a sulphonylurea only in patients who showed intolerance to metformin or for whom metformin was contraindicated. The Panel considered that the leavepiece was misleading as to the indications for the product. Insufficient detail had been given. The only mention of maximal tolerated doses was in the prescribing information. In the Panel's view this should have been stated in the flow chart. A breach of Clause 7.2 of the Code was ruled. The Panel noted that SmithKline Beecham had offered to add a footnote to the flow chart with regard to maximal tolerated doses. It was, however, a principle under the Code that otherwise misleading text could not be qualified by a footnote. In the Panel's view the addition of a footnote to the flow chart might not negate the otherwise misleading impression. The Panel requested that SmithKline Beecham be advised of its views.

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

Complaint received **9 October 2000**

Case completed **1 December 2000**

CASE AUTH/1085/10/00

PHARMACIA & UPJOHN v GLAXO WELLCOME

Zyban leaflet

Pharmacia & Upjohn complained about a leaflet for Zyban (bupropion) issued by Glaxo Wellcome, the centre page of which was headed 'Clinical trial published in The New England Journal of Medicine. Zyban – shown to be almost twice as effective, in patients motivated to stop, as a nicotine patch at one year'.

Pharmacia & Upjohn stated that the multicentre US trial by Jorenby *et al* (1999) to which this referred was pivotal in obtaining marketing authorization. It was the only trial published to date that compared bupropion with a form of nicotine replacement therapy (NRT), in this case a nicotine patch. The trial compared efficacy with respect to abstinence from smoking between placebo, a 24 hour nicotine patch, bupropion and bupropion plus nicotine patch. It was the basis for Glaxo Wellcome's comparative claims between Zyban and nicotine patch therapy. Pharmacia & Upjohn stated that there were several issues relating to the study which gave cause for concern as to the validity of the claims.

Pharmacia & Upjohn alleged that patient eligibility was such that bias in the outcomes was highly likely. Over one third had previously used a nicotine patch and approximately one third had previously used nicotine gum. Patients who had previously failed to cease smoking on NRT would be more likely to fail than if they were NRT naïve. Bupropion was an antidepressant and about 20% of patients had a history of depression and might gain benefit from it even though not currently suffering from depression. The primary outcome variable was point prevalence rate of abstinence at 6 and 12 months and not continuous abstinence, which had historically been the benchmark. The use of relatively intensive counselling support drew suspicion to the results especially for those of nicotine patch versus placebo. The leaflet was alleged to be misleading as the placebo data and the Zyban plus the patch data was not included.

In relation to patient eligibility, the Panel noted that a subgroup analysis had found no effect of prior NRT on the efficacy of any of the active treatments. In relation to antidepressant activity, on balance the Panel considered that there was evidence to support the contention that Zyban efficacy was likely to be independent of its antidepressant activity. The Panel did not consider that the data presented was misleading in relation to counselling.

The Panel considered that the efficacy of bupropion relative to NRT was an area of emerging clinical opinion. Particular care should be taken to ensure that the issue was treated in a balanced manner. The page at issue presented some of the results of the only comparative study between Zyban and the nicotine patch in the form of a bar chart. Only the point prevalence abstinence data for the nicotine patch and for Zyban was shown which indicated that Zyban was almost twice as effective as the nicotine patch. The data relating to placebo and Zyban plus the nicotine patch was not shown on the bar chart. If this data had been presented readers would have seen that in the study nicotine patches were no more effective than placebo. Such a result did not represent the balance of evidence with regard to nicotine patches. The weak effect of the nicotine patch according to the point prevalence analysis was commented upon by the study authors. Presentation of all the study data would also have shown that the addition of a nicotine patch to bupropion had no statistically significant additional effect. The Panel considered that whilst the limited amount of data presented were accurate it had not been put into context with all of the rest of the study data. The Panel questioned whether the comparative efficacy of Zyban vs nicotine patches represented the balance of the evidence given that nicotine patches appeared in this study to be no better than placebo. Insufficient information had been provided. The data was misleading in this regard. A breach of the Code was ruled.

Upon appeal by Glaxo Wellcome, the Appeal Board was concerned about the abnormally high placebo response such that the study was unable to demonstrate a statistically significant difference between the nicotine patch, a known active, and placebo with regard to point prevalence at 12 months (the primary efficacy measure in the study). A statistically significant difference had been shown between the nicotine patch and placebo with regard to continuous abstinence at all time points. The Appeal Board noted the authors' view that it was unclear why the nicotine patch produced weak effects according to the point prevalence data and that one study had suggested that the use of two placebos in a control group might produce higher smoking cessation rates than the use of a single placebo.

The Appeal Board noted the overall presentation of the data. Beneath the graph depicting the Zyban and nicotine patch data the phrase 'Placebo controlled trial' appeared. The Appeal Board considered that a reader would place reliance on this description and would be assured by the reference to a peer reviewed journal in the heading to the page. The Appeal Board considered that insufficient detail had been given about the study and its results. Although the limited amount of data presented were accurate it had not been put into context with regard to the rest of the study data. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Pharmacia & Upjohn Limited complained about a leaflet (ref HM5585 – BP/May 2000) for Zyban (bupropion) issued by Glaxo Wellcome UK Limited.

COMPLAINT

Pharmacia & Upjohn alleged that the centre page of the leaflet, headed 'Clinical trial published in The New England Journal of Medicine. Zyban – shown to be almost twice as effective, in patients motivated to stop, as a nicotine patch at one year', contravened Clause 7.2 of the Code. The company referred in particular to the supplementary information which stated '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'.

Pharmacia & Upjohn stated that the multicentre US trial by Jorenby *et al* (1999), to which the centre page referred, was pivotal in obtaining marketing authorization. It was the only trial published to date that compared bupropion with a form of nicotine replacement therapy (NRT), in this case a nicotine patch. The trial compared efficacy with respect to abstinence from smoking between placebo, a 24 hour nicotine patch (Habitrol), bupropion and bupropion plus nicotine patch. The paper formed the basis for Glaxo Wellcome's comparative claims between Zyban and nicotine patch therapy.

Pharmacia & Upjohn stated that there were several issues relating to the Jorenby trial which gave cause for concern as to the validity of the claims being used by Glaxo Wellcome when comparing Zyban to a nicotine patch. It should also be pointed out that Glaxo Wellcome in its US product information for Zyban stated that 'due to the relative lack of information at present no claims of comparison can be made between Zyban and NRT'.

1 Patient eligibility to the trial was such that bias in outcomes between the effects of a nicotine patch, bupropion and placebo was highly likely. Pharmacia & Upjohn drew attention to the fact that over one third of the patients included in the trial had previously used a nicotine patch and had subsequently failed to quit smoking and that approximately one third of those included had previously used nicotine gum (and had therefore subsequently failed to quit smoking). By including patients who had previously failed to abstain from smoking using NRT it was likely that those randomised in this trial to an arm including the use of NRT would again be more likely to fail than if they were recruited as being NRT naïve.

2 Bupropion was an anti-depressant and was licensed as Wellbutrin in the US for the treatment of depression. Almost 20% of patients enrolled into the Jorenby trial had a history of major depression (although a current diagnosis of depression was an exclusion criteria). As depression tended to be a recurring illness, it was likely that individuals with a history of major depression could gain benefit from an anti-depressant even though at the time of inclusion they were not diagnosed as suffering from a current episode of depression (according to DSM – IV criteria). It was possible that an improvement in mood in subjects with a previous history of depression could bias quitting results.

As such a large proportion of patients included into this study had historical experiences that could potentially bias the outcomes, the results should be treated with great caution.

3 The primary outcome variable used in this study was, strangely, the point prevalence rate of abstinence at 6 and 12 months and not continuous abstinence, which had historically been the benchmark efficacy parameter. Point prevalence results would clearly show greater efficacy rates than continuous abstinence. Continuous abstinence was also measured in this study but was not the primary parameter. Results for point prevalence abstinence at 12 months for placebo, nicotine patch, bupropion and bupropion plus nicotine patch were 15.6%, 16.4%, 30.3% and 35.5% respectively. There was no statistically significant difference in quit rates between placebo and nicotine patch and between bupropion and bupropion plus nicotine patch. The respective results for continuous abstinence at 12 months were 5.6%, 9.8%, 18.4% and 27.5%. Again the difference between placebo and nicotine patch and between bupropion and bupropion plus nicotine patch were not statistically significant.

This study used relatively intensive counselling support which drew suspicion to the results especially for those of nicotine patch versus placebo. At 12 months the continuous abstinence rates showed that only 9.8% of patients randomised to the nicotine patch were abstinent compared to 5.6% in the placebo arm. Previous studies using this degree of motivational support had shown much higher abstinence rates for NRT products. With respect to the point prevalence abstinence rates the odds ratio when considering the nicotine patch arm and placebo arm was 1.1%. This was clearly counter to results from previous studies and meta-analyses of the use of the nicotine patch under conditions identical to those in the Jorenby *et al* study, which reported odds ratios of 2.1 and 3.5. It had been well established in over 90 clinical trials that NRT was approximately twice as effective as placebo at helping smokers quit.

The relevant part of the leaflet was misleading as it compared Zyban with a nicotine patch and did not include the placebo data or that of Zyban plus the patch. Doing so would draw attention to the 15.6% failure [sic] rate for placebo which was clearly not statistically different from that of the patch in this study. The reader would also note that adding the nicotine patch to bupropion would not significantly enhance efficacy over bupropion alone and the reader would then question the efficacy of the nicotine patch in this trial.

Pharmacia & Upjohn noted that the US product information on Zyban stated that 'the comparisons between Zyban, NTS (nicotine transdermal system) and combination treatment in this study (Jorenby *et al*) have not been replicated and should not be interpreted as demonstrating the superiority of any of the active treatment arms over any other'. In addition the Cochrane Database of Systematic Reviews (2000 issue 2) stated that 'nicotine replacement therapy (NTR) has proven efficacy in over 80 studies (Silagy 1999) and has a very benign side-effect profile. The earlier results of several anti-depressants, especially bupropion are sufficient to endorse their use in medical practice. There is insufficient published evidence to recommend bupropion in preference to NRT or vice versa. Bupropion may also be helpful in those who fail nicotine replacement'.

RESPONSE

Glaxo Wellcome stated that it had taken particular care to ensure that the information presented was

accurate and balanced. The study referred to was the only one that had directly compared the efficacy of Zyban with that of a nicotine patch. The statement 'Zyban – shown to be almost twice as effective, in patients motivated to stop, as a nicotine patch at one year' was clearly in context and referenced to a study published in the highly respected peer-reviewed journal, The New England Journal of Medicine.

The statement appearing in the US Zyban product information was specific to the US, where it was a requirement of the FDA that statements should be supported by two similarly designed studies. It was Glaxo Wellcome's understanding that in the UK, data could be presented providing that the context was given and the data were representative of the body of evidence. Thus, the statement quoted in the US label did not appear in the UK summary of product characteristics (SPC).

Glaxo Wellcome addressed in turn the specific points raised.

Pharmacia & Upjohn claimed that, by including those patients who had previously tried nicotine replacement therapy (NRT) and failed to quit smoking, the results of the Jorenby study were biased. Pharmacia & Upjohn had assumed that such patients, if randomised to the nicotine patch arm, would be more likely to fail again. Glaxo Wellcome stated that this had been addressed in a subgroup analysis of the Jorenby study conducted to determine the influence of prior NRT use on efficacy (Durcan *et al* 1999). The results indicated that previous use of NRT had no effect on the subsequent efficacy of Zyban, the nicotine patch, or the combination of Zyban plus nicotine patch. Continuous quit rates at 12 months for patients with a history of NRT and without a history of NRT, respectively, were: Zyban 22% vs. 24%; nicotine patch 12.3% vs. 11.5%; combination 28.4% vs. 27.9%. These data confirmed that Zyban was superior to the nicotine patch in patients with and without a history of NRT in this study.

Pharmacia & Upjohn stated that, by including about 20% of patients with a history of major depression in the study, the outcome could be biased as these individuals could benefit from an antidepressant even though they were not diagnosed as having current depression. Pharmacia & Upjohn asserted that it was possible that an improvement in mood in those subjects with a previous history of depression could bias quitting results.

Glaxo Wellcome stated that in both the Jorenby study and the Zyban dose-response study, Hurt *et al* (1997), the Beck Depression Inventory (BDI) was administered at baseline, at weeks 3 and 7, and after the end of treatment to assess changes in patients' depressive symptoms during the treatment phase. In both studies, mean BDI scores at baseline were low and similar across all treatment groups and showed little change throughout the treatment period, remaining well within the normal range. This had confirmed that there was not a significant level of depression in patients taking part in these studies and that this did not change during treatment.

In a sub-group analysis of the dose-response study (Hayford *et al* 1999) baseline BDI score was not found to be associated with smoking status at the end of treatment ($p=0.89$) or at one year ($p=0.34$). In addition, a significant dose-response effect for Zyban was observed that was independent of a history of major depression. Point prevalence abstinence rates were similar for patients with and without a history of major depressive disorder at the end of treatment and at week 52, with a significant dose-response effect detected at both time points ($p<0.001$ and 0.02, respectively).

A similar analysis for the comparative study found no marked differences in abstinence rates at the end of treatment in Zyban-treated patients with or without a history of major depression.

Glaxo Wellcome stated that together, these data confirmed that Zyban's efficacy as an aid to smoking cessation was independent of its antidepressant efficacy.

Glaxo Wellcome accepted that point prevalence abstinence might be a less rigorous measure of outcome than continuous abstinence and would therefore show higher cessation rates. However, as nicotine dependence was increasingly recognised as a chronic, relapsing condition, it might be unrealistic to expect that the average smoker would maintain complete abstinence (not even a puff of a cigarette) over a prolonged period of time. In contrast, point prevalence abstinence included patients who had not smoked in the previous seven days but who might have had a few cigarettes prior to that. It accepted that some patients might have the occasional lapse after their stop date without truly relapsing, and therefore, might represent real life success rates.

The recently published US clinical practice guideline for treating tobacco use and dependence (Fiore *et al* 2000) used point prevalence abstinence as the preferred efficacy outcome in its meta-analyses of data on which its evidence-based recommendations were made. Glaxo Wellcome believed that this provided good endorsement for the validity of point prevalence data.

For these reasons, together with the fact that point prevalence abstinence at 6 and 12 months formed the primary efficacy parameter in Glaxo Wellcome's study, it had chosen to present point prevalence data in its promotional material for Zyban.

Pharmacia & Upjohn stated that the difference in continuous abstinence rates at 12 months between the nicotine patch and placebo groups was not statistically significant. This was incorrect; the Jorenby paper clearly stated that the results for the 12-month continuous abstinence rates were in fact significantly higher in all three active treatment groups, including the nicotine patch group, than in the placebo group ($p<0.001$).

In general, NRT was considered to increase the chance of stopping smoking by about 1.5 to 2-fold over placebo or no intervention, regardless of setting or the intensity of additional support, (Silagy *et al* Cochrane review, issue 3, 2000). The 12-month continuous abstinence rates reported in Glaxo Wellcome's study showed the nicotine patch to be 1.8-fold more effective than placebo (9.8% vs. 5.6%; $p<0.001$) and therefore the results fell within this range.

Jorenby *et al* had shown Zyban to be almost twice as effective as a nicotine patch in achieving smoking abstinence at one year in terms of both point prevalence and continuous abstinence rates. Pharmacia and Upjohn quoted an earlier Cochrane review (issue 2, 2000). However, the most recent Cochrane review (issue 3, 2000) of nicotine replacement therapy for smoking cessation stated in relation to the Jorenby study: 'In this study, bupropion was significantly more effective than nicotine patch or placebo. There was also a suggestion of greater efficacy for bupropion and nicotine patch compared to bupropion alone, but the difference was not statistically significant'.

Glaxo Wellcome disagreed with Pharmacia & Upjohn's comment that the counselling provided in Glaxo Wellcome's Zyban studies was intensive. The support offered to patients consisted of a short (5 to 10 minutes on average) counselling session each week during the treatment phase with three to four subsequent sessions during the follow-up phase to one year. In contrast, in the 1998 Smoking Cessation Guidelines, intensive support was described as five hours of counselling over the first month with subsequent follow up. The relative support time was therefore less than one hour over the first month for patients in the Zyban trials compared with five hours over the first month for intensive support as described in the smoking cessation guidelines.

The support provided in Glaxo Wellcome's studies was based on the US National Cancer Institute Programme which was designed to enable primary care physicians to provide brief interventions in any medical setting. The initial session was provided by a physician; however, subsequent sessions were given by a research assistant, who was not formally trained in smoking cessation counselling. It was also important to note that patients in all treatment groups received the same level of support.

The most recent Cochrane review of NRT for smoking cessation (issue 3, 2000) reported an odds ratio (OR) for abstinence at 12 months with a nicotine patch over placebo or no intervention of 1.73 (95% CI 1.56-193). The meta-analyses by Silagy *et al* (1994) and Fiore *et al* (1994) referred to by Pharmacia & Upjohn were both conducted six years ago at a time when there was only about half the current number of trials with a nicotine patch available (9 and 17 studies were included in their meta-analyses, respectively, compared with 30 studies in the most recent Cochrane review).

Whilst the provision of motivational/counselling support clearly increased absolute cessation rates with NRT, the efficacy of NRT in relation to placebo or no intervention was largely independent of the intensity of additional support provided.

Fiore *et al* (1994) stated that 'there was no indication that both low-intensity or high-intensity counselling resulted in greater efficacy of the nicotine patch in relation to placebo patch as evidenced by the considerable overlap of the 95% CIs for combined ORs… This pattern was consistent across both continuous-prevalence and point-prevalence outcome measures.'

Similarly, the current Cochrane review stated: 'The absolute probability of not smoking at 6 or 12 months was greater in trials which provided high-intensity additional support, rather than low-intensity… Although the pooled OR of abstinence was greater in the trials of gum or patch in which smokers only received low-intensity additional support, the confidence intervals overlapped.' The review concluded that 'The effectiveness of NRT intervention appears to be largely independent of the intensity of additional support provided to the smoker.'

Pharmacia & Upjohn questioned the efficacy of the nicotine patch in this study. Glaxo Wellcome stated that as pointed out above, the 12-month continuous abstinence rates for nicotine patch and placebo were 9.8% and 5.6%, respectively, giving an odds ratio of 1.8 which was well within the range quoted in the Cochrane review issue 3. Thus the efficacy of the nicotine patch in this study was confirmed.

The relatively high point prevalence abstinence rate for the placebo group in the Jorenby study might have been due to the double-dummy design whereby such patients received two placebos (placebo tablets and a placebo patch). One other study had suggested that the use of two placebos in a control group might produce higher success rates than the use of a single placebo, Fagerstrom (1994).

While Glaxo Wellcome accepted Pharmacia & Upjohn's quote from the Cochrane review of nicotine replacement therapy issue 3, 1999, the most recent Cochrane review of nicotine replacement therapy (issue 3, 2000) stated on page 10 'There is evidence from one large study that bupropion is more effective than nicotine patch…' and on page 11 'Nicotine patch was less effective than bupropion in one trial, however any decision about which pharmacotherapies to use should take into account potential adverse effects as well as benefits'. The abstract of the review concluded 'There is promising evidence that bupropion may be more effective than NRT (either alone or in combination)… However, its most appropriate place in the therapeutic armamentarium requires further study and consideration'.

The statement in Glaxo Wellcome's promotional piece reflected, carefully and in a balanced way, the results of a specific study published in a highly prestigious peer-reviewed journal. Glaxo Wellcome did not believe that the leaflet was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the page at issue featured a bar chart which showed that the percentage of patients abstinent at one year (point prevalence) treated with a nicotine patch was 16.4% compared with 30.3% of patients treated with Zyban. The Zyban data was referenced to a footnote which stated 'p<0.001 vs placebo or nicotine patch'. It was also stated that all patients received motivational support. The data and efficacy claims were referenced to Jorenby *et al* (1999).

The Panel noted that Jorenby *et al* (1999) was a double blind, placebo-controlled comparison of sustained

release bupropion (n=244), a nicotine patch (n=244), bupropion and a nicotine patch (n=245) and placebo (n=160) for smoking cessation. The primary outcome variable was the point prevalence rate of abstinence at 6 and 12 months of follow up. Patients were considered to be abstinent if they reported not smoking since the preceding clinic visit and had an expired carbon monoxide concentration of 10ppm or less; patients were considered to be continuously abstinent if they had not smoked since the quitting day, as confirmed by a carbon monoxide concentration of 10ppm or less at all clinic visits during the 12 month study. Secondary outcome measures included withdrawal symptoms, body weight and Beck Depression Inventory scores. Point prevalence rates of abstinence were based on biochemically confirmed self reports of abstinence during the seven days preceding assessment of smoking status at a given time. The abstinence rates at 12 months were 15.6% in the placebo group 16.4% in the nicotine-patch group, 30.3% in the bupropion group ($p<0.001$) and 35.5% in the bupropion and nicotine patch group ($p<0.001$). The authors concluded that treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates were higher with combination therapy than with the nicotine patch alone or placebo but the difference was not statistically significant.

The study authors noted that all subjects were volunteers and thus might not be representative of the majority of smokers. All subjects underwent weekly biochemical tests to determine whether they were still smoking. Both these factors could have enhanced cessation rates. The study authors also noted that it was unclear why the nicotine patch produced weak effects according to the point prevalence analysis (compared to analyses of continuous abstinence data). The study reprint featured subsequently published correspondence with the authors. A correspondent stated that whilst he was not questioning the efficacy of bupropion he did believe that one should be cautious in accepting the conclusions of Jorenby *et al* with respect to, *inter alia*, the superiority of bupropion over the nicotine patch until replicate studies were conducted in which the nicotine patch was found to be efficacious. In response the authors confirmed that both the point prevalence rate and the rate of continuous abstinence indicated the superiority of bupropion and, *inter alia*, stated that 'replication of [these] results was vital'. The authors stated that they preferred 'the strategy of accepting our results as they are – recognising that in the context of this study bupropion resulted in higher long-term abstinence rates than did placebo or the nicotine patch'.

The Panel first considered whether patient eligibility was such that bias in outcomes was likely with regard to previous use of the nicotine patch, prior depression and/or counselling. The Panel noted that previous use of the nicotine patch in the placebo, nicotine patch, bupropion and nicotine patch and bupropion groups was 36.5%, 38.1%, 36.9% and 34.7% respectively; the number of previous attempts to quit was 2.8 ± 3.0, 2.7 ± 2.4, 3.1 ± 4.7 and 2.5 ± 2.4 respectively. The Panel noted the subgroup analysis of the Jorenby study, Durcan *et al* 1999, stated that there was no effect of prior NRT on the efficacy of any of the active treatments.

The Panel noted patients with a history of major depression constituted 15.6%, 18%, 20.9% and 17.6% respectively of the placebo, nicotine patch, bupropion and nicotine patch with bupropion groups. The Beck Depression Inventory (BDI) score was a secondary outcome measure and was addressed at baseline, during and after treatment. BDI scores were within the range of normal at baseline. Treatment had no effect on BDI scores. A dose response study comparing placebo and bupropion was similar with regard to BDI scores before, during and after treatment (Hurt *et al* 1999). The Panel noted Glaxo Wellcome's submission that this confirmed that there was not a significant level of depression in patients taking part in these studies and that this did not change during treatment. The Panel further noted that Hayford *et al* (1999) assessed the efficacy of bupropion for smoking cessation in smokers with a history of major depression or alcoholism and changes in depressive symptoms during smoking abstinence. The study authors concluded that bupropion was efficacious for smoking cessation independently of a history of major depression or alcoholism and stated that the actual difference in mean BDI scores separating those abstinent from smoking and those who returned to smoking at end of treatment was only 2.4 points and therefore possibly not clinically meaningful. On balance, the Panel considered that there was evidence to support the contention that Zyban efficacy was likely to be independent of its antidepressant activity. However all three studies (Jorenby *et al*, Hurt *et al* and Hayford *et al*) excluded patients with a current diagnosis of depression.

The Panel then considered the issue of counselling. The Panel noted the difference in the level of counselling provided to patients in Jorenby with that mentioned in the 1998 Smoking Cessation Guidelines. The Panel noted the submission that the efficacy of NRT was largely independent of the intensity of additional support provided. The Panel also noted the conclusion of the Cochrane review (Issue 3, 2000) on this point. The Panel did not consider the data presented misleading in this regard.

The Panel noted that Glaxo Wellcome accepted that point prevalence data might be a less rigorous measure of outcome than continuous abstinence and would therefore show higher cessation rates. The Jorenby paper did not explain why point prevalence was the preferred outcome measure. The Panel noted that the point prevalence data given in the primary efficacy outcome table in the study report included patients who had smoked in the period up to 7 days before point assessment. The Panel noted the submission that such data might represent real life success rates. The Panel noted that the y axis on the page at issue was labelled '% patients abstinent at one year – point prevalence'. The final page of the leaflet in question referred to smoking cessation. The Panel queried whether a reader would necessarily be aware of the difference between point prevalence and abstinence. In this regard the Panel noted the 12

month point prevalence rate for Zyban was 30%, the continuous abstinence rate was 23% (Jorenby *et al*).

The Panel noted the author's views about the relative efficacy of the nicotine patch and placebo based on point prevalence and continuous abstinence and the submissions from Glaxo Wellcome and Pharmacia & Upjohn in this regard. The Panel was concerned that the placebo data had not been presented and there was no statistically significant difference between the placebo data and the nicotine patch with regard to point prevalence rates. The continuous abstinence rates were higher in all three active treatment groups than in the placebo group ($p<0.001$).

The Panel noted the Cochrane Review; Nicotine replacement therapy for smoking cessation, Issue 3, 2000, stated that 'There is promising evidence that bupropion may be more effective than NRT (either alone or in combination). However its most appropriate place in the therapeutic armamentarium requires further study and consideration'. The review also noted that such evidence derived from one large study.

The Panel considered that the efficacy of bupropion relative to NRT was an area of emerging clinical opinion. Particular care should be taken to ensure that the issue was treated in a balanced manner in promotional material. The page at issue presented some of the results of the only comparative study between Zyban and the nicotine patch in the form of a bar chart. Only the point prevalence abstinence data for the nicotine patch and for Zyban was shown which indicated that Zyban was almost twice as effective as the nicotine patch. The claim above the bar chart stated 'Zyban … almost twice as effective … as a nicotine patch at one year'. The data relating to placebo and Zyban plus the nicotine patch was not shown on the bar chart. If this data had been presented readers would have seen that nicotine patches were no more effective than placebo. Such a result did not represent the balance of evidence with regard to nicotine patches. The weak effect of the nicotine patch according to the point prevalence analysis was commented upon by the study authors. Presentation of all the study data would also have shown that the addition of a nicotine patch to bupropion had no statistically significant additional effect. The Panel considered that whilst the limited amount of data presented were accurate it had not been put into context with all of the rest of the study data. The Panel questioned whether the comparative efficacy of Zyban vs nicotine patches represented the balance of the evidence given that nicotine patches appeared in this study to be no better than placebo. Insufficient information had been provided. The data was misleading in this regard. A breach of Clause 7.2 was ruled.

APPEAL BY GLAXO WELLCOME

There were two aspects of Glaxo Wellcome's appeal as follows:

Zyban versus nicotine patch

Glaxo Wellcome stated that this large, well-conducted trial, published in The New England Journal of Medicine, clearly demonstrated that Zyban was almost twice as effective as a nicotine patch in helping smokers to stop, regardless of which major endpoint was selected. The primary outcome measure, point prevalence abstinence at 6 and 12 months, was decided by the investigators. First, the primary efficacy parameter, point prevalence abstinence at 12 months, was strongly in favour of Zyban compared with a nicotine patch (30.3% versus 16.4%, 1.85:1), while the same ratio (1.88:1) held for the clinically more conservative measure, continuous abstinence at 12 months (18.4% versus 9.8%). In both cases, the difference in abstinence rates between the Zyban and nicotine patch groups was statistically highly significant ($p<0.001$).

To date, this was the only study to compare Zyban with a nicotine patch and so these findings were particularly important as they represented the sum total of published evidence. As stated above, the study showed a consistent almost two-fold increase in both continuous and point prevalence 12-month abstinence rates for patients using Zyban compared with those using a nicotine patch.

Further, the most recent Cochrane review (issue 3, 2000) of nicotine replacement therapy made the following points in relation to the Jorenby study: 'In this study, bupropion was significantly more effective than nicotine patch …' and 'There is evidence from one large study that bupropion is more effective than nicotine patch …'. Similarly, a recent editorial in the BMJ stated: 'On the evidence of the only comparative study available bupropion seems to be more effective than transdermal nicotine.'

Glaxo Wellcome could have chosen to represent either the 12-month continuous abstinence rates or the 12-month point prevalence abstinence rates, as the relationship between Zyban and the nicotine patch was consistent between them (1.88:1 and 1.85:1 respectively). In the event, Glaxo Wellcome chose to present the point prevalence rates as this was the primary outcome measure. In addition, it had been recognised that continuous abstinence rates might underestimate the true percentage of patients who would actually quit and point prevalence abstinence was increasingly being considered to be a clinically more appropriate end point, particularly in the US, where this study was conducted. Glaxo Wellcome had taken great care to ensure that the statement and accompanying bar chart were in context and clearly referenced to the study publication, and that the chart was clearly and accurately labelled.

In view of all these facts, namely that the study was the only one comparing Zyban with a nicotine patch, that the difference between the efficacy of Zyban and that of the nicotine patch was consistent, regardless of which outcome measure was used, and the acceptance of the study by the Cochrane Collaboration and the BMJ editorial, Glaxo Wellcome believed that its claim was valid and represented an accurate and balanced description of the evidence.

Nicotine patch versus placebo

Glaxo Wellcome fully accepted the well-recognised efficacy of NRT in increasing smoking cessation rates

by about 1.5 to 2-fold, regardless of the setting or level of accompanying support. It believed that the readers of the item would be equally aware of the accepted efficacy of nicotine patches. The results for the nicotine patch achieved in the Jorenby *et al* study were not inconsistent with those of other NRT studies. Similarly, the efficacy of Zyban was accepted.

Essentially, the purpose of the item was to compare the efficacy of Zyban with that of a nicotine patch. As discussed earlier, the relationship between the two was consistent across both of the 12-month outcome variables in the study. Whichever Glaxo Wellcome had chosen to present, the relative positions were the same. Therefore, the inclusion of placebo data would not have provided any additional information to the reader.

To re-iterate, in the Jorenby study at 12 months, 9.8% of patients in the nicotine patch group had been continuously abstinent compared with 5.6% of those in the placebo group ($p<0.001$), giving an odds ratio of 1.8. This was well within the range reported in the most recent Cochrane NRT review which found an odds ratio for abstinence at 12 months, with a nicotine patch over placebo or no intervention, of 1.73 (95% CI 1.56 – 1.93).

The point prevalence abstinence rates also showed a statistically significant difference between the nicotine patch and placebo groups at 4 weeks (48.0% versus 33.8%; $p=0.005$). Thereafter, only the Zyban alone group and the Zyban plus nicotine patch group had significantly higher point prevalence abstinence rates than the placebo group. However, the 12-month point prevalence rate of 16.4% for the nicotine patch group found in Jorenby's study was similar to figures quoted in the Cochrane review – 17% abstinence rate for NRT overall, and 14% (CI 13 to 15%) for patches specifically, at 12 months.

Glaxo Wellcome believed that it was the apparently high value for the 12-month point prevalence abstinence rate (15.6%) in the placebo group which accounted for the lack of a statistically significantly difference between the nicotine patch and placebo groups. The Cochrane NRT review reported a 12-month cessation rate of 10% for control groups (placebo or no intervention). The exact reasons for this apparently enhanced placebo effect were not known and one could only hypothesise in order to try to understand these results from this rigorously performed study. It might be due to the double-dummy study design whereby such patients received two placebos (placebo tablets and a placebo patch) in addition to motivational support. Indeed, this observation was not unique as a previous smoking cessation study involving nicotine patch and nicotine gum suggested that the use of two placebos in the control group produced a higher success rate than was usually seen, so that placebo was similar to the nicotine patch.

Glaxo Wellcome certainly had no wish to mislead its readers into thinking that nicotine patch was no more effective than placebo, by including the placebo data for 12-month point prevalence. Had Glaxo Wellcome chosen to include the placebo 12-month point prevalence abstinence data then it might have been accused of erroneously implying that nicotine patch was no better than placebo. Had it chosen instead to present the 12-month continuous abstinence results, it would have only reinforced the fact that Zyban was almost twice as effective as a nicotine patch in achieving smoking abstinence at one year in this study. Following careful consideration of all these points and in the interests of clarity and fairness, Glaxo Wellcome decided to omit the placebo data from this bar chart and it still felt justified in having done so.

In summary, Glaxo Wellcome believed that it was not in breach of Clause 7.2 of the Code. It firmly believed that its claim and supporting bar chart were factual and fair in their reflection of the results for smoking abstinence with Zyban compared with a nicotine patch in this large, multicentre, randomised, double-blind, double-dummy, placebo-controlled comparative study. As the only comparative evidence available, Glaxo Wellcome believed that both its claim and chart accurately reflected the body of evidence for the efficacy of Zyban compared with a nicotine patch.

Glaxo Wellcome hoped that it had explained why it felt justified in making this claim and in presenting the data in the way it did.

APPEAL BOARD RULING

The Appeal Board noted that the study at issue, Jorenby *et al*, had been published in The New England Journal of Medicine. The study design included two placebos, a placebo tablet and a placebo patch. The results in the leaflet were for the nicotine patch plus placebo tablet and Zyban plus placebo patch. The Appeal Board noted that the difference in abstinence rates between the Zyban and nicotine patch groups was statistically significant with regard to both point prevalence and continuous abstinence at 12 months. Further this was the only study to compare Zyban with a nicotine patch.

The Appeal Board noted Glaxo Wellcome's submission about the study design. The Appeal Board was concerned about the abnormally high placebo response such that the study was unable to demonstrate a statistically significant difference between the nicotine patch, a known active, and placebo with regard to point prevalence at 12 months (the primary efficacy measure in the study). The Appeal Board noted that a statistically significant difference had been shown between the nicotine patch and placebo with regard to continuous abstinence at all time points. The Appeal Board noted the authors' view that it was unclear why the nicotine patch produced weak effects according to the point prevalence data and that one study had suggested that the use of two placebos in a control group might produce higher smoking cessation rates than the use of a single placebo. The Appeal Board noted however that the study had been published in a peer reviewed journal and mentioned in the Cochrane Review. The result shown for the nicotine patch was corroborated by other studies.

The Appeal Board noted the overall presentation of the data showing Zyban to be almost twice as effective as a nicotine patch; the page at issue was

headed 'Clinical trial published in The New England Journal of Medicine'. Beneath the graph depicting the Zyban and nicotine patch data the phrase 'Placebo controlled trial' appeared. The Appeal Board considered that a reader would place reliance on this description and would be assured by the reference to a peer reviewed journal. The Appeal Board considered that insufficient detail had been given about the study and its results. Although the limited amount of data presented were accurate it had not been put into context with regard to the rest of the study data. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Complaint received **10 October 2000**

Case completed **31 January 2001**

CASE AUTH/1086/10/00

SCHERING HEALTH CARE/DIRECTOR v ROCHE

Breach of undertaking

Schering Health Care alleged that Roche was in breach of the undertaking and assurance that it had given in Case AUTH/887/6/99 in that a patient information booklet on MabThera (rituximab) used at a meeting in September appeared identical to that ruled in breach.

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

The Panel noted that Roche had instructed its representatives to destroy the booklet at issue. The replacement booklet was stored in the company's medical information department and not at its distributor. Representatives were provided with copies to distribute and were instructed to order additional copies from medical information. Roche had not instructed the distributor to destroy the original material which had then been supplied when a request had been sent to the distributor and not to medical information. The Panel considered that Roche had failed to comply with the undertaking given in Case AUTH/887/6/99. A breach of the Code was ruled as acknowledged by the company.

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 important for the reputation of the industry that companies complied with undertakings. Roche had made efforts to comply with the original undertaking but although it had instructed representatives it had failed to inform the distributor. On balance the Panel considered that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The company had reviewed its procedures to ensure that such an error would not occur again. The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if its conduct in relation to the Code warranted consideration by the Appeal Board. The Panel was concerned that the company had not arranged for remaining copies of the original material retained by its distributor to be destroyed. The availability of the original material had not come to light until receipt of the present complaint. The Panel thus considered that the circumstances warranted reporting Roche to the Appeal Board.

Upon appeal by Roche of the ruling of a breach of Clause 2 of the Code, the Appeal Board noted that Roche had taken steps to comply with the undertaking but these were not sufficient. The Appeal Board considered that the company's failure to comply with its undertaking brought discredit upon and reduced confidence in the pharmaceutical industry and upheld the Panel's ruling of a breach of Clause 2 of the Code.

In relation to the report made by the Panel, the Appeal Board noted that Roche had changed its procedures. A task force of senior managers and directors had been established. New standard operating procedures relating to destruction of promotional material had been put in place. Destruction of material by the distributor was to be supervised by a manager. The company was undergoing its own internal audit. The managing director had written to all relevant staff and compulsory training for all personnel involved in the copy approval/distribution process was to take place. The Appeal Board decided in the circumstances that no further action was necessary.

Schering Health Care Limited alleged that Roche Products Limited was in breach of the undertaking and assurance that it had given in Case AUTH/887/6/99 in that a patient information booklet on MabThera (rituximab) used at a meeting in September appeared identical to that ruled in breach. The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

COMPLAINT

Schering Health Care stated that in August 1999 Roche was found in breach of Clause 20.2 of the Code for its patient information booklet 'Important information for patients being treated with MabThera (rituximab). …Your questions answered'. The Panel

ruled that the booklet had not been presented in a balanced way. It failed to inform patients of the need for pre-medication with analgesics, an antihistamine and possibly corticosteroids before administration of MabThera, and omitted to mention the risk of cytokine release syndrome, an infrequent but potentially fatal complication of MabThera therapy. Following this ruling it was Schering Health Care's understanding that, as was normally the case, all copies of the booklet had been immediately withdrawn by Roche. Schering Health Care was also aware that an amended booklet had subsequently been produced, which seemed to reflect the Panel's ruling. Schering Health Care provided an example of the amended booklet which had appeared on the Roche stand at the recent meeting.

However, at another meeting held between 29 September and 1 October, the Roche promotional stand displayed copies of a patient information booklet which appeared identical in every respect to the subject of Case AUTH/887/6/99. In particular, the information on pages 3 and 4 was unchanged from the original booklet and made no mention of premedication or additional side-effects of treatment. Schering Health Care provided copies of both the original booklet and the booklet made available at the second meeting.

Schering Health Care stated that it was clear that Roche had not complied with the Panel's ruling. The booklet was still being distributed over a year after the ruling. Schering Health Care therefore alleged a breach of Clause 21 of the Code. In view of the booklet still being in use over one year after its supposed withdrawal, and the fact that the original breach concerned serious omissions in patient safety information, Schering Health Care also believed that Roche had discredited and reduced confidence in the pharmaceutical industry. As a consequence, it additionally alleged a breach of Clause 2 of the Code.

RESPONSE

Roche stated that it had investigated the matter and regrettably it appeared that at the meeting cited the booklet had been made available.

When the original commitment was made a directive was given to all representatives to destroy the original material. In the meantime the new material was certified and printed. It was normal procedure for such material to be stored at Roche's distributor. However on this occasion, in order to control the distribution of this material, all the new material was kept and stored in Roche's medical information department. Representatives were provided with copies that they could distribute on request and were instructed to order additional copies only from the medical information department. This had been the practice up to now.

Roche was therefore extremely surprised that the older version had been distributed as it believed that all of this had been destroyed. However Roche's investigation had shown that the order to destroy the original material which had been sent to every representative had not been sent to its distributor. It seemed that when copies of the new version were needed for the second meeting, the request went directly to its distributor and not the medical information department and thus copies of the original incorrect version were inadvertently used. Clearly this should not have happened and was unacceptable. Roche had now initiated the destruction of all copies at the distributor. It had demanded its sales force to return all in their possession so that each could be checked to ensure that it was not the original version.

Roche could assure the Authority that it would be carrying out a thorough review of its procedures in order to ensure that this was not repeated in the future.

In a further response, Roche stated that its investigations suggested that none of the original version which had been the subject of the complaint had been distributed by its distributor since the time the undertaking was given up to April of this year. However it appeared that representatives subsequently placed orders for the material with the distributor from the middle of April 2000 in contravention of the directive that had been given. Consequently it was possible that copies of the leaflet had been provided to haematology nurse specialists in centres which had used MabThera for treating patients.

Accordingly the following instructions had been issued:

All hospitals that had purchased MabThera since April would be identified.

Every haematology nurse specialist (or equivalent) in the hospitals so identified would be visited by a sales specialist explaining what had happened and requesting that no MabThera booklet be given to patients and that any still in the hospital should be destroyed or returned to the company. These instructions would be confirmed in a letter delivered by the sales specialist at that time. In addition they would be requested to check with their patients at any subsequent hospital visit to ensure that they did not have any of these booklets in their possession.

In addition, each would only be provided with copies of the new version once this exercise had been completed and all old booklets had been uncovered and either destroyed or returned therefore ensuring that no further mix up could occur.

As previously advised, Roche would be reviewing what other steps to take in the future to ensure that this type of regrettable incident did not happen again.

PANEL RULING

The Panel noted that Roche had instructed its representatives to destroy the booklet at issue. The replacement booklet was stored in the company's medical information department and not at its distributor. Representatives were provided with copies to distribute and were instructed to order additional copies from the medical information department. Roche had not instructed the distributor to destroy the original material which had been supplied when a request had been sent to the

distributor and not to the medical information department.

The Panel considered that Roche had failed to comply with the undertaking given in Case AUTH/887/6/99. A breach of Clause 21 of the Code was ruled as acknowledged by the company.

The Panel noted that Clause 2 of the Code was used as a sign of particular censure. Previous cases involving breaches of Clause 21 had also been ruled to be in breach of Clause 2 when material was reused without being altered.

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 important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Roche had made efforts to comply with the original undertaking but although it had instructed representatives it had failed to inform the distributor. On balance the Panel considered that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel noted that the company had reviewed its procedures to ensure that such an error would not occur again. The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2). The Panel was concerned that the company had not arranged for remaining copies of the original material retained by its distributor to be destroyed. The availability of the original material had not come to light until receipt of the present complaint. The Panel thus considered that the circumstances warranted reporting Roche to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY ROCHE

Roche stated that it accepted that it had breached Clause 21 of the Code, ie that it had not complied with an undertaking in relation to a ruling under the Code. It sincerely regretted that this oversight had happened and gave an assurance that it had been thoroughly investigated and corrective action initiated.

However, Roche appealed the ruling of a breach of Clause 2. The company accepted a breach of Clause 21 was a serious matter and that previous cases involving such a breach had been ruled in breach of Clause 2. However, the breach in this case was due to an oversight and was not deliberate. Indeed, Roche had accepted the original ruling and amended the booklet accordingly, which, as Schering Health Care acknowledged, reflected the Panel's ruling.

Immediately after the original ruling staff were notified about the undertaking given by the company and instructions were given for the destruction of the original booklets. It was normal practice for such material to be stored at Roche's distributor's premises. However, at the time, because the booklet had been the subject of a complaint, and because Roche wanted to ensure that the amended version was distributed correctly, the decision was taken to keep the new booklets in head office within the medical information department. Representatives were instructed to order copies only from the medical information department. This clearly showed the company's genuine intention to comply with the undertaking by putting appropriate procedures in place. Unfortunately, Roche overlooked the fact that the distributor had not been instructed to destroy copies of the original booklet.

Roche accepted that there had been a breakdown in communication to the distributors. In addition, in retrospect, the decision to keep the new version within the medical department at head office, in order to be certain that it was only distributed correctly, partly led to the confusion that resulted in the error. Roche's view was that had the new version been sent to its distributor it was more likely that the existence of the old version would have been detected.

Thus, although Roche deeply regretted that this whole matter had occurred, it submitted that it was caused in error and not as a deliberate flouting of the Code. Apart from the oversight in notifying the distributor the company had otherwise complied with the undertaking. Thus the company did not feel that this had brought discredit upon or reduced confidence in the industry.

As pointed out in Roche's previous letter on this matter, the distributor had now been instructed to destroy all copies of the old booklet. Also, steps had been taken to identify whether there were any other copies of the original booklet still in existence and, if so, to retrieve and destroy them. In addition Roche had arranged for an external consultant, a physician with many years' experience of the industry and of the Code, to carry out a complete internal audit of its procedures. Furthermore, Roche had set up an internal task force comprising experienced senior managers to assist with the external review and to ensure additional training for all relevant staff. In this way Roche would ensure that such an event did not happen again.

APPEAL BOARD RULING

The Appeal Board noted the submission from Roche. There appeared to be a discrepancy as to what the distributor had been told. The appeal documents stated that the distributor had not been instructed to destroy copies of the original booklet. The company representatives said at the appeal that the distributor had been told verbally, by its customer services department, to withdraw the booklet. There was no written record of any instruction to the distributor although the company representatives stated that the booklet was deleted from the list of items from its distributor.

The Appeal Board noted that the company representatives had explained that between the time that the original booklet had been withdrawn (August 1999) and the time that it had been re-used (September 2000), Roche had created an electronic

interface between it and its distributor. It appeared that during this process the distributor had found the original booklets still in its possession and had added them to its list of available items (April 2000).

The Appeal Board considered that companies would be well advised to keep written records of the action taken to withdraw materials. The Appeal Board noted that it might have been helpful if the new booklet was easily distinguished from the old booklet. The content was of course different.

The Appeal Board considered that an undertaking was an important document. It required companies to provide details of the action taken and the date of final use of materials ruled in breach. It was signed by the chief executive or with their authority and included a statement that all possible steps would be taken to avoid a similar breach of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Appeal Board noted that Roche had taken steps to comply with the undertaking but these were not sufficient. There was no documentary evidence that the distributor had been informed of the withdrawal of the booklet. Following notification of the complaint the company had changed its procedures to ensure that the problems would not be repeated and had made every effort to remove the withdrawn booklet from use. The Appeal Board noted that the booklet was for patients.

The Appeal Board considered that the company's failure to comply with its undertaking brought discredit upon and reduced confidence in the pharmaceutical industry and upheld the Panel's ruling of a breach of Clause 2 of the Code. The appeal on this point was thus 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 Code. It noted that Roche had changed its procedures. A task force of senior managers and directors had been established. New standard operating procedures relating to destruction of promotional material had been put in place. Destruction of material by the distributor was to be supervised by a manager. The company was undergoing its own internal audit. The Managing Director had written to all relevant staff and compulsory training for all personnel involved in the copy approval/distribution process was to take place.

The Appeal Board decided in the circumstances that no further action was necessary.

Complaint received **12 October 2000**

Case completed **21 December 2000**

CASE AUTH/1087/10/00

NOVARTIS/DIRECTOR v BOEHRINGER INGELHEIM

Breach of undertaking

Novartis alleged that a double page advertisement for Micardis (telmisartan) which had appeared in the BMJ, 16 September, was in breach of the undertaking and assurance given by Boehringer Ingelheim in Case AUTH/1019/4/00.

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

The Panel noted that, following the ruling in Case AUTH/1019/4/00, the two films for journals with immediate production schedules had been amended by Boehringer Ingelheim's advertising agency but three others for later production had not been amended. Boehringer Ingelheim was responsible under the Code for acts and omissions committed on its behalf by third parties. The Panel considered that Boehringer Ingelheim had failed to comply with the undertaking given in Case AUTH/1019/4/00. A breach of the Code was ruled as acknowledged by the company.

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 important for the reputation of the industry that companies complied with undertakings. Boehringer Ingelheim had made efforts to comply with the original undertaking but although it had instructed the agency to amend materials the incorrect films had been used for the double page advertisement. On balance the Panel considered that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if its conduct in relation to the Code warranted consideration by the Appeal Board. The Panel considered that the circumstances warranted reporting Boehringer Ingelheim to the Appeal Board.

Upon appeal by Boehringer Ingelheim of the ruling of a breach of Clause 2 of the Code, the Appeal Board noted that Boehringer Ingelheim had

instructed its agency to delete a particular sentence which appeared in double page spread advertisements. Two advertisements had been changed with new material despatched to the publications. Changes to advertisements scheduled to appear in the BMJ, Doctor and Pulse had not happened. The account manager had left suddenly and shortly afterwards the closure of the agency was announced. A letter from the BMJ to Boehringer Ingelheim showed that the BMJ published the original advertisement because it had been told by the agency to repeat the film until further notice. The BMJ had received no information from the agency with regard to returning the old film or to expect a new film. No new film had been received by the BMJ.

The Appeal Board noted that Boehringer Ingelheim had taken steps to comply with the undertaking but had been let down by the unusual circumstances at the agency. The company had changed its procedures to ensure that the problems would not be repeated.

The Appeal Board considered that the circumstances did not amount to a breach of Clause 2 of the Code and therefore ruled no breach of that clause.

In relation to the report made by the Panel, the Appeal Board noted its ruling of no breach of Clause 2 of the Code. It also noted that Boehringer Ingelheim had changed its standard operating procedures to extend further its control of the activities of third parties. Films were now to be returned to the company for destruction by the product manager. The Appeal Board decided in the circumstances that no further action was necessary.

Novartis Pharmaceuticals UK Ltd complained that a journal advertisement for Micardis (telmisartan) issued by Boehringer Ingelheim Limited was in breach of the undertaking and assurance given by Boehringer Ingelheim in Case AUTH/1019/4/00. The matter was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

COMPLAINT

Novartis stated that in April 2000 it brought to the Authority's attention its concerns regarding the promotion of Micardis. Among the items at issue was a double page advertisement for Micardis in which an unfair comparison of the product with Novartis' own product Diovan (valsartan) was presented. The specific issue with regard to the advertisement was the appearance of the following statement 'In addition, Micardis 80mg has demonstrated superior efficacy in reducing diastolic blood pressure when compared to valsartan 80mg in the last 6 hours of the dosing interval'. The advertisement carrying this claim was ruled to be in breach of Clause 7.2 together with the other items submitted and the case was completed on 14 June.

Novartis believed that this would be the end of this issue. However, it had been brought to its attention that an advertisement containing the same claim had reappeared recently in the BMJ of 16 September (General Practice). As would be seen, the advertisement was prepared in December 1999 and although it carried a different reference number to the advertisement in the original complaint, it appeared to have an identical content.

Novartis believed that this represented a direct breach of Clause 21 in terms of the undertaking given by Boehringer Ingelheim in relation to the earlier case and also a continuing breach of Clause 7.2 of the Code.

When writing to Boehringer Ingelheim, the Authority stated that the matter would be considered in relation to the requirements of Clauses 2 and 21 of the Code and not Clause 7.2.

RESPONSE

Boehringer Ingelheim assured the Authority that it treated all matters regarding the Code very seriously and in this specific instance took all usual and reasonable steps to ensure compliance with the subject undertaking. Unfortunately, due to unusual circumstances involving its advertising agency, such procedures did not prevent the re-use in error of a film containing an objectionable statement.

The situation was summarised below and further detailed in two letters, copies of which were provided; one from the advertising agency and the other from the BMJ, one of the journals in which the statement related to Case AUTH/1019/4/00 recently appeared.

Following the ruling of the Panel in June 2000 all materials referencing the valsartan data were amended and reproduced (as would be seen in advertisement MIC 0001137, a copy of which was provided, which replaced MIC 00059). This specifically included removal of the statement 'Micardis 80mg has demonstrated superior efficacy in reducing diastolic blood pressure when compared to Valsartan 80mg in the last 6 hours of the dosing interval'. It was now clear that Boehringer Ingelheim's agency followed the correct instructions on two films for journals with immediate production schedules but did not follow through with three others that were scheduled for later production. When the double page advertisements started to be re-run in September 2000, the original, uncorrected films were used in error.

As noted earlier Boehringer Ingelheim followed standard procedures that had achieved satisfactory results in the past. However, in light of this unusual occurrence it intended to amend its internal procedures to introduce additional safeguards. The company would ensure that in the event that an item was found to be in breach of the Code, the Marketing Department must request that all items found in breach and the originating film and associated artwork were retrieved from all external suppliers and destroyed. The company would also ensure that details of the complaint would be inserted into the original job bag.

Boehringer Ingelheim regretted any difficulty that this error had caused and trusted that the explanation would be considered satisfactory. Boehringer Ingelheim reaffirmed its undertaking previously given in Case AUTH/1019/4/00.

PANEL RULING

The Panel noted that, following the ruling in Case AUTH/1019/4/00, the two films for journals with immediate production schedules had been amended by Boehringer Ingelheim's advertising agency but three others for later production had not been amended.

The Panel noted that Boehringer Ingelheim was responsible under the Code for acts and omissions committed on its behalf by third parties. The Panel considered that Boehringer Ingelheim had thus failed to comply with the undertaking given in Case AUTH/1019/4/00. A breach of Clause 21 of the Code was ruled as acknowledged by the company.

The Panel noted that Clause 2 of the Code was used as a sign of particular censure. Previous cases involving breaches of Clause 21 had also been ruled to be in breach of Clause 2 when material was reused without being altered.

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 important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Boehringer Ingelheim had made efforts to comply with the original undertaking but although it had instructed the agency to amend materials the incorrect films had been used for the double page advertisements. On balance the Panel considered that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2). The Panel considered that the circumstances warranted reporting Boehringer Ingelheim to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim stated that whilst acknowledging the seriousness of a breach of an undertaking, in view of the very exceptional circumstances that led to the inadvertent publication of this material, it was very surprised and disappointed that the Panel ruled that this also constituted a breach of Clause 2.

The company was also surprised that the Panel considered that the circumstances warranted reporting it to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. Paragraph 8.2 referred to Paragraphs 10.3 and 11.1, neither of which seemed appropriate in this instance. Paragraph 10.3 referred to recovering offending material, which could not be done in this case as it concerned a journal advertisement. Paragraph 11.1 referred to further sanctions by the ABPI Board of Management, which seemed totally out of place in view of the third party error that led to the breach of Clause 21.

Boehringer Ingelheim did not accept that the acknowledged breach of Clause 21 should be considered to have brought discredit upon or reduced confidence in the pharmaceutical industry. The company therefore appealed against the Panel's ruling of a breach of Clause 2. The outline of the reasons for the appeal was as follows:

1 The original complaint concerned a statement that was factually correct, but was deemed by the Panel to be an unfair comparison because the dosages quoted were not considered to be comparable. The statement was that 'Continuous ambulatory blood pressure monitoring showed that Micardis 80mg was significantly superior to valsartan 80mg in the last 6 hours of the dosing interval ($p<0.01$).' The Panel viewed this as a claim for overall superiority of Micardis.

While accepting the Panel's ruling on this matter, Boehringer Ingelheim considered that the regretted inadvertent repetition of this essentially similar, factually correct, statement was not of such a serious nature as to be capable of bringing the industry into disrepute.

2 Following the Panel's ruling of a breach of Clause 7.2 of the Code, Boehringer Ingelheim, through its advertising agency, amended its advertising to exclude the offending statement and subsequent amended advertisements appeared in journals with immediate production schedules. This confirmed that the company had taken effective steps to comply with its undertaking.

3 The advertising agency, having actioned the necessary change in the immediately published journals, failed to do so for three journals with later publication dates. This failure could be attributed to two factors. Firstly the person responsible for the account left suddenly and secondly, the agency shortly afterwards announced that it was ceasing to do business.

The impending closure of the agency clearly had a profound effect on its performance and while accepting that Boehringer Ingelheim had to take responsibility for those who produced promotional material with its authority, these very exceptional circumstances were impossible to predict.

In conclusion, Boehringer Ingelheim submitted that it acted responsibly in complying with the undertaking given, but that circumstances beyond its direct control resulted in a breach of that undertaking. The company greatly regretted this failure, but considered that the circumstances were such as to make unreasonable a ruling that the company had breached Clause 2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that Boehringer Ingelheim had instructed its agency to delete a particular sentence which appeared in double page spread advertisements. Two advertisements had been changed with new material despatched to the

publications. Changes to advertisements scheduled to appear in the BMJ, Doctor and Pulse had not happened. The account manager had left suddenly and shortly afterwards the closure of the agency was announced. The instructions to the agency were sent via email by the product manager. A copy of the email had not been kept. There was, however, a copy of a letter dated 25 October from the agency confirming that in June it had received instructions from Boehringer Ingelheim about the matter. A letter dated 19 October from the BMJ to Boehringer Ingelheim showed that the BMJ published the original advertisement because it had been told by the agency to repeat the film until further notice. The BMJ had received no information from the agency with regard to returning the old film or to expect a new film. No new film had been received by the BMJ.

The Appeal Board considered that companies would be well advised to keep written records of the action taken to withdraw materials.

The Appeal Board noted that companies were responsible for the actions of third parties acting on their behalf. This was accepted by Boehringer Ingelheim.

The Appeal Board considered that an undertaking was an important document. It required companies to provide details of the action taken and the date of final use of materials ruled in breach. It was signed by the chief executive or with their authority and included a statement that all possible steps would be taken to avoid a similar breach of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Appeal Board noted that Boehringer Ingelheim had taken steps to comply with the undertaking but had been let down by the unusual circumstances at the agency. The company had changed its procedures to ensure that the problems would not be repeated.

The Appeal Board considered that the circumstances did not amount to a breach of Clause 2 of the Code and therefore ruled no breach of that clause. The appeal on this point was thus successful.

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 Code. It noted its ruling of no breach of Clause 2 of the Code above. It also noted that Boehringer Ingelheim had changed its standard operating procedures to extend further its control of the activities of third parties. Films were now to be returned to the company for destruction by the product manager.

The Appeal Board decided in the circumstances that no further action was necessary.

Complaint received	**16 October 2000**
Case completed	**22 December 2000**

CASE AUTH/1088/10/00

SANOFI-SYNTHÉLABO v AVENTIS PHARMA

Promotion of Campto

Sanofi-Synthélabo complained about a detail aid and a 'Dear Doctor' letter for Campto (irinotecan) issued by Aventis Pharma. Both items detailed the results of a study by Douillard *et al* which was designed to assess whether the addition of Campto to fluorouracil and folinic acid (5-FU/FA) would benefit patients previously untreated with chemotherapy (other than adjuvant) for metastatic colorectal cancer. Campto was indicated for the treatment of patients with advanced colorectal cancer and was licensed for use as monotherapy in previously treated patients and as combination therapy with 5-FU/FA in previously untreated patients.

It was alleged that the claim 'Campto + 5-FU/FA significantly improves survival time while maintaining patients' quality of life v 5-FU/FA' was misleading because it suggested that quality of life did not deteriorate on Campto plus 5-FU/FA whereas the paper showed that quality of life deteriorated, though more slowly. The Panel noted that the summary of the study stated that there was 'a later deterioration in quality of life' in the Campto plus 5-FU/FA group. The Panel considered the claim misleading as alleged and ruled a breach of the Code. Upon appeal by Aventis, the Appeal Board noted the company's submission that the detail aid was to be used with oncologists who would understand the reference to maintaining quality of life. The summary of product characteristics (SPC) for Campto stated that 'Time to definitive deterioration constantly occurred later in the Campto groups. The evolution of Global Health Status/Quality of Life was slightly better in the Campto combination group although not significantly, showing that efficacy of Campto in combination could be reached without affecting the quality of life'. The authors of the cited study, however, never referred to the quality of life being maintained in the Campto group; they always stated that there was a later deterioration. The Appeal Board considered that the claim was too positive with regard to the effect of Campto on quality of life. It gave the impression that it stabilized it rather than slowed its decline. The Appeal Board considered that claim was misleading and upheld the Panel's ruling of a breach of the Code.

The statement 'No prior chemotherapy for advanced disease' appeared as a bullet point under the sub-heading of 'Inclusion Criteria' in a section of the detail aid describing the study design. Sanofi-Synthélabo noted that the statement would exclude patients with Duke C colorectal carcinoma who received adjuvant chemotherapy and subsequently went on to develop metastatic colorectal cancer. However, patients who had had previous adjuvant therapy were eligible for the study. The company alleged that the statement was misleading. The Panel noted that the paper stated that one of the inclusion criteria for the study was 'no previous (other than adjuvant) chemotherapy, finished more than 6 months before randomisation'. The inclusion criteria as stated in the detail aid had presented this as two separate bullet points which read 'No prior chemotherapy for advanced disease' and 'Adjuvant chemotherapy allowed if completed ≥ 6 months before randomisation'. The Panel considered that the separation of the two points was misleading; the first bullet point had to be qualified by the second. 'No prior chemotherapy for advanced disease' as a stand alone bullet point was incorrect. A breach of the Code was ruled. Upon appeal by Aventis, the Appeal Board noted that in advanced disease chemotherapy was palliative. The second bullet point referred to adjuvant chemotherapy which the Appeal Board noted would be given with the intention of cure. The two bullet points were thus describing two quite different clinical situations. The Appeal Board did not consider that it was misleading to separate the two points and ruled no breach of the Code.

The claim 'Significant increase (19%) in survival at one year' appeared in a section of the detail aid describing median survival. Sanofi-Synthélabo noted that the '19% increase in median survival' was based on overall survival of 17.4 months for irinotecan plus 5-FU/FA, and 14.1 months for 5-FU/FA. It would normally expect the percentage increase to be calculated by taking the difference between the two figures and dividing by the lower figure to give the percentage increase. This did not appear to be the case. Although this was not misleading as it under represented the median survival for irinotecan, it was inaccurate and undermined confidence in the validity of the statistics used. The Panel noted that the study was designed to assess whether the addition of Campto to the standard therapy for metastatic colorectal cancer, 5-FU/FA, would benefit patients. Survival in the Campto group was significantly longer than in the group treated with 5-FU/FA alone (median 17.4 months vs 14.1 months respectively p=0.031). The addition of Campto thus increased median survival time by 3.3 months which was a 23% increase over what was otherwise seen with standard therapy ie 5-FU/FA alone. The Panel considered that the claim for a 19% increase in survival was therefore inaccurate and a breach of the Code was ruled.

The statement 'Allowing for 2nd line treatment' appeared in a section of the detail aid describing time to deterioration in performance status (PS) and was the final part of a sentence which read: 'Significant delay in PS deterioration with Campto + 5-FU/FA compared to 5-FU/FA alone, allowing for 2nd line treatment'. Sanofi-Synthélabo stated that although irinotecan was licensed for second line treatment, the graph in this section and the claim 'Significant delay in PS deterioration' related to first line therapy. Therefore the graph and claim appeared to be supporting the claim 'Allowed for second line treatment'. The company alleged that this was misleading and ambiguous as it could mean 2nd line treatment with irinotecan after the failure of some other first line treatment.

The Panel considered that, read as a whole, the meaning of the claim was that because patients' performance status deteriorated later with Campto therapy, patients were fit enough to be treated with 2nd line therapy if that became necessary. The Panel considered on balance that the claim was neither misleading nor ambiguous and no breach of the Code was ruled.

A table in the summary of adverse events was headed 'Incidence of NCI WHO grade 3-4 (%) per patient' with two sub-headings for the two treatment arms of the Douillard study, 'Campto + 5-FU/FA (n=145)' and '5-FU/FA (n=143)'. Sanofi-Synthélabo noted that the title of the table had '(%)' in brackets and the title of the columns had '(n=[ ])' in brackets. It was not clear at first glance whether the numbers in the table represented percentage or numbers of patients. The company alleged that this was ambiguous. In the Panel's view the table of adverse events was set out according to common practice such that it was clear from the heading 'Incidence of NCI WHO grade 3-4 (%) per patient' that the numbers in the table were percentages of patients in each treatment group and not absolute numbers of patients. No breach of the Code was ruled.

The claims 'Predictable', 'Manageable', 'Reversible' and 'Non-cumulative' appeared as a list to one side of the table of adverse events. Sanofi-Synthélabo stated that the claims being next to the table would suggest they were descriptive of the results in the table. However, each side effect was worse for irinotecan plus 5-FU/FA, compared with 5-FU/FA. The claims did not make explicit that they referred to irinotecan or what irinotecan was being compared with. It was alleged that the claims were misleading and hanging comparisons and also that they were all encompassing. The Panel noted that the claims appeared as a list to one side of the table which compared the incidence of adverse events seen with Campto plus 5-FU/FA and with that seen with 5-FU/FA alone. In the Panel's view the claims described the adverse events observed in both groups and there was no implication that the claims were comparative or that Campto plus 5-FU/FA was better tolerated than 5-FU/FA alone. The Panel did not consider that the claims were hanging comparisons or all encompassing as alleged. No breach of the Code was ruled.

Sanofi-Synthélabo stated that the 'Dear Doctor' letter enclosed a re-print of Douillard *et al* but noted that the paper contained an important mistake; it had mis-labelled the column headings of adverse event tables 5 and 6. The column headings in tables 5 and 6 should be swapped round. This was correctly done in the corresponding table used in the detail aid. The

paper was being provided in a promotional context and therefore was subject to the Code. The reprint contained an error, which might seriously mislead the reader about the adverse event profile of irinotecan. The Panel noted that in the original paper the numbers of patients in each treatment group in Table 5 was stated to be 'Irinotecan group (n=145)' and 'No-irinotecan group (n=143)'. In Table 6 the numbers given were 'Irinotecan group (n=54)' and 'No-irinotecan group (n=43)'. Although the headings were correct with regard to the numbers of patients in each group the headings themselves appeared in the wrong tables; those in Table 5 should have headed Table 6 and vice versa. The 'Dear Doctor' letter had been accompanied by a reprint of the paper in which this mistake had been corrected. The reprint sent with the letter was thus correct and no breach of the Code was ruled.

Sanofi-Synthélabo alleged that the number of breaches involved represented a failure of Aventis' system of certification of promotional material. The Panel noted that the Code required that the certificate must certify that the signatories had examined the final form of the material and that in their belief it was in accordance with the requirements of the relevant advertising regulations and the Code, was not inconsistent with the marketing authorization and the SPC and was a fair and truthful presentation of the facts about the medicine. The Panel did not consider that there was any evidence to show that this had not been done. In the Panel's view a breach of the Code did not necessarily mean that the promotional material had not been signed off in good faith by the signatories. No breach of the Code was ruled.

The Panel did not consider that the Campto promotional materials warranted a ruling of a breach of Clause 2 of the Code as had been alleged. This was used as a sign of particular censure and was reserved for such circumstances.

Sanofi-Synthélabo complained about the promotion of Campto (irinotecan) by Aventis Pharma Ltd. There were two promotional pieces at issue, a four page detail aid (ref ONC 328109) and a 'Dear Doctor' letter (ref ONC 439030). Both pieces detailed the results of a study published in The Lancet, (Douillard *et al* 2000), which was designed to assess whether the addition of Campto to fluorouracil and folinic acid (5-FU/FA) would benefit patients previously untreated with chemotherapy (other than adjuvant) for metastatic colorectal cancer.

Campto was indicated for the treatment of patients with advanced colorectal cancer. It was licensed for use as monotherapy in previously treated patients and as combination therapy with 5-FU/FA in previously untreated patients.

A Detail Aid

1 Claim 'Campto + 5-FU/FA significantly improves survival time while maintaining patients' quality of life v 5-FU/FA'

This claim ran as a headline across the two inside pages of the detail aid.

COMPLAINT

Sanofi-Synthélabo stated that the phrase 'while maintaining patients' quality of life' suggested that quality of life did not deteriorate on Campto plus 5-FU/FA. The company noted that the Douillard paper showed that quality of life deteriorated in both groups but more slowly in the Campto plus 5-FU/FA group. It was alleged that the claim was thus misleading in breach of Clause 7.2 of the Code.

RESPONSE

Aventis Pharma submitted that the claim modestly interpreted the results of the study by Douillard *et al* in which it was stated:

> 'The analysis of variance on quality of life showed significantly better quality of life in the irinotecan group after the first imputation method was used (p=0.03). The same trend was seen with the second imputation method.
>
> Definitive deterioration in quality of life occurred consistently later in the irinotecan group, for a deterioration from baseline by 5% (p=0.03), 10% (p=0.06), 20% (p=0.04) and 30% (p=0.06).'

Aventis stated that time to tumour progression was well regarded by world experts as a surrogate for quality of life (Allen *et al* 1998). In this particular study, many patients had stabilisation of their tumour burden which explained the 'maintenance' of quality of life prior to the inevitable deterioration associated with disease progression. Aventis stated that the claim was not misleading given this data and the intended audience ie medical oncologists.

PANEL RULING

The Panel considered that the claim implied that, when treated with Campto plus 5-FU/FA, patients' quality of life was maintained ie there was no deterioration. This was not so. The results from the study by Douillard *et al* showed that patients' quality of life did deteriorate whilst receiving Campto plus 5-FU/FA but at a slower rate than in patients treated with only 5-FU/FA. In this regard the Panel noted that the summary of the study stated that there was 'a later deterioration in quality of life' in the Campto plus 5-FU/FA group. The Panel considered the claim misleading as alleged and ruled a breach of Clause 7.2.

APPEAL BY AVENTIS PHARMA

Aventis stated that the ultimate goal of cytotoxic chemotherapy was to improve survival, but not at the expense of hastening deterioration in quality of life. Over the past 40 years cytotoxic chemotherapy in advanced colorectal cancer in the UK had been 5-FU which was co-administered with folinic acid (FA) to enhance its cytotoxicity. The effectiveness of 5-FU/FA could be improved by combining it with other chemotherapeutic agents, provided that the additional agents were independently active and non-cross resistant with 5-FU/FA. Irinotecan exhibited these important properties. The concern however was that any gains in longevity might be off-set by

deterioration in quality of life due to the accumulative toxicities of these two agents.

This was tested in a randomised phase III trial by Douillard *et al*. The null hypothesis being that the combination of irinotecan plus 5-FU/FA was no more effective and impacted negatively on quality of life, compared to 5-FU/FA alone.

Aventis stated that evaluation of these parameters in palliative chemotherapy was complicated by cross-over to salvage chemotherapy in the control arm as well as the natural history of the disease, namely the inevitable decline in quality of life. It was therefore illogical to consider the control arm of this study to be constant and the observation under test was the relativity of measurements between the active and control arms.

The results of this study rejected the null hypothesis ie combination chemotherapy prolonged survival and maintained quality of life relative to 5-FU/FA alone.

Aventis stated that the Panel's assessment of this claim laid a nihilistic precedence for all palliative chemotherapy and was contrary to the view taken by experts in this area. 'In the past few years several therapeutic advances – underpinned by multi-professional, site specialised team working – have finally changed the view that advanced colorectal cancer is an untreatable disease. Although cytotoxic chemotherapy is not suitable for all patients, widespread use in appropriate situations can improve survival and quality of life' Young *et al* (2000).

APPEAL BOARD RULING

The Appeal Board noted the company's submission that the detail aid was to be used with oncologists who would understand the reference to maintaining quality of life.

The Appeal Board noted that the summary of product characteristics (SPC) for Campto stated that 'Time to definitive deterioration constantly occurred later in the Campto groups. The evolution of Global Health Status/Quality of Life was slightly better in the Campto combination group although not significantly, showing that efficacy of Campto in combination could be reached without affecting the quality of life'.

The Appeal Board noted that Douillard *et al*, the paper to which the claim was referenced, never referred to the quality of life being maintained in the Campto group; the authors always stated that there was a later deterioration.

The Appeal Board considered that the claim, 'Campto + 5-FU/FA significantly improves survival while maintaining patients' quality of life v 5-FU/FA', was too positive with regard to the effect of Campto on quality of life; it gave the impression that it stabilized it rather than slowed its decline. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

2 Statement 'No prior chemotherapy for advanced disease'

This statement appeared as a bullet point under the sub-heading of 'Inclusion Criteria' in a section of the detail aid describing the study design of Douillard *et al*.

COMPLAINT

Sanofi-Synthélabo noted that the statement would exclude patients with Duke C colorectal carcinoma who received adjuvant chemotherapy and subsequently went on to develop metastatic colorectal cancer. However, patients who had had previous adjuvant therapy were eligible for the study. The company alleged that the statement was misleading in breach of Clause 7.2.

RESPONSE

Aventis stated that the bullet point was immediately followed by the qualification statement 'Adjuvant chemotherapy allowed, if completed ≥ 6 months before randomisation'. The company stated that the inclusion criteria for Douillard *et al* were clearly stated and were therefore in no way misleading. The inclusion criteria were presented together and Aventis believed that the intended readership would consider these points together and not in isolation of each other. To have reached the conclusion that Sanofi-Synthélabo had, Aventis could only assume that it had chosen to read the inclusion criteria in isolation of each other which was not sensible.

PANEL RULING

The Panel noted that the paper by Douillard *et al* stated that one of the inclusion criteria for the study was 'no previous (other than adjuvant) chemotherapy, finished more than 6 months before randomisation'. The inclusion criteria as stated in the detail aid had presented this as two separate bullet points which read 'No prior chemotherapy for advanced disease' and 'Adjuvant chemotherapy allowed if completed ≥ 6 months before randomisation'. The Panel considered that the separation of the two points was misleading; the first bullet point had to be qualified by the second. 'No prior chemotherapy for advanced disease' as a stand alone bullet point was incorrect. A breach of Clause 7.2 was ruled.

APPEAL BY AVENTIS PHARMA

Aventis stated that the two of six bullet points qualifying the inclusion criteria for the Douillard study, 'No prior chemotherapy for advanced disease' and 'Adjuvant chemotherapy allowed, if completed ≥ 6 months before randomisation', should be read in the round and in the context of the whole promotional piece.

Advanced colorectal cancer could be defined as colorectal cancer that at presentation, or recurrence, was either metastatic or so locally advanced that surgical resection was unlikely to be carried out with curative intent. Adjuvant chemotherapy occurred at the time of tumour resection, which could be curative. However, these patients might then go on to develop advanced disease.

Essentially, this was a study in chemo-naïve patients with the exception of those who received

chemotherapy at the time of diagnosis and did not apparently cause the investigators taking part in the study any difficulty in interpretation.

APPEAL BOARD RULING

The first of the two bullet points at issue stated 'No prior chemotherapy for advanced disease'. The Appeal Board noted that in advanced disease chemotherapy was palliative. The second bullet point referred to adjuvant chemotherapy which the Appeal Board noted would be given with the intention of cure. The two bullet points were thus describing two quite different clinical situations. The Appeal Board did not consider that it was misleading to separate the two points and ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

3 Claim 'Significant increase (19%) in survival at one year

This claim appeared in a section of the detail aid describing median survival.

COMPLAINT

Sanofi-Synthélabo noted that the '19% increase in median survival' was based on overall survival of 17.4 months for irinotecan plus 5-FU/FA, and 14.1 months for 5-FU/FA. The company stated that it would normally expect the percentage increase to be calculated by taking the difference between the two figures and dividing by the lower figure to give the percentage increase. This did not appear to be the case. Although this was not misleading as it under represented the median survival for irinotecan it was inaccurate and undermined confidence in the validity of the statistics used. Sanofi-Synthélabo alleged a breach of Clause 7.2.

RESPONSE

Aventis noted the allegation regarding the inaccuracy in the methodology used in calculating the difference in median survival at one year, but as Sanofi-Synthélabo pointed out, this produced a more modest reflection of the difference in the two arms of the study which was clearly not in Aventis' interest. The statement from Sanofi-Synthélabo that 'it would normally expect the percentage increase …' also implied that the company might have different ways of presenting its data but there was no ruling to suggest that this was the only way. Aventis suggested that this was a difference in approach rather than an inaccuracy. The company agreed that there were better ways of putting across this message.

PANEL RULING

The Panel noted that the study was designed to assess whether the addition of Campto to the standard therapy for metastatic colorectal cancer, 5-FU/FA, would benefit patients. Survival in the Campto group was significantly longer than in the group treated with 5-FU/FA alone (median 17.4 months vs 14.1 months respectively p=0.031). The addition of Campto thus increased median survival time by 3.3 months which was a 23% increase over what was otherwise seen with standard therapy ie 5-FU/FA alone. The Panel considered that the claim for a 19% increase in survival was therefore inaccurate. A breach of Clause 7.2 was ruled.

4 Term 'Median survival at one year'

COMPLAINT

Sanofi-Synthélabo stated that the term 'Median survival at one year' was incorrect as acknowledged in intercompany correspondence. Sanofi-Synthélabo alleged a breach of Clause 7.2.

RESPONSE

Aventis stated that the term was incorrect as acknowledged. The company was confused and would be pleased to answer any queries after further clarification.

PANEL RULING

The Panel noted that the term 'Median survival at one year' did not appear in the detail aid. It had not been provided with sufficient information to make a ruling. The Director thus decided that there was no *prima facie* case to answer under the Code on this point.

5 Statement '…allowing for 2nd line treatment'

This statement appeared in a section of the detail aid describing time to deterioration in performance status (PS) and was the final part of a sentence which read: 'Significant delay in PS deterioration with Campto + 5-FU/FA compared to 5-FU/FA alone, allowing for 2nd line treatment'.

COMPLAINT

Sanofi-Synthélabo stated that although irinotecan was licensed for second line treatment, the graph in this section and the claim 'Significant delay in PS deterioration' related to first line therapy. Therefore the graph and claim appeared to be supporting the claim 'allowed for second line treatment'. The company alleged that this was misleading in breach of Clause 7.2. Sanofi-Synthélabo added that the statement was ambiguous as it could mean 2nd line treatment with irinotecan after the failure of some other first line treatment. The company alleged that this was still a breach of Clause 7.2.

RESPONSE

Aventis stated that Sanofi-Synthélabo's interpretation of the graph and claim was rather cynical. It was well accepted that chemotherapy for advanced colorectal cancer did not have the guarantee of cure, allowing patients with recurrence of their disease the option of second line treatment. The general condition of the patient ie co-morbidities might preclude treatment, hence the importance of performance status. In the study by Douillard *et al* 40-60% of patients went on to receive second line therapy. Given the fact that definitive deterioration in quality of life occurred consistently later in the irinotecan combination arm,

and that time to progression (surrogate for tumour stability) was significantly longer in the irinotecan combination arm, was further justification for the claim. Aventis stated that medical oncologists treating patients with colorectal cancer in the UK were familiar with the study and data and were unlikely to be misled. It was important to note that irinotecan was licensed for use in the second line setting.

PANEL RULING

The Panel noted that the claim at issue read '…allowing for 2nd line treatment' and not 'allowed for 2nd line treatment' as stated by Sanofi-Synthélabo. In addition the claim was the last part of a longer sentence which read 'Significant delay in PS [performance status] deterioration with Campto + 5-FU/FA compared to 5-FU/FA alone, allowing for 2nd line treatment'. The Panel considered that, read as a whole, the meaning of the claim was that because patients' performance status deteriorated later with Campto therapy, patients were fit enough to be treated with 2nd line therapy if that became necessary. The Panel considered on balance that the claim was neither misleading nor ambiguous and no breach of Clause 7.2 was ruled.

6 Table in the section detailing summary of adverse events

The table was headed 'Incidence of NCI WHO grade 3-4 (%) per patient' with two sub-headings for the two treatment arms of the Douillard study, 'Campto + 5-FU/FA (n=145) and '5-FU/FA (n=143)'.

COMPLAINT

Sanofi-Synthélabo noted that the title of the table had '(%)' in brackets and the title of the columns had '(n=[ ])' in brackets. It was not clear at first glance whether the numbers in the table represented percentage or numbers of patients. The company alleged that this was ambiguous in breach of Clause 7.2.

RESPONSE

Aventis submitted that the heading clearly described the source and unitage of the data tabulated and that a mere glance should tell the reader that the numbers tabulated were in percentages and not subsets of the 145/143 patients entered into the respective arms of the study.

PANEL RULING

In the Panel's view the table of adverse events was set out according to common practice such that it was clear from the heading 'Incidence of NCI WHO grade 3-4 (%) per patient' that the numbers in the table were percentages of patients in each treatment group and not absolute numbers of patients. No breach of Clause 7.2 was ruled.

7 Claims 'Predictable', 'Manageable', 'Reversible' and 'Non-cumulative'.

These claims appeared as a list to one side of the table of adverse events.

COMPLAINT

Sanofi-Synthélabo stated that the claims being next to the table would suggest they were descriptive of the results in the table. However, each side effect was worse for irinotecan plus 5-FU/FA, compared with 5-FU/FA. The claims did not make explicit that they referred to irinotecan or what irinotecan was being compared with. The company alleged that the claims were misleading and hanging comparisons in breach of Clause 7.2 and also that they were all encompassing and in breach of Clause 7.8.

RESPONSE

Aventis noted that Sanofi-Synthélabo regarded the claims predictable, manageable, reversible and non-cumulative as unintelligible. The company submitted that as the two arms from the Douillard study were shown alongside the claims they could not be regarded as hanging comparisons. The descriptive words were an accurate reflection of three large randomised control trials performed to good clinical practice with quality assurance (Douillard *et al*, Saltz *et al*, Rougier *et al*).

PANEL RULING

The Panel noted that the claims appeared as a list to one side of the table which compared the incidence of adverse events seen with Campto plus 5-FU/FA and with that seen with 5-FU/FA alone. In the Panel's view the claims described the adverse events observed in both groups, there was no implication that the claims were comparative or that Campto plus 5-FU/FA was better tolerated than 5-FU/FA alone. The Panel did not consider that the claims were hanging comparisons or all encompassing as alleged. No breach of Clauses 7.2 and 7.8 was ruled.

B 'Dear Doctor' letter

1 Reference enclosed

COMPLAINT

Sanofi-Synthélabo stated that the 'Dear Doctor' letter enclosed a re-print of Douillard *et al* but noted that the paper contained an important mistake; it had mis-labelled the column headings of adverse event tables 5 and 6. The column headings in tables 5 and 6 should be swapped round. This was correctly done in the corresponding table used in the detail aid. The paper was being provided in a promotional context and therefore was subject to the Code. The reprint contained an error, which might seriously mislead the reader about the adverse event profile of irinotecan. Sanofi-Synthélabo alleged that use of this reprint was in breach of Clause 7.6.

RESPONSE

Aventis stated that the Douillard paper was published on 25 March 2000 and a subsequent edition on 15 April published a small reprint 'Irinotecan combined with 5-FU/FA compared with 5-FU/FA alone as first line metastatic colorectal cancer'. In this article by Douillard *et al* (25 March, page 1041), in table 5 the n

value should have been irinotecan group n=54, no irinotecan group n=43, and in table six irinotecan group n=145, no irinotecan group n=144. Although this was a typographical area, there was no way that it would impact on the interpretation of the results as it only applied to the number of patients in each group. Reprints of the paper had corrected this misprint and were included in this mailing.

PANEL RULING

The Panel noted that in the original paper published in The Lancet the numbers of patients in each treatment group in Table 5 was stated to be 'Irinotecan group (n=145)' and 'No-irinotecan group (n=143)'. In Table 6 the numbers given were 'Irinotecan group (n=54)' and 'No-irinotecan group (n=43)'. Although the headings were correct with regard to the numbers of patients in each group the headings themselves appeared in the wrong tables; those in Table 5 should have headed Table 6 and vice versa. The 'Dear Doctor' letter had been accompanied by a reprint of the paper in which this mistake had been corrected. The reprint sent with the letter was thus correct and no breach of Clause 7.6 was ruled.

C Summary

1 Certification

COMPLAINT

Sanofi-Synthélabo considered that the number of breaches involved represented a failure of Aventis' system of certification of promotional material. A breach of Clause 14.3 was alleged.

RESPONSE

Aventis stated that despite Sanofi-Synthélabo's systematic scrutiny of its promotional material it did not agree that there was any breach of the Code and was of the opinion that its process of certification was satisfactory.

PANEL RULING

The Panel noted that Clause 14.3 of the Code stated that, *inter alia*, the certificate must certify that the signatories had examined the final form of the material and that in their belief it was in accordance with the requirements of the relevant advertising regulations and the Code, was not inconsistent with the marketing authorization and the summary of product characteristics and was a fair and truthful presentation of the facts about the medicine. The Panel did not consider that there was any evidence to show that this had not been done. In the Panel's view a breach of the Code did not necessarily mean that the promotional material had not been signed off in good faith by the signatories. No breach of Clause 14.3 was ruled.

2 Alleged breach of Clause 2

COMPLAINT

Sanofi-Synthélabo stated that the number of breaches involved and the fact that even when Aventis had conceded a breach of the Code it had not withdrawn the item (Point 4 above) represented a systematic failure to abide by the Code and in doing so brought discredit to the industry. A breach of Clause 2 was alleged.

RESPONSE

Aventis denied a breach of Clause 2 of the Code.

PANEL RULING

The Panel did not consider that the Campto promotional materials warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and was reserved for such circumstances.

Complaint received	**25 October 2000**
Case completed	**30 January 2001**

MEDICINES CONTROL AGENCY v SCHERING-PLOUGH

Clarityn mailing

The Medicines Control Agency (MCA) received a complaint from a consultant about a Clarityn mailing issued by Schering-Plough. The mailing, which was posted in a polythene envelope, consisted of a reprint from the BMJ which was partially enclosed in a folder such that recipients could read the journal's title banner and the citation of the study. The front cover of the folder featured a cartoon band and stated 'Take note of this major new data' and 'Important surveillance study enclosed'. Inside the folder gave brief details of the study, listed some of the features of Clarityn and included the prescribing information. The MCA stated that it had been alleged that the presentation of the document made it appear official. The MCA stated that the issue fell outside the regulations and considered that it would be more appropriately dealt with by the Authority.

The Panel considered that the design of the front cover of the folder, which was glossy, colourful and clearly visible through the polythene envelope in which it was sent, would make it unlikely that recipients would think it had come from an official source. Once opened the folder clearly promoted Clarityn. The Panel did not consider that the mailing failed to recognise the special nature of medicines or the professional standing of the recipients. It was not likely to cause offence and nor did the Panel consider that its promotional nature had been disguised. No breach of the Code was ruled.

The Medicines Control Agency (MCA) received a complaint from a consultant concerning a Clarityn mailing (ref CLA/00-637) issued by Schering-Plough Ltd. The mailing, which was posted in a polythene envelope so that its contents were clearly visible, consisted of a reprint from the BMJ which was enclosed in a folder. The front cover of the folder left the reprint partially exposed so that the recipient could read the BMJ title banner and also the citation at the bottom of the page. Above the citation appeared the statement 'Take note of this major new data'. The front cover featured a band made up of cartoon musical notes and stated 'Important surveillance study enclosed'. The inside pages of the folder gave brief details of the study enclosed (Mann *et al* 2000), listed some of the features of Clarityn therapy and included the prescribing information for the product. The mailing had originally been sent to general practitioners and then subsequently to ear, nose and throat specialists, allergists and dermatologists.

COMPLAINT

The MCA stated that it had been alleged that the presentation of the document made it appear official. The MCA stated that as the issue fell outside The Medicines (Advertising) Regulations 1994, SI 1994/1932 as amended it considered that it might be more appropriately dealt with by the Authority. Accordingly, the MCA requested that the matter be treated as a complaint under the Code.

When writing to Schering-Plough the Authority drew attention to the requirements of Clauses 9.1 and 10.1 of the Code.

RESPONSE

Schering-Plough noted that the complainant did not state which particular office they considered the document appeared to come from, and so it assumed that reference was made to a body such as the Authority, the Medicines Commission, or the Department of Health.

Schering-Plough stated that it was certainly not its intention to make the mailing appear to come from any organisation other than itself and listed some of the characteristics that would suggest to general practitioners that it was not an official document. Firstly, the exterior of the mailing portrayed a brightly coloured and cheerful picture (a cartoon of a marching band). The company's experience with official literature was that it tended to be sent in a buff, or other neutral coloured envelope. Secondly, the mailing had prescribing information for Clarityn prominently displayed. This mailing went out only to medical practitioners most of whom would associate prescribing information on a mailer as evidence that it originated from a pharmaceutical company, rather than an official body. And thirdly, the inside pages of the folder had prominent displays of the brand and non-proprietary name, as well as pictures of Clarityn syrup and tablets. Schering-Plough considered that this would suggest to a doctor that the mailing was not from an official body.

Schering-Plough stated that the mailing was sent to general practitioners to inform them of significant research findings published in the BMJ. No attempt was made to disguise the promotional nature of the mailing. The company had reviewed the piece, particularly in line with Clauses 9.1 and 10.1 of the Code, and continued to consider that it acted within the letter and spirit of the Code in the manner in which it had informed the medical community of an important piece of new research.

PANEL RULING

The Panel considered that the design of the front cover of the folder, which was visible through the clear polythene envelope in which the mailing was sent, would make it unlikely that recipients of the mailing would think that it had come from an official source. The front cover was glossy, colourful and featured a cartoon band. Once opened the inside of the folder clearly promoted Clarityn. The Panel did

not consider that the mailing failed to recognise the special nature of medicines or the professional standing of the recipients. It was not likely to cause offence and nor did the Panel consider that its promotional nature had been disguised. The Panel ruled no breach of Clauses 9.1 and 10.1 of the Code.

Complaint received **27 October 2000**

Case completed **1 December 2000**

CASES AUTH/1091/11/00 & AUTH/1092/11/00 *NO BREACH OF THE CODE*

MEDICINES INFORMATION PHARMACIST v EISAI and PFIZER

Conduct of representatives

A medicines information pharmacist at an NHS Trust alleged that an Eisai representative had gained access to the offices of a hospital directorate and had interrupted two consultants who were in conversation. When returning later the same day with a Pfizer representative he was alleged to have shouted 'Oh, it's one of those days is it?' and then passed some documents to a secretary to be photocopied. The Pfizer representative had been found sitting at a secretary's desk waiting to book an appointment and while he was there private and confidential calls with patients were being made and taken. It was also alleged that the representatives had gained access to the offices using private keypad access numbers.

The Panel noted that the parties' accounts of what took place differed and it was difficult to know exactly what had happened.

In relation to the Eisai representative, the Panel noted his submission that he had used the intercom to gain access to the offices. The two consultants had been talking in an open office and there had been no one for the representative to ask. On being told by the consultant he had come to see that he was too busy, the representative had apologised and left, leaving some documents with the consultant's secretary. With regard to the documents that had been photocopied, the representative had stated that a secretary offered to photocopy them for him on his first visit. Eisai had submitted in relation to the statement 'Oh, it's one of those days is it?' that at no time was any conversation directed to any staff in the unit. The Panel did not consider that any of these incidents amounted to a breach of the Code and ruled accordingly.

The Panel noted that the Pfizer representative had gained access to the offices for himself and his colleague from Eisai, using the keypad access code he had been given some years previously. As he had been given the code, the Panel considered that he had been given tacit permission to let himself in. Pfizer submitted that its representative had not sought access to information, confidential or otherwise. The Panel considered that it would be an everyday occurrence for representatives to be going about their business when confidential discussions were taking place. No breaches of the Code were ruled.

The medicines information pharmacist at an NHS Trust complained about the conduct of a representative from Eisai Limited and a representative from Pfizer Limited.

COMPLAINT

The complainant said that he wished to bring to the Authority's attention recent incidents involving a medical representative for Eisai and a medical representative for Pfizer. They were both involved with promoting Aricept. The complainant said that he quoted principally from a statement that one of the medical secretaries at a hospital made in late August.

'[The Eisai representative] arrived in our office at approximately 9am. I was not at my desk but a colleague (also a secretary) was in the office. He asked her to pass some documents to Dr – (a consultant psychiatrist for old age psychiatry) and then left the office. We were later informed that he had walked into Dr –'s office, interrupting Dr – and Dr – (also a consultant psychiatrist for old age psychiatry) who were in conversation.

The intercom buzzer did not sound and we did not know how he gained access to the department.

Later that morning, approximately one hour later, [the Eisai representative] reappeared in our office, this time accompanied by [the Pfizer representative]. Again the intercom buzzer had not sounded. I was talking to a patient on the telephone and my colleague was typing. [The Eisai representative] walked into our office followed by [the Pfizer representative] and shouted 'Oh, it's one of those days, is it?' presumably as we carried on working and did not acknowledge his arrival. I saw him pass documents to [my colleague] and heard him ask her to photocopy them. I was unable to intervene as the patient was talking to me at that point. My colleague photocopied the documents, handed them back to [the Eisai representative], and he and [the Pfizer representative] left. I then informed [my colleague] that we are not required to photocopy documents for medical representatives and that she should refuse future requests.'

The complainant said that in a separate statement by a second medical secretary, the Pfizer representative was found to be sitting at the secretary's desk waiting to book an appointment to see community mental health nurses or the team leader, again at the same hospital. While he was in the office private and confidential calls were being taken and made to patients.

The complainant alleged that Clauses 15.2, 15.4 and 15.10 of the Code had been contravened. The principal concerns of the Trust were that medical representatives had obtained private keypad access numbers to a department's offices and had used them to gain direct access to medical secretaries and consultant staff. Specifically the complainant found it unacceptable that the Eisai representative was incapable of displaying a modicum of discretion and that he felt it appropriate that he could invite himself into a member of staff's office, particularly when confidential discussions were taking place.

While historically a relaxed relationship had been enjoyed with medical representatives, this and other instances had forced the directorate to take draconian measures which were an inconvenience to all.

When writing to Eisai and Pfizer, the Authority drew attention to Clause 9.1 of the Code in addition to the clauses referred to by the complainant.

RESPONSE FROM EISAI

Eisai stated that its representative was able to recall the day in question. He stated that he did indeed arrive at the unit at 9am. He arrived merely to deliver an audit proposal that had been requested and chased. He proceeded entirely in accordance with practices hitherto viewed as acceptable by the unit, ie he arrived without a formal appointment because he was merely seeking to deliver a document. He buzzed the intercom and the door was opened for him. He stipulated that he had never had the code for entry to the unit. He assumed that one of the unit staff had opened the door. He entered the unit but there was nobody in evidence. He heard the voices of Dr - and Dr - and he made his way to the office where they were sitting. There was still no one else around at that time. The door was open and he knocked on the door. He asked if Dr - could take delivery of the audit proposal and was told that he was too busy. He then explained that he would leave the proposal with his secretary for him. The representative stated that he apologised for interrupting and left.

The representative agreed that he returned to the unit with the Pfizer representative and this time access was gained by the latter using a code. Eisai's representative believed the code had been given to the Pfizer representative by one of the unit staff previously. Eisai's representative also stated that at no time was any conversation directed to the staff in the unit. The purpose of the second visit was to hand a copy of the audit proposal to a nurse manager who had also requested one.

The issue of photocopying documents had been clarified by Eisai's representative. He explained that on his first visit that day Dr –'s secretary had offered to photocopy the audit proposal to save him getting it done elsewhere. He at no time requested any photocopying to be done.

Clause 15.2 of the Code stated that 'Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code.' Eisai's representative maintained that he complied with this clause at all times. Equally, he denied that he had caused a breach of the overlapping provisions of Clause 9.1 that required care to be taken to maintain high standards and avoid any activity causing offence.

Clause 15.4 stated that 'Representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and health authorities and the like, together with the manner in which they are made, do not cause inconvenience. The wishes of individuals on whom representatives wish to call and the arrangements in force at any particular establishment must be observed.' Eisai's representative had stated that he adhered to this clause on the day in question. It was now said that he interrupted two doctors but he knocked on an open door to announce himself and once he had ascertained that they were busy he made his apologies and left.

Clause 15.10 stated that 'Companies are responsible for the activities of their representatives if these are within the scope of their employment even if they are acting contrary to the instructions which they have been given.' Eisai recognised this clause but stressed that on this occasion it had no evidence to corroborate the facts set out in the complaint. Its representative's version of events, and that of the representative of Pfizer (whose response Eisai had seen), were very different and there was, therefore, a conflict of evidence that Eisai could not resolve.

Eisai accepted that if its representative's conduct was fairly and accurately described by the complainant, this would amount to a breach of Clauses 15.4 and 9.1 and, therefore, of Clause 15.10. Eisai did not believe that its representative could be held responsible for circumstances of entry by code because, if someone had a code number, the reasonable inference was that they had been given it and that entry to the unit by this method was by consent. Moreover, Eisai did not believe that a breach of Clause 15.2 arose. Eisai believed that behaviour might be inappropriate, but it did not follow that it was unethical. Failure to meet appropriate standards that might not necessarily be unethical was dealt with separately by the provisions. There was no evidence that confidentiality or other issues raising ethical concerns arose. The mere fact of being in an office where calls were being made to, or concerning, patients, was an everyday occurrence for representatives who did not by their presence breach any requirements relating to confidentiality unless they were specifically asked to remain outside and refused to do so. Here that did not appear to have been the case.

RESPONSE FROM PFIZER

Pfizer said that its representative had explained that the code for the keypad was given to him by a member of staff about three years ago. In that time, he did not recall ever being asked not to use the code nor to make appointments by telephone instead. Additionally, its representative had commented that he believed he was made welcome by the secretarial staff and that he had developed a good professional relationship with the staff, which he would not wish to jeopardise in any way. In particular he commented

that he always made appointments in order to see the consultants and did not abuse his access to the code.

Pfizer's representative had explained the incident relating to him sitting at a secretary's desk. He admitted that he was sitting at the desk, but that in all his dealings both on that day and whenever else he was there at the unit, he avoided any form of contact with any confidential information and tried to ignore any conversation that might be going on within earshot. He acknowledged that in his position he was likely to come across confidential information but that at all times he maintained a professional approach and sought no contact with such information.

In relation to the incident involving photocopying, Pfizer's representative had stated that he was not involved and that he did not request photocopying to be done for him by the secretaries.

Pfizer did not believe that its representative had acted in a manner that fell short of the high ethical standards expected of representatives in the industry. Pfizer also believed that he had respected the wishes of the staff at the centre upon whom he called. Therefore, Pfizer did not believe that there had been any breach of either Clause 15.2 or Clause 15.4.

Both Pfizer and its representative had treated this complaint seriously. Pfizer acknowledged the need for the observation of high ethical standards by its sales representatives. Pfizer was also fully appreciative of the provisions of Clauses 9.1 and 15.10 and Pfizer's responsibilities as the employing company. For this reason Pfizer ran a seminar on the content of the Code in addition to the ABPI examination which representatives must pass within two years of entering the industry. The seminar emphasised not only the content of the Code, but also the need to observe high ethical standards and follow the spirit of the Code

Although Pfizer did not believe that there had been any breaches of the Code by either its representative or the company as a whole, it apologised for any misinterpretation regarding its representative's actions and would be happy to discuss this matter with the complainant if the complainant so wished.

PANEL RULING

The Panel noted that the parties' accounts of what took place when the representatives visited the offices differed. The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel considered that in a hospital department, where in the course of a visit a medical representative might interact with several staff, it could be difficult for any one person to know the exact circumstances of the visit. The Panel noted that it had not been supplied with any information regarding what arrangements the offices had with regard to representatives' calls.

The Panel noted that the medical secretary who had written the statement regarding the initial visit by the Eisai representative had stated that she had not been at her desk at the time. The representative stated that he had used the intercom to gain entry to the department and assumed that the door had been opened for him by a member of staff. Although the representative had interrupted two consultants, one of whom he particularly wanted to see, they had been talking in an open office and on his arrival there had been no one else around to ask first. On being told that the consultant was too busy to see him the representative had apologised and left leaving some documents with a secretary on his way out. In the circumstances the Panel did not consider that in this particular case the representative's visit had been such as to cause inconvenience and nor had the representative failed to maintain a high standard of ethical conduct. No breach of Clauses 15.2 and 15.4 was ruled.

With regard to the Eisai representative's later visit to the offices, the Panel noted that as he entered he had shouted 'Oh, it's one of those days, is it?'. The Panel noted Eisai's response, however, that at no time was any conversation directed at the staff in the unit. The Panel also noted the complainant's statement that on his second visit the representative had asked a secretary to photocopy some documents for him which she did. The Panel noted Eisai's submission that the secretary had already offered to do this for him during his first visit of the morning. The Panel did not consider that either instance had been such as to cause inconvenience or represented a failure of the representative to maintain a high standard of ethical conduct. The representative had returned to the offices to deliver a document which had been requested by a member of staff. No breach of Clauses 15.2 and 15.4 was ruled.

With regard to the Pfizer representative's visit the Panel noted that he had gained entry to the offices using the keypad code which he had been given some three years' previously. The Panel questioned whether the code should have been given to a pharmaceutical company representative but considered that as it had been supplied to the representative he had thus been given tacit permission to let himself into the department. Under the circumstances the Panel did not consider that his use of the keypad code represented a failure to maintain a high standard of ethical conduct or that he was disregarding the arrangements in force in the department. No breach of Clauses 15.2 and 15.4 was ruled.

The Panel noted that a second medical secretary had found the Pfizer representative sitting at a secretary's desk. The Panel noted Pfizer's submission that he avoided any form of contact with confidential information. In a personal submission from the representative he stated that it was quite possible he had sat down as he had a back problem at the time but that if he had he would always have faced out and would never have sought access to information confidential or otherwise. The representative also stated that he would always wait until he had been asked to take a seat at a desk. The Panel did not consider that sitting at a desk *per se* represented a failure to maintain a high standard of ethical conduct or that it necessarily disregarded local arrangements. No breach of Clauses 15.2 and 15.4 was ruled.

The Panel noted that both representatives had been going about their business in the unit while

confidential discussions had been taking place. The Panel considered that this would be an every day occurrence for all medical representatives. The Panel did not consider that such a situation represented a failure to maintain a high standard of ethical conduct or that it disregarded local arrangements. No breach of Clauses 15.2 and 15.4 was ruled.

The Panel considered that the provisions of Clause 9.1 were covered in its rulings of no breach of Clauses 15.2 and 15.4 of the Code. The Panel noted that Clause 15.10 set out the responsibilities of companies for their representatives. It was not possible to breach Clause 15.10.

Complaint received **1 November 2000**

Case completed **12 January 2001**

CASE AUTH/1093/11/00 *NO BREACH OF THE CODE*

MEDICINES INFORMATION PHARMACIST v ASTRAZENECA

Conduct of representative

The medicines information pharmacist at an NHS Trust alleged that a representative from AstraZeneca was manipulative and forceful with medical secretaries. She had recently buzzed the intercom and introduced herself as a nurse manager and had been allowed access by a secretary who thought that she was a member of staff. On one occasion she had physically barred a doorway preventing a secretary from gaining access while she attempted to get information about seeing one of the consultants. In a separate incident there had been a mistake on a double booking and it was alleged that the representative had sat down with a secretary for fifteen minutes demanding to know who had changed the appointment and why it had been done, and to complain, upsetting the secretary by this confrontation.

The Panel noted that the parties' accounts differed. The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. To assist, AstraZeneca's response was sent to the complainant for further comment and the complainant's comments were then sent to AstraZeneca.

The Panel noted that it had been alleged that the representative had misled as to her identity and so gained access to the offices. The representative categorically denied ever having introduced herself as a nurse manager; the company presumed that she must have been misheard over the intercom. Given the parties' differing accounts the Panel was not in a position to determine precisely what had happened and ruled no breach of the Code.

The Panel also noted that it had been alleged that the representative had barred a doorway whilst she attempted to get some information from a secretary about one of the consultants. The representative had no recollection of any such incident. In addition it was alleged that the representative wasted a secretary's time when she had tried to find out why one of her appointments had been overwritten. The secretary had been upset by the confrontation. The representative's recollection of the exchange was of an amicable and friendly interaction. The Panel noted that the representative had subsequently admitted to being forceful and assertive in the performance of her duties and that she now realised how this could be misinterpreted. Given the parties' differing accounts the Panel was not in a position to determine what precisely had happened. The Panel therefore ruled no breach of the Code.

The medicines information pharmacist at a NHS Trust complained about the conduct of a medical representative of AstraZeneca UK Limited.

COMPLAINT

The complainant provided a statement from a medical secretary to illustrate the behaviour of the representative which read:

'[The representative] has proved manipulative and forceful with medical secretaries. She arrived at the department recently and buzzed the intercom and introduced herself as 'Nurse Manager'. She was allowed access to the department by a secretary colleague who thought she was a member of staff.'

'In the past [the representative] has physically barred the doorway, stopping me gaining access to my office, whilst she attempted to get information from me regarding seeing one of the consultant psychiatrists for old age. I had to ask her to move.'

The complainant stated that in a separate incident there was a mistake over a double booking in which the representative's appointment had been overwritten. The secretary involved had said that the representative sat down with the secretary for about 15 minutes demanding to know who had changed the appointment, why it had been done and to complain. The complainant stated that the secretary involved described herself as being upset by this confrontation.

The complainant alleged breaches of Clauses 15.2, 15.4 and 15.10 of the Code. The complainant found it quite unacceptable that a medical representative should use deceit to gain access to a department's offices and that in a separate incident she should waste staff time and verbally harass staff.

The complainant stated that while the unit had historically enjoyed a relaxed relationship with

medical representatives, this and other instances had forced it to take draconian measures which were an inconvenience to all concerned.

In addition to those clauses cited by the complainant, the Authority asked AstraZeneca to also consider the requirements of Clauses 9.1 and 15.5 of the Code.

RESPONSE

AstraZeneca stated that the representative categorically denied ever introducing herself as a nurse manager, attempting to pass herself off as a member of staff, or using deceit to gain access to the secretaries in the department. In addition, she strongly contested the accusation that she was manipulative and forceful with medical secretaries. She could only surmise that this was a case of mistaken identity.

The representative had no collection of there ever having been an incident of her barring a doorway and preventing a medical secretary gaining access to her office. The representative categorically denied that this had ever happened and, again, could only assume that this was a case of mistaken identity.

With regard to the alleged incident concerning a double booking, the representative and her manager had examined the representative's diary of appointments and could confirm that a double booking with the community mental health team did occur on 10 December 1999. The representative became aware of the double booking on the morning of the meeting when she telephoned the department to confirm the number of attendees. She was informed that another representative had been given an appointment for that day and that that representative would be holding the meeting. The representative visited the directorate a few days later to arrange with the secretary another date for her meeting.

The meeting subsequently took place on 11 February 2000. The representative's recollection of her visit to the secretary was one of an amicable and friendly interaction.

In addition, the representative stated that she had always had a professional and friendly relationship with the secretarial staff of the department. She visited the secretaries and the department only for valid business reasons and she saw the consultants in the directorate only by prearranged appointments.

In summary, AstraZeneca did not believe that the representative had misled any of the secretarial staff of the department as to her identity and, therefore, the company did not accept that a breach of Clause 15.5 had occurred.

The company did not believe that the representative's visits to the directorate or the manner of her calls had been undertaken with anything other than the professionalism and courtesy expected of a medical representative. The company, therefore, did not accept that a breach of Clause 15.4 had occurred.

AstraZeneca considered that the representative had respected the professional standing of both the medical and secretarial staff of the directorate and had maintained a high standard in her conduct and discharge of her duties. The company therefore did not accept that a breach of Clause 9.1 or Clause 15.2 had occurred.

AstraZeneca stated that it was pleased to note the complainant's comment that the directorate once enjoyed a relaxed relationship with medical representatives but was concerned to note that instances of representative behaviour had brought about changes in arrangements which were an inconvenience to all concerned. The company hoped that the matters involved in the complaint would be resolved quickly to the satisfaction of both parties and that cordial professional relationships might once again be established.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that staff had been interviewed again and their statements did not vary from those originally provided. In all instances witnesses were not available.

The complainant stated that he would fully support the staff in categorically denying the suggestion of mistaken identity. The staff who had made the complaints had worked for the trust for many years and were well acquainted with the small number of representatives that frequently visited the hospital. There was no question of a mistaken identity.

With regard to the representative being described as manipulative and forceful the complainant could understand how she could appear so to staff who were perhaps less confident in dealing with a well drilled sales force. With regard to the visit in which meeting dates were rearranged the complainant noted that the representative described the meeting as amicable and friendly, whilst the secretary found her demanding and described herself as being upset after the confrontation. The complainant interpreted the situation from personal experience and stated that he could describe the representative as assertive; as previously suggested he could easily understand how this could be misinterpreted. The complainant considered that this did not excuse behaviour that unnecessarily upset staff.

The complainant noted that specifically, the allegation that the representative wasted 15 minutes of staff time, in breach of Clause 15.4, had not been dealt with.

FURTHER COMMENTS FROM ASTRAZENECA

AstraZeneca stated that whilst making a routine call to the hospital on unrelated matters the representative was approached by the complainant and they discussed the matter of this complaint. AstraZeneca stated that the representative admitted to being focussed and assertive in the performance of her duties and, following discussions with her manager and the complainant, she now realised that this could be misinterpreted. AstraZeneca noted that in his further comments the complainant described the representative as assertive and added that he could easily understand how this could be misinterpreted. The representative was very concerned and upset that, on this particular occasion, her behaviour had

been interpreted as being forceful, manipulative or time-wasting. This had never been her intention and she would never knowingly upset, waste the time of, or jeopardise her relationships with the secretarial, administrative and medical staff on whom she called. The representative very much regretted that she had upset some members of the department staff, albeit unknowingly, and she offered her apologies to the complainant and the staff concerned.

Finally, AstraZeneca reiterated that the representative categorically denied ever having attempted to pass herself off as a member of staff (nurse manager). She had no nursing qualifications and had never been employed in any position associated with the nursing profession. The company presumed that she had been misheard over the entrance intercom.

PANEL RULING

The Panel noted that the parties' accounts of what took place when the representative visited the offices differed. The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The Panel noted that it had been alleged that the representative had arrived at the directorate offices, buzzed the intercom and introduced herself as a nurse manager. The representative was allowed into the offices by a secretary who thought she was a member of staff. The representative categorically denied ever having introduced herself as a nurse manager; the company presumed that she must have been misheard over the intercom. Given the parties' differing accounts the Panel was not in a position to determine precisely what had happened. The Panel therefore ruled no breach of Clause 15.5 of the Code.

The Panel also noted that it had been alleged that the representative had barred a doorway whilst she attempted to get some information from a secretary about one of the consultants. The representative had no recollection of any such incident. In addition it was alleged that the representative wasted a secretary's time when she had tried to find out why one of her appointments had been overwritten. The secretary said she had been upset by the confrontation. The representative's recollection of the exchange was of an amicable and friendly interaction. The Panel noted that the representative had admitted to being forceful and assertive in the performance of her duties and that she now realised how this could be misinterpreted. Given the parties' differing accounts the Panel was not in a position to determine what precisely had happened. The Panel therefore ruled no breach of Clauses 15.2 and 15.4 of the Code.

The Panel considered that the provisions of Clause 9.1 were covered in its rulings of no breach of Clauses 15.2 and 15.4 of the Code. During its consideration of this case the Panel noted that Clause 15.10 of the Code set out the responsibilities of companies for their representatives. It was not possible to breach Clause 15.10.

Complaint received	**1 November 2000**
Case completed	**17 January 2001**

CASE AUTH/1094/11/00

GENERAL PRACTITIONER v PFIZER

Lipitor journal advertisement

A general practitioner complained about a journal advertisement for Lipitor (atorvastatin) issued by Pfizer. The advertisement featured a picture of a skier, whose shirt read '10mg', going downhill having passed signs on slalom posts which read '7mmol/l', '6mmol/l' and '5mmol/l'. Beneath the visual the claim 'Going down' appeared and beneath that the claim that '77% of patients reach their LDL-C targets with 10mg starting dose'. The 77% appeared in a prominent bold typeface, the rest of the claim was much smaller. Beneath the product logo at the bottom of the advertisement was the claim 'Anything else is just another statin'.

The complainant was concerned and confused by the message portrayed. Clearly, the slalom posts were intended to signify total cholesterol values and the skier passing the lower post was meant to depict that the total cholesterol target of 5mmol/l was exceeded by Lipitor 10mg. He could not therefore understand the relevance of the statement regarding the percentage of patients reaching their LDL-C target, which was currently 3mmol/l. Surely, it would have been more appropriate for the percentage figure for patients reaching the total cholesterol target of 5mmol/l to be included. The complainant believed that this advertisement was confusing, as it would mislead physicians into believing that 77% of their patients would achieve total cholesterol targets. The percentage of patients achieving the total cholesterol target of 5mmol/l was not included anywhere in the advertisement. The complainant also alleged that the prominence of the 77% with relation to the explanatory statement below it was unacceptable. His first impression upon viewing the advertisement was that cholesterol was lowered by 77%. Clearly, Lipitor 10mg did not achieve such reductions. The complainant was also concerned that the claim regarding the percentage of patients reaching LDL-C targets was not referenced.

The Panel noted that the values on the slalom poles referred to total cholesterol whereas the 77% referred to LDL-C targets. The design of the advertisement was such that the reader's eye was drawn to the 5mmol/l slalom banner, the claim 'Going down', followed by 77%. It was not stated that 5mmol/l related to total cholesterol although the Panel noted Pfizer's submission that there should not be any confusion as to what the figures referred to given that the intended audience would be familiar with the currently recommended total cholesterol and LDL-C targets. The figure 77% appeared in bold large type face; the reference to LDL-C appeared beneath in less prominent typeface. The Panel considered that on balance the layout of the advertisement was such that the juxtaposition of values for total cholesterol levels and a claim relating to the percentage of patients achieving target levels of LDL-C was misleading. A breach of the Code was ruled. This ruling was upheld by the Appeal Board following an appeal by Pfizer.

The Panel noted the Code required that material must be capable of substantiation and that substantiation must be provided on request. There was no requirement to reference claims except when referring to published studies. The claim at issue did not mention the published study. There was no need to reference the claim and no breach of the Code was ruled.

A general practitioner complained about an A3 advertisement (ref 90986) for Lipitor (atorvastatin), issued by Pfizer Limited, which had appeared in GP, 20 October. The advertisement featured a picture of a skier, whose shirt read '10mg', going downhill having passed signs on slalom posts which read '7mmol/l', '6mmol/l' and '5mmol/l'. Beneath the visual the claim 'Going down' appeared and beneath that the claim that '77% of patients reach their LDL-C targets with 10mg starting dose'. The 77% appeared in a prominent bold typeface, the rest of the claim was much smaller. Beneath the product logo at the bottom of the advertisement was the claim 'Anything else is just another statin'.

COMPLAINT

The complainant alleged that the advertisement was misleading to prescribers and he wished to complain on three counts.

The skier was photographed passing the lower '5mmol/l' post, which presumably represented the current total cholesterol targets, as outlined in the National Service Framework for Coronary Heart Disease. The complainant was concerned and confused by the message portrayed by this advertisement. Clearly, the slalom posts were intended to signify total cholesterol values and the skier passing the lower post was meant to depict that the total cholesterol target of 5mmol/l was exceeded by Lipitor 10mg. The complainant could not therefore understand the relevance of the statement regarding the percentage of patients reaching their LDL-C target, which was currently 3mmol/l. Surely, it would have been more appropriate for the percentage figure for patients reaching the total cholesterol target of 5mmol/l to be included in the advertisement. The complainant believed that this advertisement was confusing, as it would mislead physicians into believing that 77% of their patients would achieve total cholesterol targets. The percentage of patients achieving the total cholesterol target of 5mmol/l was not included anywhere in the advertisement.

The complainant also alleged that the prominence of the 77% with relation to the explanatory statement below it was unacceptable. His first impression upon viewing the advertisement was that cholesterol was lowered by 77%. Clearly, Lipitor 10mg did not achieve such reductions. The complainant alleged that this was misleading and that other prescribers could be left with this impression.

The complainant was also concerned that the claim regarding the percentage of patients reaching LDL-C targets with the 10mg starting dose of Lipitor was not referenced.

RESPONSE

Pfizer did not believe that the picture depicting 7, 6 and 5mmol/l on the slalom posts and the skier suggested that Lipitor 10mg lowered cholesterol from 7 to 5mmol/l in the way referred to by the complainant. Pfizer believed that the picture represented the National Service Framework (NSF) and Joint British Recommendations (JBR) targets which encompassed the recognised need to lower total cholesterol, preferably to <5mmol/l.

The 5mmol/l goal was a well-known and recognised target level for total cholesterol and the picture conveyed a general message of Lipitor 10mg bringing down total cholesterol, hopefully in line with this target. Pfizer did not believe that there should be any confusion that the levels referred to on the slalom posts were LDL-C levels because of the well-recognised nature of the current total cholesterol targets contained in the NSF, a fact that the complainant appeared to acknowledge.

The complainant also referred to the much smaller part of the advertisement containing a stamp which had the quotation '77% of patients reach their LDL-C targets with 10mg starting dose' within it. This stamp was clearly labelled. Immediately underneath the '77%' figure, in clear type, there was a statement that the % figure referred to LDL-C reduction. Therefore, Pfizer did not believe that there could be any implication that the 77% figure referred to a reduction of total cholesterol.

The claim that 77% of patients reached the LDL-C target was supported by the GP Matrix Study. That study showed that following guidelines recommending a lower LDL cholesterol treatment goal of ≤ 3mmol/l in patients with coronary heart disease, 77% of patients achieved this target when on the 10mg starting dose of atorvastatin.

For the reasons stated above Pfizer believed that the advertisement was in no way misleading and it denied any breach of Clause 7.2 of the Code. Unfortunately, it must apologise for the fact that the claim in relation to the 77% reduction in LDL-C, although clearly capable of substantiation (see GP Matrix Study), was not referenced in the advertisement itself. Pfizer had now rectified this in all further advertisements of this type.

PANEL RULING

The Panel noted that the values on the slalom poles referred to total cholesterol whereas the 77% referred to LDL-C targets. The Panel noted the submission that there could be no confusion that the slalom poles referred to LDL-C levels because of the well recognised nature of the current total cholesterol targets contained in the NSF. The Panel noted that the NSF for Coronary Heart Disease stated that the interventions for people with diagnosed CHD or other occlusive arterial disease included, inter alia, 'Statins and dietary advice to lower serum cholesterol concentrations either to less than 5mmol/l (LDL-C to below 3mmol) or by 30% (whichever is greater)'. Identical cholesterol targets were mentioned in relation to people without diagnosed CHD or other occlusive arterial disease with a CHD risk greater than 30% over ten years. Similarly the Joint British recommendations on prevention of coronary heart disease in clinical practice stated that in relation to patients with CHD or other major artherosclerotic disease a rigorous control of lipids was recommended to a target of total cholesterol less than 5mmol/l (LDL-C less than 3mmol/l). Identical lipid targets were recommended in relation to primary CHD prevention in high risk individuals. The Panel noted that the Prescribing Notes to the hypolipidaemic agents section in MIMS November 2000 referred to a desirable total cholesterol target of no more than 5.2mmol/l and a LDL-C target of ≤ 3.5mmol/l for those with multiple risk factors (British Hyperlipidaemia Association (BHA) and European Artherosclerosis Society (EAS) Guidelines).

The Panel noted that Neil *et al* (1999), the GP Matrix Study, was an open label non comparative 17 week trial preceded by a five week dietary run-in period designed to investigate in a primary care setting the ability of atorvastatin to achieve LDL-C target levels. A total of 554 patients entered the diet only phase of the study. Of the original study population 155 patients were discontinued during the run-in period. A total of 399 patients received atorvastatin and of the 379 patients remaining in the study after 5 weeks of treatment 94% reached their LDL-C target ≤ 3.4mmol/l on the 10mg starting dose. After completion of the study new guidelines recommended a lower LDL-C treatment goal of ≤ 3mmol/l. The study authors stated that reanalysis of the data showed that 77% of patients achieved this lower treatment target on the 10mg starting dose.

The Panel noted that the design of the advertisement was such that the reader's eye was drawn to the 5mmol/l slalom banner, the claim 'Going down', followed by 77%. It was not stated that 5mmol/l related to total cholesterol although the Panel noted Pfizer's submission that there should not be any confusion as to what the figures referred to given that the intended audience would be familiar with the currently recommended total cholesterol and LDL-C targets. The figure 77% appeared in bold large type face; the reference to LDL-C appeared beneath in less prominent typeface. The Panel considered that on balance the layout of the advertisement was such that the juxtaposition of values for total cholesterol levels and a claim relating to the percentage of patients achieving target levels of LDL-C was misleading. A breach of Clause 7.2 was ruled.

The Panel noted the Code required that material must be capable of substantiation and that substantiation must be provided on request (Clauses 7.2 and 7.3). There was no requirement to reference claims except when referring to published studies (Clause 7.5). The claim at issue did not mention the published study, Neil *et al* (1999). There was no need to reference the claim. No breach of Clause 7.5 was ruled. This ruling was not appealed.

APPEAL BY PFIZER

Pfizer did not agree that the advertisement was misleading in the way described by the Panel.

Pfizer noted that the complainant alleged that the advertisement was misleading in two ways. Firstly,

the GP alleged that the advertisement was confusing because it would mislead physicians into believing that 77% of their patients would achieve total cholesterol targets. The percentage of patients achieving a total cholesterol target of 5mmol/l was not included anywhere in the advertisement. And secondly, that the prominence of the 77% in relation to the rest of explanatory statement was not acceptable. His first impression was that cholesterol was lowered by 77% and that Lipitor 10mg did not achieve such reductions.

Pfizer stated that the Panel had noted in its ruling that the values on the slalom posts in the advertisement referred to total cholesterol levels and that there could be no confusion that these values referred to LDL-C levels because of the well recognised nature of the current total cholesterol targets. These targets represented the need to lower total cholesterol, preferably to <5mmol/l as recommended by the NSF and JBR.

Underneath the picture of the skier, the reader's eye would be drawn to the claim 'Going down'. Next to the claim on the right bottom corner was a stamp with the quote '77% of patients reach their LDL-C targets with the 10mg starting dose' in clear typeface.

Pfizer believed the visual image was not misleading to physicians because the nature of the 5mmol/l target would be well understood by the intended audience, the exact meaning of the '77%' reference was clearly visible and in any event, Lipitor was capable of (and licensed to) reduce both LDL-C and total cholesterol. It was not therefore misleading to claim that the product would reduce cholesterol in the general sense or, in addition, to claim that Lipitor 10mg would enable 77% of patients to reach their LDL-C targets, as substantiated by the GP Matrix Study.

Although Pfizer firmly believed that healthcare professionals reading the advertisement would not believe that the 77% figure related to total cholesterol, since it was explicitly stated to relate only to LDL-C, in fact, significant reductions in LDL-C would inevitably reduce total cholesterol also.

Total cholesterol levels could be calculated from LDL-C and HDL-C levels plus a factor of about 15% of the total amount to account for VLDL-C. VLDL-C was not commonly measured. Therefore, total cholesterol could be estimated from (LDL-C + HDL-C) + 15%. It was not possible for patients to have reductions of LDL-C independent of total cholesterol.

In the GP Matrix Study, the objective was not to assess the number of patients reaching total cholesterol targets and, therefore, this was not referred to in the advertisement. However, on the basis set out above, since 77% of patients achieved the LDL-C target, it was highly likely that a similar proportion would also achieve their total cholesterol target of <5mmol/l, given that the mean HDL-C level recorded in this study was 1.23mmol/l.

Pfizer did not believe that the advertisement was misleading to healthcare professionals.

APPEAL BOARD RULING

The Appeal Board considered that the layout of the advertisement was such that the juxtaposing of values for total cholesterol levels and the claim relating to the percentage of patients achieving target levels of LDL-C was misleading. Readers would be misled into assuming that total cholesterol was reduced by 77% and this was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Complaint received **2 November 2000**

Case completed **30 January 2001**

CASE AUTH/1095/11/00

PHARMACIST v PFIZER

Lipitor journal advertisement

A pharmacist complained about a journal advertisement for Lipitor (atorvastatin) issued by Pfizer Limited. Apart from size and layout the advertisement was similar to that at issue in Case AUTH/1094/11/00. The advertisement featured a picture of a skier, whose shirt read '10mg', going downhill having passed signs on slalom posts which read '7mmol/l', '6mmol/l' and '5mmol/l'. Beneath the visual the claim 'Going down' appeared and beneath that the claim that '77% of patients reach their LDL-C targets with 10mg starting dose'. The 77% appeared in a prominent bold typeface, the rest of the claim was much smaller. Beneath the product logo at the bottom of the advertisement was the claim 'Anything else is just another statin'.

The complainant alleged that the advertisement was ambiguous and misled clinicians by omission. The advertisement stated that '77% of patients reach their LDL-C targets …'. However, the particular therapeutic target to which this statement referred was not clearly stated. This would suggest that 77% of patients should always achieve a therapeutic target irrespective of what this target actually was. Clearly, for 10mg of Lipitor, this was not the case, particularly for any therapeutic target below 3mmol/l. The claim 'Anything else is just another statin' was disparaging of other statins, unsubstantiable, an unqualified comparison, exaggerated and suggested unique benefits for Lipitor 10mg. The complainant believed that the advertisement was irresponsible and unacceptable.

The Panel considered that its general comments regarding the widespread publication of nationally agreed lipid target levels made in Case AUTH/1094/11/00 also applied here. The Panel noted that the allegation in this case was different to that at issue in Case AUTH/1094/11/00 and concerned the claim for LDL-C targets rather than the layout of the advertisement. On balance, the Panel considered that as the intended audience would be familiar with LDL-C target levels it was not necessary to restate them. No breach of the Code was ruled.

The Panel considered that the claim 'Anything else is just another statin' implied that Lipitor was generally superior to the other statins and gave the impression that all other statins were all much the same as each other. The Panel noted that the licensed indications were not exactly the same for all of the statins. The Panel considered the unqualified claim was exaggerated and disparaging as alleged and breaches of the Code were ruled.

A pharmacist complained about an A4 advertisement (ref 90986) for Lipitor (atorvastatin) issued by Pfizer Limited which had appeared in Prescriber, 19 October. Apart from size and layout the advertisement was similar to that the subject of Case AUTH/1094/11/00. The advertisement featured a picture of a skier, whose shirt read '10mg', going downhill having passed signs on slalom posts which read '7mmol/l, '6mmol/l' and '5mmol/l'. Beneath the visual the claim 'Going down' appeared and beneath that the claim that '77% of patients reach their LDL-C targets with 10mg starting dose'. The 77% appeared in a prominent bold typeface, the rest of the claim was much smaller. Beneath the product logo at the bottom of the advertisement was the claim 'Anything else is just another statin'.

COMPLAINT

The complainant alleged that the advertisement was ambiguous and misled clinicians by omission. The advertisement stated that '77% of patients reach their LDL-C targets …'. However, the particular therapeutic target to which this statement referred was not clearly stated. This would suggest that 77% of patients should always achieve a therapeutic target irrespective of what this target actually was. Clearly, for 10mg of Lipitor, this was not the case, particularly for any therapeutic target below 3mmol/l.

The claim 'Anything else is just another statin' was alleged to be disparaging of other statins, unsubstantiable, an unqualified comparison, exaggerated and suggested unique benefits for Lipitor 10mg.

The complainant believed that the advertisement was irresponsible and unacceptable.

RESPONSE

Pfizer noted that the complainant commented that the advertisement could be misleading in relation to the claim '77% of patients reach their LDL-C targets with 10mg starting dose', because the advertisement did not contain a clear statement of what the target was.

The claim was substantiated by reference to the GP Matrix Study. This study showed that following guidelines recommending a lower LDL-C treatment goal of ≤ 3mmol/l in patients with coronary heart disease, 77% of patients achieved this target when on the 10mg starting dose of atorvastatin.

The 3mmol/l target for LDL-C was a well-established target in the CHD National Service Framework (NSF), Joint British Recommendations (JBR), Clinical Resource Efficiency Support Team (CREST) and Scottish Intercollegiate Guidelines Network (SIGN). These bodies were well-known and their guidelines accepted for the treatment of hypercholesterolaemia/ prevention of coronary heart disease. Pfizer did not, therefore, consider it necessary to expressly to refer to the 3mmol/l level.

Given the well-recognised nature of the 3mmol/l target for LDL-C and the supporting study (GP Matrix Study), Pfizer did not believe that the claim was in any way misleading or ambiguous and specifically it denied any breach of either Clause 7.2 or Clause 7.3 of the Code.

Pfizer also noted that the complainant referred to the claim 'Anything else is just another statin' as being potentially disparaging of other statins. However,

Pfizer did not believe this to be the case and certainly it was not its intention in initially using the statement. Pfizer believed that Lipitor did have additional merits over other statins at the 10mg dose in that it reduced LDL-C by more than any other statin, at their respective starting dosages.

The advertisement was clearly for Lipitor 10mg (starting dose for atorvastatin). The bracketing of other statins as being outside of the LDL-C lowering ability of Lipitor was not intended to be disparaging of the other statins, but was merely intended to express the special capabilities of the product in lowering LDL cholesterol at the 10mg dose.

Pfizer therefore denied that the statement was either disparaging or exaggerated and specifically denied any breach of either Clause 7.8 or Clause 8.1 of the Code.

Despite Pfizer's express denial of any breach of the Code with regard to this advertisement, it had taken due consideration of the complainant's comments and had been in discussion with its fellow pharmaceutical companies. Pfizer now appreciated that there was a possibility that this statement might be open to some misinterpretation. Therefore, Pfizer had already amended future advertisements of this type accordingly so that they did not include this particular statement.

PANEL RULING

The Panel considered that its general comments regarding the widespread publication of nationally agreed lipid target levels made in Case AUTH/1094/11/00 were relevant here. In this regard the Panel noted that the NSF for Coronary Heart Disease stated that the interventions for people with diagnosed CHD or other occlusive arterial disease included, *inter alia*, 'Statins and dietary advice to lower serum cholesterol concentrations either to less than 5mmol/l (LDL-C to below 3mmol) or by 30% (whichever is greater)'. Identical cholesterol targets were mentioned in relation to people without diagnosed CHD or other occlusive arterial disease with a CHD risk greater than 30% over ten years. Similarly the Joint British recommendations on prevention of coronary heart disease in clinical practice stated that in relation to patients with CHD or other major artherosclerotic disease a rigorous control of lipids was recommended to a target of total cholesterol less than 5mmol/l (LDL-C less than 3mmol/l). Identical lipid targets were recommended in relation to primary CHD prevention in high risk individuals. The Panel noted that the Prescribing Notes to the hypolipidaemic agents section in MIMS November 2000 referred to a desirable total cholesterol target of no more than 5.2mmol/l and a LDL-C target of ≤ 3.5mmol/l for those with multiple risk factors (British Hyperlipidaemia Association (BHA) and European Artherosclerosis Society (EAS) Guidelines).

The Panel noted that the allegation was different to that at issue in Case AUTH/1094/11/00 and concerned the claim '77% of patients reach their LDL-C targets with 10mg starting dose' rather than the layout of the advertisement.

On balance, the Panel considered that as the intended audience would be familiar with LDL-C target levels it was not necessary to restate them. The Panel did not consider that the claim was misleading as alleged and ruled no breach of Clause 7.2 of the Code.

The Panel considered that the claim 'Anything else is just another statin' implied that Lipitor was generally superior to the other statins and gave the impression that all other statins were all much the same as each other. The Panel noted that the licensed indications were not exactly the same for all of the statins. The Panel did not accept Pfizer's submission that the claim was merely intended to express the special capabilities of Lipitor in lowering LDL-C at the 10mg dose. The Panel considered the unqualified claim was exaggerated and disparaging as alleged and ruled breaches of Clauses 7.8 and 8.1 of the Code.

The Panel was concerned to note that the advertisement in this case and that the subject of Case AUTH/1094/11/00 each bore the same reference number. One was A3 size and the other A4 and the layouts were different. The guidelines on company procedures at the back of the Code of Practice Booklet recommended that a particular reference number should relate to only one item of promotional material. The Panel requested that this be drawn to Pfizer's attention.

Complaint received **2 November 2000**

Case completed **5 January 2001**

CASE AUTH/1098/11/00

PHARMACEUTICAL ADVISER v WYETH

Arrangements for a meeting

A pharmaceutical adviser to a primary care group complained about a letter of invitation to attend a meeting on the management of depression which he had received from the local university's school of neurosciences and psychiatry. The complainant alleged that it seemed likely that the meeting was sponsored by Wyeth as the file name Wyeth appeared in the bottom left hand corner of the reply slip but the company's support was not clearly acknowledged. The complainant also alleged that the hospitality did not meet the requirements of the Code.

The Panel noted that the complainant had received a mailing comprising three separate documents, the letter of invitation, the speakers' CVs and the programme. The letter contained a clear and unambiguous statement of sponsorship. The Panel considered that both the CVs and the programme should each have contained a declaration of sponsorship. The file reference on the programme was insufficient in this regard. A breach of the Code was ruled.

The Panel noted that the Code required hospitality to be secondary to the purpose of the meeting. The overall impression created by the arrangements had to be borne in mind. The programme had to attract delegates and not the venue. The Panel noted that the educational part of the meeting lasted from 7 to 9pm and was followed by a buffet dinner, the cost of which was less than £20 per head. The Panel did not consider the hospitality provided unreasonable and ruled no breach of the Code.

A pharmaceutical adviser to a primary care group submitted a complaint about a letter of invitation to attend a meeting on the management of depression which he had received from the local university's school of neurosciences and psychiatry. The letter stated that the meeting had been sponsored by Wyeth Laboratories and was accompanied by the speakers' CVs and the programme. The programme stated that the venue for the meeting was a local hotel. The reference X:/Wyeth appeared in the bottom left-hand corner of the programme.

COMPLAINT

The complainant stated that the material might not comply with Clause 19.3. The complainant also referred to Clause 9.9 and its supplementary information and stated that it seemed likely that the meeting advertised was to be supported by Wyeth Laboratories, as the file name Wyeth appeared in the bottom left hand corner of the reply slip, but the company's support was not clearly acknowledged.

The complainant stated that he might be mistaken; the meeting might not be sponsored by a pharmaceutical company and the university's school might have a large enough budget to be able to treat local health professionals to a pre-Christmas beanfeast at a four-star hotel. The complainant stated he would not usually dine at the hotel in question after a professional meeting and referred to Clause 19.1 of the Code.

RESPONSE

Wyeth stated that The British Association for Psychopharmacology (BAP) had recently published some independent evidenced-based guidelines on the treatment of depression. These covered all aspects of depression, and treatment using pharmacological agents was only a small part of the document. There were a couple of sentences in the guidelines which suggested that venlafaxine (Wyeth's antidepressant, Efexor) might be more efficacious than the selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression.

Some members of BAP had held a meeting a few months ago in which the guidelines were introduced and explained. As the guidelines suggested that venlafaxine might be more effective than the SSRIs, one of Wyeth's local senior representatives approached one of the BAP members and asked if they would like to give the same talk at a venue sponsored by Wyeth. Naturally the BAP members were keen to go ahead as it gave them further opportunities to promote the guidelines. A meeting was therefore set up at a local hotel. The purpose of the meeting was to improve the recognition and treatment of depression for local people using the BAP guidelines. The meeting had been granted PGEA approval.

Wyeth stated that it had had no input into the talks at all. The letter of invitation jointly sent out by the university clearly made the point that the meeting was sponsored by Wyeth. This letter was sent out at the same time as the CVs and programme. No other documents were sent out. The only 'handout' that Wyeth was proposing to circulate was a reprint of the guidelines. The cost of the buffet dinner was less than £20 a head which was not excessive. No company personnel would be at the meeting itself, though Wyeth would have a stand outside the main meeting room.

In view of the fact that the invitation letter clearly stated that the meeting was sponsored by Wyeth (Clauses 9.9 and 19.3) and that the cost of the buffet dinner was not excessive, Wyeth did not consider that this meeting breached the Code.

PANEL RULING

The Panel noted that the purpose of the meeting was to improve the recognition and treatment of depression for local people using the BAP guidelines. The Panel understood that the BAP guidelines made favourable comments about Wyeth's product venlafaxine compared with SSRIs. A local representative had originally suggested the meeting take place at a venue sponsored by Wyeth; Wyeth had no further involvement. The Panel considered that given Wyeth had initiated this particular meeting and provided sponsorship it was responsible for the

arrangements under the Code. The Panel noted that Clause 19.3 required sponsorship of meetings to be disclosed in the papers relating to the meetings and in any published proceedings. Clause 9.9 required that all material relating to medicines and their uses, sponsored by a pharmaceutical company, must clearly indicate that it has been sponsored by that company. The Panel noted that the complainant had received a mailing comprising three separate documents, the letter of invitation, the CVs and the programme. The letter contained a clear and unambiguous statement of sponsorship. The Panel considered that both the CVs and the programme should each have contained a declaration of sponsorship. The file reference on the programme was insufficient in this regard. A breach of Clause 19.3 was ruled. The Panel considered that the alleged breach of Clause 9.9 was covered by its ruling.

The Panel noted that Clause 19.1 of the Code required, *inter alia*, that hospitality must be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion and costs involved must not exceed those which participants would normally adopt when paying for themselves. The overall impression created by the arrangements had to be borne in mind. The programme had to attract delegates and not the venue. The Panel noted that after registration at between 6.30 and 7pm the educational part of the meeting lasted from 7 to 9pm and was followed by dinner. The Panel noted the submission that the cost of the buffet dinner was less than £20 per head. In the circumstances the Panel did not consider the hospitality provided unreasonable and ruled no breach of Clause 19.1 of the Code.

Complaint received **10 November 2000**

Case completed **19 December 2000**

CASE AUTH/1099/11/00

MEDICINES INFORMATION PHARMACIST v TRINITY

Provision of Brexidol samples

The medicines information pharmacist at a hospital complained that samples of Brexidol had been left in the anaesthetics department by a representative from Trinity, contrary to regional policy.

The Panel noted that the representative had met with the complainant in August. Trinity had submitted that the representative was adamant that no mention was made at that time, or since, of any restrictions on sampling. Nonetheless the Panel considered that the representative should have established what the hospital policy was regarding samples whilst meeting with the complainant or before leaving the samples with hospital doctors. Failure to do this had resulted in a breach of the Code and the Panel ruled accordingly.

The medicines information pharmacist at a hospital complained directly to Trinity Pharmaceuticals Ltd about the provision of samples of Brexidol by the company, copying his letter to the Authority.

COMPLAINT

The complainant stated that he was concerned that samples of Brexidol had been left in the anaesthetics department of the hospital. This had come to light when a member of staff from that department was admitted to the hospital with samples of Brexidol tablets in their possession.

All pharmaceutical companies had been informed that samples could not be left in any hospital in the region. The leaving of these samples was clearly a breach of Clause 17.8 of the Code.

RESPONSE

Trinity stated that it had written independently to the complainant in reply to his letter to the company; a copy was provided. The representative involved had not only passed his ABPI examination with distinction but was also a qualified pharmacist. He was thus well aware of the ABPI Code and of the correct use of sample packs.

The representative had stated that:

i) When working in any new hospital he, wherever possible, began by visiting the pharmacy both to introduce himself and the company and to explain his intentions when meeting the hospital's staff.

ii) As per this policy he met with the complainant in August together with another of Trinity's representatives. He was adamant that no mention was made at the time, or since, of any restrictions imposed by the hospital on sampling.

iii) Certain hospitals in the region had a printed sheet which new representatives were given detailing the specific hospital etiquette. The hospital in question did not appear to have such a document.

iv) The representative left sample packs with hospital doctors on his strict understanding that they were for their own personal evaluation only and to familiarise themselves with the product.

Trinity was confident that this highly professional representative would not flout the Code. If he had left samples in contravention of the region's general instruction then he was not aware of it. Trinity stated

(having made internal enquiries) that it had no record of ever having received any such guidelines from the region and had asked the complainant to provide a copy of the instruction and given an undertaking that Trinity would, of course, comply with it in the future.

In summary Trinity did not believe that it had breached the Code since the representative had made all of the appropriate approaches at the hospital, was not informed directly, nor indirectly via the company, of any restrictions in sampling.

Following a request from the Authority for further information, the complainant provided a copy of a letter sent in March 2000 to all companies supplying medicines to hospitals in the region. The complainant stated that in addition to the letter all representatives were repeatedly told of the policy regarding the leaving of samples in wards.

The letter was from the pharmacy department at the hospital. It stated that the health board operated a strict policy on samples. No samples should be left at any hospital in the region. This applied to pharmacy departments as well as wards, clinics and community hospitals. The letter also stated that representatives who failed to adhere to the policy would be reported to the ABPI.

PANEL RULING

The Panel noted that the representative had met with the complainant in August. Trinity had submitted that the representative was adamant that no mention was made at that time, or since, of any restrictions on sampling imposed by the hospital. Nonetheless the Panel considered that the representative should have established what the hospital policy was regarding samples whilst meeting with the complainant or before leaving the samples with hospital doctors. Failure to do this had resulted in a breach of Clause 17.8 of the Code. The Panel ruled accordingly.

Complaint received	**10 November 2000**
Case completed	**9 January 2001**

CASE AUTH/1102/11/00

UNIVERSITY CLINICAL LECTURER v NAPP

Zanidip journal advertisement

A university clinical lecturer complained about a journal advertisement for Zanidip (lercanidipine) issued by Napp. Above the words 'sweet heart', the advertisement stated 'Diabetes is no barrier to saving lives. In fact, type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts' and beneath 'sweet heart', 'With proven efficacy in diabetic hypertensives, and a tolerability profile comparable with placebo, Zanidip tablets offer sweet relief to patients in whom diuretics and beta blockers may be contra-indicated'. At the bottom, beneath the Zanidip logo, the advertisement stated 'Treating diabetic hypertensives saves lives'.

The complainant stated that there was no evidence from clinical trials to substantiate the key claim of the advertisement that treatment of diabetic patients with lercanidipine saved lives. There had been no properly conducted clinical trials to demonstrate that lercanidipine saved lives in any patient group, including diabetic or non-diabetic hypertensive patients. The Panel considered that in the context of an advertisement for Zanidip the claim 'Treating diabetic hypertensives saves lives' would be seen as a specific claim for the product rather than as a general statement of the benefits of lowering blood pressure. The Panel considered that the material was misleading and not capable of substantiation and breaches of the Code were ruled.

The complainant stated that the claim 'With proven efficacy in diabetic hypertensives and a tolerability profile comparable with placebo …' implied that lercanidipine was of proven efficacy in diabetic patients. Given the key claim above, this was very misleading. Efficacy had been demonstrated in the context of blood pressure reduction (surrogate end-point). However, the claim implied that lercanidipine was somehow effective in reducing clinical events (primary end-point). No data existed to support the latter. The tolerability profile claim was inaccurate and misleading. Observational data collected from clinical studies of lercanidipine had not demonstrated a significantly higher adverse event rate than placebo, but none of these studies were sufficiently powered to demonstrate such equivalence. The Panel considered that the implication that Zanidip had proven efficacy in diabetic hypertensives in conjunction with the claim 'Treating diabetic hypertensives saves lives' was again that Zanidip saved lives. The Panel considered that its ruling above of breaches of the Code also applied here. The Panel noted Napp's submission that the overall incidence of adverse events in the ELYPSE study at 7.6% was close to the incidence of adverse events of 7% for patients on placebo in the global analysis. No statistical analysis appeared to have been undertaken on any of the adverse event data. On balance the Panel considered that given the data the comparability claim was not unreasonable and no breach of the Code was ruled in this regard.

The complainant alleged that the claim '…type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts' was again misleading, inaccurate and potentially dangerous. To date there had been no clinical trials designed to

compare the response (blood pressure lowering as a surrogate end-point, or clinical outcome end-points) in diabetic and non-diabetic hypertensive patients, treated with any antihypertensive. The sole reference was to an abstract, not published in a peer reviewed journal, relating to a retrospective sub-group analysis of the Syst-Eur study, a placebo controlled study of nitrendipine (not lercanidipine), the design of which did not allow sufficient statistical power for this sub-group analysis. Applying this sort of improper ad hoc analysis to the data from the same abstract could be used to support the view that diabetics responded less favourably to calcium channel blocker treatment (–8.5/–3.9mmHg) than their non-diabetic counterparts (–10.3/–4.6mmHg). The Panel noted that the statement was referenced to a post hoc analysis of the Syst-Eur data which looked at the diabetic sub-group of patients. The Syst-Eur study had compared nitrendipine (with the possible addition or substitution of enalapril or hydrochlorothiazide or both) with placebo. The Panel noted its comments above and again considered that in the context of an advertisement for Zanidip the claim 'type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts' would be seen as a specific claim for the product rather than as a general statement about the response to therapy by diabetic hypertensives. The Syst-Eur study had been published in a peer reviewed journal – The New England Journal of Medicine – but the claim was referenced to a sub-group analysis of the data which appeared as an abstract in the proceedings of a European Conference. The Panel was concerned that the data to support the claim involved the use of nitrendipine and not Zanidip. The Panel noted that 43% of the diabetics in the trial received additional treatment with enalapril or hydrochlorothiazide or both. Readers would assume that there was data for Zanidip comparing diabetic and non-diabetic patients. This was not so. The claim was misleading and a breach of the Code was ruled.

The complainant regarded certain aspects of the advertisement as reckless and without foundation. Cardiovascular disease remained the leading global cause of death, and treatment of hypertension would undoubtedly go some way to alleviating this burden. With the ever-increasing number of antihypertensives available it was more important than ever to select those that had demonstrated not only safety and tolerability, but also the ability to reduce long-term consequences of hypertension. Lercanidipine appeared to be acceptably safe, tolerable and effective in blood pressure reduction. However, the promotional message made claims beyond this, which were not only misleading and inaccurate, but also potentially dangerous. The Panel considered that Napp had failed to maintain a high standard and a breach of the Code was ruled in that regard. The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such circumstances. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

A university clinical lecturer complained about a journal advertisement for Zanidip (lercanidipine) issued by Napp Pharmaceuticals Limited. Above the words 'sweet heart', the advertisement stated 'Diabetes is no barrier to saving lives. In fact, type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts' and beneath the words 'sweet heart', 'With proven efficacy in diabetic hypertensives, and a tolerability profile comparable with placebo, Zanidip tablets offer sweet relief to patients in whom diuretics and beta blockers may be contra-indicated'. At the bottom, beneath the Zanidip logo, the advertisement stated 'Treating diabetic hypertensives saves lives'. The advertisement included the Recordati logo. Napp advised that the marketing authorization holder was Recordati with Napp having an exclusive licence to market and sell Zanidip in the UK. Recordati did not co-promote the product in the UK. The matter was therefore taken up with Napp.

The complainant was concerned about the advertisement, the example he provided having been taken from the British Journal of Cardiology, October 2000.

1 Claim 'Treating diabetic hypertensives saves lives.'

COMPLAINT

The complainant stated that the key claim of the advertisement was that treatment of diabetic patients with lercanidipine saved lives. There was no evidence whatsoever from clinical trials which would substantiate this claim; there had been no properly conducted clinical trials to demonstrate that lercanidipine saved lives in any patient group, including diabetic or non-diabetic hypertensive patients.

RESPONSE

Napp stated that the complainant referred to the combination of product information 'Zanidip lercanidipine HCl tablets' and the strapline underneath 'Treating diabetic hypertensives saves lives'. The complainant observed that the inference was that treatment with lercanidipine saved lives and stated that there was no evidence that lercanidipine saved lives in any group of patients. Napp had already presented evidence on this point in Case AUTH/1061/8/00 where the Code of Practice Appeal Board ruled that although lercanidipine could not claim to have the same degree of cardiovascular protection as that shown in the Syst-Eur (systolic hypertension – Europe) study, 'a reduction in cardiovascular events would be a potential benefit of lowering blood pressure'.

Napp submitted that it was beyond question that the only reason to treat essential hypertension (a largely asymptomatic condition) was to prevent the long-term sequelae of the disease. These included coronary heart disease, cerebrovascular disease, eye disease and renal disease. These were very common but serious medical conditions that could frequently lead to the death of the patient. The complainant alluded to this. There could be no doubt that treating hypertension saved lives, which was the simple message of this

strapline. The only debate could be over the reduction in the proportion of cardiovascular events, and hence lives, that each agent produced with continued use, and over what time period these reductions might be seen. The strapline did not make any claims in this regard.

It had been repeatedly shown that diabetic hypertensives had a high rate of cardiovascular morbidity and mortality compared to that of the general public, and indeed that of the non-diabetic hypertensive group. It had also been shown that blood pressure reduction was even more beneficial in this group than those without diabetes. Potentially even more lives could be saved over time. This was reflected in the Government's National Service Framework (NSF) for coronary heart disease which, because of this frequent and well-known observation, stated in a dedicated section on diabetes 'Diabetes increases someone's risk of developing and dying from coronary heart disease (CHD) two to five fold. People with CHD who have diabetes will benefit from particularly meticulous attention to their modifiable risk factors and even more stringent blood pressure targets' (… than other hypertensive patients). The same page also highlighted 'meticulous control of blood pressure and glucose in people who also had diabetes' as an intervention necessary in those people without CHD.

This was also emphasised in the British national guidelines for the treatment of hypertension (British Hypertension Society) which listed diabetes as a critical risk factor with hypertension, smoking and hypercholesterolaemia for the development of coronary heart disease. The guidelines then went on to discuss the choice of antihypertensive family for each sub-group of hypertensive diabetics in a dedicated section, further underlining the importance of this sub-group. Within this section, these guidelines stated 'Subgroup analysis of outcome trials have shown that other classes of antihypertensive drugs, ie diuretics and dihydropyridine calcium channel antagonists' (of which lercanidipine was a member) 'also improve the prognosis of diabetic patients with hypertension. Thus, the optimal first-line drug is yet to be established but there is evidence from sub-group analyses of outcome trials in diabetic people for the safety and efficacy of ACE-inhibitors, dihydropyridine calcium antagonists, low dose thiazide diuretics and beta-blockers'. A number of large international studies were cited. It was of note that the guidelines recognised there was unlikely to be a significant difference in the protection afforded by individual dihydropyridines, and so did not recommend a specific calcium channel antagonist. This theme was also seen in the US national guidelines for treating hypertension (Joint National Committee on Prevention, Detection, Evaluation and Treatment), where after analysing the results of the Syst-Eur outcome data using nitrendipine as the dihydropyridine, they stated 'because nitrendipine is not available in the United States, other long acting dihydropyridine calcium antagonists are considered to be appropriate alternatives in these patients'.

This strapline simply reinforced the message from national guidelines and the British Government's own position that treating hypertension in diabetics did indeed save lives (by reducing cardiovascular events). This was neither misleading nor unsubstantiated under Clauses 7.2 or 7.3 of the Code.

PANEL RULING

The Panel considered that in the context of an advertisement for Zanidip the claim 'Treating diabetic hypertensives saves lives' would be seen as a specific claim for the product; it would not be seen as a general statement of the benefits of lowering blood pressure. The Panel noted that it had not been given any data to support the claim that 'Treating diabetic hypertensives [with Zanidip] saves lives'. In support of its claim Napp had cited the Syst-Eur study which had used nitrendipine not Zanidip. The Panel considered that the material was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

2 Claim 'With proven efficacy in diabetic hypertensives and a tolerability profile comparable with placebo …'

COMPLAINT

The complainant stated that this claim implied that lercanidipine was of proven efficacy in diabetic patients. Given the key message (point 1 above) of the advertisement, this statement was very misleading. Efficacy had been demonstrated in the context of blood pressure reduction (surrogate end-point), however, in the context of this promotion, the claim implied again that lercanidipine was somehow effective in reducing clinical events (primary end-point); no data existed to support the latter.

The tolerability profile claim was inaccurate and misleading. Observational data collected from clinical studies of lercanidipine had not demonstrated a significantly higher adverse event rate than placebo, but none of these studies were sufficiently powered to demonstrate such equivalence.

RESPONSE

Napp stated that the first portion of this complaint regarding the reduction of clinical events (presumably cardiovascular events) by treating hypertension with lercanidipine, despite the complaint's recognition that lercanidipine was effective at reducing blood pressure, was dealt with in point 1 above.

The second portion of this complaint referred to the statement 'tolerability profile comparable with placebo'. This was supported by data already reviewed and upheld by the Appeal Board in Case AUTH/1061/8/00 in the form of the global safety analysis on lercanidipine submitted to and accepted by the Medicines Control Agency as a requirement for registration of the product. This report looked at the adverse events in all studies available at the time and compared them to the placebo population appearing in that cohort of studies.

The term 'comparable' was defined as: (i) 'worthy of comparison' and (ii) 'able to be compared with' (Collins English Dictionary). This term was used

rather than the term 'equivalent' as used by the complainant, or 'equal to', to avoid the impression that the adverse event profile of Zanidip tablets was identical to that of a cohort taking placebo.

More recent data from the ongoing ELYPSE study looking at a much larger cohort (7469 patients) had demonstrated an overall incidence of adverse events of 7.6%, even closer to the 7% seen in the placebo group in the global safety report of 1995.

Although the adverse event profile was not 'equivalent' to placebo, Napp did not state this in the advertisement. Napp believed the adverse event profile was comparable to placebo. Even the complainant stated that 'observational data from clinical studies had not demonstrated a significantly higher adverse event rate than placebo' but commented on the power to detect equivalence in individual studies, precisely the term deliberately avoided.

Napp submitted the claim 'comparable to placebo' was not misleading, it was capable of substantiation and as evidenced by the ELYPSE study (Barrios *et al* 2000) was reflected in ongoing clinical experience.

PANEL RULING

The Panel considered that the implication of the claim that Zanidip had proven efficacy in diabetic hypertensives in conjunction with the claim at issue in point 1 'Treating diabetic hypertensives saves lives' was again that Zanidip saved lives. The Panel considered that its ruling in point 1 above of breaches of Clauses 7.2 and 7.3 applied here. The Panel therefore ruled breaches of Clauses 7.2 and 7.3 of the Code.

With regard to the claim that Zanidip had a tolerability profile comparable with placebo, the Panel noted that this had not been the subject of complaint in the previous case, Case AUTH/1061/8/00. A complaint had been made about the data depicted beneath the claim but not about the claim itself.

The data referred to in the previous complaint was a clinical safety report for lercanidipine based on data from 20 placebo controlled comparative studies. A total of 1316 patients received lercanidipine during the studies with 86% receiving the 10mg dose. A total of 227 patients received placebo. 156 (12%) patients on lercanidipine reported at least one adverse event compared with 16 (7%) of patients on placebo. The total numbers of adverse events reported were 277 for lercanidipine (mean 1.8 per patient) and 21 for placebo (mean 1.3 per patient). Overall 75% of the adverse events for lercanidipine were mild to moderate. For the 10mg dose the percentage of mild to moderate adverse events was the same as placebo (81%).

The Panel noted Napp's submission that the overall incidence of adverse events in the ELYPSE study at 7.6% was close to the incidence of adverse events of 7% for patients on placebo in the global analysis. No statistical analysis appeared to have been undertaken on any of the adverse event data.

On balance the Panel considered that given the data the comparability claim was not unreasonable. The Panel therefore ruled no breach of Clause 7.2 of the Code in this regard.

3 Claim '… type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts'

COMPLAINT

The complainant alleged that this claim was again misleading, inaccurate and potentially dangerous. To date there had been no clinical trials designed to compare the response (blood pressure lowering as a surrogate end-point, or clinical outcome end-points) in diabetic and non-diabetic hypertensive patients, treated with any antihypertensive. The sole reference was to an abstract, not published in a peer reviewed journal, relating to a retrospective sub-group analysis of the Syst-Eur study; this was a placebo controlled study of nitrendipine (not lercanidipine), the design of which did not allow sufficient statistical power for this sub-group analysis. Applying this sort of improper ad hoc analysis to the data from the same abstract could be used to support the view that diabetics responded less favourably to calcium channel blocker treatment (–8.6/3.9mmHg) than their non-diabetic counterparts (–10.3/–4.6mmHg).

RESPONSE

Napp stated that this had been partially dealt with in its response to point 1 above.

This complaint was centred on the assumption that the abstract concerned was not published in a peer-reviewed journal. This was not so. This paper had statistically analysed the population of diabetic hypertensives and found a statistically significant difference in cardiovascular end-points between this group and that of non-diabetic hypertensive patients. Given that this was published in one of the leading peer-reviewed journals, and was itself a ground breaking paper, Napp was surprised the complainant was unaware of its existence.

In summary Napp believed that the advertisement was not in breach of Clauses 7.2, 7.3 or 7.7 of the Code, but simply reflected available data for lercanidipine and promoted the advice of Government and national guidelines with regard to this very important sub-set of hypertensive patients.

PANEL RULING

The Panel noted that the statement was referenced to a post hoc analysis of the Syst-Eur data which looked at the diabetic sub-group of patients. The Syst-Eur study had compared nitrendipine (with the possible addition or substitution of enalapril or hydrochlorothiazide or both) with placebo.

The Panel noted its comments in point 1 above and again considered that in the context of an advertisement for Zanidip the claim 'type II diabetics respond better to antihypertensive therapy than their non-diabetic counterparts' would be seen as a specific claim for the product; it would not be seen as a general statement about the response to therapy by diabetic hypertensives.

The study included 4695 patients 492 had diabetes mellitus 240 received placebo and 252 received active treatment. The Panel noted that the study had been

published in a peer reviewed journal – The New England Journal of Medicine. The claim, however, was referenced to a sub-group analysis of the Syst-Eur data which appeared as an abstract in the proceedings of a European Conference.

The Panel was concerned that the data to support the claim involved the use of nitrendipine and not Zanidip. The Panel noted that 43% of the diabetics in the trial received additional treatment with enalapril or hydrochlorothiazide or both products.

Readers would assume that there was data for Zanidip comparing diabetic and non-diabetic patients. This was not so. The claim was misleading and a breach of Clause 7.2 of the Code was ruled.

4 General comments

COMPLAINT

The complainant believed that the advertisement contravened the Code and regarded certain aspects as reckless and without foundation. Cardiovascular disease remained the leading global cause of death, and treatment of hypertension would undoubtedly go some way to alleviating this burden. With the ever-increasing number of antihypertensive drugs available it was more important than ever to select those that had demonstrated not only safety and tolerability, but also the ability to reduce long-term consequences of hypertension. Lercanidipine appeared to be acceptably safe, tolerable and effective in blood pressure reduction. However, the promotional message made claims beyond this, which were not only misleading and inaccurate, but also potentially dangerous.

RESPONSE

Napp stated that the Authority had asked it to consider Clauses 2 and 9.1 of the Code. Napp could not see anything in the advertisement which would demean the professional standing of the readership, undermine the special nature of medicines, or cause offence. Napp did not believe there was a breach of Clause 9.1. As the advertisement merely promoted available safety experience for lercanidipine and an important message shared by the UK Government in conjunction with the major opinion leaders, Napp believed that the advertisement could not either being discredit upon or reduce confidence in the pharmaceutical industry. Thus there was no breach of Clause 2.

PANEL RULING

The Panel considered that Napp had failed to maintain a high standard. A breach of Clause 9.1 of the Code was ruled.

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

Complaint received **14 November 2000**

Case completed **25 January 2001**

CASE AUTH/1104/11/00

PRIMARY CARE GROUP HEAD OF PRESCRIBING v ASTRAZENECA

Conduct of representative

The head of prescribing at a primary care group (PCG) alleged that an AstraZeneca representative had been misinforming practices that it was PCG policy, as agreed by the complainant, that patients taking 20mg of Losec (omeprazole) should be switched to 20mg of Nexium (esomeprazole). Losec and Nexium were both AstraZeneca products.

The Panel noted that a general practitioner present at a meeting of the PCG had told the representative that the complainant was recommending the use of Nexium for patients on high dose (20mg) Losec. AstraZeneca had stated that the representative did not interpret this information as PCG policy. The Panel noted, however, that when subsequently asked by another general practitioner what the PCG thought of Nexium, the representative had mentioned the complainant by name and stated that he had no objection to GPs looking at patients on high dose Losec with a view to placing them on Nexium if appropriate. In the Panel's view, the complainant's opinion on such matters would be considered by local general practitioners as likely to represent official PCG policy. In this regard the Panel assumed that the second general practitioner had gained such an impression and discussed it with the complainant as he said he would. The Panel considered that the representative had not sufficiently qualified her response to the second general practitioner and it was misleading in this regard. A breach of the Code was ruled.

COMPLAINT

The head of prescribing at a primary care group (PCG) complained that a representative from AstraZeneca UK Limited had been misinforming

practices that it was the PCG's policy, as agreed by the complainant, that patients taking 20mg of Losec (omeprazole) should be switched to 20mg of Nexium (esomeprazole). Losec and Nexium were both AstraZeneca products.

This was not the PCG's policy and at no time had the complainant ever discussed it with an AstraZeneca representative.

RESPONSE

AstraZeneca stated that the representative categorically denied that she had informed any general practitioner that it was the PCG's policy, as agreed by the complainant, that patients taking Losec 20mg should be switched to Nexium 20mg.

On 31 October, AstraZeneca sponsored a meeting for the PCG which was attended by the representative and one of her AstraZeneca colleagues. At this meeting, one of the general practitioners present informed the representative and her colleague that the complainant was recommending the use of Nexium for patients on high dose (20mg) Losec. The representative did not interpret this information as being PCG policy. Had it been PCG policy, she would have been informed of this by her other AstraZeneca colleagues whose duties included calling on prescribing advisors such as the complainant.

The representative did not discuss this information with any of the doctors present at that meeting. Since the meeting, she had had interviews with seven general practitioners within the PCG and, to the best of her knowledge, she could recall only one discussing the subject of PCG policy on Nexium.

The representative visited that doctor at his surgery in November and, during the course of her interview with him, the doctor asked her what the PCG thought of Nexium. The representative replied that, to the best of her knowledge, the complainant had no objection to general practitioners looking at patients on high dose Losec with a view to placing them on Nexium if appropriate. At no time did the representative state that this was PCG policy as she was not aware of there being a policy on the prescribing of proton pump inhibitors from the PCG and, therefore, could not give an opinion on the matter. At the end of the interview, the doctor stated that he would be seeing the complainant in three day's time and would discuss the matter with him then. The representative was convinced that the statements she made in her interview with the doctor could not, in any way, have been interpreted as representing a statement of the PCG's policy.

It was, perhaps, worth stating that the representative was well known to doctors in the area and consequently was often associated, by name, with matters relating to Losec and Nexium. It was conceivable that comments made elsewhere had been wrongly attributed to her. Any additional information on how this perceived statement of policy came to the notice of the complainant would be helpful in investigating the matter further.

AstraZeneca had no reason to believe that the representative had, in any way, misled doctors on matters of the PCG's policy and nor did AstraZeneca have any reason to believe that she had at all times maintained anything other than a high standard of ethical conduct in the discharge of her duties. AstraZeneca did not accept that there had been any breach of Clauses 7.2 or 15.2.

The representative was both shocked and surprised that this complaint had been brought against her and she shared AstraZeneca's concern and the hope that the matter would be resolved satisfactorily as soon as possible.

PANEL RULING

The Panel noted that a general practitioner present at a meeting of the PCG had told the representative that the complainant was recommending the use of Nexium for patients on high dose (20mg) Losec. AstraZeneca stated that the representative did not interpret this information as PCG policy. The Panel noted, however, that when subsequently asked by another general practitioner what the PCG thought of Nexium, the representative had mentioned the complainant by name and stated that he had no objection to GPs looking at patients on high dose Losec with a view to placing them on Nexium if appropriate. In the Panel's view the complainant's opinion on such matters would be considered by local general practitioners as likely to represent official PCG policy. In this regard the Panel assumed that the second general practitioner had gained such an impression and discussed it with the complainant as he said he would. The Panel considered that the representative had not sufficiently qualified her response to the second general practitioner and it was misleading in this regard. A breach of Clause 15.2 was ruled. The Panel considered this ruling covered the alleged breach of Clause 7.2.

Complaint received	**22 November 2000**
Case completed	**18 January 2001**

CASE AUTH/1111/12/00

ALLERGAN v PHARMACIA

Promotion of Xalatan

Allergan complained about a promotional item for Xalatan (latanoprost) issued by Pharmacia which was headed 'Xalatan – 1st choice monotherapy*'. The asterisk related to the statement beneath it 'when patients are intolerant or insufficiently responsive to ß-blockers'.

Referring to the strapline 'Xalatan – 1st choice monotherapy*', Allergan stated that Pharmacia had said that it intended this to mean that Xalatan was the most commonly prescribed monotherapy, based on IMS data. Allergan accepted that this was accurate. However, unless the strapline was clearly and prominently referenced to IMS data and not associated in any way with efficacy data, it constituted an exaggerated claim. In addition, the strapline appeared immediately above a graph showing the effect of Xalatan on intraocular pressure (IOP). This gave the misleading impression that Xalatan was 'first choice' for reasons beyond frequency of prescribing and therefore constituted an exaggerated claim. The strapline was followed by an asterisk, which did not appear to relate to any other statement in the piece. In Allergan's view, however, even if there were an asterisked statement, this would not be sufficient to correct the misleading impression.

The Panel noted that Xalatan was indicated to reduce elevated IOP in patients with open angle glaucoma and ocular hypertension who were intolerant or insufficiently responsive to another IOP lowering medication. The claim 'Xalatan – 1st choice monotherapy' was followed by an asterisk which referred the reader to a statement beneath the claim 'when patients are intolerant or insufficiently responsive to ß-blockers'. Allergan was incorrect in stating that there was no statement linked to the asterisk. The claim appeared above a graph which showed the reduction in morning IOP, from untreated baseline, using Xalatan monotherapy over two years. The data to support the claim at issue was based on the number of prescriptions but this was not made clear. The qualification was not acceptable. It was not appropriate to correct a misleading impression by use of a footnote and in any event the explanation was not sufficient. The Panel considered that the claim was exaggerated as it implied more than that after beta-blockers Xalatan was, based on usage, the medicine most often prescribed to reduce IOP pressure. The claim appeared above a graph depicting efficacy from an untreated baseline. Some readers might assume that the claim meant that Xalatan was the first choice first line therapy whereas it was a second line therapy when patients were intolerant or insufficiently responsive to other medication. A breach of the Code was ruled.

Allergan Ltd complained about a promotional item for Xalatan (latanoprost) issued by Pharmacia Limited. The item (ref P5306 390-0092) took the form of a folded up card which could be opened up to reveal a Calotherm impregnated lenscloth. The front of the item was headed 'Xalatan – 1st choice monotherapy*'. The asterisk related to the statement beneath it 'when patients are intolerant or insufficiently responsive to ß-blockers'. The item in question had been used by representatives following individual calls or at promotional meetings.

COMPLAINT

Allergan stated that its complaint related to the use of the strapline 'Xalatan – 1st choice monotherapy'. In previous discussion, Pharmacia had stated that it intended this strapline to mean only that Xalatan was the most commonly prescribed monotherapy, based on IMS data. Allergan accepted that this was accurate. However, it considered that unless the strapline was clearly and prominently referenced to IMS data and not associated in any way with efficacy data, it constituted an exaggerated claim.

In the promotional piece at issue, no reference was made to IMS data. In addition, the strapline appeared immediately above a graph showing the effect of Xalatan on intraocular pressure (IOP). This gave the misleading impression that Xalatan was 'first choice' for reasons beyond frequency of prescribing and therefore constituted an exaggerated claim. Allergan alleged a breach of Clause 7.8 of the Code.

The strapline was followed by an asterisk, which did not appear to relate to any other statement in the piece. In Allergan's view, however, even if there were an asterisked statement, this would not be sufficient to correct the misleading impression. It had been ruled on several previous occasions that a footnote could not correct an otherwise misleading impression.

RESPONSE

Pharmacia stated that it was both surprised and disappointed to receive this complaint. Pharmacia had had several communications with Allergan during the year to agree a mutually acceptable way to reference the strap line, 'Xalatan 1st choice monotherapy', and had agreed that '1st choice monotherapy' would not be used as a strap line against any comparative efficacy data showing Xalatan in relation to beta-blockers. As a result of this, a leavepiece (P5307 390-0091), a copy of which was provided, was withdrawn in September 2000. Secondly, Pharmacia had also agreed to include the reference to the DIN-LINK data. Allergan had indicated that it was happy with this adjustment and the reference had been added to all new materials on reprint. Pharmacia had also informed Allergan that the item in question in this case would be reproduced with the reference added. Indeed, the item was no longer in use.

To re-state Pharmacia's case, it was an accepted fact that Xalatan was the first choice anti-glaucoma medicine when patients were intolerant to beta-blockers. Pharmacia provided the DIN-LINK data which showed usage across all prescribed anti-glaucoma products on the UK market. 47,470 patients were on monotherapy (calculated from 38.5% of 123,300). This figure exceeded any other product excluding beta-blockers.

Pharmacia therefore submitted that there was no breach of Clause 7.8 of the Code.

PANEL RULING

The Panel noted that Xalatan was indicated to reduce elevated IOP in patients with open angle glaucoma and ocular hypertension who were intolerant or insufficiently responsive to another IOP lowering medication.

The Panel noted that the claim 'Xalatan – 1st choice monotherapy' was followed by an asterisk which referred the reader to a statement beneath the claim 'when patients are intolerant or insufficiently responsive to ß-blockers'. The Panel noted that Allergan was incorrect in stating that there was no statement linked to the asterisk. The claim appeared above a graph which showed the reduction in morning IOP, from untreated baseline, using Xalatan monotherapy over two years.

The Panel noted that the data to support the claim at issue was based on the number of prescriptions. This was not made clear. The Panel considered that the qualification was not acceptable. It was not appropriate to correct a misleading impression by use of a footnote and in any event the explanation was not sufficient. The Panel considered that the claim was exaggerated as it implied more than that after beta-blockers Xalatan was, based on usage, the medicine most often prescribed to reduce IOP pressure. The claim appeared above a graph depicting efficacy from an untreated baseline. Some readers might assume that the claim meant that Xalatan was the first choice first line therapy whereas it was a second line therapy when patients were intolerant or insufficiently responsive to other medication. The Panel ruled a breach of Clause 7.8 of the Code.

The Panel queried whether the promotional aid, a Calotherm impregnated lenscloth, met the requirements of Clause 18.1 of the Code in that the relevance to the practice of medicine might be questionable. The Panel requested that its concerns be drawn to the attention of Pharmacia.

Complaint received **4 December 2000**

Case completed **31 January 2001**

CASES AUTH/1112/12/00 and AUTH/1113/12/00 *NO BREACH OF THE CODE*

NURSE v PFIZER and SEARLE

Meeting in St Andrews

A nurse complained about a meeting held by Pfizer and Searle at The Old Course Hotel, St Andrews. The complainant was concerned that the meeting was only for prescribers and not for others interested in arthritis care, such as nurses, and that the level of hospitality was not appropriate, the meeting being held at a five star hotel. Searle had become part of Pharmacia which responded on its behalf.

The Panel considered that it was not necessarily a breach of the Code for companies to hold meetings which were not open to all health professionals. It was for the company or companies to decide who to invite to their meetings. The Panel noted that there was a discrepancy between the responses. Pfizer had stated that nurses with an interest in arthritis would be welcome to attend whereas Pharmacia had stated that groups other than doctors and pharmacists would not be well served by the meeting. Nevertheless the Panel considered that it was acceptable to limit the meeting in question to doctors and pharmacists. There was no requirement to invite nurses to such meetings. No breach of the Code was ruled.

The Panel noted that the Code required that hospitality be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed that level which the recipients would normally adopt when paying for themselves. The cost per attendee was just over £40. The Panel considered that the level of hospitality, although on the limits of acceptability, was, on balance, not unreasonable. The Panel therefore ruled no breach of the Code.

A nurse complained by telephone about a meeting organised by Pfizer Limited and Searle at The Old Course Hotel, St Andrews.

COMPLAINT

The complainant had two concerns. Firstly, that the meeting was restricted only to prescribers and was not for others interested in the area of arthritis care, such as nurses. Secondly, that the level of hospitality was not appropriate, the meeting being held at a five star hotel.

When writing to Pfizer and Searle, the Authority drew attention to Clauses 2, 9.1 and 19.1 of the Code.

Searle had become part of Pharmacia Limited which responded to the complaint on behalf of Searle.

RESPONSE FROM PFIZER

Pfizer stated that the subject of the meeting held at The Old Course Hotel, St Andrews, was 'Rheumatic Diseases and the way Forward', part of a series of speaker meetings organised and funded by Searle and Pfizer on the subject of osteoarthritis and rheumatoid arthritis. Pfizer and Searle (now part of Pharmacia Limited) co-promoted the product Celebrex (celecoxib) which was indicated for the symptomatic treatment of these conditions. A copy of the invitation/agenda was provided. The speaker was a consultant rheumatologist and the chairperson was a local general practitioner. The speaker gave a

presentation on the burden of arthritis and the current and future management of osteoarthritis and rheumatoid arthritis, including discussions of three case scenarios. PGEA for one and a half hours was applied for and, in fact, two hours were awarded. Twenty-three healthcare professional delegates were expected but, in the event, 17 attended. These were 14 general practitioners, 2 practice pharmacists and one hospital consultant. Three representatives from the companies attended also. No promotional materials were displayed in the meeting room.

Pfizer submitted that the venue, whilst famous, was not lavish. The hotel was frequently used by other pharmaceutical companies because it was suitable in terms of size, conference/meetings facilities and geographical location. It was within easy reach of GPs in the Dundee and East Neuk area, who were the audience invited by local Pfizer and Searle representatives. The only suitable alternative venue in the area was the Hilton in Dundee, which was rejected in this instance as being more expensive than The Old Course Hotel in St Andrews.

The hospitality offered to the delegates comprised soft drinks and tea and coffee on arrival and dinner after the presentation and discussion ended. The cost of the meeting was set out in the response from Pharmacia.

Pfizer stated that the meeting was restricted to healthcare professionals in accordance with the Code and nurses were not excluded.

RESPONSE FROM PHARMACIA

Pharmacia stated that the meeting convened at 7-10pm, with dinner arranged for 9pm. The educational content of the meeting was clear.

The concerns were twofold and Pharmacia addressed each in turn.

1 The meeting was restricted only to prescribers with invites not issued to others such as nurses interested in the treatment of arthritis

The content of the meeting was structured primarily towards the clinical needs and interests of GPs. Pharmacia fully appreciated the role of other health professionals in the treatment of arthritis and indeed two pharmacists did attend the meeting. It was considered though at the time the meeting was arranged that other professional groups would not be well served by the proposed format of this particular meeting and invitations were thus not issued. The company submitted that this was in line with the spirit of Clause 9.1 of the Code.

2 The level of hospitality was inappropriate

The breakdown of costs for the event was: room hire costs, £205; food/drink supplied at the time of the meeting itself, £66; cost of 26 set price dinners (previously agreed based on proposed attendees), £742.75; cost of beverages supplied at dinner, £172.50; giving a total of £1,186.25. At such, the cost per intended attendee, including the cost of room hire was £45.63. The cost per intended attendee, excluding room hire, was £37.74 (£981.25 ÷ 26).

Pharmacia contended, in line with the Code, that the hospitality was secondary to the purpose of the meeting, appropriate and not out of proportion to the occasion, and did not exceed the level which recipients would normally adopt if paying for themselves.

PANEL RULING

The Panel considered that it was not necessarily a breach of the Code for companies to hold meetings, which were not open to all health professionals. Companies had to ensure that meetings complied with the Code but it was for the company or companies to decide who to invite to their meetings. The Panel noted that there was a discrepancy between the responses. Pfizer stated that nurses with an interest in arthritis would be welcome to attend whereas Pharmacia stated that groups other than doctors and pharmacists would not be well served by the meeting. Nevertheless the Panel considered that it was acceptable to limit the meeting in question to doctors and pharmacists. There was no requirement to invite nurses to such meetings. No breach of Clause 9.1 of the Code was ruled.

The Panel noted that Clause 19.1 of the Code required that hospitality be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed that level which the recipients would normally adopt when paying for themselves.

The Panel considered that the cost per attendee was just over £40 (dinner plus drinks before and during dinner) and not £37.74 as submitted by Pharmacia. In the Panel's view the cost of the drinks etc had to be divided by the number attending (20) and not the intended number (26). The Panel considered that the level of hospitality, although on the limits of acceptability, was, on balance, not unreasonable and did not exceed the level which the recipients would normally adopt when paying for themselves. The Panel therefore ruled no breach of Clause 19.1 of the Code. In the circumstances there was no breach of Clause 2 of the Code and the Panel ruled accordingly.

Complaint received **6 December 2000**

Case completed **1 February 2001**

CODE OF PRACTICE REVIEW – FEBRUARY 2001

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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1061/8/00	**Bayer v Napp**	**Zanidip detail aid**	**Breach Clause 3.2 Nine breaches Clause 7.2 Breach Clause 7.8**	**Appeal by respondent**	**Page 35**
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1066/8/00	Bristol-Myers Squibb v Glaxo Wellcome	Combivir leavepiece	No breach	Appeal by respondent	Page 61
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1078/9/00	**General Practitioner v Allen & Hanburys**	**'Dear Doctor' letter and reply paid card about the Accuhaler**	**Three breaches Clause 7.2**	**No appeal**	**Page 93**

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1080/9/00	**Wyeth v AstraZeneca**	**Promotion of Nexium**	**Three breaches Clause 7.2 Breaches Clauses 7.3 & 7.8**	**No appeal**	**Page 100**
1081/10/00	Consultant Physician v Pfizer	Radio advertisement	No breach	No appeal	Page 109
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1098/11/00	**Pharmaceutical Adviser v Wyeth**	**Arrangements for a meeting**	**Breach Clause 19.3**	**No appeal**	**Page 149**
1099/11/00	**Medicines Information Pharmacist v Trinity**	**Provision of Brexidol samples**	**Breach Clause 17.8**	**No appeal**	**Page 150**
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PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply 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 in connection therewith
- the provision of information to the general public either directly or indirectly
- 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).