PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW
NUMBER 26 NOVEMBER 1999

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.

Provision of medical and educational goods and services

At the suggestion of the Code of Practice Appeal Board and with the support of the ABPI Board of Management, a working party established by the Authority has reviewed the provision of medical and educational goods and services by pharmaceutical companies in relation to the requirements of the Code. A number of cases relating to this area had exposed uncertainties. Guidance drafted by the working party has now been agreed, subject to some changes along the way, by the Appeal Board, the ABPI Board and the Medicines Control Agency, and is reproduced below in the hope and expectation that it will assist companies in this difficult area.

Pharmaceutical companies operate in a commercial environment and it could be argued that everything a pharmaceutical company does is for a commercial purpose. There is however a difference between the promotion of a company and the promotion of specific products. Clause 18.1, Gifts and Inducements, and the supplementary information to Clause 18.1, Provision of Medical and Educational Goods and Services, set out that difference. The promotion of specific medicines must be completely separate from the provision of medical and educational goods and services in order to comply with the Code. The Code prohibits the offering or giving of any gift, benefit in kind or pecuniary advantage to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer or buy any medicine. Promotional aids within the parameters of Clause 18.2 are permitted. The requirements of the Code reflect the provisions of The Medicines (Advertising) Regulations 1994, as amended.

The pharmaceutical industry already offers numerous goods and services to enhance patient care and benefit the NHS. These include facilitating audits, sponsorship of posts in health authorities/trusts etc, provision of specialist nurses, provision of equipment, provision of diagnostic kits/services and the supply of textbooks. Such activities can be acceptable. Pharmaceutical companies must ensure that their arrangements comply with all relevant requirements of the Code. The industry also receives requests for various goods and services from its customers.

In the event of a complaint each case would be judged on its own merits. The following guidance is to assist companies in relation to the requirements of Clause 18.1 of the Code.

1 (i) The role of medical/generic representatives in relation to the provision of goods and services supplied in accordance with the supplementary information to Clause 18.1 needs to be in accordance with the principles set out below. In this context companies should consider using staff other than medical/generic representatives.

(ii) If medical/generic representatives provide, deliver or demonstrate medical and educational goods and services then this must not be linked in any way to the promotion of products.

(iii) The acceptability of the role of medical/generic representatives will depend on the nature of the goods and services provided and the method of provision.

(iv) The nature of the service provider, the person associated with the provision of medical and educational goods and services, is important ie is the service provider a medical/generic representative or is the service provider some other appropriately qualified person, such as a sponsored registered nurse? If the goods and services require patient contact, for example, either directly or by identification of patients from patient records and the like, then medical/generic representatives must not be involved. Only an appropriately qualified person, for example a sponsored registered nurse, not employed as a medical/generic representative, may undertake activities relating to patient contact and/or patient identification. Medical/generic representatives could provide administrative support in relation to the provision of a screening service, but must not be present during the actual screening and must not discuss or help interpret individual clinical findings.

(v) Neither the company nor its medical/generic representatives may be given access to data/records that could identify, or could be linked to, particular patients.

(vi) Sponsored health professionals should not be involved in the promotion of specific products. Registered nurses, midwives and health visitors are required to comply with the United Kingdom Central Council for Nursing, Midwifery and Health Visiting Code of Professional Conduct. This Code requires, *inter alia*, that registration status is not used in the promotion of commercial products or services.

2 The remuneration of those not employed as medical/generic representatives but who are sponsored or employed as service providers in relation to the provision of medical and educational goods and services must not be linked to sales in any particular territory or place or to sales of a specific product or products and, in particular, may not include a bonus scheme linked to such sales. Bonus schemes linked to a company's overall national performance, or to the level of service provided, may be acceptable.

3 Companies must ensure that patient confidentiality is maintained at all times and that data protection legislation is complied with.

4 Service providers must operate to detailed written instructions provided by the company. It is recommended that these should be similar to the briefing material for representatives as referred to in Clause 15.9 of the Code. The written instructions should set out the role of the service provider and should cover patient confidentiality issues. Instructions on how the recipients are to be informed etc should be included. The written instructions must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code.

5 Service providers must abide by the principle set out in Clause 15.5 of the Code that in an interview, or when seeking an appointment, reasonable steps must be taken to ensure that they do not mislead as to their identity or that of the company they represent.

6 A recipient of a service must be provided with a written protocol to avoid misunderstandings as to what the recipient has agreed. The identity of the sponsoring pharmaceutical company must be given. For example, a general practitioner allowing a sponsored registered nurse access to patient records should be informed in writing of any data to be extracted and the use to which those data will be put.

7 Any printed material designed for use in relation to the provision of medical and educational goods and services must be non-promotional. It is not acceptable for such materials to promote the prescription, supply, sale or administration of the sponsoring company's medicines. Nor is it acceptable for materials to criticise competitor products as this might be seen as promotional. All printed materials must identify the sponsoring pharmaceutical company.

8 Materials relating to the provision of medical and educational goods and services, such as internal instructions, external instructions, the written protocol for recipients and printed material etc, must be examined by the Code of Practice signatories within companies to ensure that the requirements of the Code are met as recommended in the supplementary information to Clause 14.1 of the Code. A copy of the materials must be made available to the Prescription Medicines Code of Practice Authority on request.

9 Companies are recommended to inform relevant parties such as NHS trusts, health authorities, health boards and commissioning groups of their activities where appropriate. This is particularly recommended where companies are proposing to provide medical and educational goods and services which would have budgetary implications for the parties involved. For example the provision of a screening service for a limited period might mean that funds would have to be found in the future when company sponsorship stopped. Another example might be the provision of diagnostic or laboratory services and the like, which the NHS trust, health authority, health board or commissioning group would normally be expected to provide.

Mr Philip Cox QC retires

Mr Philip Cox QC retired as Chairman of the Code of Practice Appeal Board at the end of October but will continue to attend meetings until the end of the year. Mr Cox was appointed Chairman of the then Code of Practice Committee in 1978. The Authority and the ABPI are extremely grateful to Mr Cox whose contribution to the success of self-regulation over the years cannot be overestimated. He has been a wise, thoughtful and capable Chairman. Our best wishes go to him for a long and happy retirement.

New Appeal Board Chairman welcomed

Mr Cox's successor as Chairman of the Code of Practice Appeal Board is Mr James Hunt QC. Mr Hunt was leader of the Midland and Oxford Circuit and a member of the General Council of the Bar. He is legal assessor to the Royal College of Veterinary Surgeons. His experience of crime includes acting for the defence in Matrix Churchill, 1992, and Beverley Allit, 1993. He has experience in personal injury and professional negligence cases. Mr Hunt is a worthy successor to Mr Cox and the Authority looks forward to working with him.

New independent member of the Appeal Board

Dr Joy Edelman has been appointed to the Code of Practice Appeal Board as an independent medical member and is welcomed by the Authority. Dr Edelman is a consultant cardiologist who has recently retired from her full time position. She is a member of the BMA Council.

The vacancy now filled by Dr Edelman arose due to the death at the beginning of the year of Dr Brian Lewis who was one of the first two independent medical members appointed to the then Code of Practice Committee in 1978.

MCA guidance note published

The Medicines Control Agency has now published 'Advertising and Promotion of Medicines in the UK' (Guidance Note No.23, ISBN 0-11-702438-4).

Copies can be obtained from the Stationery Office, price £15.

The full text can also be found on the Internet at https://www.the-stationery-office.co.uk/mca/gnotes/medic.htm

To access the site user name: adpromuk and password: wckyabt are required.

Company not complying

As will be seen from the report on Case AUTH/801/11/98 at page 21 in this issue of the Review, Eastern Pharmaceuticals Ltd which, according to the Authority's records, had agreed in 1994 to comply with the Code and accept the jurisdiction of the Authority, though the Company disputed this, declined to give the requisite undertaking and assurance in acceptance of rulings of breaches of the Code The company did indicate, however, that it would change its procedures so as to conform with the Code.

The case in question, which involved the supply of unsolicited samples through the post without a signed order being obtained, was reported to the Code of Practice Appeal Board and then on to the ABPI Board of Management. The ABPI Board decided that the Authority should remove Eastern from the list of companies which had agreed to comply with the Code and advise the Medicines Control Agency (MCA) that responsibility for the company under the Code could no longer continue to be accepted. Any complaints about Eastern which may be received in the future will be passed to the MCA for it to take such action as it sees fit.

Complying with the Code and accepting the jurisdiction of the Authority are obligatory for ABPI member companies and in addition more than seventy non members of the ABPI have agreed to do so. Nearly the entirety of the prescription medicines industry thus supports the Code.

Representative examinations should be taken early

The appropriate ABPI examination has to be passed by medical representatives and generic sales representatives before two years in such employment have elapsed.

Companies are reminded that representatives should normally be entered for the appropriate examination during their first year of employment. This will help to avoid the problems which sometimes arise when representatives do not take the examination for the first time until their second year and then fail to pass or are unable to attend for the examination for some reason.

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, 14 January

Monday, 28 February

Friday, 10 March

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

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

Answers to specific questions

Clause 1.2 of the Code excludes from its requirements replies made in response to individual enquiries or comments from health professionals, but only if the replies relate solely to the subject matter of the enquiry or comment, are accurate and do not mislead and are not promotional in nature.

It should be noted that this limited exception applies not only to letters and telephone calls but also to e-mail. Companies should retain copies of such e-mail enquiries and of their replies to them.

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/796/11/98

LILLY v LUNDBECK

Promotion of Cipramil

Lilly complained about the promotion of Cipramil (citalopram) by Lundbeck, referring to six promotional items. Citalopram was a selective serotonin re-uptake inhibitor (SSRI) for the treatment of depressive illness and panic disorder. Lilly marketed fluoxetine (Prozac) which was also an SSRI.

Lilly alleged that the claim 'Cipramil – the most selective SSRI' in a clinical compendium was a hanging comparison and did not describe the way in which it was 'most selective'. It was unclear what clinical benefit derived from such selectivity. The Panel noted that a hanging comparison was a phrase whereby a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared and considered that the phrase in question was not a hanging comparison. The summary of product characteristics (SPC) for Cipramil stated that it was the most selective serotonin re-uptake inhibitor yet described with no or minimal effect on noradrenaline, dopamine and gamma aminobutyric acid uptake. The SPC also stated that it had a low potential for clinically relevant interactions. A series of five SSRIs, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline had been characterized in a study with regard to their selectivity for 5-HT uptake. Citalopram had been shown to be the most selective 5-HT re-uptake inhibitor whilst paroxetine was the most potent. The Panel considered that the claim was not misleading as alleged and ruled no breach of the Code. Upon appeal by Lilly, the Appeal Board noted that the Cipramil SPC stated that it was the most selective serotonin re-uptake inhibitor yet described. The Appeal Board also noted the submission by Lilly that in studies where Cipramil had been compared with other SSRIs there was no evidence that there were significant differences in the reported adverse events which negated the theoretical application on which the claim that Cipramil was the most selective SSRI was made. However, given the SPC and the data, the Appeal Board considered that the claim at issue was not misleading as alleged and upheld the Panel's ruling of no breach of the Code.

A bar chart on a page headed '… proven efficacy in severe major depression' detailed the results of a study comparing the efficacy of citalopram with placebo in severe major depression. At baseline citalopram treated patients had a mean Hamilton Depression Rating Scale (HAMD) of 24 which was reduced to 18.8 at week 1. Beneath the bar chart was the claim 'Effective from week 1'. Lilly alleged that it was misleading as the dose of citalopram was not given, it was not explained by what criteria efficacy from week 1 was measured and a fall in HAMD score from 24 to 18 did not imply efficacy. The Panel considered that the study demonstrated that Cipramil exerted an effect measurable on the HAMD scale from week 1 but did not accept that the claim implied efficacy in terms of a full response from week 1. The Panel noted, however, that the dose of Cipramil used in the study was higher than that recommended in the SPC. Most readers would assume that Cipramil had been used at its licensed dose which was not so. The failure to give dosage details was misleading and a breach of the Code was ruled.

Lilly stated that the implication of a section headed 'Comparison of onset of action' was that half life determined 'onset of action' by a delay in reaching steady state concentrations. This was not the case and it was therefore misleading. The Cipramil SPC stated that 'there is no clear relationship between citalopram plasma levels and therapeutic response or side effects'. The Panel noted Lundbeck's submission that a certain threshold plasma concentration was required before sufficient serotonin re-uptake inhibition occurred at the pre-synaptic neurone. The Panel considered that half life and time to steady state concentration were relevant data in relation to onset of action. The Panel did not accept that this page gave the impression that half life was the sole determinant of onset of action, did not accept that the page was misleading as alleged and ruled no breach of the Code.

A page headed 'Cipramil 20mg versus fluoxetine 20mg' featured a bar chart which compared the percentage of severely depressed patients with a 50% reduction in the Montgomery-Ashberg Depression Rating Scale (MADRS) score after two weeks and which showed a statistically significant reduction in favour of Cipramil. Lilly alleged that the presentation of the data was misleading. The Panel noted that the mean baseline score was 29.7 for the citalopram treated group and 29.4 for the fluoxetine treated group. The paper involved gave clear details of the statistical analysis and the reasons for patients withdrawing from the study. The Panel considered that overall the study substantiated the claim that Cipramil had a significantly faster early onset of action than fluoxetine 20mg and ruled no breach of the Code. Upon appeal by Lilly, the Appeal Board noted that the study showed a reduction of MADRS mean total scores in both treatment groups with no statistically significant differences between treatments. Citalopram showed an earlier onset of recovery than fluoxetine. The Appeal Board noted that the efficacy analyses were based on an efficacy population as opposed to an intention-to-treat population and the claim 'Cipramil 20mg had a significantly faster early onset of action than fluoxetine' was based upon this sub-group. The claim was clearly related to those patients with a 50% reduction in MADRS score after two weeks. On balance the Appeal Board considered that the presentation of the data was not misleading and upheld the Panel's ruling of no breach of the Code.

A number of allegations were made by Lilly about bullet points relating to side effects and to a section referring to Cipramil's cardiovascular effects. With regard to the claim 'No effect on weight' the Panel noted that in a section headed 'Undesirable effects' the Cipramil SPC stated that the adverse effects were in general mild and transient. Weight increase and decrease were listed in the SPC as adverse events reported in clinical trials with a frequency of

1-<5%. The Panel considered that given the statement in the SPC, the claim was misleading and a breach of the Code was ruled.

With regard to the claim 'No or minimal anticholinergic effects', the Panel noted that the examples of anticholinergic effects listed adjacent to the claim were dry mouth, blurred vision, constipation and urinary retention. According to the SPC, amongst the most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo treated patients was dry mouth, although its incidence in excess over placebo was low (<10%). Dry mouth and constipation were listed in the SPC as frequent adverse events reported in clinical trials with a frequency of 5-20%. Given the statements in the SPC the Panel considered the claim was misleading and a breach of the Code was ruled. Upon appeal by Lundbeck, the Appeal Board considered that the claim was misleading. It gave the impression that there would be no or minimal incidence of the adverse events listed and this was not consistent with the statements in the SPC. The Panel's ruling of a breach of the Code was upheld.

With regard to the claim 'Low level toxicity in LD50 testing', the Panel noted that the adjacent page was headed 'Cipramil – low level of toxicity in LD50 testing' and featured a graph which compared the oral LD50 in rats (mg/kg) of Cipramil, sertraline, fluoxetine and paroxetine. The Panel considered that it would be clear to the reader that lethal dose testing referred to animal work. The Panel noted the submission that data appeared to show a correlation between fatal toxicity index and LD50 suggesting relevance to the clinical setting although the data did not show it was of direct relevance. A breach of the Code was ruled. The phrase 'The cardiovascular safety of Cipramil has been documented…' was considered by the Panel to amount to a statement that Cipramil was safe from a cardiovascular point of view. The Panel considered that the use of this phrase together with the overall impression that there was no cardiovascular risk associated with Cipramil created a misleading impression about the safety of the product and a breach of the Code was ruled.

Under the heading 'Considering the options for treating a refractory patient' and a subheading 'Combination with another antidepressant' it was stated that 'Case reports and trials demonstrate a significant adverse interaction between SSRIs and TCAs with the probable exception of Cipramil'. Lilly alleged that this was potentially misleading. The Panel noted that the section referred to the probable exception of Cipramil and this was immediately followed by the claim 'All currently available SSRIs may cause an increase in the serum levels of concurrent TCAs'. There was little well-conducted research to support the combination. The Panel did not consider that the material was misleading as alleged and no breach of the Code was ruled.

The claim 'Cipramil – an effective and well tolerated treatment for depression associated with stroke and dementia' headed a page featuring the graphical results of two studies. Both graphs were alleged to be misleading. The Panel noted that the first graph and adjoining text featured the results of Anderson, Stroke (1994), but cited Anderson *et al* Acta Psychiatrica Scandinavica (1994). The Panel considered that the information was thus inaccurate and so ruled a breach of the Code. The second graph was labelled 'Depression in demented patients' but showed the mean Gottfrie-Brane-Steen (GBS) geriatric rating scale at baseline and after 4 weeks' treatment with Cipramil. The GBS scale assessed the level of dementia by measuring motor, intellectual and emotional impairment and six common dementia symptoms. The specific items of the GBS scale shown on the graph were emotional bluntness, confusion, irritability , depressed mood and restlessness. All were significantly reduced by Cipramil. In the Panel's view, despite the inclusion of 'Depressed mood,' the GBS scale was not designed to measure depression per se. The description of the study which accompanied the graph referred to 98 demented patients whereas the graph was relevant only to a sub-set of 27 patients with AD/SDAT treated with Cipramil. Overall the Panel considered that the presentation of the data gave the impression that depression was decreased in 98 patients treated with Cipramil whereas what the data actually showed was that dementia was decreased in 27 patients treated with Cipramil. Cipramil was not licensed for the treatment of dementia. The Panel considered that the data was confusing and ruled a breach of the Code.

Lilly alleged that on a page headed 'Why is selectivity important?' *in vitro* data was being extrapolated to the clinical setting, referring to the statement 'A highly selective antidepressant has the potential to target the depression and not the patient'. The Panel considered that it was neither stated nor implied that no side effects would occur. In the Panel's opinion the section attempted to explain the scientific theory behind selectivity. No breach of the Code was ruled.

In a detail aid under the heading 'Mood disorders: Common cause' reference was made to anxiety and panic and Lilly submitted that it was questionable whether psychiatrists would classify these as 'mood disorders'. In the opinion of the Panel 'mood' was used to indicate a class or group of disorders which might come within the licensed indication for the use of Cipramil. The Panel considered that the use of the term 'mood disorders' was not misleading in this context. The Panel ruled no breach of the Code.

Lilly alleged that it was unclear what convenient half life meant in a page in the detail aid which stated that one of the features of Cipramil was a convenient half life as opposed to a long half life for SSRIs. The Panel noted that the adjacent page featured a table which compared the pharmacokinetic parameters of four SSRIs. Paroxetine displayed the shortest half life at 24 hours and fluoxetine the longest at 132 hours. Cipramil had a half life of 36 hours. The Panel noted Lundbeck's submission that convenience referred to dosage requirements and the washout period. Whilst the Panel considered that further

explanation of the term might have been provided, it did not consider the term to be misleading and ruled no breach of the Code.

Other allegations in relation to the detail aid had been covered by earlier rulings.

In a mailer, beneath a sub-heading 'Cipramil: the most cost-effective SSRI', Cipramil was described as the least expensive SSRI. Lilly agreed that citalopram at 20mg a day was now the cheapest SSRI per tablet but disputed the claim that it was also therefore the most 'cost-effective SSRI'. What the promotional piece showed was that at the doses selected, irrespective of the relative clinical efficacy, it was less expensive than the other antidepressants highlighted. Lilly submitted that it was a cost-minimisation analysis, not a cost-effective analysis. Leaving aside the applicability of such a methodology to compare 'modern' antidepressants, this did not demonstrate relative cost-effectiveness. The costs were more than just the acquisition costs of the medicine and could include direct medical costs, medicine costs, days in hospital, nursing time, GP visits, concomitant medications, direct non-medical costs, carer time and indirect costs. The Panel considered that a reader would assume that the phrase cost-effectiveness did not merely refer to the acquisition cost of the medicine but included an evaluation of the resource cost implications of using a particular medicine and its effectiveness, including effects on a patient's health as a result of side effects. A cost-effectiveness analysis allowed one to incorporate both costs and differing degrees of effectiveness and compare them. Cost-minimisation analysis could be used when the alternative treatments being evaluated had identical health outcomes and the comparison could therefore be limited to analysing the costs. The Panel considered that given the study assumptions about health costs, probabilities and the similarities between efficacy, tolerability and side effect profiles noted by the study authors, the acquisition cost of the medicine was the significant variable in the calculation of the cost-effectiveness ratio. The Panel considered that it would have been helpful if the significance of the medicines acquisition cost in the calculation had been brought to the reader's attention. The Panel did not consider however that there was a breach of the Code as alleged and no breach was ruled.

Lilly alleged that the statement in the mailer 'When we realised that our future research projects can be financed with less revenue from product sales, we decided to pass the benefit on to you and your patients' was inappropriate. The Panel considered that this was a declaration of corporate intent and was not unacceptable. No breach of the Code was ruled.

Other allegations in relation to the mailer had been covered by earlier rulings. An allegation concerning a reply paid card sent with the mailer had been covered by an earlier case (AUTH/770/10/98).

An abbreviated advertisement featured the heading 'Cipramil: Makes a real difference to your prescribing costs' above a bar chart which compared the treatment cost per 28 days of stated doses of five marketed SSRIs. The text beneath and adjacent to the graph referred to 'the most selective and cost-effective SSRI'. Lilly alleged that this was not permitted in an abbreviated advertisement. The Panel noted that cost should not be included in abbreviated advertisements unless it was given as a reason why the medicine was recommended for the indication or indications referred to. The Panel considered that the advertisement was recommending Cipramil because it was the most cost-effective SSRI and thus the provision of comparative cost information did not render the advertisement in breach of the Code.

In another mailer, the claim '… Efficacy with the potential for cost savings' appeared above a table which compared the annual cost of treating 122 patients with stated doses of five SSRIs, one of which was Cipramil 20mg OD. For each of the other four SSRIs the annual saving if Cipramil had been administered was stated as were the number of additional patients who could be treated annually if this saving was spent on Cipramil. Lilly stated that the implication was that the average GP with a list of 2000 patients would have approximately 122 patients suffering from depression. The extrapolation was that if all patients were treated with citalopram then considerable costs savings could be made over the use of existing or other antidepressant treatment. This assumed a 100% response rate to citalopram and did not take into account individual patient differences with regard to severity of depression or previous response to other antidepressants and was therefore completely unrealistic. It also gave the impression that all antidepressants were equivalent at the doses stated. The Panel considered that there was a difference between the phrase 'Efficacy with the potential for cost savings' and 'cost-effectiveness', the latter phrase implied that a pharmacoeconomic evaluation had been undertaken, the former would be interpreted as referring to the acquisition cost of the medicine unless otherwise stated. The Panel noted that the data presented beneath the phrase in question and adjacent to it was based on the acquisition cost of each medicine at stated doses. The assumptions were clearly set out. The Panel ruled no breach of the Code.

Allegations in relation to a leavepiece and two further journal advertisements had been covered by earlier rulings.

Eli Lilly and Company Limited complained about the promotion of Cipramil (citalopram) by Lundbeck Ltd. Citalopram was a selective serotonin re-uptake inhibitor (SSRI) for the treatment of depressive illness and panic disorder. Lilly marketed fluoxetine (Prozac) which was also an SSRI for the treatment of depression.

A CLINICAL COMPENDIUM – 0998/CIP/525/152

The clinical compendium contained a summary of product information to support formulary applications. It was divided into 14 sub-sections dealing with issues such as onset of action,

tolerability, treating refractory depression, selectivity etc. Lundbeck stated it was issued to its sales force for use in discussions with general practitioners, psychiatrists and geriatricians.

1 Claim 'Cipramil – the most selective SSRI'

This claim appeared as a heading on page 2 of the compendium which introduced Cipramil as a product. The claim occurred again as a heading in the final section of the compendium which discussed the selectivity of antidepressants.

COMPLAINT

Lilly alleged that this was a hanging comparator and did not describe the way in which citalopram was 'most' selective. In terms of serotonin re-uptake, paroxetine was in fact the most selective SSRI. It was also unclear what clinical benefit actually derived from such supposed 'selectivity'. This was therefore misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Lundbeck stated that this was not a hanging comparison. It was clear that Cipramil was compared to the other SSRIs. To be the most selective 'selective serotonin re-uptake inhibitor' a medicine must be the most selective for inhibition of serotonin re-uptake, and so the way in which Cipramil was the most selective was also clear. Selectivity was discussed in the papers by Hyttel (1994) and Stahl. Hyttel presented data for selectivity in terms of the ratio of the IC50 NA (noradrenaline) uptake/IC505-HT (serotonin) uptake. Cipramil was 3400 times more potent on 5-HT that on NA uptake and was more selective than the other SSRIs. Selectivity was also determined by Cipramil's lack of effects at other neurotransmitter receptors such as acetylcholine, histamine, noradrenaline, 5-HT or dopamine. Paroxetine was a more potent SSRI which was quite different (in fact sertraline would appear to be the most potent SSRI). If a medicine was selective for the pharmacological action which was responsible for efficacy it would have little activity at other receptor sites or systems which would not contribute to efficacy but might have the potential to cause unwanted effects. This was of clinical benefit.

PANEL RULING

The Panel noted that a hanging comparison was described in the supplementary information to Clause 7.2 as a phrase whereby a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared. The Panel considered that the phrase in question was not a hanging comparison, as alleged.

The summary of product characteristics (SPC) for Cipramil stated that it was the most selective serotonin re-uptake inhibitor yet described with no or minimal effect on noradrenaline, dopamine and gamma aminobutyric acid uptake. The SPC also stated that it had a low potential for clinically relevant medicine interactions.

Hyttel stated that SSRIs were those which preferably inhibited 5-HT uptake compared with NA, and which at the same time had no or only slight effect on other uptake mechanisms, neurotransmitter receptors, enzymes etc. A series of five SSRIs, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline were characterized with regard to their selectivity for 5-HT uptake. Citalopram was shown to be the most selective 5-HT re-uptake inhibitor whilst paroxetine was shown to be the most potent.

The Panel noted Lundbeck's submission that the lack of activity at other receptor sites or systems which would not contribute to efficacy but might have the potential to cause unwanted side-effects would be of clinical benefit.

The Panel considered that the claim was not misleading as alleged and ruled no breach of Clause 7.2 of the Code.

APPEAL BY LILLY

Lilly stated that it had already been noted by Lundbeck that the lack of activity of Cipramil at some brain receptor sites would not affect efficacy. It was, however, claimed in the Lundbeck response that this brain receptor selectivity would have the potential to reduce unwanted effects. This was perceived as a clinical benefit.

Such a claim might be acceptable if there was limited clinical experience with Cipramil. However it had been on the UK market since 1995 and experience in other countries was longer. The side effect profile was now well known and did not appear to differ significantly from other SSRIs.

Lilly had examined papers where Cipramil had been compared with other SSRIs and found no evidence that there were significant differences in the reported adverse events which negated the theoretical application on which the claim had been made. In addition, on review of material distributed by Lundbeck, Lilly found claims of adverse event equivalence when comparing Cipramil with some other SSRIs. This was at odds with the interpretation that Lundbeck had given in response to the initial complaint. Lilly maintained that this claim was misleading in terms of clinical implications and thus a breach of Clause 7.2.

Bougerol *et al* (1997) described two comparative studies between fluoxetine and citalopram. The first was a study of patients with depression seen by psychiatrists in an in-patient or out-patient setting where the effects of 20mg/day of fluoxetine were compared to those of 40mg/day of citalopram. It was noted that the frequency of adverse events was generally low. A higher frequency of adverse events was reported with citalopram (which might have been dose dependent), with the only significant difference being in patients taking citalopram who had a statistically significant increased incidence of vomiting. This settled after the first 2 weeks. No statistically significant differences were observed between the treatment groups in relation to serious adverse events.

The second study compared fluoxetine with citalopram (both at a dose of 20mg/day) in a general

practice setting. Few differences were noted between the groups as far as adverse events were concerned. There was, however, a statistically significant increased incidence of back pain in patients treated with citalopram. While trends were present in the reports of dry mouth and weight loss in patients treated with fluoxetine, these failed to reach statistical significance. Global evaluation of the interference of adverse events on outcome showed that there were no statistical or clinical differences between the groups. Again, with serious adverse events there were no statistically significant differences noted between the treatments.

A double-blind multicentre trial comparing sertraline and citalopram in patients with major depression in general practice (Ekselius *et al* (1997)) compared citalopram (20-60mg/day) with sertraline (50-150mg/day). Patterns of spontaneously reported adverse events reported were similar although no statistical analyses had been reported. A side effect scale was used to elucidate adverse events. Again the pattern of reported events was similar with no statistically significant differences reported.

'Citalopram An evidence-based review' by JB Medical (distributed by Lundbeck), was a review of information on citalopram and stated when reviewing comparative studies 'Citalopram and fluoxetine have comparable efficacy and side-effect profile', 'Citalopram and sertraline have comparable efficacy and side-effect profile' and 'a slight difference compared with fluvoxamine with regard to GI [gastro-intestinal] side effects, but apart from vomiting this was only significant at week 1'.

Lilly stated that the pre-clinical receptor binding data suggested a potential clinical benefit which was not borne out in the clinical efficacy or safety data. Therefore the use of the phrase 'The most selective SSRI' was misleading.

RESPONSE FROM LUNDBECK

Lundbeck stated that Lilly contended that the claims made regarding receptor selectivity should translate into an improved clinical safety profile to justify the use of such a phrase, it appeared that this was the only way that Lilly believed the claim could be justified.

Lundbeck provided two papers by Stahl where the author contended that SSRI activity was a relative rather than an absolute property.

In the first paper (Stahl (1998a)) it was contended that selectivity was only a relative concept and that secondary pharmacological properties must be understood to optimise patient treatment. This was further developed in a second paper (Stahl (1998b)), where citalopram was described as the 'purest' SSRI with no significant drug interactions, no significant activation/anxiety/insomnia (short-term) and an advantageous GI tolerability/irritable bowel.

Lundbeck therefore contended that 'the most selective SSRI' was a statement that could be supported and that by focussing on simply the issue of clinical tolerability Lilly was trying to narrow down a complex concept into simply adverse event comparisons alone.

Lundbeck submitted that its data fully supported the claim.

FURTHER COMMENTS FROM LILLY

Lilly stated that in its response Lundbeck claimed that Lilly contended that the claims made regarding receptor selectivity should translate into an improved clinical safety profile to justify the use of such a phrase. It appeared that this was the only way that Lilly believed the claim could be justified. Whilst this was not a wholly accurate representation of Lilly's position, it was certainly its belief that by prominently displaying the statement 'Cipramil – the most selective SSRI' on the promotional material, Lundbeck was implying that this claimed selectively translated into some clinical benefit, else why was it included on the material?

Lundbeck quoted Stahl (1998b) where citalopram was described as the 'purest' SSRI 'with no significant drug interactions, no significant activation/anxiety/insomnia and an advantageous GI tolerability'. Any claim that Cipramil offered an advantageous adverse event profile over other SSRIs was not, however, borne out by the body of evidence, eg Bougerol *et al* (1997), Citalopram An evidence-based review and many others.

Lundbeck's claim that 'By focusing simply on the issue of clinical tolerability … Lilly was trying to narrow down a complex concept into simply adverse event comparisons alone' was missing the point – promotional materials carrying the offending claim were designed to be read by healthcare professionals in order to inform and influence their prescribing habits. On such materials, claims of superior selectivity were highly likely to be interpreted by those reading them as conferring clinical benefits, most likely a superior adverse event profile (just as the class of SSRIs as a whole had come to be known for their more favourable side effect profile on account of their selectively). Despite this, however, the body of literature did not support claims of such benefits with Cipramil.

Lilly therefore maintained that Lundbeck had breached Clause 7.2 with its 'most selective' claim, as in the context that it was presented, the statement was highly likely to mislead and implied benefits not supported by the body of evidence.

APPEAL BOARD RULING

The Appeal Board noted that the Cipramil SPC stated that it was the most selective serotonin re-uptake inhibitor yet described with no or minimal effect on noradrenaline, dopamine and gamma aminobutyric acid uptake. The Appeal Board also noted that Hyttel *et al* stated that Cipramil was shown to be the most selective 5-HT re-uptake inhibitor whilst paroxetine was shown to be the most potent. The Appeal Board noted the submission by Lilly that in studies where Cipramil had been compared with other SSRIs there was no evidence that there were significant differences in the reported adverse events which negated the theoretical application on which the claim that Cipramil was the most selective SSRI was made.

However given the statement in the SPC and the data the Appeal Board considered that the claim at issue was not misleading as alleged and upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal was thus unsuccessful.

2 Claim '... proven efficacy in severe major depression'

The claim appeared as a heading to page 4 which detailed the results of a four week double-blind parallel group study which compared the efficacy of citalopram with placebo in patients with severe major depression. A bar chart showed the mean total Hamilton Depression Rating Scale (HAMD) score at baseline and at weekly intervals throughout the study. At baseline citalopram treated patients had a mean total HAMD score of 24 which was reduced to 18.8 at week 1. Beneath the bar chart was the claim 'Effective from week 1'.

COMPLAINT

Lilly stated that the dose of citalopram was not given to accompany this graph. Efficacy from week 1 was stated but it was not explained by what criteria this efficacy was measured. A fall in HAMD score from 24 to 18 did not imply 'efficacy'. This was alleged to be misleading in breach of Clause 7.2.

RESPONSE

Lundbeck said that the piece stated clearly that efficacy was measured by reduction in the 17-item HAMD score. Cipramil was 'effective' from week one in terms of a statistically significant reduction in the mean HAMD score from 24 to 18. This was not the same as claiming 'efficacy' which implied a full response.

PANEL RULING

The Panel noted that most patients in the study had started therapy on citalopram 20mg daily; the dose was increased as necessary to a maximum daily dose of 80mg. The average daily dose of citalopram in the first week was 33mg and at week four was 63mg. The Cipramil SPC stated that in depression patients should begin therapy with 20mg daily. Dependent upon individual patient response this dose could be increased to a maximum of 60mg daily.

The bar chart illustrated the reduction in mean total HAMD scores achieved in the study. The Panel considered that the graph and accompanying text clearly stated that depression was measured using the HAMD total score. The study showed in terms of HAMD score, that citalopram was significantly more effective than placebo at all time points including week 1.

The Panel considered that the study demonstrated that Cipramil exerted an effect measurable on the HAMD scale from week one. The Panel did not accept that the claim implied efficacy in terms of a full response from week 1. The Panel noted, however, that the dose of Cipramil used in the study was higher than that recommended in the SPC. Most readers would assume that Cipramil had been used at its licensed dose which was not so. The failure to give dosage details was misleading and a breach of Clause 7.2 was ruled.

3 Section headed 'Comparison of onset of action'

Beneath this heading on page 8 were three general points regarding onset of action and clinical response. These were followed by two tables; the first containing data on half-life and time to steady state of five SSRIs and the second comparing the time interval to percentage of steady state concentration for Cipramil and fluoxetine.

COMPLAINT

Lilly stated that the implication of this section was that half life determined 'onset of action' by a delay in reaching steady state concentrations. This was not in fact the case and this was therefore misleading and in breach of Clause 7.2. Indeed the Cipramil SPC stated that 'there is no clear relationship between citalopram plasma levels and therapeutic response or side effects'.

RESPONSE

Lundbeck stated that it agreed that antidepressants did not have to reach steady-state plasma concentrations before they started to exert their antidepressant effects. However, they had to reach a certain threshold plasma concentration before sufficient serotonin re-uptake inhibition occurred at the pre-synaptic neurone. The time taken for the antidepressant to reach this threshold would, to some extent, depend upon half life.

PANEL RULING

The Panel noted Lundbeck's submission that a certain threshold plasma concentration was required before sufficient serotonin re-uptake inhibition occurred at the pre-synaptic neurone and that the Cipramil SPC stated that there was no clear relationship between citalopram plasma levels and therapeutic response or side effects. The Panel considered that half life and time to steady state concentration were relevant data in relation to onset of action. The Panel did not accept that this page gave the impression that half life was the sole determinant of onset of action. The Panel did not accept that the page was misleading as alleged and ruled no breach of Clause 7.2 of the Code.

4 Page comparing onset of action of Cipramil and fluoxetine

Page 9 of the compendium was headed 'Cipramil 20mg versus fluoxetine 20mg' and featured a bar chart which compared the percentage of severely depressed patients with a 50% reduction in the Montgomery-Ashberg Depression Rating Scale (MADRS) score after two weeks. The bar chart was referenced to Patris *et al* (1996) and showed a statistically significant reduction in favour of Cipramil (P=0.048).

COMPLAINT

Lilly noted that the page stated that the study was of severely depressed patients with a MADRS score of >22. This was not a criterion for severity, being a common entry criterion for depression studies. This was also a general practice population, again suggesting that it was not a severe group. In fact the discussion section of the referenced paper stated '... patients treated in general practice are less severely ill than those referred for specialist treatment'.

Review of the statistical analysis of the data in the Patris paper indicated that the authors chose to define two populations for analysis – the ITT (intention to treat population) and the EFF ('efficacy group'). Use of an EFF group was a most unusual way to interpret trial data and suggested that there might be some issues with the trial results being presented in the traditional ITT manner. The EFF population was a group 'which had completed at least 14 days of double-blind treatment' and 'all efficacy analyses were made on the basis of this population'. If patients therefore completed 13 days of treatment (and then withdrew) they would not be included in the time to onset analysis. It was not clear why this cut off was made, and would therefore not allow realistic extrapolation of the data to an average general practice setting.

'Equivalence of treatments' was also assessed but the study was not powered for equivalence.

Despite the above deficiencies, the promotional piece claimed that citalopram showed a 'significantly faster onset of action' based on a 50% reduction of MADRS score after 2 weeks (p=0.048). This was based on the EFF population (defined above) and not on ITT population as one would expect. 53 out of 153 patients on citalopram and 39 out of 161 patients on fluoxetine had a 'faster onset of action' at week 2. Lilly did not know anything about patients who dropped out before 2 weeks (20 patients in the citalopram group and 23 in the fluoxetine group). Lilly also did not know whether the improvement at the two week time-point was maintained in these individual patients beyond week 2. In addition, there was in fact no difference in the mean results for the two groups over the duration of the study.

The presentation of the data was therefore misleading and in breach of Clause 7.2.

RESPONSE

Lundbeck stated that although a MADRS score of greater than 22 was a study inclusion criterion, the mean baseline MADRS score was above 29 in both groups.

It was the explicit intention of the study to demonstrate the equivalence of Cipramil and fluoxetine in the treatment of depression and the sample size was calculated in accordance with this intention. The two one-sided tests procedure by Schuirmann was chosen over the t-test procedure by Hauck and Anderson as the latter was often more likely to point to equivalence than the former while the former was the procedure statisticians tended to recommend at the time the protocol was written (ICH Guideline: Statistical Principles for Clinical trials).

Patients who withdrew early from either treatment group would mostly not have responded to treatment and an ITT analysis might be biased towards demonstrating equivalence. Similarly, any major protocol violations including violation of inclusion criteria might also tend to bias the results towards a conclusion of equivalence. In an equivalence study it was therefore good statistical practice to use an efficacy or per protocol population. The efficacy population defined a sub group of patients who were more compliant with the protocol and the scientific model behind the protocol. It provided the two treatments with equal chances of showing efficacy and it increased the probability of drawing the right conclusion as to whether or not the two treatments were comparable.

In more general terms, to assess response at two weeks it was reasonable to include patients who received two weeks of treatment. A clinician would not expect to see any meaningful response to two weeks' treatment unless the patient actually received treatment throughout those two weeks. In any case the number of drop outs in both groups before two weeks was very similar (20 in the Cipramil group and 23 in the fluoxetine group) and was unlikely to have influenced the results.

The fact that both treatments produced comparable results over the course of the study was stated clearly.

PANEL RULING

The Panel noted that beneath the bar chart it clearly stated that the patient population consisted of 314 severely depressed patients, defined as a MADRS score of more than 22. The Panel considered that as the MADRS score had been given readers would interpret for themselves where on the scale of mild to severe depression such a score lay. The Panel noted that the mean baseline MADRS score for patients was 29.7 for the citalopram treated group and 29.4 for the fluoxetine treated group. The Panel did not consider the description of the study population misleading as alleged and ruled no breach of Clause 7.2 of the Code.

The Panel noted that all efficacy analyses had been based on an efficacy population as opposed to the intention-to-treat population. The paper gave clear details of the statistical analysis and the reasons for patients withdrawing from the study. The Panel noted that there was no statistically significant difference between those who withdrew from the citalopram group (n=24; 14%) and those who withdrew from the fluoxetine group (n=21; 11%). Lundbeck had submitted that the two groups were also similar with regard to the number of drop outs before two weeks. The Panel noted that the efficacy population was more compliant with the study protocol. The Panel considered that given the similarity of the two groups the use of an efficacy population was justified.

The Panel considered that overall the study by Patris *et al* substantiated the claim that Cipramil 20mg had a significantly faster early onset of action than fluoxetine 20mg. No breach of Clause 7.2 was ruled.

APPEAL BY LILLY

Lilly stated that it considered that the interpretations made by Patris *et al* did not reflect a clinical difference, further confirming the company's belief that a breach of Clause 7.2 had occurred.

In addition to the Patris *et al* (1996) paper, Lilly had now identified a further study (Patris *et al* (1998)) comparing fluoxetine and citalopram, where no earlier onset of action with citalopram was claimed. The claim that citalopram had a faster onset of action was therefore not reflected by the total body of evidence and as such was misleading and a breach of Clause 7.2.

Within the original Patris paper, it was stated that 'a between group difference of at least 4 points in the mean change of MADRS total score from baseline to endpoint was considered to be clinically relevant'. From the graph of mean MADRS scores it was clear that this difference was not achieved at any time point. Table III indicated that 27% citalopram patients and 16% fluoxetine patients had MADRS scores of 12 or lower at week 2 (with the assumption that this was a clinically relevant event). In order for the week 2 mean scores to be similar for the two groups (as demonstrated by Figure 1), there must have been a greater number of subjects on citalopram with higher MADRS scores at week 2 (compared with those on fluoxetine) in order to counteract the greater number of 'full responders' on citalopram.

The displays in Table III and Figure 1 did not demonstrate the full range of scores at the week 2 time points which made the full distribution unclear. Therefore this study demonstrated no clinically relevant differences between these treatments.

Bougerol *et al* (1997) described two comparative studies between fluoxetine and citalopram. The first was a study of patients with depression seen by psychiatrists in an in-patient or out-patient setting where the effects of 20mg/day of fluoxetine were compared to those of 40mg/day of citalopram. No clinically relevant or statistically significant differences were identified at any point in changes in MADRS score between the groups. As citalopram was being used at a higher dose (40mg/day) than in the initial referenced study (Patris), it might be the case that if a true difference in onset of action were present this would have been identified, but despite this, no comments were made about individual patient responses at any time point other than comparing baseline to endpoint.

The second study was further reporting of the Patris study above. Within Table III mean MADRS scores at each time point were noted confirming that there were no clinically significant differences (difference of 4 points) between the treatments at any time.

Therefore in light of the evidence above, the balance of scientific data did not support an earlier onset of action for citalopram and to quote a single measure at a single time point was misleading.

RESPONSE FROM LUNDBECK

Lundbeck stated that Lilly contended that the statements concerning speed of onset of action were not supported by the two references from Patris and Bougerol.

In the Bougerol paper, the authors reported 'the numbers of patients with a 50% reduction in MADRS total score after 2 weeks was 35% in the citalopram group and 24% in the fluoxetine group. This difference was statistically significant. This effect was also seen in those with a baseline MADRS >25 (more severe patients). It was further noted that those showing a total MADRS score ≤12 after 2 weeks was also statistically significantly greater in the GP study. All the data were thus fully supportive of an earlier onset of action with citalopram compared to fluoxetine.

Lundbeck disputed that there were no statistically significant differences in the Patris paper. The authors stated that 'a statistically significant difference in favour of citalopram was observed after 2 weeks of treatment where 53 patients in the citalopram group and 39 patients in the fluoxetine group showed a 50% reduction in MADRS total score'. Since the baseline score was 29 in both groups, such a reduction was also clinically significant. Reductions in HAMD scores were also statistically significantly in favour of citalopram in the same time frame. The data were also cited in a review article, Feighner (1997), where the study was cited as being well designed. The view that fluoxetine was slower in terms of onset of action was further supported by a recent review by Edwards and Anderson (1999).

Lundbeck contended that the speed of onset of action was faster for citalopram and that there had been no breach of Clause 7.2.

FURTHER COMMENTS FROM LILLY

Lilly stated that Lundbeck's claim that Cipramil showed a more rapid onset of action than fluoxetine was based upon data taken from papers by Patris *et al* and Bougerol *et al*.

Lilly had stated its criticisms of Lundbeck's interpretation of data from these papers in its appeal. Briefly, the Patris paper revealed no statistically significant difference in mean MADRS or HAMD scores between subjects treated with Cipramil or fluoxetine at any time during the eight-week treatment period. Not only were claims of a faster onset of action based on just a single statistically significant difference between the treatment groups in a specific sub-grouping of subjects, but even then this analysis failed to take into account a higher drop-out rate in the Cipramil group (due to adverse events). Furthermore, the highlighting of this sole possible difference when the study showed a distinct lack of statistically significant difference between treatment groups at any other time point in any other measure was hardly the balanced representation of the paper demanded by Clause 7.2.

Similar criticisms could be levelled at Lundbeck's treatment of data from the Bougerol study, where again there was no overall difference in mean MADRS scores at any time point. Lundbeck had based its claim of faster onset of action on one single

statistically significant difference between scores in a subgroup of the general practice sample.

In its most recent response, Lundbeck stated that its claims for a faster onset of action were supported by a recent review by Edwards and Anderson. This review, however, appeared to be basing its conclusion largely on the same Patris paper discussed above, and Lilly noted that its analysis appeared to include not one single other paper comparing the speed of onset of action of Cipramil and fluoxetine. Lilly's own literature search revealed no other papers claiming a faster onset of action for Cipramil over fluoxetine either.

In summary, Lilly maintained that Lundbeck had breached Clause 7.2 as its claims for a faster onset of action of Cipramil were based on a single statistically significant difference between treatment groups from a sub-set of subjects where the overall analysis revealed no statistically significant difference between the treatment groups. At the very least, Lundbeck was generalising what it perceived to be a treatment difference in a specific sub-group of subjects to the entire patient population by not qualifying its claims. There were no other robust data to support Lundbeck's position. Lundbeck was therefore making a claim which was not supported by the available evidence and was thus misleading.

APPEAL BOARD RULING

The Appeal Board noted that Patris *et al* showed a reduction of MADRS mean total scores in both treatment groups with no statistically significant differences between treatments. Citalopram showed an earlier onset of recovery than fluoxetine. The Appeal Board noted that in Patris *et al* all efficacy analyses were based on an efficacy population as opposed to an intention-to-treat population and the claim at issue 'Cipramil 20mg had a significantly faster early onset of action than fluoxetine' was based upon this sub-group. The claim was clearly related to those patients with a 50% reduction in MADRS score after two weeks. On balance the Appeal Board considered that the presentation of the data was not misleading as alleged and upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal was thus unsuccessful.

5 Claim 'Cipramil lifts depression with patient safety in mind'

The claim appeared as a heading on page 12 of the compendium indexed with the word 'safety'. Eight bullet points referred to different side effects. In addition two subsequent pages (14 and 15) were also indexed 'safety' and referred to detailed aspects of Cipramil's cardiovascular effects including one bullet point which read 'No effect on QTc'.

COMPLAINT

With regard to the bullet point 'No effect on weight' Lilly noted that the SPC stated weight increase or decrease at a rate of between 1 and 5% in clinical trials. Lilly alleged that the bullet point 'No or minimal anticholinergic effects' did not make sense – either there were or there were not anticholinergic effects. The company noted that the SPC stated that dry mouth was a 'frequent' adverse event at a rate of 5-20% in clinical trials. With regard to the bullet point 'Low level toxicity in LD50 testing' Lilly stated that use of this data was in breach of Clause 7.2 – extrapolation of *in vitro* data to the clinical situation should only be made where it could be shown that it was of direct relevance or significance. Lilly stated that in previous correspondence with Lundbeck challenging the use of this statement, a reply was received in which Lundbeck correlated the LD50 data with Fatal Toxicity Indices for antidepressants (from Power *et al* (1995)). The paper quoted 'a weak but significant correlation' between the FTI values for antidepressants in humans and their median lethal dose in mice. However the table in this paper included no reference to SSRIs at all. With regard to claims about cardiovascular safety Lilly noted that there were a number of case reports in the literature of fatalities caused by citalopram overdose, in particular 6 cases reported in Sweden (Öström *et al*) with a postulated mechanism of death due to cardiac arrhythmias due to QTc prolongation.

RESPONSE

Lundbeck stated that weight increase was mentioned on the Cipramil SPC but the SPC also made it clear that the incidence of weight increase associated with Cipramil in clinical studies was no different from that associated with placebo.

Cipramil had minimal affinity for anticholinergic receptors (as shown in the study by Hyttel (1994) and referred to in A1 above) and so produced minimal anticholinergic effects. Dry mouth was associated with Cipramil treatment but was more likely a serotonin-mediated effect.

Several investigators had attributed a Fatal Toxicity Index (FTI) to antidepressants by relating coroner's data to number of prescriptions dispensed (Power *et al* (1995)). It was significant that there appeared a correlation between FTIs and LD50 data suggesting that the latter were useful in predicting potential toxicity in the clinical setting. The ranking of antidepressants using the ratio of the oral LD50 to the clinical dose correlated with the ranking of antidepressants using the FTI. Lundbeck agreed that the animal data should be used with caution, but it contended that these data had clinical relevance and their inclusion was therefore justified.

Of the six cases reported by Öström only one was an apparently pure Cipramil overdose. Although the authors of this report speculated about the role of a minor metabolite of citalopram, it had to be stressed that no cause of death was identified. This metabolite could cause QT prolongation in dogs when it was present in high concentrations, but it was present in comparatively very low concentrations in man, even after overdose. This point was made by the authors themselves. There was no evidence of cardiovascular risk associated with Cipramil. In particular, Christensen *et al* (1985) reported no postural hypertension, while Elsborg *et al* (1991) and Overo *et al* (1991) found no clinically significant effects on ECG.

PANEL RULING

With regard to the claim 'No effect on weight' the Panel noted that in a section headed 'Undesirable effects' the Cipramil SPC stated that the adverse effects observed with citalopram were in general mild and transient. Weight increase and decrease were listed in the SPC as adverse events reported in clinical trials with a frequency of 1-<5%. The Panel considered that given the statement in the SPC, the claim was misleading and a breach of Clause 7.2 was ruled.

With regard to the claim 'No or minimal anticholinergic effects', the Panel noted that the examples of anticholinergic effects listed adjacent to the claim were dry mouth, blurred vision, constipation and urinary retention. According to the SPC amongst the most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo treated patients was dry mouth although its incidence in excess over placebo was low (<10%). Dry mouth and constipation were listed in the SPC as frequent adverse events reported in clinical trials with a frequency of 5-20%, and abnormal vision was listed as less frequent at 1-<5%. Given the statements in the SPC the Panel considered the claim was misleading and a breach of Clause 7.2 was ruled.

'Low level toxicity in LD50 testing' – The Panel noted that the page adjacent to the claim in question was entitled 'Cipramil – low level of toxicity in LD50 testing' and featured a graph which compared the oral LD50 in rats (mg/kg) of Cipramil, sertraline, fluoxetine and paroxetine. The supplementary information to Clause 7.2 provided that care must be taken with data derived from animal studies so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel considered that it would be clear to the reader that lethal dose testing referred to animal work. The Panel noted the submission that data appeared to show a correlation between FTIs and LD50 suggesting relevance to the clinical setting although the data did not show it was of direct relevance. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel considered that the complaint regarding cardiovascular safety related to the double page spread of pages 14 and 15 of the compendium.

It was stated that the cardiovascular safety of Cipramil had been documented in normal volunteers (n=12) and patients (n=798) and by the evaluation of over 5,000 ECGs and that these studies represented the largest investigation of an SSRI on ECG yet to be published. Four bullet points appeared beneath including the claim 'Minimal effects on pulse, blood pressure or ECG.' The heading on the opposite page read 'Cipramil – no effect on ECG' beneath which a graph featured the results of Elsborg (1991) which compared the percentage of patients with ECG changes on Cipramil, placebo and tricyclic antidepressants. The adjacent text stated that the frequency of ECG changes were the same for Cipramil and placebo.

The Panel noted that Christensen *et al* (1985) which examined the orthostatic side effects of clomipramine and citalopram during treatment for depression conceded that no significant changes in orthostatic blood pressure or heart rate were demonstrated during treatment of the Cipramil group and these patients had no orthostatic complaints. Elsborg (1991) concluded that ECG recordings from short term and long term evaluations indicated that citalopram did not induce conduction disturbances or activate ectopic foci. A slight effect on blood pressure was recorded and a minimally decreased pulse rate of little clinical relevance was observed.

The Panel noted that Öström *et al* (1996) which reported on six forensically investigated suicides where overdose with citalopram was found, postulated that one possible mechanism of death was cardiac arrhythmias. The letter stated that in dogs, didesmethyl-citalopram prolonged the QT interval, and high levels of citalopram and didesmethyl citalopram produced fatal ventricular arrhythmias and torsade des pointes. This statement was referenced to van der Burgh, Citalopram product monograph, Denmark (1994).

The Panel noted that the SPC stated that palpitation occurred in 5-20% of patients in clinical trials with postural hypotension and tachycardia being less frequent (1-<5%). The Panel noted that in its response Lundbeck stated that 'There was no evidence of cardiovascular risk associated with Cipramil'. The text on page 14 began with 'The cardiovascular safety of Cipramil has been documented…'. The Panel considered that this phrase amounted to a statement that Cipramil was safe from a cardiovascular point of view. The Panel considered that the use of this phrase together with the overall impression that there was no cardiovascular risk associated with Cipramil created a misleading impression about the safety of the product a breach of Clause 7.7 was ruled.

APPEAL BY LUNDBECK

Lundbeck appealed the ruling that the claim 'No or minimal anticholinergic effects' was in breach of Clause 7.2.

Lundbeck stated that it was unreasonable to expect a clear distinction of any anticholinergic effects to be made in terms of their presence or absence. Cipramil, due to its lack of affinity for cholinergic receptor sites exhibited minimal anticholinergic effects (Hyttel (1994)). It would, however, be difficult to quantify the exact size of any effect and hence the qualification used in the claim remained justified and appropriate.

Furthermore, adverse effects which were more usually associated with the older tricyclic antidepressants and attributed to their anticholinergic activity but had now been reported with some SSRIs, eg Cipramil, were thought to be produced by different mechanisms. For example, dry mouth might be caused by indirect enhancement of noradrenaline innervation of the salivary gland, and blurred vision might be attributable to enhancement of the serotonin innervation of the pupil (Skerritt (1997)).

It was also well documented that somatic symptoms that commonly occurred in depressed patients such as

constipation (60% of depressed patients), were frequently erroneously regarded as side effects of medication (Nelson (1997)).

Adverse events such as dry mouth, constipation and visual disturbances were listed in the Cipramil SPC, however, it was very unlikely that these could be attributed to activity at cholinergic receptors. Lundbeck therefore disagreed with the ruling that this statement was misleading.

APPEAL BOARD RULING

The Appeal Board noted the examples listed next to the claim 'no or minimal anticholinergic effects' were dry mouth, blurred vision, constipation and urinary retention. This cluster of side effects were considered to be typically due to anticholinergic effects. The Appeal Board noted that dry mouth and constipation were listed in the SPC as frequent adverse events and abnormal vision was listed as a less frequent adverse event. The Appeal Board noted Lundbeck's submission that some effects, such as constipation, commonly occurred in depressed patients and were erroneously regarded as side effects of the medication.

The Appeal Board considered that the claim was misleading. It gave the impression that there would be no or minimal incidence of the adverse events listed and this was not consistent with the statements in the SPC. The pharmacological basis of the adverse events was immaterial. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The appeal by Lundbeck was thus unsuccessful.

6 Heading 'Considering the options for treating a refractory patient'

Page 29 listed treatment options for refractory patients. Beneath a sub-heading 'Combination with another antidepressant' was a discussion on the combined use of SSRIs and tricyclic antidepressants (TCA). It was stated that 'Case reports and trials demonstrate a significant adverse interaction between SSRIs and TCAs with the probable exception of Cipramil'. This was referenced to Taylor (1995).

COMPLAINT

Lilly noted that the statement that a combination of an SSRI and TCA might cause severe adverse events 'with the probable exception of citalopram' was referenced to a paper published in 1995 when Cipramil had only just been licensed (June 1995). Despite the fact that citalopram's metabolism was only partly dependent on CYP2D6 and it was only a weak inhibitor of it, there was still a theoretical risk of interaction with TCAs. This information was therefore potentially misleading and in breach of Clause 7.2.

RESPONSE

Lundbeck said that at the time the cited paper was published Cipramil had only just been licensed in the UK, but had been available in other markets from 1989. The quotation referred to severe adverse events, not to the possibility of minor pharmacokinetics interactions. Indeed the item stated that all SSRIs might cause an increase in the serum levels of concurrent TCAS and that this combination was supported by little research.

PANEL RULING

The Panel noted that the statement 'Case reports and trials demonstrate a significant adverse interaction between SSRIs and TCAs with the probable exception of Cipramil' was followed by the claim that 'All currently available SSRIs may cause an increase in the serum levels of concurrent TCAs.' Both were referenced to Taylor (1995).

Taylor (1995) was a review of 35 articles which discussed SSRI/TCA interactions and evaluated the therapeutic use of SSRI/TCA combinations in treating refractory depression. Taylor recorded that there were no reports of clinical adverse interactions when citalopram was co-administered with a TCA, but noted that this medicine had only recently (June 1995) been marketed in the UK. A similar comment was made with reference to paroxetine where there was one report of an interaction with a TCA. The study concluded that 'There are many case reports and trials demonstrating a significant adverse interaction between SSRIs and TCAs. With the probable exception of citalopram, all concurrently available SSRIs may raise the serum levels of concurrent TCAs...'

The Panel noted that the compendium did not accurately reflect this conclusion. The first part of the second sentence 'With the probable exception of Cipramil…' had been added to the end of the preceding sentence thus referring to significant medicine interactions between SSRIs and TCAs rather than serum levels of TCAs as in the paper. In a section headed 'Limitations of the review' the study stated that 'Data on paroxetine, sertraline and particularly citalopram are too limited to make firm conclusions about their interaction potential'. The Panel considered that the discussion of significant adverse medicine interactions did not fairly reflect the findings of Taylor (1995) although there was no allegation on this point.

The Panel noted that the section referred to the probable exception of Cipramil and this was immediately followed by the claim 'All currently available SSRIs may cause an increase in the serum levels of concurrent TCAs' and that there was little well-conducted research to support the combination. The Panel did not consider that the material was misleading as alleged and no breach of Clause 7.2 of the Code was ruled.

7 Claim 'Cipramil – an effective and well tolerated treatment for depression associated with stroke and dementia'

This claim appeared as a heading to page 39 which featured the graphical results of two studies. The first graph, subtitled 'Cipramil – effective treatment for post-stroke depression' was referenced to Anderson *et al* Acta Psychiatrica Scandinavica (1994). The second

graph subtitled 'Depression in demented patients' was referenced to Nyth and Gottfrie (1990). Each graph was accompanied by a brief description of the relevant study.

COMPLAINT

With regard to the first graph Lilly noted that the description of the study stated that 66 consecutive patients from an unselected population of 285 stroke patients were treated with citalopram. Firstly the graph showed only 27 patients on citalopram and 32 on placebo, not 66 on citalopram. Secondly, the reference cited had no mention of the data presented. Therefore it was misleading and in breach of Clause 7.2.

Lilly noted that also presented in this section was a study (Nyth and Gottfrie (1990)) of 98 demented patients in whom citalopram 'effectively treated emotional bluntness, restlessness, irritability and depressed mood'. The description of the study did not say how many patients had depression and also data was presented on only 27 patients. Once again the way the data was presented was misleading and thus in breach of Clause 7.2.

RESPONSE

Lundbeck stated that the first graph should have stated that 66 patients were treated with Cipramil or placebo and the reference was incorrectly cited (the correct reference was Andersen, Stroke (1994)). This was an error and Lundbeck thanked the Authority for bringing it to its attention. The graph provided data on the efficacy population (27 patients on Cipramil and 32 on placebo).

The study described by Nyth and Gottfrie involved patients with a mean baseline MADRS score of 8.307 and the 27 patients referred to in the graph were a subset of patients with Alzheimer's dementia and senile dementia of Alzheimer type.

PANEL RULING

The Panel noted that Clause 7.2 of the Code required claims, information and comparisons to be, *inter alia*, accurate. The Panel noted that the first graph and adjoining text featured the results of Anderson, Stroke (1994) but cited, Anderson *et al* Acta Psychiatrica Scandinavica (1994). The Panel considered the information was thus inaccurate and so ruled a breach of Clause 7.2 of the Code.

The Panel noted that the second graph was labelled 'Depression in demented patients' but showed the mean Gottfrie-Brane-Steen (GBS) geriatric rating scale at baseline and after 4 weeks' treatment with Cipramil. The GBS scale assessed the level of dementia by measuring motor, intellectual and emotional impairment and six common dementia symptoms. The specific items of the GBS scale shown on the graph were emotional bluntness, confusion, irritability, depressed mood and restlessness. All were significantly reduced by Cipramil. In the Panel's view, despite the inclusion of 'Depressed mood', GBS scale was not designed to measure depression *per se*.

The Panel noted that in the discussion section of the paper by Nyth and Gottfrie it was stated that this was the first controlled study reporting that an SSRI seemed to benefit patients with dementia disorders and that the study suggested that citalopram might be valuable in elderly demented patients with Alzheimer's disease or senile dementia of Alzheimer type (AD/SDAT). The Panel also noted that the description of the study which accompanied the graph referred to 98 demented patients whereas the graph was relevant only to a sub-set of 27 patients with AD/SDAT treated with Cipramil. Overall the Panel considered that the presentation of the data gave the impression that depression was decreased in 98 patients treated with Cipramil whereas what the data actually showed was that dementia was decreased in 27 patients treated with Cipramil. Cipramil was not licensed for the treatment of dementia. The Panel considered that the data was confusing and ruled a breach of Clause 7.2 of the Code.

8 Heading 'Why is selectivity important?'

This statement appeared on page 40 as a heading to a section which discussed the concept of selectivity with reference to *in vitro* studies.

COMPLAINT

Lilly stated that once again *in vitro* data was being extrapolated to the clinical setting. A statement was made that 'A highly selective antidepressant has the potential to target the depression and not the patient'. All medicines which affected neurotransmitter receptors and enzyme systems present in the brain would also have effects on those systems elsewhere. Whether relative affinity for one receptor type at an order of magnitude of 1000 times higher *in vitro* had clinical implications was unclear. Clearly Cipramil was not a medicine which was devoid of adverse effects (see the SPC) which might be attributable to other transmitter systems. This presentation was therefore potentially misleading and in breach of Clause 7.2.

RESPONSE

Lundbeck said that the same arguments applied here as provided in A1 above. The claim related to a lack of effects at receptor sites, receptor systems or enzyme systems other than those on which the pharmacological benefits of the medicine were based. Effects on these other systems might cause unwanted effects.

PANEL RULING

The Panel considered that its ruling at A1 above was relevant. It was neither stated nor implied that no side effects would occur. In the opinion of the Panel the section attempted to explain the scientific theory behind selectivity. No breach of Clause 7.2 of the Code was ruled.

B DETAIL AID – 0898/CIP/525/142

Lundbeck said that this 16 page item was provided to its sales force for use in discussions with general practitioners, psychiatrists and geriatricians.

1 Claim 'Mood disorders'

Page 3 of the detail aid was headed 'Mood disorders: Common cause'. A solid circle in the middle of the page was labelled 'Serotonin disturbances' and had three arrows pointing outward to 'Anxiety/panic', 'suicidal behaviour' and 'depression'. Page 5 was headed 'Cipramil: A logical choice for mood disorders' and referred to the treatment of depression, anxiety and panic disorder. Page 16 (back page) was headed 'Cipramil – makes a real difference in mood disorders' and referred to panic disorder and anxiety symptoms of depression.

COMPLAINT

Lilly submitted that it was questionable whether psychiatrists would classify anxiety and panic as 'mood disorders'.

RESPONSE

Lundbeck submitted that this had been addressed above.

PANEL RULING

In the opinion of the Panel 'mood' was used to indicate a class or group of disorders which might come within the licensed indication for use of Cipramil. The Panel considered that the use of the term 'mood disorders' was not misleading in this context. The Panel considered that the allegation came within Clause 7.2 and ruled no breach of that clause.

2 Claim 'Cipramil: Speed to onset of action'

Page 7 of the detail aid was headed 'Cipramil: Speed to onset of action' underneath which appeared a graph comparing fluoxetine and Cipramil in relation to the percentage of patients with a full response over 8 weeks.

COMPLAINT

Lilly noted that this was the same study presented in the Clinical Compendium and challenged under point A4 above.

RESPONSE

Lundbeck submitted that it had responded to this point above.

PANEL RULING

The Panel noted that the graph in the detail aid was different to the graph in the clinical compendium considered under point A4. The Panel noted that no breach of the code had been ruled in point A4. The Panel considered that in the absence of any specific allegations about the graph at issue, it was obliged to rule no breach of the Code.

3 Claim 'Cipramil: The most selective SSRI'

This claim appeared as a heading to page 15 (inside back cover) of the detail aid.

COMPLAINT

Lilly referred to its complaint in point A1 above.

RESPONSE

Lundbeck referred to its response in point A1 above.

PANEL RULING

The Panel considered that its ruling of no breach of clause 7.2 of the Code in point A1 above also applied here.

4 Claim 'Convenient half-life'

Page 12 of the detail aid was headed 'Cipramil: Minimal potential for drug interactions'. Two boxes of text favourably compared, in general terms, the pharmacokinetic properties of Cipramil with SSRIs. One of the features of Cipramil was a convenient half life as opposed to a long half life for SSRIs.

COMPLAINT

Lilly alleged that it was unclear what convenient half-life meant and it was hence misleading and in breach of Clause 7.2.

RESPONSE

Lundbeck stated that convenient half life referred to a half life which was neither so short as to necessitate more than once daily dosing which was less convenient for the patient, or so long as to necessitate a long washout period if adverse events occurred or a change in treatment became necessary.

PANEL RULING

The Panel noted that the adjacent page featured a table which compared the pharmacokinetic parameters of four SSRIs. Paroxetine displayed the shortest half life at 24 hours and fluoxetine the longest at 132 hours. Cipramil had a half life of 36 hours. The Panel noted Lundbeck's submission that convenience referred to dosage requirements and the washout period.

Whilst the Panel considered that further explanation of the term might have been provided it did not consider the term to be misleading and ruled no breach of Clause 7.2 of the Code.

5 Claim 'Low level of toxicity in LD50 testing'

The claim appeared on page 8 of the detail aid under the heading 'Cipramil: Established safety profile.'

COMPLAINT

Lilly referred to its complaint in point A6.

RESPONSE

Lundbeck referred to its response in point A5.

PANEL RULING

The Panel noted that the point at issue was discussed at point A5, not point A6 as stated by Lilly. The Panel considered that its ruling of a breach of Clause 7.2 in point A5 also applied here.

C MAILER – 0998/CIP/511/067/L

The mailer was entitled 'Cipramil: Now makes a real difference to your prescribing costs' and informed the recipient that the cost of Cipramil had been reduced. The mailer also referred to the cost-effectiveness of Cipramil, the selectivity of the medicine and the fact that Lundbeck was a specialist CNS company.

Lundbeck said that this mailing was sent to all general practitioners, psychiatrists, geriatricians, retail pharmacists, hospital pharmacists, trust chief executives, trust medical directors, trust pharmacy managers and FHSA medical advisors.

1 Claim Cipramil the 'most selective …. SSRI'

COMPLAINT

Lilly referred to its complaint in point A1 above.

RESPONSE

Lundbeck referred to its response in point A1 above.

PANEL RULING

The Panel considered that its ruling of no breach of clause 7.2 of the Code in point A1 above also applied here.

2 Claim 'Most cost effective'

Beneath the sub-heading 'Cipramil: the most cost-effective SSRI', Cipramil was described as the least expensive SSRI and monthly cost savings in percentage terms of Cipramil 20mg OD compared with fluoxetine 20mg OD, paroxetine 20mg OD and setraline 50mg OD were provided.

COMPLAINT

Whilst Lilly would agree that citalopram at 20mg a day was now the cheapest SSRI per pill, Lilly disputed the claim that it was also therefore the most 'cost-effective SSRI'.

What the promotional piece showed was that at the doses selected, irrespective of the relative clinical efficacy, it was less expensive that the other antidepressants highlighted. This was not a cost-effectiveness analysis. There were four main types of economic evaluation. Their conventional definitions were discussed in detail by Drummond and Jefferson (1996) and well described by Greenhalgh (1997) as follows:

Cost-minimisation analysis; used when the effect of both interventions was known (or might be assumed) to be identical. The methodology used no outcome measure.

Cost-effectiveness analysis; used when the effect of the interventions could be expressed in terms of one main variable. The outcome measure used was in natural units, eg life years gained.

Cost-utility analysis; used when the effect of the interventions on health status had two or more important dimensions, for example, benefits and side effects of medicines. The outcome measures used were utility units, eg quality adjusted life years.

Cost-benefit analysis; used when it was desirable to compare an intervention for this condition with an intervention for a different condition. This used monetary units, eg estimated cost of loss in productivity.

Lilly submitted that this piece was a cost-minimisation analysis. Leaving aside the applicability of such a methodology to compare 'modern' antidepressants, this did not demonstrate relative cost-effectiveness. What was the outcome measured, ie effect? Outcomes which could be used to compare the effectiveness of treatments included symptom resolution, return to functioning and rate of relapse.

The costs were more than just the acquisition costs of the medicine and could include direct medical costs, medicine costs, days in hospital, nursing time, GP visits, concomitant medications, direct non-medical costs, carer time and indirect costs.

Obviously, much would depend on the type(s) of patient to be treated and the setting.

In conclusion, this was a cost-minimisation analysis. The data presented did not permit the statement that citalopram was the 'most cost-effective SSRI'.

Therefore Lilly believed that this statement was in breach of Clause 7.2 relating to the use of data from the economic evaluation of medicines.

RESPONSE

Lundbeck provided a copy of the study report 'Citalopram: Cost/Effectiveness Analysis in Acute Phase for Major Depression Treated in Primary Care in United Kingdom', which described a model which analysed costs involved in the treatment of depression with the currently available SSRIs and venlafaxine. The report concluded that Cipramil was the most cost-effective SSRI in the UK.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 provided that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data available and did not exaggerate its significance. Assumptions made in an economic evaluation must be clinically appropriate and consistent with the marketing authorization. Attention was drawn to the guidance on good practice in the conduct of economic evaluation of medicines which had been given by the Department of Health and the ABPI. The guidance provided that the study should use a recognised technique. These included cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analysis. Any one of these

could be appropriate according to the purpose of the study. The report of the study should include justification of the technique chosen.

The Panel considered that a reader would assume that the phrase cost-effectiveness did not merely refer to the acquisition cost of the medicine but included an evaluation of the resource cost implications of using a particular medicine and its effectiveness, including effects on a patient's health as a result of side effects. A cost-effectiveness analysis allowed one to incorporate both costs and differing degrees of effectiveness and compare them. Cost-minimisation analysis could be used when the alternative treatments being evaluated had identical health outcomes and the comparison could therefore be limited to analysing the costs. The Panel noted Lilly's allegation that the claim was based upon a cost-minimisation study rather than a cost-effectiveness study.

The Panel examined the study report (data on file) submitted by Lundbeck. The study sought to evaluate the cost effectiveness of Cipramil, fluoxetine, venlafaxine, paroxetine, sertraline and fluvoxamine based on a six week economic decision tree model. After 2-3 weeks of treatment the decision tree split into two arms; the first comprising patients who dropped out and who either switched treatment or discontinued treatment, and the second group, patients who continued treatment at the same or an increased dose. Seven potential outcomes were identified. The total cost of each outcome was calculated. Only direct costs were considered. It was assumed that the health care cost was the same for all the SRRIs, except the costs of the medicines themselves. The total expected cost per patient for each SSRI was calculated by multiplying the cost for each potential outcome in the model by the probability of that outcome occurring. When discussing the probability of a patient responding to treatment the authors noted that in terms of efficacy it was extremely difficult to differentiate between the compounds. The Panel noted that for patients who had dropped out of treatment at 2-3 weeks the probabilities of each outcome were assumed to be the same. The Panel noted that in this arm of the decision tree the only variable in the expected cost would thus be the acquisition cost of medicines.

The response rate for each SSRI was obtained from a meta analysis of studies that compared SSRIs using a parallel group design. The Panel noted that effectiveness ranged from 0.44 for Cipramil to 0.38 for fluoxetine and fluvoxamine. The study concluded that Cipramil was the most cost-effective SSRI. The study authors noted that SSRIs were almost equivalent in terms of overall efficacy, safety and tolerability, only differences in the side effect profile could be found but the rate of patients experiencing side effects or drop outs remained very close for all compounds.

It was noted that the cost of the medicine appeared to be a major issue in the comparison of the cost-effectiveness ratio.

The Panel considered that given the study assumptions about health costs, probabilities and the similarities between efficacy, tolerability and side effect profiles noted by the study authors the acquisition cost of the medicine was the significant variable in the calculation of the cost-effectiveness ratio. The Panel considered that it would have been helpful if the significance of the medicines acquisition cost in the calculation had been brought to the reader's attention. The Panel did not consider however that there was a breach of Clause 7.2 of the Code as alleged and ruled no breach of the Code.

3 Claim 'More can benefit…'

This claim was part of the sub-heading 'More can benefit from the most selective SSRI'.

COMPLAINT

Lilly made no specific allegations referring only to its allegations with respect to the mailer, 0998/CIP/511/068M (F1 and F2 below).

RESPONSE

Lundbeck did not respond to this point.

PANEL RULING

The Panel noted that it did not appear to have a specific allegation about the phrase 'more can benefit' and made no ruling on this point.

The reference to the mailer 0998/CIP/511/068M appeared to refer to the claim 'the most selective' (F1) and 'the most cost effective' (F2). The Panel considered that its rulings at A1 and C2 covered these points.

4 Inappropriate statement

COMPLAINT

Lilly believed that the statement 'When we realised that our future research projects can be financed with less revenue from product sales, we decided to pass the benefit on to you and your patients', was inappropriate.

RESPONSE

This was very subjective. Lundbeck was owned by a foundation and had no shareholders. This meant the company could pass on reduced internal costs to customers in the form of reduced prices in a way a conventional company could not.

PANEL RULING

The Panel considered that this was a declaration of corporate intent. Such statements were not unacceptable so long as they otherwise complied with the Code. The Panel ruled no breach of Clause 9.1 of the Code.

D REPLY CARD 0998/CIP/511/067/RC

This reply card was sent with the mailer above. The card was headed 'Price reduction acknowledgement'. Readers were required to tick a box which followed

the statement 'I am now aware that, following its price reduction, Cipramil is the least expensive SSRI'. In addition the card featured two cartoon characters with one character stating 'Cipramil is now the least expensive SSRI'. Readers were invited to add their reaction to that statement to the empty thought bubble of the second character. It was stated that for every completed reply card returned to Lundbeck, the company would donate £1 to a named charity.

COMPLAINT

Lilly stated that the 'thought bubble' cartoon and tick box with the offer of a £1 donation to Depression Alliance appeared rather inappropriate to the practice of medicine, and hence in breach of Clause 18.1.

RESPONSE

Lundbeck submitted that the price reduction acknowledgement card was the subject of a recent ruling by the Panel of no breach (Case AUTH/770/10/98).

PANEL RULING

The Panel noted that this complaint had been received before the previous case, AUTH/770/10/98, had been completed. In the previous case the complainant considered it to be unethical for a pharmaceutical company to require pharmacists to read and acknowledge marketing material in order to ensure a donation to a charitable body from that company.

During its consideration of Case AUTH/770/10/98, the Panel noted the supplementary information to Clause 18.1 'Donations to Charities' which stated that 'Donations to charities made by companies in return for health professionals' attendance at company stands at meetings or offered as rewards for completing and returning quiz cards in mailings … are not unacceptable … provided that the level of donation for each individual is modest, the money is for a reputable charity and any action required by the health professional is not inappropriate. … At all times the provisions of Clauses 2 and 9.1 must be kept in mind'.

Clause 9.1 required that all materials and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained at all times. The supplementary information to Clause 9.1 stated that certain types, styles and methods of promotion, even where they might be acceptable for the promotion of products other than medicines, were unacceptable.

The Panel noted that the reply card in question asked the reader to acknowledge the fact that Cipramil was the least expensive SSRI. In the Panel's view the cartoon which was to be completed was more likely to elicit a flippant response than to provide the company with genuine feedback. In effect the payment to charity was for reading the mailing. The Panel had reservations about the mailing but decided that as the supplementary information to Clause 18.1 of the Code permitted donations to charities in return for health professionals' attendance at company stands at meetings it was difficult to draw a distinction between this and the mailing in question. The level of donation of £1 per card was not unreasonable. The Panel therefore ruled no breach of Clauses 9.1 and 18.1 of the Code in Case AUTH/770/10/98.

The ruling was not appealed by the complainant.

Turning to the case now before it, the Panel considered that the allegation was similar to that in Case AUTH/770/10/98. Lilly had alleged only a breach of Clause 18.1 and no breach of that clause was ruled.

E ABBREVIATED ADVERTISEMENT IN MIMS OCTOBER 1998 – 0998/CIP/501/053

The advertisement featured the heading 'Cipramil: Makes a real difference to your prescribing costs', above a bar chart which compared the treatment cost per 28 days of stated doses of five marketed SSRIs. The text beneath and adjacent to the graph referred to 'the most selective and cost-effective SSRI'.

COMPLAINT

Lilly alleged that this advertisement was in breach of Clause 5.4 which listed the permitted contents of an abbreviated advertisement. Dosage particulars and cost were specifically excluded and this advertisement included both of these, in both text and artwork.

RESPONSE

Lundbeck stated that the Code stated that cost or dose particulars might be included in abbreviated advertisements if they were the reasons why the medicine was recommended. This was the position with this advertisement.

PANEL RULING

The Panel noted that the content of abbreviated advertisements was set out in Clause 5.4 of the Code and its supplementary information. The supplementary information provided that cost should not be included in abbreviated advertisements unless it was given as a reason why the medicine was recommended for the indication or indications referred to. The Panel considered that the advertisement was recommending Cipramil because it was the most cost-effective SSRI and thus the provision of comparative cost information did not render the advertisement in breach of Clause 5.4 of the Code and no breach of that Clause was ruled.

F MAILER – 0998/CIP/511/068 M

Lundbeck said that this item was sent to general practitioners, psychiatrists and geriatricians.

1 Claim 'Most selective'

COMPLAINT

See A1 above.

RESPONSE

As A1 above.

PANEL RULING

The Panel considered that its ruling at A1 above applied here.

2 Claim 'Most cost effective'

COMPLAINT

As C2 above.

RESPONSE

As C2 above.

PANEL RULING

The Panel considered that its ruling at C2 above applied here.

3 Claim 'Efficacy with the potential for cost savings'

This claim appeared above a table which compared the annual cost of treating 122 patients with stated doses of five SSRIs, one of which was Cipramil 20mg OD. For each of the other four SSRIs the annual saving if Cipramil had been administered was stated as was the number of additional patients who could be treated annually if this saving was spent on Cipramil.

COMPLAINT

Lilly said that the implication of this mailer was that the average GP with a list of 2,000 patients would have approximately 122 patients suffering from depression. The extrapolation made from this epidemiological picture was that if all patients were treated with citalopram then considerable costs savings could be made over the use of existing or other antidepressant treatment. This assumed a 100% response rate to citalopram and did not take into account individual patient differences with regard to severity of depression or previous response to other antidepressants and was therefore completely unrealistic. It also gave the impression that all antidepressants were equivalent at the doses stated.

It also suggested that 'an additional number of patients could be treated with citalopram' with the money thus saved. Where would these patients come from - it had already been stated that all the GP's patients were being treated!! Hence this information was in breach of Clause 7.2.

RESPONSE

Lundbeck stated that this item addressed potential savings and the assumptions behind these savings were clear. In particular, any assumptions regarding response rates and drop outs were the same for all the medicines presented. The treatment of 'extra' patients might appear paradoxical but it was generally accepted that depression was under recognised in general practice. The estimated number of patients with a depressive illness (around 6%) was very conservative and it was highly likely that an average GP with a list of 2000 patients would have more than 122 patients in need of antidepressant treatment. In addition to these 'extra' previously undiagnosed patients, Cipramil might also be used to treat patients with panic disorder.

PANEL RULING

The Panel considered that there was a difference between the phrase 'Efficacy with the potential for cost savings' and 'cost-effectiveness'; the latter phrase implied that a pharmacoeconomic evaluation had been undertaken, the former, would be interpreted as referring to the acquisition cost of the medicine unless otherwise stated.

The Panel noted that the data presented beneath the phrase in question and adjacent to it was based on the acquisition cost of each medicine at stated doses. The assumptions were clearly set out. The Panel ruled no breach of Clause 7.2 of the Code.

G 0998/CIP/525/171 – LEAVEPIECE

Lundbeck stated that this leavepiece was distributed to its salesforce to be left with GPs, psychiatrists and geriatricians.

Complaints about two claims in the leavepiece were considered to have been covered by the Panel's rulings in A1 and C2 above.

H 0998/CIP/501/051 – ADVERTISEMENT

Lundbeck stated that this advertisement first appeared on 1 October 1998.

Complaints about two claims in the advertisement were considered to have been covered by the Panel's rulings in A1 and C2 above.

I 0998/CIP/501/049 – ADVERTISEMENT

Lundbeck stated that this advertisement appeared on 16 September 1998.

A complaint about a claim in the advertisement was considered to have been covered by the Panel's rulings in A1 above.

Items C and D were last used in October 1998. Item F was last used in November 1998. Items A, B, C, and G were last used in January 1999 and Item I was last used in March 1999.

Complaint received **6 November 1998**

Case completed **23 July 1999**

CASE AUTH/801/11/98

CONSULTANT CARDIOLOGIST v EASTERN

Sampling of Isocard Transdermal Spray

A consultant cardiologist complained that he had received an unsolicited sample of Isocard Transdermal Spray from Eastern Pharmaceuticals. An accompanying letter offered further samples by either telephone or written request.

The Panel noted that Eastern had acknowledged that the sample had been sent out in error. An unsolicited prescription only medicine had been sent in the post to a health professional and the Panel ruled a breach of the Code in that regard. A further breach was ruled because the company had failed to obtain a signed and dated written request for the sample.

A consultant cardiologist complained about an unsolicited free sample of Isocard Transdermal Spray which he had received by post from Eastern Pharmaceuticals Ltd. An accompanying letter offered further samples by either telephone or written request.

COMPLAINT

The complainant said that he had received an unsolicited free sample of Isocard Transdermal Spray which had been accompanied by a letter. The complainant's understanding was that this was contrary to Clause 17.10 of the Code.

RESPONSE

Eastern pointed out that it noticed this error only recently and would strongly confirm that this was not normal practice. The mailing in question had been stopped and it would not be repeated.

Eastern supplied copies of the letters which it normally sent out. From those it could be noted that general practitioners were invited to complete a request slip for samples and only then did Eastern deliver samples to them.

Eastern apologised to the consultant cardiologist who brought this to the Authority's attention and would only assure him that it had made a genuine error. The company stated that the error would never be repeated and that the persons responsible had been severely reprimanded.

PANEL RULING

The Panel noted that Eastern had acknowledged that the sample had been sent out in error. An unsolicited prescription only medicine had been sent in the post to a health professional. The Panel ruled a breach of Clause 17.10 of the Code as alleged.

The Panel noted that the company had failed to obtain a signed, dated, written request for the sample as required by Clause 17.3 of the Code. The Panel also ruled a breach of that clause.

REPORT TO APPEAL BOARD

In response to the notification of the rulings, Eastern stated that it had put procedures in place to ensure that the principles of the Code were adhered to and to ensure that there were no further grounds for complaint. It further stated that while it accepted the principles of the Code it did not consider itself contractually bound to participate in future adjudications. It did not provide the requisite undertaking and assurance as required by the Constitution and Procedure when a breach is ruled.

Eastern was not a member of the ABPI but according to the Authority's records it was a company which had agreed to comply with the Code and accept the jurisdiction of the Authority. This was now disputed by Eastern.

The Authority informed Eastern that the situation was incompatible with it remaining in the system. In accordance with Paragraph 8 of the Constitution and Procedure, the matter was reported by the Panel to the Appeal Board which decided that, in accordance with Paragraph 11 of the Constitution and Procedure, the matter should be reported to the Board of Management of the ABPI.

REPORT TO THE ABPI BOARD

The ABPI Board decided that the Authority should delete Eastern from the list of companies which had agreed to abide by the Code and advise the Medicines Control Agency (MCA) that responsibility for the company under the Code could no longer continue to be accepted.

Any complaints about Eastern which may be received in the future will be passed to the MCA for it to take such action as it sees fit.

Complaint received	**18 November 1998**
Panel ruling	**4 December 1998**
Report considered by Appeal Board	**24 June 1999**
Report considered by ABPI Board	**13 July 1999**

PIERRE FABRE v RHÔNE-POULENC RORER and CHUGAI PHARMA

Promotion of Taxotere

Pierre Fabre complained about a booklet entitled 'Which is the most effective chemotherapy option for Advanced Breast Cancer?'. The booklet, issued by Rhône-Poulenc Rorer and Chugai Pharma, compared Taxotere (docetaxel) with vinorelbine monotherapy for patients with metastatic breast cancer who had received previous anthracycline treatment. Pierre Fabre supplied vinorelbine (Navelbine).

The booklet used non-comparative clinical trials. Pierre Fabre stated that comparisons between two products could not be made from two different non-comparative trials. Rhône-Poulenc Rorer, responding on behalf of both itself and Chugai, stated that only patients treated within the licensed indications for the medicines had been included. There was no direct comparison of Taxotere and Navelbine in their licensed indications. It was routine practice for conclusions to be drawn in oncology between different anti-cancer agents in Phase II studies. The Panel noted that the booklet was aimed at oncologists. Oncology was a complex therapy area. The booklet clearly set out on page 3 that the trials were non-comparative and the audience, in the Panel's view, would understand the limitations of this. Given the therapy area and the intended audience the Panel did not consider that page 3 was misleading as alleged. No breach was ruled. On appeal from Pierre Fabre the Appeal Board considered that the use of non-comparative data might be acceptable in certain circumstances. Relevant factors would be the therapy area, the intended audience, how the data was presented and the conclusions drawn. The audience would understand the limitations of the data and be able to assess its significance. The Appeal Board did not consider that the use of non-comparative data was misleading *per se* as alleged and upheld the Panel's ruling of no breach.

The booklet stated that 'The best available data at the time of preparation of the booklet was used'. Pierre Fabre referred to data on its product that had not been used. Rhône-Poulenc Rorer commented in detail on the data. The Panel ruled no breach of the Code as Rhône-Poulenc Rorer had only used data where vinorelbine had been administered according to its UK marketing authorization.

Pierre Fabre alleged that the use of the term 'second line treatment' in relation to patients with anthracycline – pre-treated metastatic breast cancer was ill understood. The Panel considered that the term might be open to interpretation but the whole sentence clearly defined the population for which Taxotere was licensed. No breach of the Code was ruled.

Pierre Fabre alleged that the references to support the claim 'higher overall tumour response rates' were not from direct comparisons of the products. Rhône-Poulenc Rorer stated that the references chosen were the highest published objective response rate data which used the products within their licensed indications. The Panel considered that the page clearly referred to the use of non-comparative data. Given the therapy area and the intended audience no breach of the Code was ruled. Upon appeal by Pierre Fabre, the Appeal Board noted the response rates for Taxotere and vinorelbine used in the booklet. The response rate for Taxotere provided by Pierre Fabre in its appeal was disputed by Rhône-Poulenc Rorer and Chugai as it referred to widely different groups of patients. The Appeal Board did not consider that the data was such as to allow a clear determination of the comparative efficacy of Taxotere and vinorelbine to be made. It was inappropriate to refer only to the best available data. The claim was ruled to be misleading and not capable of substantiation. Breaches of the Code were ruled. This ruling also applied to the claims 'longer time to disease progression' and 'longer median survival' which the Panel had ruled not to be in breach.

A claim relating to quality of life was ruled to be misleading and in breach by the Panel. It was referenced to a pharmacoeconomic study but appeared under a clinical heading.

A claim 'more convenient administration' was alleged to be misleading, not capable of substantiation and not referenced. Rhône-Poulenc Rorer referred to the more detailed information given later in the booklet. The Panel ruled no breach of the Code with regard to the failure to reference the claim. The claim did not refer to a published study so there was no need to cite a reference. In the Panel's view the administration of Taxotere was more convenient than vinorelbine, there was no need for venous washout post infusion and the frequency of administration was once every three weeks for 6 cycles as opposed to once a week for 9 weeks. No breach of the Code was ruled. Further allegations in relation to the convenience of the products are considered below, some of which were ruled in breach.

The Panel did not consider that page 3 of the booklet, which included all the claims referred to above, was disparaging of vinorelbine and no breach of the Code was ruled.

Pages 4 and 5 of the booklet dealt with overall response rates in Phase II trials.

Pierre Fabre alleged that a claim referring to the presentation of the highest available overall response rate data in Phase II trials was untrue and misleading. The overall response rate for vinorelbine was stated as 20.5%. Data which showed a response rate for vinorelbine of 65% had not been used. Rhône-Poulenc Rorer stated that the data had not been published and was only supplied by Pierre Fabre when making the complaint. It was unclear whether all patients had been pre-treated with an anthracycline and therefore whether vinorelbine was used within the UK approved indications. The Panel noted that the pre-treatment

position was not clear and that the dosage regimen was not consistent with the licence. No breach of the Code was ruled.

Pierre Fabre alleged that a claim that the overall response rate to Taxotere was superior to vinorelbine was untrue, misleading and could not be substantiated. 'Superior' was a superlative which could not be used. Rhône-Poulenc Rorer stated that it applied the same criteria to both medicines, selecting the highest response rate reported in Phase II studies. The word 'superior' was not a superlative. The Panel noted that the audience would understand the limitations of Phase II data. The Panel considered that the claim was not misleading. It could be substantiated and no breach was ruled. The word 'superior' was not a superlative and no breach was ruled in that regard. Upon appeal by Pierre Fabre, the Appeal Board noted that the two studies involved limited numbers of patients and thus the claim was more definite and positive about the comparative efficacy of Taxotere and vinorelbine than the data would allow. It was ruled to be misleading and not substantiated and in breach of the Code. The Appeal Board upheld the Panel's ruling of no breach with regard to the allegation that the word 'superior' was a superlative.

Pierre Fabre alleged that data presented in graphs from a non-comparative Phase II study did not provide a basis for a fair comparison. The profiles of the patients in each of the studies were not the same. The proximity of the graphs within the same illustration and under a common title was misleading. Rhône-Poulenc Rorer stated that the graphs were on separate axes to show clearly that they were not head-to-head comparisons and were referenced to separate studies. The same criteria had been used for the selection of the studies from the available data. The Panel noted that some of the issues had been raised in earlier allegations. The patients had been treated within the product licence. Although the bar charts were placed side by side the audience would know that the Phase II results were not from a direct head-to-head study. No breach of the Code was ruled. Upon appeal by Pierre Fabre, the Appeal Board considered that the presentation of the graphs invited a direct comparison of the products that was misleading given the data upon which they were based. Breaches of the Code were ruled.

Similar allegations to those made about the Phase II data were made about Phase III data which appeared on pages 6 and 7 of the booklet. The Panel considered that it was misleading not to state that separate studies had been used as Phase III studies could have been comparative. Breaches of the Code were ruled. No breach was ruled regarding an allegation that the word 'superior' was a superlative and the Appeal Board upheld that ruling upon appeal by Pierre Fabre.

Pages 8 and 9 referred to disease progression and survival in Phase III trials. Data presented were from separate studies. The Panel considered that the allegations were similar to those already raised in relation to pages 6 and 7. The Panel's rulings of breaches of the Code made there also applied to pages 8 and 9.

The side effect profiles of the products were compared on pages 10 and 11. The side effects listed were taken from the summaries of product characteristics (SPCs) plus data from two other named sources. A comparison of the severity of neutropenia was not fair. In addition the failure to include information about the nature of neutropenia associated with Navelbine, having included comparable information about Taxotere, was misleading. A breach of the Code was ruled. The Panel ruled that the failure to include detailed information about fluid retention with Taxotere was misleading. The SPC referred to the incidence of fluid retention with and without pre-medication with steroids whereas the booklet only referred to the incidence with pre-medication. A breach of the Code was ruled. The Panel ruled that the information given about Taxotere in relation to hypersensitivity reactions was overly reassuring and did not reflect the information given in the SPC. A breach of the Code was ruled. The Panel ruled that the comparison of the incidence of cardiac events was misleading. The Taxotere data was not an accurate reflection of the SPC. The vinorelbine data had been taken from Phase II data not the SPC. The nature of the events had not been further defined nor had their causal relationship with vinorelbine been established. The SPC did not refer to cardiac events. A breach of the Code was ruled. The Panel ruled a breach of the Code as the booklet did not refer to the cutaneous and hepatic reactions that could occur with Taxotere therapy. The Panel considered that to make no mention of a group of reactions which affected more than half of those who received the medicine and which could, rarely, be severe enough to interrupt therapy was misleading. Comparisons in relation to the incidence of neuropathy, alopecia and diarrhoea were ruled not to be in breach of the Code.

Pages 12 and 13 were headed 'Taxotere The convenience advantages' under which was a comparison of the two products. A breach of the Code was ruled with regard to the statement 'No extravasation injuries have been reported in the UK'. This might be true but implied that no extravasation injuries had ever been reported with docetaxel which was not true. Extravasation was mentioned in the SPC. Pierre Fabre alleged that the information about pre-medication with Taxotere could not be substantiated as a convenience advantage for the product. The Panel considered that it might have been misleading to omit information about pre-medication. It was one element of administration data that was relevant to convenience as a whole. No breach of the Code was ruled. A similar allegation was made about cold capping and no breach of the Code was ruled. A statement relating to nursing observation in relation to Taxotere administration was ruled to be misleading as it was not consistent with the SPC. A statement implying that patient, doctor and nursing convenience related only to the number of visits a patient made to receive therapy was too simplistic, misleading and not capable of substantiation. Breaches of the Code were ruled.

Pages 14 and 15 were headed 'Taxotere The economic advantage'. The Panel noted that the results of the pharmacoeconomic study were presented in clinical language giving the impression that they were from a direct clinical comparison. The quality of life data was from nurses not patients. A breach of the Code was ruled as not sufficient information had been given to allow the reader to fully understand the basis of the comparison. No breach was ruled with regard to an allegation that the opinion of the authors had not been accurately stated. The presentation of a claim as a direct quote was misleading as none of it was a quotation from the paper. It did reflect the findings but it had been incorrectly presented as a quotation and a breach of the Code was ruled. Pierre Fabre alleged that a table comparing costs and progression-free days was in breach as it was not clear that it had been adapted from the reference. Pierre Fabre alleged that there were significant differences between the data used in the comparison and the current indication for vinorelbine in the UK. It was also alleged that the claim 'Taxotere dominates vinorelbine' was exaggerated and not substantiated. The Panel noted that the table was a composite of two tables and some text. It had not been taken from the paper as such. There was no need to state that it had been adapted and no breach of the Code was ruled. This was upheld by the Appeal Board on appeal by Pierre Fabre. The Panel did not accept that the patient population was inconsistent with the licensed indication for vinorelbine and no breach of the Code was ruled. The Appeal Board upheld the Panel's ruling on appeal by Pierre Fabre. The Panel ruled that the claim 'Taxotere dominates vinorelbine' was misleading as it might be assumed that this was a clinical claim. It was a pharmacoeconomic claim. A breach of the Code was ruled.

Pierre Fabre alleged that in view of the nature and frequency in which the Code had been breached the booklet was in breach of Clause 2 of the Code as it had reduced confidence in and brought discredit upon the pharmaceutical industry. The Panel did not accept that this was so and ruled no breach of Clause 2.

Pierre Fabre Ltd complained about the co-promotion of Taxotere (docetaxel) by Rhône-Poulenc Rorer Limited and Chugai Pharma UK Ltd. The material at issue was a twenty page A5 booklet entitled 'Which is the most effective chemotherapy option for Advanced Breast Cancer?'. The booklet compared Taxotere with vinorelbine (Pierre Fabre's product Navelbine).

Rhône-Poulenc Rorer responded on behalf of both itself and Chugai. The company explained that the booklet had been used as exhibition support material at a meeting of physicians involved in cancer trials. It had also been mailed to specialists in the delivery and provision of cancer care.

A PAGE 3 OF THE BOOKLET

Page 3 of the booklet bore the following text:

'In non-comparative clinical trials, an analysis of the available data for Taxotere and vinorelbine monotherapy* for the second-line treatment of patients with anthracycline – pretreated metastatic breast cancer, shows that Taxotere gives:

- Higher overall tumour response rates
- Longer time to disease progression
- Longer median survival
- Better quality of life
- More convenient administration'

'*This booklet compares Taxotere with vinorelbine monotherapy for patients with metastatic breast cancer who have received a previous anthracycline treatment. The best available data at the time of preparation of this booklet was used.'

1 'In non-comparative clinical trials…'

COMPLAINT

Pierre Fabre stated that comparisons between two products could not be made from two different non-comparative clinical trials. Clause 7.2 of the Code stated that 'comparisons must be accurate, balanced, fair, objective and unambiguous' and therefore the text of the page did not comply with the Code. Additionally, the booklet stated that the trials were 'non-comparative'. However, the booklet proceeded to make comparisons as if the trials were comparative and further, drew conclusions as a result of those comparisons. The booklet therefore created a misleading impression.

Pierre Fabre alleged a breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer submitted that it was the practice throughout medicine, and specifically within oncology, to draw limited conclusions from side-by-side comparison of Phase II clinical trial results. Whilst clinicians would agree these were never as good as direct comparative Phase III studies, it was clear that some information could be drawn from such comparisons, provided that they were accurate, balanced, fair and objective. In terms of accuracy, the data had in every case either been published in a peer reviewed journal or been subjected to a detailed audit. In order to ensure balance, only patients treated within the licensed indication for the medicines had been included.

With regard to the non-comparative nature of these studies, Rhône-Poulenc Rorer agreed that there was no direct comparison of single agent Taxotere and single agent Navelbine in the licensed indication for both products. As stated previously, it was routine practice for conclusions to be drawn within oncology between different anti-cancer agents in Phase II studies within the same indication. Indeed, this applied not only to pharmaceutical agents, but also to all modalities of treatment for cancer. Rhône-Poulenc Rorer noted that, what was arguably regarded as the single most authoritative textbook on oncology, 'Cancer: Principles and Practice of Oncology, fourth edition', edited by Vincent T DeVita Jr *et al* (1995)

showed comparative results from several clinical studies of the surgical management of carcinoma in situ of the breast, and similarly provided a ranking of 48 cytotoxic agents based on non-head-to-head activity data.

The latter was particularly relevant, since Pierre Fabre itself used the data in this table in its own promotion for treatment comparisons.

PANEL RULING

The Panel noted that the booklet was aimed at oncologists and specialists in cancer care. Oncology was a complex therapy area and the Panel noted Rhône-Poulenc Rorer's submission that it was not unusual for comparisons to be made without head-to-head data. The text on page 3 clearly set out that the trials were non-comparative and the Panel considered that the audience would understand the limitations of this. Given the therapy area and the intended audience the Panel did not consider that page 3 of the booklet was misleading as alleged. No breach of Clause 7.2 was ruled.

Pierre Fabre appealed the Panel's ruling.

2 'The best available data at the time of preparation of this booklet was used.'

COMPLAINT

Pierre Fabre submitted that additional data on the use of vinorelbine within the licensed indication for the UK was available to Rhône-Poulenc Rorer at the time the booklet was devised. The company referred to the Navelbine product monograph 'Focus on Navelbine' produced by Pierre Fabre which included comprehensive data on the use of the product in the treatment of advanced breast cancer. Therefore, neither 'all' nor the 'best' of the available data for vinorelbine had been considered in this analysis as claimed. These statements were thus inaccurate and misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that it proved extremely difficult for it to extract data on patients treated within the licensed indication for vinorelbine from most of the studies referred to. For example, the tables of data in the product monograph referred to 8 published papers/abstracts. Where discrete data was available on patients treated within the licensed indication for Navelbine, the highest reported overall 'best' response rate was identified and used in the booklet. Rhône-Poulenc Rorer commented on each of the eight references individually.

The first reference, Extra *et al* (1991) was a Phase II study of 33 patients with breast cancer; 27 patients had received previous anthracycline therapy in the form of doxorubicin or epidoxorubicin. The remaining 6 patients had not received an anthracycline (mitoxantrone was not an anthracycline but rather an anthracenedione) and were therefore treated outside the terms of the summary of product characteristics (SPC) for Navelbine. The patients pre-treated with an anthracycline were not identified as a distinct sub-group on which discrete data were presented. Therefore, Rhône-Poulenc Rorer concluded that this paper included data from patients treated outside the terms of the SPC for Navelbine and so it was unable to use it.

The second reference in the table, Tresca *et al* (1990), was also a Phase II study. Thirty eight breast cancer patients were eligible for response assessment each of whom had received no more than one previous chemotherapy regimen for metastatic breast cancer. It was not stated whether all patients received an anthracycline or not, but it was stated that out of the 9 responding cases, although all were considered resistant to CMF related medicines, 5 were resistant to mitoxantrone or anthracyclines. In the absence of information to the contrary, Rhône-Poulenc Rorer assumed that the term 'resistant to' indicated that patients had received these medicines and had failed to continue to respond to them: therefore, the company suspected in the absence of other evidence, that many of the patients had received mitoxantrone rather than an anthracycline. Therefore, it was beyond reasonable doubt that this study was not carried out within the terms of the marketing authorisation for Navelbine. Not withstanding this, the response rate, even at 20%, was not the highest response rate available, and was actually lower than the one quoted for what Rhône-Poulenc Rorer regarded as the best response rate.

The third reference cited in 'Focus on Navelbine' was Gasparini *et al* (1994). In this study, 67 assessable patients with pre-treated breast cancer were treated with Navelbine at a dose of 20mg/m^2 by one hour infusion. This was not the same dose or infusion schedule as licensed in the UK. The licensed dose was 25-30mg/m^2 either by bolus injection or by infusion of no more than 30 minutes. Therefore, the medicine was not administered in accordance with the marketing authorisation for Navelbine which was clearly stated as a term of reference for the booklet, and therefore, this paper was not eligible to be considered.

The fourth reference, Degardin *et al* (1994), was a study of 100 patients with advanced or metastatic adenocarcinoma of the breast. The dose was 30mg/m^2 of Navelbine weekly and all patients had received palliative treatment with an anthracycline. Therefore, this study was within the licensed indication for Navelbine, and Rhône-Poulenc Rorer included it in its analysis for the booklet. However, the response rate recorded in this was 16%, and this was less favourable than the 20.5% response rate recorded in the Dogliotti paper discussed below. Therefore, it was not the 'best' or 'highest' response rate recorded in Phase II studies and for Rhône-Poulenc Rorer to have presented this data would have presented Navelbine in an unfairly compromised position. Therefore, to ensure fairness, and a balanced comparison, this study was not included.

The fifth reference, Demicheli *et al* (1993) was a review of 20 patients with progressive metastatic breast cancer treated with vinorelbine. Of these 20 patients, only 17 patients had received prior chemotherapy, some of whom had received only cyclophosphamide,

methotrexate and 5-FU and had not therefore been exposed to an anthracycline. Therefore, many of these patients were not treated within the licensed indication for Navelbine and this paper therefore, could not be used.

The sixth paper was Fernandes *et al* (1995). Three separate searches to the British Library over a twelve month period had failed to identify any copy of this reference, and an approach made to Pierre Fabre for supply of all publications concerning patients with advanced breast cancer treated within the now licensed indication for Navelbine yielded several of the papers referred to before, but not this item. Therefore, it was not available to Rhône-Poulenc Rorer at the time of production of the booklet. The company noted that the piece clearly stated on page 3 that this was an analysis of the available data for Taxotere and vinorelbine monotherapy. Very recently, Rhône-Poulenc Rorer had for the first time been able to review this abstract, since it was sent to the Authority by Pierre Fabre as supplemental information to the complaint. The text of this abstract from Argentina was not completely clear, since it actually referred to '33 patients with metastatic breast cancer, all pre-treated with one or more chemotherapeutic regimens, including anthraciclines (sic)' and from this it was unclear whether in fact all patients had received an anthracycline. In any case, patients were treated with vinorelbine 30mg/m^2 on days 1 and 8 of a three weekly regimen, rather than on a weekly basis. Therefore, it was unlikely that the patients were treated within the UK licensed indication for Navelbine.

The seventh paper in the product monograph was Dogliotti *et al* (1993). This paper was a review of 48 patients with anthracycline pre-treated breast cancer who were treated with vinorelbine 30mg/m^2. Of these 44 patients, 9 achieved at least a partial response, giving a response rate of 20.5%. Rhône-Poulenc Rorer stated that this was the highest available objective response rate data for patients treated within the licensed indication and therefore was selected for use in the booklet.

The eighth and final paper referred to in 'Focus on Navelbine' was Nistico *et al* (1995). This abstract was a preliminary report on 20 previously treated advanced breast cancer patients. The nature of the previous treatment was not identified. The abstract certainly did not identify that they were pre-treated with anthracyclines. Therefore, Rhône-Poulenc Rorer was unable to confirm that these patients had been treated within the now licensed indication for Navelbine, and therefore, this particular preliminary report was not included in the booklet. Rhône-Poulenc Rorer had been unable to trace any evidence that a full paper was ever published on this study.

Rhône-Poulenc Rorer submitted that, for the reasons stated above, most of the papers referred to in the product monograph 'Focus on Navelbine' actually involved the use of Navelbine outside its UK licensed indication and dosage schedule, and the use of results obtained with the use of Navelbine outside the terms of its marketing authorisation would not have been a fair comparison against the use of Taxotere within the terms of its marketing authorisation. The result used in the booklet was the highest response rate reported in a Phase II study of Navelbine used within its licensed breast cancer indication at its licensed dosage and schedule.

Therefore, Rhône-Poulenc Rorer denied the allegation that neither 'all' nor the 'best' of the available data for vinorelbine had been considered. The company further denied that the statements were inaccurate and misleading and in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that eight published papers/abstracts had been cited in the Navelbine product monograph. Rhône-Poulenc Rorer had taken account of all of the publications but had only used those where vinorelbine had been administered according to its UK marketing authorization. The Panel did not consider this to be misleading and ruled no breach of Clause 7.2 of the Code.

3 '…for the second-line treatment of patients with anthracycline – pretreated metastatic breast cancer, …'

COMPLAINT

Pierre Fabre noted that the first sentence attempted to select a specific sub-population of patients with breast cancer and submitted that the term 'second-line' was ill-understood. It might be interpreted by some as treatment of metastatic breast cancer following anthracycline-based adjuvant chemotherapy (an increasingly accepted clinical practice), ie first-line treatment for metastatic disease. Or, by others, as re-treatment of metastatic disease following initial treatment with anthracycline for first-line metastatic disease irrespective of any previous adjuvant treatment, ie third-line chemotherapy. This selection of an ill-defined sub-population of patients was also inconsistent with the title of the booklet, which implied that the most effective chemotherapy for all patients could be defined and the result was contained within the booklet. Pierre Fabre alleged that the statement was misleading and in breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer agreed that the first sentence selected a specific sub-group of patients with breast cancer 'for the second-line treatment of patients with anthracycline-pretreated metastatic breast cancer'. The company also accepted that the term 'second line' was interpreted by some as a second treatment for metastatic breast cancer, and by others that it might be second treatment with chemotherapy after adjuvant chemotherapy. Nevertheless, the term was in widespread clinical usage, and for the purposes of this document it was immaterial whether previous chemotherapy had been given in the adjuvant setting or in the metastatic disease setting so long as it had contained an anthracycline. To fail to define a population in this way would be to include patients who had been treated outside the licensed indication

for Navelbine, which would clearly be both inappropriate and misleading. Rhône-Poulenc Rorer denied that the statement was misleading and in breach of Clause 7.2.

PANEL RULING

The Panel considered that although the term 'second-line' might be open to interpretation it was further defined by the subsequent text ie '…second-line treatment of patients with anthracycline-pretreated metastatic breast cancer…'. The Panel considered that the whole sentence clearly defined the population for which Taxotere was licensed. In the Panel's opinion the term 'second-line' as used was not misleading and no breach of Clause 7.2 was ruled.

4 Claim 'higher overall tumour response rates'.

COMPLAINT

Pierre Fabre noted that the two references cited in support of this claim were Ravdin *et al* (1995) which was a selected, non-comparative Phase II study of docetaxel, and data on file Rhône-Poulenc Rorer which was from a selected arm of an unpublished Phase III study which was not a comparison with vinorelbine.

Pierre Fabre stated that these references did not provide a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel and this statement was in breach of Clause 7.2 of the Code. In addition the claim could not be substantiated and was in breach of Clause 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that the Ravdin reference was indeed a Phase II study of docetaxel which was identified using exactly the same criteria as those used for the identification of the highest response rate in Phase II studies for Navelbine. All patients were treated within the licensed indication for docetaxel using the licensed dosage and schedule. The data on file referred to in the piece was the only arm containing docetaxel in a Phase III study, which had not yet been published in journal form. Since randomised controlled trials in this population directly between vinorelbine and docetaxel as single agents were not yet available, the highest published objective response rate data in Phase III trials was used in second-line monotherapy for patients with metastatic breast cancer who had received a previous anthracycline treatment for metastatic disease, between the drugs administered at the licensed doses and schedules in the UK. The comparison of study results in this way was not uncommon, as demonstrated by DeVita, and exactly the same criteria were used for selection of the Taxotere and the vinorelbine results supplied. Rhône-Poulenc Rorer considered that this analysis was balanced, fair, objective and unambiguous. The company therefore denied breach of Clause 7.2 or 7.3 of the Code.

PANEL RULING

The Panel considered that the page clearly stated that non-comparative trials were being used as the basis for the claims. Given the therapy area and the intended audience the Panel did not consider the claim to be misleading and ruled no breach of Clause 7.2 of the Code.

The Panel noted that data on file and a paper by Ravdin *et al* had been cited in support of the claim. Subsequent pages of the booklet dealt with response rate in detail (see B and C below) and the Panel considered that the claim could be substantiated. No breach of Clause 7.3 was ruled.

Pierre Fabre appealed the Panel's rulings.

5 Claim 'longer time to disease progression'

COMPLAINT

Pierre Fabre noted that the reference quoted in support of the claim was Nabholtz *et al* (1998) which was from a selected arm of a Phase III study which was not a comparison with vinorelbine.

Pierre Fabre noted that this reference did not provide a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel and the claim was in breach of Clause 7.2 of the Code. This claim could not be substantiated and was in breach of Clause 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that exactly the same situation applied as in point A4 above, since the same study had been identified. Once again, the company considered that this provided a basis for a balanced, fair, objective and unambiguous comparison, and that this claim was not in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel considered that the matter was, in principle, the same as in point A4 above. The Panel considered that its rulings of no breach of Clauses 7.2 and 7.3 applied and ruled accordingly.

Pierre Fabre appealed the Panel's rulings.

6 Claim 'longer median survival'

COMPLAINT

Pierre Fabre noted that the reference quoted in support of the claim was Nabholtz *et al* (1998) which was from a selected arm of a Phase III study which was not a comparison with vinorelbine.

Pierre Fabre noted that this reference did not provide a basis for a balanced, fair, objective and unambiguous comparison of Vinorelbine with docetaxel and the claim was in breach of Clause 7.2 of the Code. This claim could not be substantiated and was in breach of Clause 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that exactly the same situation applied as in point A4 above, since the same study had been identified. Once again, the company considered that this provided a basis for a balanced, fair, objective and unambiguous comparison, and that this claim was not in breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel considered that the matter was, in principle, the same as in point A4 above. The Panel considered that its rulings of no breach of Clauses 7.2 and 7.3 applied and ruled accordingly.

Pierre Fabre appealed the Panel's rulings.

7 Claim 'better Quality of Life'

COMPLAINT

Pierre Fabre noted that the reference quoted in support of this claim was Launois *et al* (1996) which was a report on a constructed, pharmaco-economic model. Pierre Fabre stated that the reference was not a clinical trial comparing vinorelbine, docetaxel and paclitaxel. The reference did not contain any data from a prospective comparison of quality of life during treatment with vinorelbine or docetaxel using recognised methods. This reference did not, therefore, provide a basis for a balanced, fair, objective and unambiguous comparison of quality of life during treatment with vinorelbine or docetaxel. The claim was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer agreed that this reference was not a clinical trial comparing vinorelbine, docetaxel and paclitaxel, and that it did not contain data from a prospective comparison of quality of life during treatment with vinorelbine or docetaxel. The company understood that data might be drawn from a number of sources, including, but not exclusively, clinical trials. Rhône-Poulenc Rorer did not agree that a reference for an economic evaluation had to be based upon clinical trials only. As described in the booklet, the analysis was based upon a classification of utilities as a function of state of health and used a health-related quality of life analysis, measured via a survey using a standard Gamble method. The company therefore denied the allegation that this reference did not provide a basis for a balanced, fair, objective and unambiguous comparison and that the claim was misleading or in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim was referenced to a pharmaco-economic study. The claim appeared under a heading which began 'In non-comparative clinical trials…'. The Panel considered that it was misleading to put a claim based on economic data under a clinical heading. A breach of Clause 7.2 was ruled.

8 Claim 'More convenient administration'

COMPLAINT

Pierre Fabre noted that no reference was provided for this claim. This claim could not be substantiated and was misleading. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Rhône-Poulenc Rorer stated that it was not a condition of the Code that all claims had to be referenced, only that they must be capable of substantiation. The company considered that the arguments presented on pages 12 and 13 of the booklet, drawn from nine separate references, were more than adequate. Taken together, the references substantiated the claim. The company submitted that there had been no breach of either Clause 7.2 or 7.3.

PANEL RULING

The Panel noted that the Code only required references to be cited when promotional material referred to published studies. The claim in question did not refer to a published study and so there was no need to cite a reference.

In the Panel's view, given the context of the claim it could be reasonably considered to refer to the administration of the medicine. In this respect the Panel noted that, compared to vinorelbine, administration of Taxotere did not require a venous washout post-infusion and the frequency of administration was once every three weeks for 6 cycles as opposed to once a week for 9 weeks. The Panel considered that the claim was not misleading and that it could be substantiated. No breach of Clauses 7.2 and 7.3 was ruled.

9 Disparagement of vinorelbine

COMPLAINT

Pierre Fabre stated that page 3 of the booklet contained 8 breaches of Clause 7.2 and 4 breaches of Clause 7.3. It was misleading and inaccurate and disparaged vinorelbine. A breach of Clause 8.1 of the Code was alleged.

RESPONSE

Rhône-Poulenc Rorer noted that it had already denied that there were any breaches of Clause 7.2 or 7.3 in the booklet, or that it was misleading or inaccurate. Therefore, the company considered that it did not disparage vinorelbine, and that no breach of Clause 8.1 of the Code had occurred.

PANEL RULING

The Panel did not consider that page 3 disparaged vinorelbine as alleged. No breach of Clause 8.1 was ruled.

B PAGES 4 AND 5 OF THE BOOKLET

The double page spread of pages 4 and 5 of the booklet dealt specifically with overall response rates (ORR) in Phase II trials. Text on page 4 explained that the highest available ORR data for each product had been presented and page 5 showed two bar charts, one for vinorelbine and one for Taxotere. ORR for vinorelbine was given as 20.5% (ref Dogliotti *et al* 1993) and that for Taxotere was given as 54.5% (ref Ravdin *et al* (1995)). The conclusion, given on page 4, was that '…the overall response rate to Taxotere is superior to that of vinorelbine'.

1 Claim 'The highest available ORR data in Phase II trials for each drug are presented'

COMPLAINT

Pierre Fabre stated that on the basis of comparisons used by Rhône-Poulenc Rorer, additional information was available to Rhône-Poulenc Rorer in which higher response rates were observed when using vinorelbine within the approved UK indication (eg Fernandez *et al* who reported on overall response rate of 64%). Pierre Fabre alleged that the statement was therefore untrue and misleading in breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer stated that it had already identified that all of the additional information was in fact associated with, or confounded by, the use of Navelbine either outside its approved indication of metastatic breast cancer previously treated with an anthracycline or a dosage or schedule that was not licensed in the UK. The company repeated that the Fernandez abstract was not available to it despite extensive searching of the British Library on three occasions, and was not supplied by Pierre Fabre until the receipt of this complaint, and was not therefore available at the time of preparation of the piece. In any case, the Fernandez abstract was unclear as to whether all patients had received an anthracycline or not and therefore, whether vinorelbine was used within the UK approved indication. Rhône-Poulenc Rorer therefore denied the allegation that it had not used the best available ORR data in Phase II trials for each drug, and denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the ORR given for vinorelbine was 20.5% compared with 54.5% for Taxotere. The abstract by Fernandez *et al* had quoted an ORR of 64% for vinorelbine. In the Panel's view it was ambiguous as to whether the patients in the study had all been pre-treated with an anthracycline in accordance with the vinorelbine product licence. The abstract of the study stated 'all pre-treated with one or more chemotherapeutic regimens including anthraciclines (sic)'. The Panel noted that Rhône-Poulenc Rorer, in its response to point A2 above, had incorrectly quoted from the study and had inserted a comma after 'regimens' which would alter the interpretation. Notwithstanding the issue of pre-treatment, however, the Panel noted that the Fernandez study had used a dosage regimen of vinorelbine which was not consistent with the UK product licence ie 30mg/m^2 on days 1 and 8 every three weeks and not the licensed regimen of weekly dosing.

The Panel noted that the 20.5% ORR quoted for vinorelbine had been taken from a paper by Dogliotti *et al* (1993). This study was conducted in patients pre-treated with anthracycline but the dosage regimen (30mg/m^2 on day 1 and day 8 every 21 days) was the same as that used by Fernandez *et al* and therefore also not consistent with the UK licence. The Panel therefore questioned the use of the Dogliotti data and noted that if, as stated on page 4, only results from studies which strictly complied to the UK licensed doses and schedules were to be quoted then an ORR of 16%, from Degardin *et al* should have been shown for vinorelbine. There was, however, no allegation in this respect. The Panel did not consider that the comparison was misleading as alleged and ruled no breach of Clause 7.2.

2 Claim 'Conclusion: In phase II trials as second-line monotherapy in patients who have previously received anthracyclines for metastatic disease, the overall response rate to Taxotere is superior to that of vinorelbine.'

COMPLAINT

Pierre Fabre stated that this statement was untrue, misleading and could not be substantiated. It was in breach of Clauses 7.2, 7.3 and 7.8 for the following reasons:

i) Comparisons could not be drawn from a single, selected, non-comparative trial for each product. This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel.

ii) The data quoted was not a proper comparison as the booklet did not use the highest available ORR for vinorelbine.

iii) The statement had breached Clause 7.8 by using the word 'superior' which was a superlative, when from the figures quoted by the booklet it was not possible to form a view that Taxotere was superior.

RESPONSE

Rhône-Poulenc Rorer denied that the claim was in breach of Clauses 7.2, 7.3 or 7.8. Specifically the company stated that it was extremely difficult to obtain from the published data available to it, any results on a reasonably homogenous cohort of anthracycline pre-treated breast cancer patients, with vinorelbine given within its licensed dosage and schedule. It was not therefore, possible to produce either a meta-analysis or a table showing many different results. The company therefore applied the same criteria to both medicines, selecting the highest response rate reported in Phase II studies, so that the comparison could be balanced, fair and objective.

Rhône-Poulenc Rorer disputed the allegation that the booklet did not use the highest available objective response rate for vinorelbine used within the terms of

its SPC. The company had already identified that previous attempts to obtain the Fernandez abstract had been unsuccessful and in any case the abstract, as now supplied to the company for the first time, did not clearly state that all patients had received anthracyclines.

Rhône-Poulenc Rorer noted that the Shorter Oxford English Dictionary provided a number of definitions of 'superior', of which three were relevant. The first was 'of higher rank', the second was 'above the average in quality etc' and the third was 'better or greater in some respect'. In each definition, it was clear that the word superior was not a superlative, but a comparative term. The superlative derivation of the comparative 'superior' could be either 'supreme' or 'superlative'. Therefore, Rhône-Poulenc Rorer considered that the word 'superior' was a comparative and not a superlative and therefore, there had been no breach of the Code.

PANEL RULING

The Panel noted that pages 4 and 5 clearly related to the results obtained from Phase II studies. In the Panel's view Phase II studies were unlikely to compare two active products. The Panel considered that the specialist audience to whom the booklet was distributed would understand the limitations of Phase II data and would not expect it to include direct head-to-head comparative studies. The Panel considered that the conclusion was not misleading and that it could be substantiated. No breach of Clause 7.2 and 7.3 was ruled.

The Panel noted its comments made in B1 above regarding the ORR figures for vinorelbine. With regard to the highest available ORR for vinorelbine the Panel noted that, according to the criteria used to select the studies, a lower figure than shown should have been quoted. No breach of Clause 7.2 was ruled.

The Panel did not consider that the word 'superior' was a superlative, it was a comparative term and the comparison had been clearly stated. No breach of Clause 7.8 was ruled.

Pierre Fabre appealed the Panel's rulings.

3 Graph entitled 'Overall response rates (ORR) in Phase II trials.'

COMPLAINT

Pierre Fabre stated that the data presented by the graphs had been selected from a different, non-comparative Phase II study for each product and, therefore, did not provide a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel. Additionally, Clause 7.2 was breached because the profiles of patients included in each of the selected studies was not the same and were not a basis for a balanced, fair, objective and unambiguous comparison of Vinorelbine with docetaxel. In addition the company stated that the proximity of the graphs within the same illustration and under the common title was misleading. Pierre Fabre alleged breaches of Clauses 7.2 and 7.6 of the Code.

RESPONSE

Rhône-Poulenc Rorer agreed that the data presented by the graphs were selected from different non-comparative Phase II studies for each product. All of the graphical representations of the studies were depicted on separate axes, to show clearly that they were not head-to-head comparative studies. They were also clearly referenced as separate studies. As had previously been explained, the company considered that this practice of comparison was a normal practice within oncology, and was, for example, used to select medicines for further development within oncology. Furthermore, Pierre Fabre endorsed this by way of using such data. Exactly the same criteria had been used for the selection of these particular studies from the ones available, for both medicines. Rhône-Poulenc Rorer therefore considered that this was a balanced, fair, objective and unambiguous comparison. It was clearly identified on page 4 of the booklet that these were not head-to-head clinical studies. Since exactly the same criteria had been used for selection of the studies for both medicines, the company denied that this was not balanced, fair, objective or unambiguous, and denied breaches of Clauses 7.2 and 7.6 of the Code.

PANEL RULING

The Panel noted that the issues raised had some commonality with those in point B2 above. The Panel referred to its comments in B2 above.

With regard to patient profiles the Panel noted that the vinorelbine-treated group was described as having received 'prior anthracyclines' and could thus be considered to include both anthracycline-resistant and anthracycline-refractory patients. The majority of the Taxotere-treated patients were resistant to the anthracycline doxorubicin (22/35) while the rest were resistant to mitoxantrone (an anthracycline derivative). The ORR quoted for Taxotere only applied to those patients who had been pre-treated with the anthracycline (doxorubicin) ie those patients who had been treated in accordance with the UK product licence.

The Panel considered that although the two bar charts were placed side-by-side, and therefore invited comparison, the audience would accept that the Phase II results presented were not from a direct head-to-head study. The Panel did not consider the bar charts were misleading and ruled no breach of Clauses 7.2 and 7.6.

Pierre Fabre appealed the Panel's rulings.

C PAGES 6 AND 7 OF THE BOOKLET

The double page spread of pages 6 and 7 of the booklet dealt specifically with overall response rates (ORR) in Phase III trials. Text on page 6 explained that the highest available ORR data for each product had been presented and page 7 showed two bar charts, one for vinorelbine and one for Taxotere. ORR for vinorelbine was given as 15% (ref Jones *et al* (1995)) and that for Taxotere was given as 33% (ref data on file Rhône-Poulenc Rorer). The conclusion,

given on page 6, was that '… the overall tumour response rate to Taxotere is superior to that of vinorelbine'.

1 Claim 'Conclusion: In phase III trials as second-line monotherapy in patients who have previously received anthracyclines for metastatic disease, the overall response rate to Taxotere is superior to that of vinorelbine.'

COMPLAINT

Pierre Fabre noted that the references quoted in support of the claim were Jones *et al* (1995) which was a Phase III comparison of vinorelbine and melphalan, and data on file. The data on file was an unpublished comparison of docetaxel versus mitomycin plus vinblastine.

Pierre Fabre stated that these did not relate to any Phase III trial in which vinorelbine and docetaxel were compared to each other. These data were drawn from selected arms of different Phase III studies and did not provide a basis for a comparison from which this conclusion could be drawn. This statement was misleading and could not be substantiated. Pierre Fabre alleged breaches of Clauses 7.2 and 7.3 of the Code.

Pierre Fabre added that the statement had breached Clause 7.8 by using the word 'superior' which was a superlative, when from the references quoted in the booklet it was not possible to form a view that docetaxel was superior.

RESPONSE

Rhône-Poulenc Rorer agreed that the data did not relate to any Phase III trial in which vinorelbine and docetaxel were directly compared. The data certainly were drawn from selected arms of different Phase III studies. The company noted that it had already identified that it was important to present data from Phase II and Phase III studies separately, since clinicians were aware that response rates in Phase II studies were normally higher than in than in Phase III studies. It was clearly identified on the piece that each of these results were taken from separate Phase III studies using different comparator arms, and therefore, Rhône-Poulenc Rorer denied that the statement was misleading and could not be substantiated. Therefore, the company denied breaches of Clause 7.2 and 7.3 of the Code. In addition, Rhône-Poulenc Rorer also denied a breach of Clause 7.8, since it had already identified that the word 'superior' was not a superlative but rather a comparative.

PANEL RULING

The Panel noted that pages 6 and 7 of the booklet did not specifically state that the Phase III studies from which the data were derived to compare vinorelbine with Taxotere were not direct comparisons of the two products. The Panel considered that, as Phase III studies were likely to be comparative studies, it was misleading not to state that, in this case, separate studies had been used to draw an indirect comparison between vinorelbine and Taxotere. The Panel considered that the claim could not be substantiated and was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that Pierre Fabre had repeated its allegation as set out in point B2 above regarding the use of the word 'superior'. The Panel considered that its ruling of no breach of Clause 7.8 in point B2 also applied here.

Pierre Fabre appealed the Panel's ruling of no breach of Clause 7.8.

2 Title of bar charts 'Overall response rates (ORR) in Phase III trials'

COMPLAINT

Pierre Fabre stated that the title implied that the data would be drawn from Phase III trials in which vinorelbine and docetaxel were compared to each other in the same patient population. The references quoted did not relate to Phase III trials in which vinorelbine and docetaxel were compared to each other. The patient population in each trial was different by nature of the comparative agents chosen (melphalan or mitomycin/vinblastine). There was, therefore, no statistical or scientific basis for this comparison, which was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that the title did not imply that the data would be drawn from Phase III trials in which vinorelbine and docetaxel were compared to each other in the same patient population. It stated that data would be presented on time to disease progression and survival in Phase III trials. Each piece was clearly identified as being referenced to a different study. The nature of the comparative agents chosen was indeed different, but this did not imply a difference in the patient population at all. It was a difference in the treatment used in the comparator arms. Rhône-Poulenc Rorer therefore denied that this was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the title of the bar charts did not convey the fact that the data had been drawn from separate Phase III studies for each medicine. The Panel considered that failure to point this out was misleading as Phase III studies could have been a direct comparison of vinorelbine and Taxotere. A breach of Clause 7.2 was ruled.

3 Graphical presentation

Two separate bar charts on page 7 depicted the ORRs in Phase III trials for vinorelbine (15%) and Taxotere (33%). The two bar charts were side by side and drawn to the same scale but were in different colours. Beneath each bar chart was a brief description of the studies from which the results had been taken.

COMPLAINT

Pierre Fabre noted that these data were drawn from selected arms of different Phase III studies (see point C1 above). These were not Phase III trials in which vinorelbine and docetaxel had been compared with each other. The patient population in each trial was different by nature of the comparative agents chosen (melphalan or mitomycin/vinblastine). There was no statistical or scientific basis for this comparison and these graphs should not be placed in proximity within the same illustration, which was misleading. Pierre Fabre alleged breaches of Clauses 7.2 and 7.6.

RESPONSE

Rhône-Poulenc Rorer agreed that these data were drawn from selected arms of different Phase III studies. They were clearly referenced to different studies, and the populations were similar as in each arm all patients were treated as second line monotherapy for metastatic breast cancer with a previous anthracycline treatment for metastatic disease with the medicines administered at the licensed doses and schedules in the UK. Rhône-Poulenc Rorer noted that it had not drawn any statistical conclusions from these studies. As stated above, the company denied that making a comparison between two data sets was without scientific merit or was misleading. The company denied breaches of Clauses 7.2 and 7.6.

PANEL RULING

The Panel noted that the two bar charts, drawn to the same scale, were placed side by side and so invited direct comparison. The data had been taken from Phase III studies which could have been expected to be a head-to-head comparison of vinorelbine and Taxotere. The Panel noted that brief study details were given below each bar chart and each was in a different colour. Nonetheless the Panel considered that the visual impact of the bar charts was such that many readers would assume that the data was from a direct comparison of vinorelbine and Taxotere which was not the case. The Panel considered that the presentation of the bar charts was misleading in breach of Clauses 7.2 and 7.6 of the Code.

D PAGES 8 AND 9 OF THE BOOKLET

The double page spread of pages 8 and 9 of the booklet referred to disease progression and survival in Phase III trials. Text on page 8 explained that the longest available time to disease progression and survival in Phase III trials for each product was presented and page 9 showed four bar charts, two showing time to disease progression (3 months and 4.5 months for vinorelbine and Taxotere respectively) and another two showing survival time (8.1 months and 11.4 months for vinorelbine and Taxotere respectively). Data for vinorelbine had come from a paper by Jones *et al* (1995) and that for Taxotere was from Nabholtz *et al* (1998).

1 Claim 'Conclusion: In phase III trials as second-line monotherapy in patients who have previously received anthracyclines for metastatic disease, Taxotere gives longer time to disease progression and increased median survival benefit versus vinorelbine.'

COMPLAINT

Pierre Fabre noted that the references cited in support of the claim were Jones *et al* (1995) which was a Phase III comparison of vinorelbine versus melphalan and Nabholtz *et al* (1998) a Phase III comparison of docetaxel versus mitomycin plus vinblastine.

Pierre Fabre stated that these data were drawn from selected arms of different Phase III studies which were not Phase III trials in which vinorelbine and docetaxel were compared to each other. There were significant differences in the patient populations in each study. There was no scientific or statistical basis for this claim. This statement was inaccurate, misleading and could not be substantiated. Pierre Fabre alleged breaches of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer agreed that these data were drawn from different Phase III studies in which the two medicines vinorelbine and docetaxel were not directly compared. Review of the papers did not lead to the conclusion that there was either a qualitative or quantitative difference in the patient populations in each study: the only differences were those in the comparator arm. The company therefore denied breaches of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that it was difficult to determine whether or not there were any significant differences in the two patient populations. The paper by Jones *et al* was a full paper while Nabholtz *et al* was an abstract. The Panel noted that the ages of the two patient groups were almost identical.

The Panel considered that overall the other issues raised were similar to those in C1 above regarding the use of data which were not directly comparative. The Panel noted its comments in point C1 that as Phase III studies were likely to be comparative it was misleading not to state that separate studies had been used to draw an indirect comparison between vinorelbine and Taxotere and considered that its ruling of breaches of Clauses 7.2 and 7.3 also applied here.

2 Title of bar charts 'Time to disease progression and survival in phase III trials'.

COMPLAINT

Pierre Fabre referred to its complaint in C2 above.

RESPONSE

Rhône-Poulenc Rorer referred to its response in C2 above.

PANEL RULING

The Panel noted its comments in point C2 that the title of the bar charts did not convey the fact that the data had been drawn from separate Phase III studies for each medicine. The Panel considered that its ruling of a breach of Clause 7.2 also applied here.

3 Graphical representation

Four separate bar charts on page 9 depicted for vinorelbine and Taxotere time to disease progression (3 months and 4.5 months respectively) and survival (8.1 months and 11.4 months respectively) from Phase III trials. The presentation of the bar charts, together with data from the studies from which the results were taken, was similar in layout to that described in C3 above.

COMPLAINT

Pierre Fabre referred to its complaint in C3 above.

RESPONSE

Rhône-Poulenc Rorer referred to its response in C3 above.

PANEL RULING

The Panel noted that the issues raised were the same as those in point C3 above. The Panel noted its comments in point C3 that the visual impact of the bar charts was such that many readers would assume that the data was from a direct comparison of vinorelbine and Taxotere which was not so. The Panel considered that its ruling of breaches of Clauses 7.2 and 7.6 also applied here.

E PAGES 10 AND 11 OF THE BOOKLET

The double page spread of pages 10 and 11 of the booklet detailed, in tabular form, the side-effect profiles of vinorelbine and Taxotere. It was stated that the side-effects listed were taken from the SPC for each product (Taxotere: Sept '98; Navelbine: Jan. '97) unless otherwise specified.

Pierre Fabre noted that it had not been possible to obtain a copy of the Taxotere (docetaxel) SPC dated September 1998 from Rhône-Poulenc Rorer. The SPC requested and obtained in December 1998 was dated 10th November 1997. This was the most recent version available to Pierre Fabre and had been used as the basis for its complaint.

Rhône-Poulenc Rorer noted that it had already apologised to Pierre Fabre for the delay in supplying the Taxotere SPC dated September 1998 which arose due to an administrative error. This was rectified as soon as the company was made aware of the error.

The Authority noted that Pierre Fabre had based its complaint on the SPC text of November 1997. An SPC supplied to the Authority by Rhône-Poulenc Rorer in response to the complaint had been prepared in October 1998 with text which had been revised in July 1998. The Panel assumed that it was this text which would have been current when the booklet was prepared in September 1998. In consideration of the following allegations the Panel, therefore, referred to the SPC dated October 1998.

1 Neutropenia

The vinorelbine entry read 'Grade 3+4: 52.1%'. The entry for Taxotere stated 'Severe: 76.4% (This is usually of short duration [median 7 days], non-cumulative and reversible)'.

COMPLAINT

Pierre Fabre stated that severe neutropenia was defined in the docetaxel SPC as less than 500 cells/mm^3 which corresponded to World Health Organisation (WHO) grade 4 toxicity. A comparison had therefore been made between the incidence of WHO grade 3 + 4 neutropenia for vinorelbine (24.3% grade 3 plus 27.8% grade 4) and WHO grade 4 neutropenia for docetaxel (76.4% of patients). This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel in breach of Clause 7.2 of the Code.

Pierre Fabre noted that the incidence of grade 3 + 4 neutropenia was reported in 97.5% patients treated with docetaxel in a study by Ravdin *et al* (1995). As this reference had been used elsewhere in the booklet, it could be assumed that Rhône-Poulenc Rorer knew of this and chose not to use it.

Pierre Fabre also noted that Rhône-Poulenc Rorer stated that a statement relating to the duration and nature of this toxicity was included for docetaxel ('This is usually of short duration (median 7 days), non-cumulative and reversible'). A similar statement relating to the duration and nature of this toxicity associated with vinorelbine had been omitted (Rapidly reversible (5 to 7 days) and non-cumulative). This was, therefore, an incomplete comparison that was misleading.

Pierre Fabre alleged a breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer did not understand how the direct comparison of the approved SPC could be unfair. Rhône-Poulenc Rorer stated that in all tables, it had directly compared the texts of the SPCs unless stated otherwise and this was clearly identified to the reader in the text directly opposite the table.

The company agreed that the table contained WHO grade 3 + 4 neutropenia for vinorelbine, and severe neutropenia for docetaxel. Rhône-Poulenc Rorer stated that it had clearly identified WHO grade 3 + 4 for vinorelbine, and severe neutropenia, which was the term used in the Taxotere SPC. All the company was doing was comparing the SPCs. For Rhône-Poulenc Rorer to have used another descriptive term regarding myelotoxicity would have been outside the

legitimacy of its SPC. The company therefore denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the two SPCs for Navelbine and Taxotere used different nomenclature to describe the severity of neutropenia. The Navelbine SPC used WHO grades 1 to 4 while the Taxotere SPC referred only to severe neutropenia which it defined as <500 cells/mm^3. The Panel understood that only WHO grade 4 was equivalent to the description 'severe'. The table of adverse events, however, had compared the incidence of neutropenia WHO grades 3 and 4 (vinorelbine) with 'severe' (Taxotere).

The Panel noted that additional information regarding the short duration, non-cumulative nature and reversibility of the neutropenia associated with Taxotere had been given. Similar positive information appeared in the Navelbine SPC but had not been included in the table.

The Panel considered that the comparison of WHO grade 3 and 4 with severe neutropenia was not fair and the failure to include the additional information regarding the nature of the neutropenia associated with Navelbine, having included the comparable information for Taxotere, was misleading. A breach of Clause 7.2 was ruled.

2 Fluid retention

There was no entry for vinorelbine. The entry for Taxotere stated 'Severe: 6.5%' and gave details of the median cumulative dose shown to cause the onset of moderate or severe fluid retention.

COMPLAINT

Pierre Fabre stated that the overall incidence of fluid retention associated with docetaxel administration was 81.6% (22.4% severe). Only with pre-medication could the incidence and severity of fluid retention be reduced to 64.1% patients (6.5% severe). The data relating to this toxicity was thus incomplete for docetaxel in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that it considered it appropriate to quote a rate of severe fluid retention (agreed with Pierre Fabre and as quoted in the Taxotere SPC) of 6.5%. All patients who received Taxotere should routinely receive pre-medication with steroids unless absolutely contraindicated. Therefore, it was extremely unlikely that patients would receive docetaxel without steroid pre-medication, and the company was not aware of any cases in which docetaxel had been given without steroid pre-medication in the UK since the drug had been commercially available. Rhône-Poulenc Rorer considered it inappropriate to include toxicity results relating to the inadvisable use of Taxotere. The company considered that this was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the Taxotere SPC gave the incidence of severe fluid retention with and without pre-medication with steroids (6.5% and 22.4% respectively). In the Panel's view, a small number of patients, ie those for whom steroids were contraindicated, would receive Taxotere therapy without pre-medication. Given that the SPC stated both figures and given the importance of pre-medication on the incidence of severe fluid retention the Panel considered that the brief statement in the booklet was misleading. A breach of Clause 7.2 was ruled.

3 Peripheral neuropathy, neuromotor effects and autonomic neuropathy

The entry for vinorelbine read 'Grade 3 + 4: peripheral neuropathy 2.7%' and that for Taxotere stated 'Severe peripheral neuropathy 4.1%'.

COMPLAINT

Pierre Fabre noted that the term 'severe' was not defined for docetaxel toxicity. A comparison had therefore been made between the incidence of WHO grade 3 + 4 neuropathy for vinorelbine and undefined 'severe' toxicity for docetaxel. This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel and this was in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer agreed that the term 'severe' was not precisely defined for docetaxel toxicity, either in the booklet or in the SPC. The SPC clearly stated that severe peripheral neuropathy occurred in 4.1% of cases treated with Taxotere and this was therefore used in the piece. Similarly, the company had presented the WHO grade 3 and 4 data for vinorelbine, and clearly identified it as such. Therefore, the data had been presented in a balanced, fair, objective and unambiguous way, and Rhône-Poulenc Rorer denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the figures given for both medicines had been accurately quoted from the two SPCs which used different nomenclature to describe the severity of peripheral neuropathy. The Navelbine SPC referred to grades 3 and 4 combined. Separate incidence figures for each grade were not stated. The Panel understood that the WHO definition for grade 3 neuropathy was 'intolerable paraesthesia and/or marked motor loss'. The definition of grade 4 was 'paralysis'. 'Severe' peripheral neuropathy as referred to in the Taxotere SPC was not further defined. In the Panel's view 'severe' and 'grade 3 and 4' peripheral neuropathy would be seen as being roughly equivalent particularly as the Navelbine SPC referred to grades 3 and 4.

In the circumstances the Panel did not consider that the comparison was misleading and ruled no breach of Clause 7.2 of the Code.

4 Alopecia

The vinorelbine entry stated 'Grade 3 + 4: 4.1%' and that for Taxotere stated 'Severe: 67%. ('Coldcap is 'very effective' in preventing alopecia.')'.

COMPLAINT

Pierre Fabre stated that the term 'severe' was not defined for alopecia associated with docetaxel. A comparison had therefore been made between the incidence of WHO grade 3 + 4 alopecia for vinorelbine (4.1%) and an undefined 'severe' alopecia for docetaxel (67%). This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer referred to its submission in point E3 above.

PANEL RULING

The Panel noted that the figures given for both medicines had been accurately quoted from the two SPCs which used different nomenclature to describe the severity of alopecia. The Navelbine SPC referred to grades 3 and 4 combined. Separate incidence figures for each grade were not stated. 'Severe' alopecia as referred to in the Taxotere SPC was not further defined. The Panel noted that there was a marked difference between the products. The Panel did not consider that the comparison was inaccurate or misleading as alleged and no breach of Clause 7.2 was ruled.

5 Hypersensitivity reactions

The vinorelbine entry read 'Occasionally' while that for Taxotere stated 'Overall: 25.9% Severe: (generally reversible, manageable) 5.3%'.

COMPLAINT

Pierre Fabre noted that the docetaxel entry included the additional information 'generally reversible, manageable' that did not appear in the SPC and was not referenced to another source. The SPC for docetaxel stated that '… severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.' The SPC went on to describe that severe hypersensitivity reactions occurred in 5.3% of patients and were a contra-indication for re-administration of docetaxel. The omission of this information and insertion of the above statement might compromise patient safety and understate the significance and severity of this toxicity and was therefore misleading. Pierre Fabre alleged a breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer submitted that there were two issues in this allegation: first that it had omitted information and secondly that it had inserted additional information, namely 'general reversible, manageable'. The company agreed that the SPC for docetaxel stated that 'severe reactions … require immediate discontinuation of docetaxel and appropriate therapy', and that it indicated that severe hypersensitivity reactions occurred in 5.3 % of patients. This information was also included in an abridged form within the prescribing information printed on page 18 of the booklet, and was referred to on the pages concerned. The company supported the insertion of the phrase 'generally reversible, manageable' by the wealth of clinical data available and its pharmacovigilance database. Therefore, Rhône-Poulenc Rorer considered that this information had not been omitted and that there had been no breach of Clause 7.2.

PANEL RULING

The Panel noted that the SPC for Taxotere stated that 'Severe reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema were observed in 5.3% of patients. They resolved after discontinuing the infusion and instituting appropriate therapy'. The SPC also stated that a history of severe hypersensitivity reactions to Taxotere was a contra-indication to further treatment with the medicine. On balance the Panel considered that the statement 'generally reversible, manageable' with regard to severe hypersensitivity reactions was overly reassuring and did not accurately reflect the information given in the SPC. It was immaterial that additional data was included in the prescribing information as it was an accepted principle under the Code that misleading claims etc could not be qualified by the small print. A breach of Clause 7.2 was ruled.

6 Nausea and vomiting

The entry for vinorelbine read: 'Overall: 30.4% Grade 3 + 4: 2.2%'; that for Taxotere read 'Nausea: (overall) 40.5%, severe 4% Vomiting: (overall) 24.5%, severe 3%.'

COMPLAINT

Pierre Fabre stated that the term 'severe' was not defined for nausea or for vomiting associated with docetaxel. A comparison could not be drawn between these agents when toxicity was expressed according to WHO grades 3 + 4 for vinorelbine (nausea and vomiting) and reported separately (nausea: vomiting) with undefined measures, for docetaxel. Also the reporting of these two side effects separately might serve to reduce the significance of this side effect associated with docetaxel. This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel and this was in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that it had directly compared the terminology of the two SPCs. The company considered that the issue here was one of

confused semantics. Rhône-Poulenc Rorer had reported severe nausea and vomiting for Taxotere (defined by the European Medicines Evaluation Agency as grades 3 and 4). The same argument applied as for point E1 above. The company denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the information given for both medicines had been accurately quoted from the two SPCs which dealt differently with nausea and vomiting. The Navelbine SPC combined them as a single entity and graded such reactions as grade 1, 2, 3 or 4. Combining the figures for grades 3 and 4 gave an incidence of nausea and vomiting of 2.2%. The SPC stated that 'severe nausea and vomiting may occasionally occur'. With regards to vomiting the Panel understood that grade 3 was 'vomiting requiring therapy' and grade 4 was 'intractable vomiting'. Taxotere reported the incidences of nausea and vomiting separately and gave a figure for severe reactions. 'Severe' as referred to in the Taxotere SPC was not defined. In the Panel's view 'severe' and grades 3 and 4 nausea and vomiting would be seen as being roughly equivalent. In the circumstances the Panel did not consider that the comparison was misleading and ruled no breach of Clause 7.2 of the Code.

7 Diarrhoea

The entry for vinorelbine read 'Overall: 12%, Grade 3 + 4: 0.8%', while that for Taxotere stated 'Overall: 40.6% Severe: 4%'.

COMPLAINT

Pierre Fabre stated that the term 'severe' was not defined for diarrhoea associated with docetaxel. A comparison had therefore been made between the incidence of WHO grade 3 + 4 diarrhoea for vinorelbine (0.8%) and an undefined 'severe' diarrhoea for docetaxel (4%). This was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that it had directly compared the terminology of the two SPCs. Furthermore, the term 'severe diarrhoea' as used in the Taxotere SPC was defined by the European Medicines Evaluation Agency as grades 3 and 4 ie identical to the measures used in vinorelbine.

PANEL RULING

The Panel noted that the two SPCs for Navelbine and Taxotere used different nomenclature to describe severity of diarrhoea. The Navelbine SPC used WHO grades 1 to 4 and stated that 'severe diarrhoea is uncommon' while the Taxotere SPC referred only to an overall incidence and the incidence of severe diarrhoea. The Panel understood that the WHO definition of grade 3 diarrhoea was 'intolerable, requiring therapy' and for grade 4 'haemorrhagic dehydration'. 'Severe' diarrhoea as referred to in the Taxotere SPC was not further defined but the Panel noted Rhône-Poulenc Rorer's submission that the European Medicines Evaluation Agency had defined it as grades 3 and 4. In the Panel's view 'severe' and 'grades 3 + 4' diarrhoea were equivalent. The Panel did not consider that the comparison was misleading and ruled no breach of Clause 7.2 of the Code.

8 Cardiac events

The entry for vinorelbine read '2.6%' while that for Taxotere read: 'Hypotension: 3.8% Rare cases of myocardial infarction reported'.

COMPLAINT

Pierre Fabre stated that only the figures for hypotension were quoted for docetaxel whereas no qualification was given for the figures quoted in respect of vinorelbine and therefore it could be assumed by the reader to cover the whole range of possible cardiac events. The figures produced for docetaxel implied that the only adverse events documented were hypotension and 'rare cases of myocardial infarction'. The list of cardiac events listed within the docetaxel SPC3 included hypotension, 3.8%; dysrhythmia, 4.1%; hypertension, 2.4%; heart failure, 0.46%.

Only hypotension was reported in this table. This analysis was therefore incomplete and was not a basis for a balanced, fair, objective and unambiguous comparison of vinorelbine with docetaxel in breach of Clause 7.2 of the Code.

RESPONSE

Rhône-Poulenc Rorer noted that cardiac adverse events were not mentioned in the Navelbine SPC, and therefore it was not possible to directly compare the SPCs because data were not available for comparison. Importantly, the Pierre Fabre publication 'Focus on Navelbine' reported 39 cardiac events in Phase II clinical trials, an overall incidence of 2.6%. The nature of these events, nor their casualty, was not mentioned in the piece, even in the case of the grade 3 and 4 events. To tabulate all of the events possibly associated with Taxotere and not to do so for Navelbine (Pierre Fabre had chosen not to share this data with the clinical community in their international monograph) would have been unfairly unbalanced against Taxotere. However, Rhône-Poulenc Rorer stated that it took the responsible course and alerted clinicians to the most frequent cardiac event associated with Taxotere (ie hypotension) and the most severe, although rare (myocardial infarction) even though it did slightly bias the piece against its own product. The company noted that the Taxotere SPC highlighted the fact that in most cases the causality of the cardiac events associated with Taxotere treatment was in doubt.

As a result of the above, Rhône-Poulenc Rorer considered the piece was balanced and fairly represented the facts. The company therefore denied a breach of the Code.

PANEL RULING

The Panel noted that incidence figures for hypotension and dysrythmia were stated in the Taxotere SPC. Incidence figures were also given for hypertension and heart failure although it was stated that the relationship of these reactions to the administration of docetaxel had not been clearly defined. Venous thromboembolic events and myocardial infarction had both been rarely reported. The Panel noted that the booklet referred only to hypotension and myocardial infarction and considered that this was not an accurate reflection of the Taxotere SPC. The Panel noted that the figure of 2.6% for vinorelbine had been taken from Phase II clinical trials not the product SPC. It appeared that the nature of the adverse events had not been further defined nor had their causal relationship with vinorelbine therapy been established. The SPC did not refer to adverse cardiac events. Overall the Panel considered the comparison was misleading. A breach of Clause 7.2 was ruled.

9 Omission of major toxicity associated with docetaxel

COMPLAINT

Pierre Fabre noted that other toxicity associated with docetaxel was listed in the SPC but not reported on pages 10 and 11 of the booklet. These included: stomatitis, 41.8% (5.3% severe); asthenia, 62.6% (11.2% severe); cutaneous reaction, 56.6% (5.9% severe). All of these toxicities might have a significant effect on patient wellbeing and the omission of these side effects from this table was misleading. Pierre Fabre alleged a breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer stated that asthenia, stomatitis and cutaneous reactions were common to most anticancer agents and since it was not possible to quantitate any of them from the Navelbine SPC, it was not possible to produce a balanced comparison in this context. The company stated that it was not its intention to list all known side-effects of both agents, and indeed, there were a number of side effects of vinorelbine eg anaemia (7.4% grade 3 and 4) and thrombocytopenia (2.5% grade 3 and 4) that were not used. In the absence of data, therefore, it would not have been a balanced comparison. Rhône-Poulenc Rorer therefore denied breaches of Clause 7.2.

PANEL RULING

The Panel noted that there was no indication that the comparative list of side-effects was intended to be exhaustive. In the Panel's view the target audience would not assume this to be the case. Page 10 of the booklet stated that the side-effects listed had been taken from the relevant SPC. The Taxotere SPC listed side-effects according to body system. Reactions from each body system listed had been included in the table with the exception of cutaneous reactions and hepatic reactions. Hepatic reactions occurred in less than 5% of patients. Cutaneous reactions had been observed in 56.6% of patients and were generally considered to be mild or moderate. The Panel noted, however, that less frequently (5.9%) severe reactions occurred which in rare cases led to interruption or discontinuation of Taxotere therapy. The Panel considered that to make no mention of a group of reactions which affected more than half of those who received Taxotere therapy, and which could, rarely, be severe enough to interrupt therapy, was misleading. A breach of Clause 7.2 of the Code was ruled.

F PAGES 12 AND 13 OF THE BOOKLET

The double page spread of pages 12 and 13 of the booklet were headed 'Taxotere The convenience advantages'. A table of data comparing various administration data for vinorelbine and Taxotere was given. The page included a claim that 'Taxotere is more convenient to administer than vinorelbine'. It was stated that the information presented in the table had been taken from the relevant SPCs (Taxotere: September 1998; Navelbine: January 1997) unless otherwise stated.

Pierre Fabre noted that certain categories of data had been selected (eg cold capping, pre-medication) to imply 7 advantages for docetaxel over vinorelbine. Pierre Fabre stated that, based on the following allegations, this was not an accurate, fair, objective and unambiguous comparison, could not be substantiated and was disparaging.

1 Extravasation

The Taxotere entry in the table of data read 'Non-vesicant: No extravasation injuries have been reported in the UK' and was referenced to Padzur *et al* (1992). In text alongside the table of data the stab point 'non-vesicant [Padzur *et al* (1992)]: no injuries have been reported in the UK [Data on file RPR]' appeared.

COMPLAINT

Pierre Fabre referred to the statement in the table and noted that the reference cited in support (Padzur *et al*) was published before the introduction of docetaxel into the UK (January 1996) and was therefore, unable to substantiate this claim and was misleading. Injection site reactions, including extravasation, were reported in 5.6% patients as noted in the docetaxel SPC. Rhône-Poulenc Rorer had chosen to ignore this data from the SPC and the statement was therefore misleading. Pierre Fabre alleged breaches of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that Padzur *et al* was not a justification that no extravasation injuries had been reported in the UK; it was a reference for the statement that Taxotere was non-vesicant. Padzur *et al* was a study in which docetaxel was administered by bolus injection, a route of administration much more likely to lead to substantial extravasation of concentrated medicine than the licensed intravenous infusion. Even in the circumstances in which the medicine was directly extravasated in concentrated form in 5 patients, no vesicant activity was

demonstrated. Rhône-Poulenc Rorer therefore considered that this substantiated the claim that docetaxel was non-vesicant and trusted that there had been no breach of either Clause 7.2 or 7.3 of the Code. The claim that no extravasation injuries had been reported in the UK (at the time of preparation of the piece) was based upon a review of the company's UK adverse reaction database and was referenced as such.

PANEL RULING

The Panel noted that the information given in the table had been referenced such that it appeared that Padzur *et al* supported the whole statement which was not so. References had been correctly cited in the text alongside the table.

The Panel noted that the claim non-vesicant was supported by Padzur *et al*. The Taxotere SPC, however, included the statement 'Infusion site reactions were generally mild, occurred in 5.6% of patients, and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein'. The Panel considered, therefore, that while the statement 'No extravasation injuries have been reported in the UK', might be factually correct, reflecting the time that the medicine had been available in the UK, the implication was that no extravasation injuries had ever been reported with docetaxel which was not true. Extravasation was mentioned in the SPC. The Panel considered that the statement was misleading and ruled a breach of Clause 7.2. The Panel noted the response from Rhône-Poulenc Rorer that the statement was factually correct and could be substantiated by UK adverse reaction data. The Panel noted that the data had not been supplied. It therefore ruled a breach of Clause 7.3.

2 Premedication

The entry for vinorelbine read 'None' and that for Taxotere read '8mg dexamethasone bd po x 3 d (Days-1, 1 and 2)'.

COMPLAINT

Pierre Fabre stated that premedication with steroids was an intervention to reduce the frequency and severity of fluid retention associated with docetaxel use. This procedure extended the clinical or nursing time required for the administration of docetaxel and also increased the cost of treatment. There was no need for this premedication with vinorelbine monotherapy. The need for premedication could not be substantiated as 'a convenience advantage' for docetaxel as proposed in the title of this page and was in breach of Clause 7.3. The presentation of the data in this way was, therefore, misleading and Pierre Fabre alleged a breach of Clause 7.2.

RESPONSE

Rhône–Poulenc Rorer disagreed that premedication with steroids extended the clinical or nursing time required for the administration of docetaxel. The steroid pre-medication was in the form of 8mg of dexamethasone taken by mouth twice daily for three days starting the day before Taxotere administration and normally provided as tablets for the patient to take at home. Therefore, there was no extension of clinical or nursing time required. The company could not therefore, see how this was in breach of Clause 7.2 or Clause 7.3.

PANEL RULING

The Panel noted that the information given in the table about premedication was accurate. In the Panel's view the heading 'Taxotere The convenience advantages' did not imply that every comparison with vinorelbine would be in favour of Taxotere. Indeed the Panel noted that to have constructed the table such that only data favourable to Taxotere had been included might in itself have been misleading in breach of the Code. The Panel considered that information about premedication was one element of administration data that was relevant to convenience as a whole. The Panel did not consider it misleading. No breach of Clauses 7.2 and 7.3 was ruled.

3 Cold capping

The vinorelbine entry read 'Not stated'. The entry for Taxotere read 'Yes, prevents alopecia (< Grade 2) in 86% of patients' This statement was referenced to Lemenager *et al* (1997).

COMPLAINT

Pierre Fabre stated that cold capping was an intervention to reduce the frequency and severity of alopecia associated with docetaxel use. This procedure extended the clinical or nursing time required for the administration of docetaxel and also increased the cost of treatment and the level of discomfort experienced by the patient. Alopecia associated with vinorelbine monotherapy was mild and might appear progressively with extended courses of treatment and cold capping was not recommended or routinely used.

The need for cold capping could not be substantiated as 'a convenience advantage' for docetaxel as proposed in the title of this page and was in breach of Clause 7.3. The presentation of this data in this way was, therefore, misleading and Pierre Fabre alleged a breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer agreed that cold capping reduced the severity and frequency of alopecia associated with docetaxel use. Docetaxel-induced alopecia appeared early and cold capping was effective in preventing it in the majority of cases in which it was used. It could be administered simply by placing the patient underneath a machine, which resembled a salon hairdryer, which blew cold air over the scalp during the time immediately before docetaxel was administered, during the actual administration, and for 15 minutes afterwards. No special nursing care was required if the cold capping was administered in this way. By comparison, the

alopecia associated with vinorelbine therapy became progressively worse with extended courses of treatment, and Rhône-Poulenc Rorer considered that the reason cold capping was not recommended or routinely used was that it was ineffective with vinorelbine. The company considered that Pierre Fabre was not only confused over its assertion that Taxotere was inconvenient to use, but it had also misunderstood the nature of additional benefits when compared with treatment convenience. Rhône-Poulenc Rorer considered that the ability to maintain patient confidence by prevention of alopecia in the majority of cases treated with Taxotere was of considerable advantage for docetaxel and so the claim was not in breach of either Clause 7.2 or 7.3.

PANEL RULING

The Panel noted that cold capping, although not referred to in the Taxotere SPC, had been shown to prevent alopecia in some patients (Lemenager *et al* 1997). The Panel appreciated that such a procedure could be viewed as inconvenient but the fact that there was a procedure which could be used to prevent Taxotere-induced alopecia might also be seen as an advantage. The Panel did not consider the statement misleading. The Panel ruled no breach of Clauses 7.2 and 7.3.

4 Nursing observation per cycle

The entry for vinorelbine read 'Occasionally during 30 minutes infusion' and that for Taxotere read 'Beginning and end of one hour infusion'.

COMPLAINT

Pierre Fabre noted that the SPC for docetaxel stated that 'Patients should be observed closely especially during the first and second infusion of docetaxel because of the risk of hypersensitivity reactions'. The company also noted that infusion site reactions (reported in 5.6% of patients) included inflammation, phlebitis, extravasation and swelling of the vein all of which might become apparent during the infusion of docetaxel. Pierre Fabre submitted that regular checks throughout the infusion was good nursing practice. This was inconsistent with the advice 'Beginning and end of one hour infusion'.

Pierre Fabre stated that administration of any cytotoxic chemotherapy should only be undertaken with close haematological monitoring and careful patient assessment by trained staff. In addition, haematological monitoring was always required to assess patients for re-treatment and to calculate dosage adjustments if required (eg patients who experienced neutrophils < 500 cells/mm^3 for more than one week during docetaxel therapy should have the dosage reduced). Patients should also be monitored for signs and symptoms of infection which with docetaxel were serious in 5.7% of patients and fatal in 1.7%. Appropriate emphasis on monitoring for signs and symptoms of infection should reflect the information in the docetaxel SPC and should be included in any assessment for nursing observation required for each cycle of treatment.

Pierre Fabre noted that other pre-medication procedures recommended in the SPC for docetaxel included: dexamethasone, 8mg bd for three days starting one day prior to the start of therapy and cold capping. Interaction with medical and/or nursing staff during pre-medication procedures was likely.

Pierre Fabre stated that the statement 'Beginning and end of one-hour infusion' was therefore a gross understatement of the nursing effort required to administer docetaxel safely. This was a breach of Clause 7.2 and the Code.

RESPONSE

Rhône-Poulenc Rorer agreed that the administration of any cytotoxic chemotherapy should only be undertaken with close haematological monitoring. However, haematological monitoring did not require any nursing or medical time apart from the time taken to look at laboratory results. Only neutropenia which resulted in clinical symptomatology required assessment and the patient information leaflet for Taxotere clearly advised patients to report any symptoms, either of infection, or even a raised temperature. Taxotere treatment was a three-weekly, 1 hour, outpatient treatment and it was not routine practice for patients treated with Taxotere even to be required to re-attend on a weekly basis for nursing assessment, and the company would not consider that this was necessary. Corticosteroid pre-medication, as already outlined, was normally taken as an outpatient and therefore, did not impact upon medical or nursing staff. Rhône-Poulenc Rorer therefore did not consider that the nursing effort required to administer docetaxel had been grossly understated, or that there had been a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that the statement 'Beginning and end of one hour infusion' was not consistent with the SPC which read 'Patients should be observed closely especially during the first and second infusion of docetaxel because of hypersensitivity reactions.' The Panel considered that the statement in the table was thus misleading in breach of Clause 7.2 of the Code.

5 Patient, doctor and nursing convenience

The entry for vinorelbine stated 'Once a week for 9 weeks (range 1-66) = 9 visits'. The Taxotere entry read 'Once every 3 weeks x 6 cycles (range 1-12) = 6 visits'.

COMPLAINT

Pierre Fabre stated that it was difficult to understand the meaning of this comparison and convenience might be interpreted differently by a patient, a doctor and a nurse. Even on the basis of the comparison made by Rhône-Poulenc Rorer, if the number of visits was to be used as a surrogate for convenience then the number of visits should accurately reflect what was required during treatment. The frequency of contact with healthcare professionals was affected by many factors other than the administration of the

cytotoxic agent. These included: assessment of response to treatment; pre-medication, if required; haematological monitoring; toxicity, including infection and neutropenia.

Pierre Fabre stated that this was a meaningless and inaccurate summary, which gave a misleading impression that docetaxel was more convenient than vinorelbine and the claim could not be substantiated. Pierre Fabre alleged breaches of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Rhône-Poulenc Rorer stated that it was generally accepted that weekly visits were less convenient than three weekly visits. The company agreed that the frequency of contact with healthcare professionals was affected by many different factors, but clearly the baseline was affected by the fact that more visits were required for chemotherapy administration for Navelbine than for Taxotere. The assessment of response to treatment was normally made at the time of the clinical administration of chemotherapy, and pre-medication for the next cycle was dispensed at the time that chemotherapy was given for the preceding cycle, so that it might be taken as an outpatient. Haematological monitoring did not require patient, doctor or nursing time, apart from the time taken to look at results of blood samples taken by a phlebotomist. In view of the above, Rhône-Poulenc Rorer did not consider that this was a meaningless and inaccurate summary, or that it could not be substantiated and denied breaches of Clause 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that this particular entry in the table of information implied that patient, doctor and nursing convenience was related only to the number of visits a patient had to make to receive either vinorelbine or Taxotere therapy. By comparing 9 visits (vinorelbine) with 6 visits (Taxotere) the impression was that that Taxotere was more convenient to administer than vinorelbine. In the Panel's view patient, doctor and nursing convenience was related to more than the number of times the medicine had to be administered. The Panel considered that the statement was too simplistic and could not be substantiated; it was also misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

G PAGES 14 AND 15 OF THE BOOKLET

The double page spread of pages 14 and 15 of the booklet was headed 'Taxotere The economic advantage' and detailed an economic evaluation of the two medicines (Launois *et al* 1996). A table of comparative costs was included.

1 Claim 'A French pharmacoeconomic model based on actual patient data from 153 medical reports from 5 hospitals showed that:

'Docetaxel reduces the time spent with, and decreases the number of complications due to, progressive disease and thereby provides better quality of life (compared with vinorelbine). It brings a benefit equivalent to an extra 57 disease- and discomfort-free days, compared with vinorelbine."

COMPLAINT

Pierre Fabre stated that this claim implied that the actual patient data from the medical records of 153 patients was used as a basis for the construction of this pharmacoeconomic model. It was the only data source mentioned. The quotation from the paper implied differences in the clinical outcome with respect to response, quality of life and survival. A reader would reasonably assume that these 153 patient records were the source of comparative data on treatment with the medicine being evaluated, including response rates, survival, quality of life and actual economic consumption.

Pierre Fabre noted that in the paper Launois *et al* reported that the clinical data came from the following sources:

- docetaxel: The drug registration master file (111 patients pooled from 3 Phase II studies)
- paclitaxel: interim results of the BMTSG trial (123 patients)
- vinorelbine: from the trial conducted routinely in a clinical department by Degardin *et al* (100 patients)

Quality of life was estimated. No measurement of quality of life was conducted with patients. The expected progression free survival was calculated. Cost of treatment with docetaxel or paclitaxel was estimated by substituting for the actual chemotherapy used (which was not necessarily with single agent vinorelbine).

A retrospective analysis of 153 patient records from patients receiving any form of second-line chemotherapy for metastatic breast cancer (not necessarily with any of the single-agent medicines being compared) was used to estimate the mean number of related procedures and hospital admissions.

Pierre Fabre stated that the claim that this model was '… based on actual patient data from 153 medical reports from 5 hospitals' was an exaggeration and therefore misleading in breach of Clause 7.2 of the Code.

Pierre Fabre noted that the quotation had been taken from a paper discussing a constructed, French, pharmacoeconomic model. It was not a clinical trial comparing vinorelbine and docetaxel (and paclitaxel) and no prospective clinical, survival or quality of life data was measured. Any claims of clinical benefit or 'better' quality of life were inappropriate and were misleading in breach of Clauses 7.2 and 11.2 of the Code.

Pierre Fabre also noted that it was not made clear that the words '… compared with vinorelbine' had been added to the quotation. This was misleading in breach of Clause 7.2.

RESPONSE

Rhône-Poulenc Rorer stated that the Launois paper used standard and validated techniques for estimating quality of life in patient care. The statement 'Docetaxel reduces the time spent with, and decreases the number of complications due to, progressive disease and thereby provides better quality of life… equivalent to an extra 57 disease- and discomfort-free days, compared with vinorelbine', was an accurate reflection of this independent peer-reviewed article.

The progression free survival was calculated as was the cost of treatment used, using standard and well-validated techniques. The page was headed 'economic advantage' and the economic data in the model was based upon actual patient data from 153 reports from 5 hospitals as stated in the text. Rhône-Poulenc Rorer therefore denied a breach of Clause 7.2 of the Code.

Rhône-Poulenc Rorer considered that pages 14 and 15 made it explicitly clear that the Launois paper discussed an economic model, it was nowhere claimed that this was a clinical trial. The quotation, which was an accurate reflection of the context of the paper, qualified better quality of life in the form of a benefit equivalent to an extra 57 disease- and discomfort-free days. Therefore, the company did not consider that there had been a breach of Clauses 7.2 of 11.2.

Rhône-Poulenc Rorer explained that the words 'compared to vinorelbine' were added in order to ensure that the reader could interpret the quotation correctly. The company therefore denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim referred to a French pharmacoeconomic model. Notwithstanding this, the results were presented in clinical language and the Panel considered that the impression given was that they were from a direct clinical comparison of vinorelbine and Taxotere which was not so. The pharmacoeconomic model was based on a retrospective study of 153 case records from patients treated with a second-line therapy for metastatic breast cancer. Having established the model, data from patients who had been treated with vinorelbine (n=100) or Taxotere (n=91) was applied. Thus the respective costs and merits of the two medicines had been indirectly compared. The data regarding quality of life had been gathered from asking nurses not the patients themselves. The Panel did not consider that sufficient information had been given to allow the reader to fully understand on what basis the comparison had been made. The Panel considered the claim was misleading and ruled a breach of Clause 7.2.

The Panel noted that the conclusions of the study were as given in the booklet. The opinion of the authors had thus been accurately stated and no breach of Clause 11.2 was ruled.

With regard to that part of the claim in the booklet which was in quotation marks, the Panel noted that none of it, irrespective of whether '(compared with vinorelbine)' had been added or not, was a quotation from Launois *et al*. The Panel considered that although the claim reflected the findings of the study it was inaccurate and misleading to present it as a direct quote. A breach of Clause 7.2 was ruled.

2 Table comparing costs and progression-free days

COMPLAINT

Pierre Fabre noted that the table as presented in the booklet had been adapted from the publication by Launois *et al* and this should have been made clear. The company alleged a breach of Clause 7.6 of the Code.

Pierre Fabre noted that the clinical data for vinorelbine used to build this pharmacoeconomic model was a clinical paper published by Degardin *et al* (1994). In this clinical paper, vinorelbine was used as a salvage treatment for 100 heavily pre-treated patients (up to 3 previous chemotherapy regimens) with 44% having a performance status (PS) <2 (PS 2 was resting up to 50% daylight hours, PS 3 was confined to bed or chair for more than 50% daylight hours). The company submitted that significant differences existed between the clinical experience and patient selection reported by Degardin and the current indication for vinorelbine in the UK. This was, therefore, a misleading economic comparison of vinorelbine with docetaxel in relation to clinical practice in the UK and a breach of Clause 7.2 of the Code.

Pierre Fabre considered that the phrase 'Taxotere dominates vinorelbine' was an exaggerated claim not substantiated for UK clinical practice and alleged a breach of Clause 7.8.

RESPONSE

Rhône-Poulenc Rorer noted that vinorelbine was licensed in the UK for the 'treatment of advanced breast cancer stages 3 and 4 relapsing after or refractory to an anthracycline containing regimen'. Therefore the patients treated by Degardin *et al* were all within the current therapeutic indication for vinorelbine in the UK. Consequently, Rhône-Poulenc Rorer could not understand the objection raised by Pierre Fabre and denied a breach of Clause 7.2 of the Code.

Rhône-Poulenc Rorer submitted that the phrase 'Taxotere dominates vinorelbine' was not a clinical term, and was a fair representation of the reference. It was clearly identified that this was a pharmacoeconomic argument taken from an pharmacoeconomic model and was language used in that context to describe superiority. As this was the verbatim quote, it was not appropriate to modify it. The company denied a breach of Clause 7.8.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.6 of the Code stated, *inter alia*, that if a table was taken from a published paper but had not

been reproduced in its entirety it must be clearly labelled as having been adapted from the paper in question. The Panel noted that the table in the booklet was a composite of two tables and some text from the Launois paper. The table had, therefore, not been taken from the paper as such and so there was no need to state that it had been adapted from it. The Panel ruled no breach of Clause 7.6 of the Code.

The Panel noted that the vinorelbine data in the Launois paper had been taken from the study by Degardin *et al*. Degardin had treated patients with refractory advanced and/or metastatic breast cancer all of whom had previously received treatment with an anthracycline. In the Panel's view such a population was not inconsistent with the licensed indication of 'advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen'. The Panel, therefore, did not consider that the Degardin study provided a misleading comparison as alleged and ruled no breach of Clause 7.2.

The Panel noted Rhône-Poulenc Rorer's submission that 'Taxotere dominates vinorelbine' was a pharmacoeconomic claim not a clinical claim. In the Panel's view, however, some readers would not be familiar with pharmacoeconomic terms and might assume that, in a booklet which otherwise dealt with the clinical aspects of vinorelbine and Taxotere, this was a clinical claim. The Panel considered that, in the context in which it had been used, the claim was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that Taxotere was indicated for the treatment of advanced breast cancer after the failure of previous chemotherapy. However, of the Taxotere-treated patients included in the Launois study, only 90% had received previous chemotherapy which meant that 10% were being treated with the medicine outwith its licensed indication. In addition the Panel noted that all patients had received premedication with oral dexamethasone (8mg bd) for five days and not three days as recommended in the Taxotere SPC. In the Panel's view the Taxotere-treated patients had not been treated in accordance with the SPC. There was, however, no allegation in this respect but the Panel requested that Rhône-Poulenc Rorer and Chugai be advised of its views.

During its consideration of this matter the Panel noted that the economic model used in the Launois paper had been based on the French health system. The Panel questioned whether this was wholly applicable to the NHS in the UK and asked that Rhône-Poulenc Rorer and Chugai be advised of its concerns.

Pierre Fabre appealed the Panel's rulings of no breach of the Code.

H PAGES 17 OF THE BOOKLET

Page 17 of the booklet bore the following text:

'In non-comparative clinical trials, an analysis of the available data for Taxotere and vinorelbine monotherapy for the second-line treatment of patients with anthracycline-pretreated metastatic breast cancer, shows that Taxotere gives:

- higher overall tumour response rates
- longer time to disease progression
- longer median survival
- better Quality of Life
- more convenient administration'

COMPLAINT

Pierre Fabre referred to its complaints in A above (A1 to A9 inclusive).

RESPONSE

Rhône-Poulenc Rorer referred to its responses in A above (A1 to A9 inclusive).

PANEL RULING

The Panel noted that the text on page 17 was almost identical to that at issue on page 3 and considered in A above. The Panel noted that page 17 did not refer to 'The best available data …' (point A2). With the exception of its ruling in point A2 the Panel therefore considered that all of its comments and rulings similarly applied to page 17.

I OVERALL IMPRESSION OF THE BOOKLET

COMPLAINT

Pierre Fabre stated that the treatment of cancer patients with cytotoxic chemotherapy was a pharmaceutical intervention associated with significant morbidity and mortality. Clinicians must be confident that promotional material produced by the pharmaceutical industry was accurate and designed to ensure the safe administration and use of these agents. In view of the nature and frequency in which the Code had been breached throughout the booklet, this material had served to reduce confidence in, and bring discredit upon, the pharmaceutical industry and was, therefore, in breach of Clause 2 of the Code.

RESPONSE

Rhône-Poulenc Rorer noted that it had denied breaches of the Code with this material. The company considered that it was a fair, accurate, balanced and unambiguous reflection of the two agents as licensed for the treatment of metastatic breast cancer. It certainly did not believe that it had brought discredit on the pharmaceutical industry, and therefore Rhône-Poulenc Rorer also denied a breach of Clause 2 of the Code of Practice.

PANEL RULING

The Panel did not consider that the booklet was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

APPEAL BY PIERRE FABRE

Pierre Fabre stated that the management of advanced breast cancer with cytotoxic chemotherapy required a

partnership between patient, clinician and carer. Information supplied to healthcare professionals involved in the care of cancer patients should always adhere to the highest standards of the pharmaceutical industry and be clear, accurate and unambiguous.

Pierre Fabre disputed the contention stated in the Panel ruling that '… the audience would understand the limitations …' of non-comparative trial data (point A1 above). The interpretation of promotional material should rely on the scientific credibility of data contained within it rather than assumed expertise of a multidisciplinary audience that might include nurses, doctors in training and NHS managers.

Pierre Fabre stated that in the booklet Rhône-Poulenc Rorer had made comparisons and drawn conclusions from data selected from a sub-group analysis from a single Phase II study for docetaxel against a single Phase II study of Navelbine, these studies having different patient populations. It had also made comparisons between single arms of different Phase III studies. Pierre Fabre did not accept that the processes or methodologies followed in making these comparisons were balanced, fair, objective or accurate.

This point of principle was the basis of the Panel rulings made on the following points, A1, A4, A5, A6, (and corresponding items H1, H4, H5, H6), B2, B3, C1 and G2.

Basis of the appeal

Pierre Fabre stated that in the booklet, Rhône-Poulenc Rorer had published an analysis of two different products based upon selected data from different studies, conducted in unmatched patient populations. None of these data were derived from a properly conducted, prospective Phase III comparison of the two products. Further, it had used this analysis as a basis for drawing specific conclusions and claims regarding the 'superiority' of one treatment over another in the context of response rates, time to progression and median survival. Pierre Fabre considered that this was an unscientific and unfairly biased analysis and the conclusions drawn were inaccurate and misleading.

The role of clinical trials in improving outcomes from cancer

Pierre Fabre stated that clinical trials were of fundamental importance in the practice of oncology in that they were the core component of clinical research. The methodology of clinical trials had been pioneered in oncology and examples of all the key approaches and issues in clinical research could be found in cancer clinical trials. Clinical trials resulted in the generation of data which would answer the questions posed in the design of the study and which had been fully elucidated in the protocol.

Phase II clinical trials for a new medicine involved a preliminary evaluation of the activity sufficient to allow a reasonable decision about proceeding to large-scale randomised studies (Phase III). Phase II studies were only a basis for generating new hypotheses that could then be tested in the context of large, randomised Phase III clinical trials.

Phase III trials were designed to answer a clinical question definitively. From the research perspective, this involved the validation of a meaningful hypothesis. As a result of the potential definitive nature of Phase III studies, they should be large, controlled, randomised and adequately powered to give confidence in the result. Only in this way could one ensure that the comparison between treatments was valid, ie in the same patient population using the same evaluation criteria for response assessment (survival, quality of life or response rate).

It was not routine practice in oncology to draw detailed conclusions between different treatments on the basis of different Phase II clinical studies. Nor was it the practice within the pharmaceutical industry that the interpretation of promotional material should rely on the assumed expertise of a multidisciplinary audience rather than the scientific credibility of evidence contained within it.

Variability of response rates in cancer clinical trials

Pierre Fabre stated that overall objective response rates in published studies with any cytotoxic drug were linked not only to the dose intensity of the treatment schedule but also to important prognostic factors within a given study population such as site of metastatic disease, number of metastatic sites, hormone receptor status (ER+/-), menopausal status, age <35 years, performance status, and most importantly previous chemotherapy. Regarding previous chemotherapy, the most important prognostic factors were:

1 Number of different treatment episodes (adjuvant, 1st line metastatic, 2nd line metastatic, etc).

2 Type and number of medicines used previously (eg CAF, CMF, MMM) as this limited choice of regimen.

3 Drug resistance, cross-resistance or irreversible toxicity from previous treatment.

4 Disease-free interval: the expected outcome might improve with a long treatment-free I interval.

The effect of these prognostic factors could be very significant '…patients that benefit from chemotherapy may be treated successfully with other regimens at the time of progression. However, the chance of response decreases by about half with each subsequent treatment.' (Cancer: Principles and Practice of Oncology, 5th Edition, 1997). Trials performed in different patient populations could clearly lead to a wide variation in reported response rates, even with the same medicine.

Pierre Fabre stated that confidence intervals were broad whenever the patient numbers were small in a given study, (Principles of clinical trials: Textbook of Medical Oncology, edited by Cavalli *et al*). This further limited the reliability of any conclusions drawn from studies with small patient populations.

Response rates published for docetaxel within the licensed indication showed overall response rates between (less than) 16% and 54.5%. Some examples were:

a) Trandifir *et al* (1996), 17/107 patients (16% 'response') anthracycline-resistant patients (this response rate included patients with only a minor response)

b) Ravdin *et al* (1995), 12/22 patients (ORR 54.5%) anthracycline-resistant patients

c) Ravdin, (1997) overview of three Phase II studies, overall response 41% (n=134 anthracycline-resistant patients)

Similarly with Navelbine, a range of response rates was published in the monograph, Focus on Navelbine (second edition). In patients within the UK indication, examples were:

a) Degardin *et al*, 16/100 patients (ORR 16%) previous anthracycline treatment

b) Fumoleau *et al*, 17/44 patients (ORR 38.6%) previous anthracycline treatment

c) Terenziani *et al*, 14/32 patients (ORR 44%) previous anthracycline treatment or anthracycline-resistant

These data on both products (within the UK approved indications) demonstrated that response rates varied in Phase II studies where characteristics of patient populations were not identical.

Even De Vita only broadly grouped the activity of different agents based on a comprehensive review of the world literature. Only limited classifications of the activity of different agents used in the treatment of breast cancer was attempted.

Summary

Pierre Fabre stated that comparisons between different treatments were extremely important throughout the industry and in clinical practice. On the basis of a properly conducted comparison, decisions regarding the regulatory approval, local adoption or funding (purchaser support) for a specific treatment might be taken. The industry must ensure that any comparison between different products was conducted according to accepted scientific principles and any unfair methodology or bias was avoided. The standard procedure for comparing two treatments was through a prospective, Phase III clinical trial that was adequately powered to give confidence in the result. Only in this way could the bias of patient selection be eliminated.

The analysis presented in the booklet had been constructed by Rhône-Poulenc Rorer to promote its product, docetaxel. Although the original data was drawn from peer reviewed publications, the analysis had not been peer reviewed and would not withstand any such scrutiny. The comparison of the two treatments was not a proper scientific assessment and the subsequent 'conclusions' were inappropriate and without foundation. This analysis by Rhône-Poulenc Rorer created a misleading impression of the two treatments and the methodology used was not accepted practice.

This unfair principle had been used as a basis for the following Panel rulings: A1, A4, A5, A6 (and corresponding items H1, H4, H5, H6), B2, B3, C1 and G2.

RESPONSE FROM RHÔNE-POULENC RORER AND CHUGAI PHARMA

Rhône-Poulenc Rorer responded on behalf of both companies. It agreed with Pierre Fabre that Phase III randomised studies were often referred to as the gold standard by which to compare different cytotoxic agents and different combinations of cytotoxic agents within a defined tumour type and patient population. During the last 35 years approximately 100 cytotoxic drugs had been tested in patients with metastatic breast cancer, of which around 30 had demonstrated substantial activity. No other solid tumour was responsive to such a wide array of cytotoxic agents as well as to multiple types of endocrine therapy, immuno-modulation and radiation therapy. Most of these agents could be given by different routes and dosage schedules, either as single agents or in combination with other agents and therapies. It was therefore impractical to compare each of the agents and combinations of agents against all of the others in Phase III studies before one or both of the agents were licensed or in a Phase IV setting, post licensing.

Rhône-Poulenc Rorer stated that it was important to note that many anti-cancer drugs, like Taxotere, were granted marketing authorizations in the European Union purely on the basis of Phase I and II toxicity data and Phase II activity data. Rhône-Poulenc Rorer submitted that if the Appeal Board found in favour of Pierre Fabre and concluded that it was not possible to compare activity and toxicity on the basis of Phase II data, then it would not be possible to compare the SPCs of many different anti-cancer agents because, in many cases, that was the only clinical data included within the SPCs. A copy of the first Taxotere SPC as issued by the European Medicines Evaluation Agency was provided as an illustration.

Clinicians who were faced with real-life clinical problems needed to be in a position to make an informed decision as to which agent or combination of agents to use in the treatment of a patient with metastatic breast cancer. In order to be able to make informed judgements, clinicians required access to the best available data.

In the absence of randomised, directly comparative Phase III trials, which was the normal situation in oncology, clinicians had to draw conclusions between different treatments on the basis of Phase II and Phase III clinical trials. Interpreting data that used 'bridges' with other products or with broadly similar patient populations was not only a necessity but was also a scientific and intellectually sound practice. Pierre Fabre supported its appeal that drawing meaningful conclusions from studies that were not directly comparative was unsound, by referring to Cavelli F *et al* in which the editors discussed the methodology and purpose of clinical studies in oncology practice. The Appeal Board would note that the same editors went on to compare the efficacy of 31 cytotoxic agents in metastatic breast cancer from Phase II clinical trials.

In addition, Rhône-Poulenc Rorer drew the attention of the Appeal Board to another of the standard textbooks for the management of breast diseases, Breast Diseases, Harris *et al* 2nd edition 1991, that the section 'Chemotherapy for Metastatic Disease'

contained no less than 7 tables, each comparing the activity and/or toxicity results, of up to 69 different anti-cancer agents or regimens, taken either from Phase II studies, or from comparisons of non-bridged Phase III studies.

Rhône-Poulenc Rorer did not consider it was appropriate to externalise an internal disagreement within the pharmaceutical industry by obtaining testimonials from reputable opinion leaders that this practice of comparing the activity of agents using Phase II and Phase III non-bridged data was a necessary and normal part of the routine practice of oncology. Therefore, it had deliberately not sought such testimonials, and believed that the evidence supplied should be sufficient to enable the Appeal Board to reach the same conclusion. However, Rhône-Poulenc Rorer would have no objection to such opinions being sought by the Appeal Board should it be considered appropriate, indeed it would welcome it.

Rhône-Poulenc Rorer agreed with Pierre Fabre's statement *'there is a potential for a variability of different response rates in published studies, linked to important prognostic factors within a given study population'*. Indeed, Rhône-Poulenc Rorer was careful to select only comparable groups of patients in which the medicines were used as:

- second line monotherapy
- for patients with metastatic breast cancer
- who had received a previous anthracycline treatment for metastatic breast cancer
- who received treatments at the licensed dose and dose schedule in the UK
- in an identical clinical phase of study

It should be noted that the Phase II studies referred to by Pierre Fabre illustrating variations in activity of Taxotere were based upon widely different groups of patients and therefore compared 'apples with pears'. For example, the paper Trandifir *et al* was not a Phase II clinical study at all; this abstract was an analysis of an open, uncontrolled, compassionate use programme. The second paper Ravdin *et al* was a report of a controlled Phase II study with an anthracycline- resistant patient population. The third 'study' also by Ravdin was a review of three separate studies one of which was the study mentioned previously. In this review, the author noted that the two North American Phase II trials which used similar patient selection 'showed nearly identical results (ORR 48%)'.

The three quoted vinorelbine papers referred to by Pierre Fabre included three different patient populations. In two of the three papers, the majority of patients were treated outside the UK licensed dosage or dose schedule for Navelbine. The paper by Degardin *et al* was a Phase II study within the licensed UK dosage regimen, whereas the paper by Fumoleau *et al* (which had not been submitted previously by Pierre Fabre) was within the licensed indication, but not within the carefully defined patient population which Rhône-Poulenc Rorer had used to compile the booklet at issue. The patients in this paper had received no previous chemotherapy for metastatic disease. In the last paper, Terenziani *et al*, the majority of patients were treated using a non-licensed dosage regimen (days 1 and 8 of a 21 day regimen) rather than the UK licensed weekly dosage regimen for Navelbine.

Rhône-Poulenc Rorer stated that it was not surprising that, given that the substantial differences in patient population and/or study regimen used in the papers presented above, that varying results had been obtained for activities. Informed well educated cancer specialists were able to appreciate the subtleties as a matter of course. In the piece in question, Rhône-Poulenc Rorer was scrupulously careful to ensure that the patient populations in each study were as similar as possible.

Rhône-Poulenc Rorer concluded that the basis of the appeal by Pierre Fabre was fundamentally flawed and lacking in substance.

FURTHER COMMENTS FROM PIERRE FABRE

Pierre Fabre stated that the Appeal Board should be reminded that the basis for this complaint was that Rhône-Poulenc Rorer had compared docetaxel and vinorelbine using selected data from different non-comparative clinical trials for the promotion of docetaxel. It had used this comparison to draw specific claims of superiority of docetaxel over vinorelbine with respect to response rate, time to progression and survival. This appeal was based on the fact that this data selection and comparison was unfairly biased and the subsequent claims were misleading and inaccurate.

Pierre Fabre had demonstrated that the observed response rate with cytotoxic treatment varied greatly according to important prognostic factors (previous treatment etc) and entry criteria used to select patients for a study.

As an example, Pierre Fabre had shown that, according to the published data on docetaxel (within the UK licensed indication), the response rate might vary from 16% (n=107, Trandifir *et al*) to 54.5% (n=22, Ravdin *et al*). Even when an essentially similar protocol was used in different areas of the world, the overall response rate was reported to vary between 29% (Europe) and 50% (USA) (Ravdin (1997)). It would be clearly biased to select any of these lower response rates for docetaxel as a basis for a comparison with other agents.

In its response to the appeal and the presentation of this data, Rhône-Poulenc Rorer had commented on the above examples of variable response rates with docetaxel with the following statement:

'… variations in activity of Taxotere are based upon widely different groups of patients and therefore compare 'apples with pears' …'

Interestingly this was precisely the basis of the complaint and appeal. Commercial bias in the selection of which Phase II data was used for the comparison would pre-determine the result. This was unfair.

Conclusions about the superiority of one treatment over any other could only be made on the basis of

large prospective Phase III (randomised) clinical trials that were sufficiently well-powered to give significance to the results. If Rhône-Poulenc Rorer wished to draw any of these conclusions within this booklet, it had an obligation to properly conduct this research. This comparison, using samples of selected data from small Phase II trial results was unscientific, biased and misleading. In the context of this disease and within oncology generally, this was an unacceptable practice.

Other issues within the response by Rhône-Poulenc Rorer

Administration schedule for vinorelbine

Whilst Pierre Fabre welcomed this late acceptance of the data on vinorelbine published by Fumoleau *et al* (which, in Pierre Fabre's view, was previously well-known to Rhône-Poulenc Rorer) it was disappointed that Rhône-Poulenc Rorer claimed to not understand the dosing schedule for vinorelbine, as described by Terenziani *et al*.

The SPC for vinorelbine, section 4.2 (Posology and method of administration), clearly stated that Navelbine was usually given at 25-30mg/m≈ weekly and that administration was expected to be delayed by 1 week in about 35% of treatment courses.

In the schedule described by Terenziani *et al*, Navelbine was administered for two weeks out of three with a planned dose delay (omission) at the start of week 3, ie 33% dose delay. This was clearly within the scope of this dosage recommendation in Pierre Fabre's SPC and reflected the clinical practicalities of managing neutropenia, the dose limiting toxicity. As this schedule could greatly enhance patient convenience and clinical efficiency, it was frequently adopted in routine clinical practice throughout Europe. The Appeal Board might also note that the MRC and UKCCCR had also adopted this schedule in their studies as evidence of the widespread clinical interpretation and validity of this schedule within the oncology community.

In excluding data from Phase II studies with legitimate and commonly adopted vinorelbine schedules, Rhône-Poulenc Rorer further increased the selection bias in this 'analysis'.

Use of Phase II data by oncologists

Pierre Fabre stated that Rhône-Poulenc Rorer had attempted to justify its actions in this matter by claiming that it was common practice to draw detailed and specific conclusions about the merits of different chemotherapy agents on the basis of Phase II, non-comparative data. It claimed to have provided examples of this.

Although many textbooks would present tabulated results from an overview of all published Phase II studies (usually with a range of published response) as a basis for a discussion within the accompanying text, they contained no examples of any specific conclusions about the superiority of one treatment over another. Even when Phase III studies were reported, only limited conclusions were drawn when statistical significance was clearly demonstrated. Where statistical significance was not demonstrated, additional Phase III studies were required to confirm a result. Oncologists rigorously applied the rules of scientific and statistical evaluation and any impression created by Rhône-Poulenc Rorer that was contrary to this was misleading.

Summary

Comparisons between treatments had many important consequences with respect to adoption, use and funding. In view of this importance, the industry must ensure that when comparisons were made, they were done according to rigorous scientific methodology, were fair, accurate and without bias. The only accepted methodology for comparing different treatments was with a prospective, randomised Phase III clinical trial with sufficient patients to ensure statistical confidence in the result.

Pierre Fabre had shown that the reported response to any cytotoxic chemotherapy treatment could vary significantly according to a range of prognostic variables within a study population. In permitting Rhône-Poulenc Rorer to select single study Phase II data (or data from single arms of different Phase III studies) as a basis for this comparison, the Panel had allowed an unfair bias in the 'analysis' which resulted in misleading and inaccurate 'conclusions' being drawn.

Pierre Fabre asked the Appeal Board to prevent the use of this biased and unfair methodology.

Pierre Fabre referred to rulings in a previous case, Case AUTH/378/11/95, when the Appeal Board had ruled that comparisons between two products in a product monograph were misleading. The data was not from studies in which the products were directly compared. The impression given was that the data were from directly comparable studies and this was not so.

APPEAL BOARD RULING

A PAGE 3

1 'In non-comparative clinical trials …'

In the Appeal Board's view oncology was a very complex therapy area. Oncologists were a sophisticated and innovative group of clinicians in terms of their use of treatment regimens. Some of the medicines they would use would have been licensed on the basis of Phase II data and it would be unlikely that particular regimens would have been directly compared in double-blind controlled trials. The Appeal Board noted that Taxotere had been licensed on Phase II data. In terms of their use of published clinical data oncologists could not be viewed in the same way as the average prescriber.

The Appeal Board noted that the Taxotere SPC stated that Taxotere monotherapy was indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent. The SPC also stated that the use of the product should be

confined to units specialised in the administration of cytotoxic chemotherapy and that it should only be administered under the supervision of a qualified oncologist. The Appeal Board noted that Navelbine was licensed for the treatment of advanced breast cancer stage 3 and stage 4 relapsing after or refractory to an anthracycline containing regimen. Navelbine was usually given at 25-30mg/m^2 weekly. If the neutrophil count reached a certain level then treatment should be delayed until recovery. Drug administration was expected to be delayed by one week in about 35% of treatment courses.

The Appeal Board noted that the booklet in question had been used at a Royal College of Physicians Cancer Trials meeting and had also been mailed to oncology specialists and used by sales representatives to detail oncology specialists. The booklet had not been used to detail nurses or pharmacists.

The Appeal Board considered that the use of non-comparative data might be acceptable in certain circumstances; relevant factors would be the therapy area, the intended audience, how the data was presented and the conclusions drawn. In this case the audience would understand the limitations of the data presented in what was a complex therapy area and be able to assess its significance. In that regard the Appeal Board did not consider that the use of non-comparative data was misleading *per se* as alleged and upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal on this point was thus unsuccessful.

4 Claim 'higher overall tumour response rates'

The Appeal Board noted that two references were cited in support of this general claim. Ravdin *et al* (1995), a Phase II study, demonstrated that the overall response rate to Taxotere was 54.5% (12/22 patients). The second reference, data on file, was a selected arm of an unpublished Phase III study which demonstrated an overall response rate to Taxotere of 33% (59/179 patients). The Appeal Board noted the range of reported response rates for Taxotere, 33% – 54.5%; the higher figure had been observed in a very small group of patients.

The Appeal Board noted that page 3 began 'In non-comparative clinical trials, an analysis of the available data … shows that Taxotere gives:' and then continued by listing a number of comparative claims in favour of Taxotere. The best available data at the time of preparation of the booklet was used. The Appeal Board noted its comments regarding the use of non-comparative data in point A1 above but did not consider that the data was such as to allow a clear determination of the comparative efficacy of Taxotere and vinorelbine to be made. It was inappropriate to base the booklet on the best available data. The Appeal Board thus considered that the claim 'higher overall tumour response rates' was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

The appeal on this point was thus successful.

5 Claim 'longer time to disease progression'

The Appeal Board noted that one reference was cited in support of this claim, Nabholtz *et al* (1998). The Appeal Board considered that the matter was, in principle, the same as in point A4 above ie that a positive claim for Taxotere compared with vinorelbine had been based on a limited amount of data. The Appeal Board did not consider that the data was such as to allow an accurate and fair comparison to be made and the claim could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

The appeal on this point was thus successful.

6 Claim 'longer median survival'

The Appeal Board noted that the same reference was cited in support of this claim as in support of the claim at issue in point A5 above.

The Appeal Board considered that the matter was, in principle, the same as in point A4 above and that its ruling of a breach of Clauses 7.2 and 7.3 also applied. The Appeal Board ruled accordingly.

The appeal on this point was thus successful.

B PAGES 4 AND 5 OF THE BOOKLET

2 Claim 'Conclusion: In Phase II trials as second-line monotherapy in patients who have previously received anthracyclines for metastatic disease, the overall response rate to Taxotere is superior to that of vinorelbine'

The Appeal Board noted its comments in A4 above. The Appeal Board noted that the claim was based on the outcome of two published studies. Dogliotti *et al* (1993) demonstrated an overall response rate for vinorelbine of 20.5% based on the results from 44 patients. The study by Ravdin *et al* (1995) demonstrated an overall response rate for Taxotere of 54.5% based on the results from 22 patients. The Appeal Board noted that the two studies involved limited numbers of patients and thus, in its view, the claim was more definite and positive about the comparative efficacy of Taxotere and vinorelbine than the data would allow. The Appeal Board considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

The appeal was thus successful on this point.

With regard to the use of the word 'superior' the Appeal Board did not consider that it was a superlative as alleged; it was a comparative term. The Panel's ruling of no breach of Clause 7.8 was upheld.

The appeal on this point was thus unsuccessful.

3 Graph entitled 'Overall response rates (ORR) in Phase II trials'

The Appeal Board noted its comments and ruling in point B2 above. The Appeal Board considered that the presentation of the graphs invited a direct comparison of vinorelbine and Taxotere that was

misleading given the data on which they were based. Breaches of Clauses 7.2 and 7.6 were ruled.

The appeal on this point was thus successful.

C PAGES 6 AND 7 OF THE BOOKLET

1 Claim 'Conclusion: In Phase III trials as second-line monotherapy in patients who have previously received anthracyclines for metastatic disease, the overall response rate to Taxotere is superior to that of vinorelbine'

The Appeal Board noted that the claim had been ruled in breach of Clauses 7.2 and 7.3 by the Panel. This ruling had been accepted by Rhône-Poulenc Rorer and Chugai.

With regard to the use of the word 'superior' the Appeal Board did not consider that it was a superlative as alleged; it was a comparative term. The Panel's ruling of no breach of Clause 7.8 was upheld.

The appeal on this point was thus unsuccessful.

G PAGES 14 AND 15 OF THE BOOKLET

2 Table comparing costs and progression-free days

The Appeal Board noted that the table (referenced to the Launois paper), although based on information contained within the Launois paper, had not been taken from it as such. An entirely new table had been created, it had not been adapted from one in the paper and there was no need to state that the table had been adapted from it. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 7.6 of the Code.

The appeal on this point was thus unsuccessful.

With regard to the patient population featured in the Launois paper the Appeal Board considered that it was not inconsistent with that for which Taxotere was licensed. In that regard the Appeal Board did not consider that the paper provided a misleading comparison as alleged. The Panel's ruling of no breach of Clause 7.2 was upheld.

The appeal on this point was thus unsuccessful.

H PAGES 17 OF THE BOOKLET

The Appeal Board considered that its comments and rulings in points A1, A4, A5 and A6 similarly applied to page 17.

During its consideration of this case the Appeal Board noted that the question which appeared on the front page as the title of the booklet was 'Which is the most effective chemotherapy option for Advanced Breast Cancer'. The Appeal Board was concerned that 'advanced breast cancer' was too broad a term given that Taxotere was only licensed for use in patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy which should have included an anthracycline or alkylating agent. The Appeal Board requested that the companies be notified of its concerns.

The booklet was last used on 12 May.

Complaint received **15 January 1999**

Case completed **7 October 1999**

CASE AUTH/832/1/99

ALLERGAN v PHARMACIA & UPJOHN

Sponsored meeting report

Allergan complained about a meeting highlights report sponsored by Pharmacia & Upjohn. The meeting had been held by a group of ophthalmologists and the report was entitled 'Setting new targets in glaucoma management'. It gave a summary of seven presentations, the final one of which was entitled 'New concepts in medical treatment' and featured three graphs showing the efficacy in terms of the lowering of intraocular pressure (IOP) of four types of eye drops, one of which was latanoprost (Pharmacia & Upjohn's product Xalatan) and another of which was brimonidine (Allergan's product Alphagan). Allergan alleged that the report was a promotional item and was in breach of the Code as prescribing information had not been provided. The three graphs were also alleged to be in breach.

The Panel noted Pharmacia & Upjohn's submission that the views and recommendations of the group were entirely independent. The Panel noted that the report was of a meeting sponsored by Pharmacia & Upjohn and reference was made to the use of products including its product Xalatan. The report had been made available by Pharmacia & Upjohn representatives and had been on the company's stand at a meeting. The report had thus been used for a promotional purpose. In the circumstances the Panel considered that the company's use of the report meant that it had to be regarded as coming within the scope of the Code. A breach of the Code was ruled due to the lack of prescribing information for Xalatan.

The Panel considered that the graphs were inadequately labelled. All of them used suppressed zeros. It appeared to the Panel that graph one showed IOP data for which there was no appreciable peak or trough effect after each dose. The second and third graphs appeared to compare trough data although they were not so labelled. The Panel also noted that the graphs were arranged in such a way that readers would be tempted to compare them with each other. The latanoprost line on graph one was closer to the x axis than any line on any of the other graphs and it appeared therefore that latanoprost produced a greater lowering of IOP than the other eye drops. No indication was given as to whether the differences shown on each individual graph were statistically significant or not. Overall the Panel considered that the graphs were misleading. A breach of the Code was ruled.

Upon appeal by Pharmacia & Upjohn, the Appeal Board noted that there was no criticism of the activities of the group of ophthalmologists; they could hold meetings, produce and circulate reports without reference to the Code. It was the involvement and role of Pharmacia & Upjohn which was being considered. The Appeal Board accepted that 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 its promotional purposes. This was not what had happened in this case. The Appeal Board considered that by supplying its representatives with a number of copies for distribution and by placing it on the company's stand in such as way as to be promotional, the report was not solely available in response to individual enquiries. Pharmacia & Upjohn was using the item for a promotional purpose which brought it within the scope of the Code. If it was to be used in that way, the report should have included prescribing information for Xalatan. The Appeal Board upheld the Panel's ruling of a breach of the Code in that regard.

The Appeal Board noted that graphs used to illustrate the final presentation detailed in the report were taken from three separate clinical papers. Two of the graphs had actually appeared in the papers in question and the third had been derived from a table of results given in the paper. The Appeal Board noted that while each graph on its own was an accurate representation of the results of each study, the presentation of the graphs invited readers to make comparisons across all three studies. Given the inadequate labelling of the graphs and the fact that two of them depicted trough data while the other one did not, the Appeal Board considered that such a comparison was unfair. The graphs, as presented, did not give a clear, balanced view of the matter with which they dealt, as required by the Code. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Allergan Ltd complained about a meeting highlights report sponsored by Pharmacia & Upjohn Limited. The meeting had been held on 5 June 1998 by a group of ophthalmologists and the report was entitled 'Setting new targets in glaucoma management'. The report consisted of four A3 pages and gave a summary of seven presentations which had been delivered at the meeting. Use had been made of colour, diagrams and boxed text and associated with each resumé was a small colour photograph of the speaker. The final presentation detailed in the report was entitled 'New concepts in medical treatment' and featured three graphs showing the efficacy in terms of the lowering of intraocular pressure (IOP) of four types of eye drops, one of which was latanoprost (Pharmacia & Upjohn's product Xalatan) and another of which was brimonidine (Allergan's product Alphagan).

The report was distributed by Pharmacia & Upjohn's representatives and had been made available from a company stand at a meeting held on 6 November 1998 at a hospital postgraduate centre.

COMPLAINT

Allergan alleged that the report was a promotional item and was in breach of Clause 4.1 of the Code as prescribing information was not included.

Allergan referred to the three graphs featured in the final section of the report which showed the change in

IOP (mmHg) over time with various eye drops. The first graph compared the mean IOP of latanoprost and timolol at 8.00 hr over 6 months (Camras *et al* (1996)). The second graph compared the mean IOP of dorzolamide, betaxolol and timolol at 8.00 hr over 6 months (Strahlman *et al* (1995)) and the third graph compared IOP of brimonidine 0.2% with timolol 0.5% over 12 months (Schumann (1996)). IOP was shown on the y axis of each graph which started at 17mmHg on the first two graphs and at 16mmHg on the last graph.

Allergan alleged that the graphs contained suppressed zeros which overemphasised the differences in IOP reduction between the various treatments. A breach of Clause 7.6 of the Code was alleged.

Allergan also pointed out that the latanoprost summary of product characteristics (SPC) stated that the maximum IOP lowering effect was reached after 8-12 hours. Therefore, peak data had been used in the latanoprost graph while trough data was shown for the other two products. The graphs had not been labelled as such and therefore the information was misleading. Furthermore, the fact that the graphs were side by side invited the reader to compare the data. As peak data for latanoprost had been compared with trough data for the other two products, this constituted an unfair comparison and breaches of Clauses 7.2 and 7.6 of the Code were alleged.

RESPONSE

Pharmacia & Upjohn explained that the group was composed of UK ophthalmologists who were leaders in the field of glaucoma at both European and local level. The aim of the meeting was an attempt to establish the groundwork for the development of guidelines for glaucoma management in what was an increasingly complex area. The meeting was sponsored by an educational grant from Pharmacia & Upjohn but the views and recommendations of the group were entirely independent. As a consequence, the presentations delivered at the meeting were not subject to any editorial controls by Pharmacia & Upjohn, nor did they go through the company's approval process.

The publication from this meeting, the highlight report in question, took the form of an abstract of each specialist's presentation from the meeting. This report was prepared by the same public relations agency responsible for the set-up of the meeting, again sponsored by an educational grant from Pharmacia & Upjohn. It should be emphasised that, as in the case of the meeting, Pharmacia & Upjohn had no editorial input or control over either the presentations or abstracts presented in the report. Once again, due to the editorial independence of the group, the contents of this report were not judged to be promotional and therefore did not go through the company's normal approval process but, in compliance with Clause 9.9 of the Code, the piece was reviewed to ensure the declaration of sponsorship was prominently displayed.

The report was sent to the delegates at the meeting and the Pharmacia & Upjohn salesforce circulated it to non-delegates only upon request. This was done with the agreement of the group.

The report was not therefore a promotional piece and did not require prescribing information. Furthermore, as the presentations delivered at the meeting were the editorial property of the ophthalmologists and not Pharmacia & Upjohn, the contents were not covered by the Code and therefore no breach of Clauses 7.2 or 7.6 could be inferred. In addition, the company drew attention to the fact that as the content of the meeting and subsequent report were independent, Pharmacia & Upjohn was not in a position to control withdrawal of the piece and any such action would have to involve discussion with the members of the group.

Following a request for further information Pharmacia & Upjohn explained that it was the sole sponsor of the meeting through a medical communications agency. The group directed that the delegates should include ophthalmologists, optometrists, nurses and all other paramedical specialities associated with the management of glaucoma, and the invitations were duly sent out by Pharmacia & Upjohn.

The medical manager, clinical research manager, product manager, sales manager, marketing director and five sales representatives of Pharmacia & Upjohn attended the meeting in the capacity of delegates for educational purposes and did not speak at, or contribute to, the content of the meeting in any way. Furthermore, neither a trade stand nor promotional items for Xalatan or any other product were available at the meeting.

With regard to the alleged breach of Clause 7.6, the company was aware of the prohibition of suppressed zeros in this clause but as Pharmacia & Upjohn had absolutely no editorial control over the contents of any of the presentations, it was not in a position to enforce the Code. Furthermore, as the graphs used were taken directly from peer reviewed papers, the presenter was perfectly entitled to use them in this or any other independent presentation.

With regard to the alleged breach of Clause 7.2, once again the speaker had taken the information presented directly from peer reviewed papers and editorial control was out of the remit of Pharmacia & Upjohn.

The company re-iterated that neither the meeting nor the proceedings were promotional, and the whole attempt behind both was to expand the debate on glaucoma management. Again, the proceedings were only distributed to delegates and then supplied upon request to other interested parties. The piece in question did not promote any one product over another and the company was confident that such promotion was definitely not the intention of the group. The industry provided a valuable service to the medical community in sponsoring meetings such as the one under discussion and the company was firmly of the opinion that this meeting was conducted in the spirit of the Code.

PANEL RULING

The Panel noted that the pharmaceutical industry provided a useful service to the medical community

in sponsoring meetings. In this case Pharmacia & Upjohn had sponsored the meeting via a third party.

The Panel referred to previous cases concerning meetings which had been directly sponsored by companies, Cases AUTH/270/2/95 and AUTH/551/5/97 & AUTH/552/5/97. The Panel accepted that speakers at meetings were entitled to hold their own views and to express them. It would be inappropriate for companies inviting speakers to meetings to control the content of their presentations. To do so would detract from the value of industry sponsored educational meetings. It was not, however, possible for a company to completely disassociate itself from the content of meetings that it sponsored, especially where the meetings were initiated by the sponsoring company. The question was not whether it was appropriate for the speaker to have made the presentations but whether or not it was appropriate for the company to have sponsored them. The Panel considered that the same principles applied to meetings sponsored through a third party. There was no complaint about Pharmacia & Upjohn's sponsorship of the meeting. The complaint focused on the report of the meeting.

In relation to published material, Clause 9.9 required material relating to medicines to so declare if it had been sponsored by a pharmaceutical company and this applied even if the material was non-promotional. 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 favorable 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 content, 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 its promotional purposes. The Panel noted Pharmacia & Upjohn's submission that the views and recommendations of the group were entirely independent. The Panel noted that the report was of a meeting sponsored by Pharmacia & Upjohn and reference was made to the use of products including its product Xalatan (latanoprost). The report had been made available by Pharmacia & Upjohn representatives and had also been on the company's stand at a subsequent meeting. The report had thus been used for a promotional purpose. In the circumstances the Panel considered that the company's use of the report meant that it had to be regarded as coming within the scope of the Code. A breach of Clause 4.1 of the Code was ruled due to the lack of prescribing information for Xalatan.

With regard to the allegation concerning the comparison of peak data for latanoprost (Xalatan) and trough data for dorzolamide and brimonidine, the Panel examined the papers to which the graphs were referenced. The Camras (1996) study compared twice daily timolol with once daily latanoprost. Patients were instructed to instil their eye drops at 8am and 8pm (the latanoprost assigned group received active medication at 8pm and the vehicle at 8am). The IOP was measured at 8am, 12 hours after the last dose. The paper stated that both medicines provided approximately 24 hours of IOP control with minimal diurnal fluctuation; there was no appreciable peak or trough effect after each dose. The greater efficacy of latanoprost compared with timolol was unlikely to be due to differences in the timing of the IOP measurements.

The second graph was referenced to Strahlman *et al* (1995) and compared three times daily dorzolamide with twice daily betaxolol and timolol eye drops. IOP was measured 2, 5 and 8 hours following the morning dose. Two hours after instillation of the medication dorzolamide reduced IOP by approximately 23% during a 1 year period, timolol reduced IOP by approximately 25% and betaxolol reduced IOP by approximately 21%. The relative magnitude of effect was the same at hours 5 and 8 for the three treatment groups with each treatment having its peak ocular hypotensive efficacy at 2 hours post dose and its trough effect at 8 hours post dose. The Panel noted that the second graph was thus showing the trough effect of each medicine.

The third graph was referenced to Schuman (1996) and compared brimonidine and timolol. IOP was measured at peak (2 hours after the morning dose) and trough (12 hours after the evening dose). No significant between groups differences were shown at peak except for weeks 1 and 2 and month 3 when brimonidine had a lower mean IOP. A significant between group difference was seen at trough at all visits when timolol had a lower mean IOP. It was the trough data that was shown in the graph in the report although this was not made clear.

The Panel considered that the graphs were inadequately labelled. All of them used suppressed zeros. It appeared to the Panel that graph one, based on Camras *et al*, showed IOP data for which there was no appreciable peak or trough effect after each dose. The second and third graphs appeared to compare trough data although they were not so labelled. The Panel also noted that the graphs were arranged in such a way that readers would be tempted to compare the graphs with each other. The latanoprost line on graph one was closer to the x axis than any line on any of the other graphs and it appeared therefore that latanoprost produced a greater lowering of IOP than the other eye drops. No indication was given as to whether the differences shown on each individual graph were statistically significant or not. Overall the Panel considered that the graphs were misleading. A breach of Clause 7.6 of the Code was ruled.

APPEAL BY PHARMACIA & UPJOHN

Pharmacia & Upjohn said that fundamentally the complaint hinged on whether or not the piece was a promotional item and whether or not it was subject to the requirements of the Code. It was Pharmacia & Upjohn's contention that this report was not a promotional item, was intellectually and editorially independent of the company and was therefore not subject to the Code. That was the basis for the appeal.

The group in question was an independent group of ophthalmologists which came together last year with the objective of establishing standards of glaucoma

management. This initiative was sponsored by an educational grant from Pharmacia & Upjohn but it was clearly established at the outset that the group, its meetings, opinions, proceedings and publications would be entirely independent of the company.

The Panel had noted in its ruling that 'It would be inappropriate for the companies inviting speakers to meetings to control the content of their presentations ……[and] … the question was not whether it was appropriate for the speaker to have made the presentations but whether or not it was appropriate for the company to have sponsored them'.

The speakers at the meeting were members of the group, chosen by the group and the publishing company and not Pharmacia & Upjohn. Similarly the abstracts in the published meeting report were not subject to any intellectual or editorial control on the part of Pharmacia & Upjohn. Pharmacia & Upjohn believed, therefore, that the method of sponsorship of this meeting was similar to the sponsorship of educational meetings undertaken by most ethical pharmaceutical companies (eg the 'Key Advances' series of The Royal Society of Medicine). In these cases the sponsoring company did not choose the speakers, view the presentations in advance or have any input into the published abstracts of the meeting. Furthermore, the sponsoring company's prescribing information did not appear on the published abstracts as these proceedings were not viewed as promotional material.

Pharmacia & Upjohn submitted that the publication 'Setting new targets in glaucoma management', which emanated from a meeting sponsored by an educational grant from Pharmacia & Upjohn, was editorially and intellectually an independent publication of the group. It was not a promotional item for Xalatan and therefore was not subject to the requirements of the Code in relation to promotional items – in the case of this complaint, prescribing information and content of independent speakers' abstracts.

Given the independent nature of this publication, Pharmacia & Upjohn had used it in the same way as other publications/papers were used by the industry in accordance with the Code, namely distribution to clinicians upon request and availability on company stands along with other published data or disease information.

Pharmacia & Upjohn had stated from the outset that this meeting and the subsequent published report were the property of the group, an independent group whose activities were currently sponsored by an educational grant from Pharmacia & Upjohn. The group was, of course, free to obtain sponsorship or enter discussions with any other potential industry or academic collaborators. Pharmacia & Upjohn further stated in all correspondence on this matter that since any publications were not the property of Pharmacia & Upjohn, it was not in a position to control either the distribution or withdrawal of these items and that this issue would ultimately have to be referred to the group.

In the light of the Panel's ruling, Pharmacia & Upjohn had informed the group of the case. The group wished to assert its intellectual independence from Pharmacia & Upjohn as well as its ownership of any and all publications. A letter from the chairman of the group was provided.

The chairman stated that he was surprised and quite shocked that Allergan had taken such a partisan attitude over the publication. He was also very surprised that the complaint had been upheld. None of the members of the panel or contributors had any interest in or connection with marketing a Pharmacia & Upjohn product. The Allergan complaint and the ruling implied that the report of the consensus debate was intended to market Xalatan. The chairman could state with absolute confidence that this was not the case. The content of the discussions and the consensus reached was entirely independent. It followed therefore that the publications produced by the group were the property of the group and were likewise independent of Pharmacia & Upjohn. The chairman trusted that having understood the implications of the accusation to the reputation of the many senior clinicians in the group, the erroneous ruling would be seriously reconsidered.

APPEAL BOARD RULING

The Appeal Board noted the comments from the chairman of the group. There was no criticism of the activities of that group which could hold meetings, produce and circulate reports without reference to the ABPI Code. It was the involvement and role of Pharmacia & Upjohn which was being considered. The Appeal Board accepted that 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 its promotional purposes. This was not what had happened in this case.

The Appeal Board considered separately the content of the meeting report and the use to which it had been put.

With regard to the content of the report, the Appeal Board noted that it was a record of presentations which had been delivered at one of the group's meetings. The meeting had been sponsored by Pharmacia & Upjohn. The report had been attractively presented and Pharmacia & Upjohn had not had any editorial control over what had been published. The report stated that it had been sponsored by Pharmacia & Upjohn.

With regard to Pharmacia & Upjohn's use of the report, the Appeal Board noted that copies of it had been available from the company stand and that representatives had been given copies to distribute. The Appeal Board considered that such circumstances would inevitably lead to representatives making use of the item.

The Appeal Board noted that Pharmacia & Upjohn had viewed the meeting report as independent and used it in the same way as it used other publications/papers. The Appeal Board considered that whilst a medical journal might publish the results of a company sponsored study, actual publication of

such a paper would not be so sponsored and the paper would often have been subject to peer review. In the Appeal Board's view the meeting report was quite different; both the meeting and the report had been sponsored by Pharmacia & Upjohn. Clause 11.1 of the Code permitted the provision of an unsolicited reprint of a refereed article. The supplementary information stated that the provision of an unsolicited reprint of an article about a medicine constituted promotion and all relevant requirements of the Code should be observed. Particular attention needed to be paid to Clause 3 and the reprint should be accompanied by the prescribing information.

The Appeal Board noted that Clause 1.2 of the Code stated that the term 'promotion' did not include replies made in response to individual enquiries from health professionals or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they related solely to the subject matter of the letter or enquiry, were accurate and did not mislead and were not promotional in nature.

The Appeal Board considered that by supplying its representatives with a number of copies for distribution and by placing it on the company's stand in such as way as to be promotional, the report was not solely available in response to individual enquiries. Pharmacia and Upjohn was using the item for a promotional purpose which brought the report within the scope of the Code. If it was to be used in that way, the report should have included prescribing information for the product. The Appeal Board upheld the Panel's ruling of a breach of Clause 4.1 of the Code.

The appeal on this point was thus unsuccessful.

The Appeal Board noted that graphs used to illustrate the final presentation detailed in the report were taken from three separate clinical papers. Two of the graphs had actually appeared in the papers in question (Camras *et al* (1996) and Schuman (1996)). The graph from Strahlman *et al* (1995) had been derived from a table of results given in the paper. The Appeal Board noted that while each graph on its own was an accurate representation of the results of each study the presentation of the graphs invited readers to make comparisons across all three studies. Given the inadequate labelling of the graphs and the fact that two of them depicted trough data while the other one did not, the Appeal Board considered that such a comparison was unfair. The graphs, as presented, did not give a clear, balanced view of the matter with which they dealt, as required by the Code. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.6 of the Code.

The Appeal on this point was thus unsuccessful.

Complaint received **25 January 1999**

Case completed **22 July 1999**

CASE AUTH/837/1/99

BIOGEN/DIRECTOR v SCHERING HEALTH CARE

Promotion of Betaferon and failure to comply with an undertaking

Biogen complained about the promotion of Betaferon (interferon beta-1b) by Schering Health Care.

A statement regarding the effect of Betaferon on disability progression in a detail aid was alleged to be misleading as the Betaferon summary of product characteristics (SPC) stated at that time that there was no evidence of an effect on disability or on the progression of the disease. A breach of the Code was ruled by the Panel. It was considered that the claim was sufficiently similar to one ruled in breach in a previous case for it to represent a failure to comply with the undertaking. A further breach was ruled.

Allegations were made about a reprint of a journal article made available at a meeting of the Multiple Sclerosis Society. The reprint included an advertisement for Betaferon. The article was ruled to be misleading as it implied that Betaferon had a positive effect on disability. A further breach of the Code was ruled as Schering Health Care had failed to comply with the undertaking given in the previous case. The availability of the reprint meant that promotional literature for a prescription only medicine which might give rise to unfounded hopes of successful treatment had been made available to the public. Breaches of the Code were ruled by the Panel.

Biogen alleged that a Schering Health Care spokesperson had made an unqualified statement to the lay press that Betaferon delayed the progression of disability. No press release had been issued to the newspaper although a journalist had spoken to someone at Schering Health Care. Schering Health Care submitted that the journalist created a composite article from various sources. On balance the Panel considered there was not sufficient evidence to determine what exactly had been said to the journalist and ruled no breach of the Code.

Biogen alleged that a chart in the detail aid gave a misleading impression about the reduction in relapse rates for its product Avonex (interferon beta-1a). The reduction in relapse rate given in the detail aid was 18% and this related to all patient data. The Avonex SPC referred to a one third reduction in annual relapse rate. Schering Health Care submitted that the one third reduction was based on a subset analysis of only those patients completing two years of treatment. The Panel ruled that the chart gave a misleading impression about the reduction in relapse rates. The basis of the data had not been explained. The Panel also ruled a breach of the Code as Schering Health Care had failed to comply with the undertaking given in the previous case. The Appeal Board upheld the Panel's rulings on appeal by Schering Health Care.

Biogen Limited complained about the promotion of Betaferon (sub-cutaneous (sc) interferon beta-1b) by Schering Health Care Limited alleging in particular that Schering Health Care did not respect the limitations of the Betaferon summary of product characteristics (SPC) and the ruling in Case AUTH/569/6/97.

Biogen explained that in November 1995 Betaferon was given centralised approval. The Betaferon SPC stated:

'Betaferon is indicated for the reduction of frequency and degree of severity of clinical relapses in ambulatory patients … with relapsing, remitting multiple sclerosis … Patients receiving Betaferon showed a reduction in frequency (30%) and severity of clinical relapses… There is no evidence of an effect of Betaferon on the duration of exacerbations, on symptoms in between exacerbations, or of the progression of the disease. There are also no data on the effect of Betaferon on performance of daily activities or in the social field. …there is no evidence of an effect on disability.'

In March 1997, Biogen's product Avonex (interferon beta-1a) was given centralised approval with broader indications than those approved for Betaferon. The Avonex SPC stated:

'Avonex (intramuscular (IM) interferon beta-1a) is indicated for the treatment of ambulatory patients with relapsing multiple sclerosis … Avonex slows the progression of disability and decreases the frequency of relapses over a 2-year period … It was also shown that there was a one-third reduction in annual relapse rate.'

In March 1997, Schering Health Care issued a press release that, among other things, implied that Betaferon could delay the progression of disability in relapsing/remitting multiple sclerosis (MS) and presented misleading comparative information regarding the reduction in relapse rates for Betaferon and Avonex. In September 1997 in Case AUTH/ 569/6/97, the Panel ruled that Schering Health Care's press release breached Clauses 7.2 and 9.1 of the Code.

The Authority noted that it was alleged that the undertaking given by Schering Health Care in Case AUTH/ 569/6/97 had been breached. In accordance with advice given by the Appeal Board, allegations of breaches of undertaking were taken up as complaints by the Director as the Authority itself was responsible for ensuring compliance with undertakings. This case was not straightforward, however, as other allegations were involved. It would not be possible to establish the position until the response was received from Schering Health Care.

1 Statements suggesting that Betaferon could delay disability progression

A Statement: 'Disability progression was not a primary endpoint in the Betaferon nor the sc 1a study. Compared with other studies, the overall progression of the sc 1b study population was very low. Due to the design and power of the study, the detection of a statistically significant slowed disability progression was not expected.'

This statement appeared in a detail aid which discussed the use of Betaferon in relapsing/ remitting MS. On a page headed 'Summary of disability data' three graphs showed the percentage of patients in whom a disability score worsened by at least one point. The data had been taken from three separate placebo-controlled trials of three different forms of interferon. The graph for Betaferon showed that in placebo-treated patients disability score worsened in 28% of patients compared with 20% of the Betaferon group (p=0.16). The other two graphs showed that the results, in favour of the interferons, were statistically significant.

COMPLAINT

Biogen stated that as discussed above, Betaferon had not been proven to delay disability progression in relapsing/remitting MS. The disclaimers included did not cure the fact that this statement was misleading and inconsistent with the product's SPC. Furthermore, this statement was extremely similar to the one found in breach of the Code in Case AUTH/569/6/97.

In Case AUTH/569/6/97, a breach of Clause 7.2 had been ruled in relation to the statement: 'The Betaferon study was not designed to show a significant effect on the progression of disability. Nevertheless a strong 'trend' towards a slowing of disease progression was observed in the Betaferon trial'.

Biogen alleged breaches of Clauses 3.2 and 7 of the Code; in light of the ruling in Case AUTH/569/6/97 it was alleged that the detail aid was also in breach of Clauses 2, 9.1 and 21.

RESPONSE

Schering Health Care stated that the detail aid was designed to compare data from the three placebo-controlled pivotal trials involving the three forms of interferon beta (Betaferon; Biogen's interferon beta-1a and Ares-Serono's interferon beta-1a). Had the data on disability progression from these trials been excluded from the detail aid, the piece would have been unbalanced in favour of Betaferon and could have attracted a complaint under Clause 7.2 of the Code. It was made clear in the item that Schering Health Care's competitors' trials demonstrated a significant effect on disability progression whereas the Betaferon relapsing/remitting MS study did not. Possible reasons for this were presented and were a faithful representation of the facts. The detail aid did not claim that Betaferon slowed disability and was therefore in full concordance with the Betaferon SPC in use at the time. The current SPC now included the information that Betaferon had been shown to significantly delay disability progression in secondary progressive MS. The earlier ruling in Case AUTH/569/6/97 concerned a comparison of Biogen's placebo group with published natural history data, and these claims had never been repeated by Schering Health Care.

PANEL RULING

The Panel noted that, at the date of preparation of the detail aid, the Betaferon SPC (dated 5 February 1998) stated that it was indicated for the reduction of frequency and degree of severity of clinical relapses in ambulatory patients (ie patients who were able to walk unaided) with relapsing, remitting multiple sclerosis, characterized by at least two attacks of neurological dysfunction over the preceding two year period, followed by complete or incomplete recovery. There was no evidence of an effect of Betaferon on the progression of the disease. There was no evidence of an effect on disability.

The Panel noted that the statement at issue in Case AUTH/569/6/97 was 'The Betaferon study was not designed to show a significant effect on progression of disability. Nevertheless a strong 'trend' towards a slowing of disease progression was observed in the Betaferon trial.' The Panel had noted that the statement was based on the results of a trial which was not designed to show a significant effect on progression of disability. The SPC stated that there was no evidence of an effect on disability or on the progression of the disease. The Panel had considered that the claim was misleading and had ruled a breach of Clause 7.2 of the Code which had been accepted by Schering Health Care.

Turning to the present case, the Panel considered that the statement now at issue in the detail aid was similar to the statement at issue in Case AUTH/569/6/97 which had been ruled to be misleading in breach of Clause 7.2 of the Code. In the Panel's view the statement in the detail aid was similarly misleading. The Panel ruled a breach of Clause 7.2.

The Panel did not consider that the statement constituted promotion of Betaferon outside its marketing authorization. No breach of Clause 3.2 was ruled.

The Panel noted that although the statement was different from the statement in the previous case it nonetheless was sufficiently similar such that it represented a failure to comply with the undertaking given in Case AUTH/569/6/97. The Panel therefore ruled a breach of Clause 21 of the Code.

The Panel noted that Schering Health Care had amended the statement at issue in Case AUTH/569/6/97 but the amendment had not been adequate. In the circumstances the Panel ruled no breach of Clauses 9.1 and 2.

B Reprint: 'Patients' views of interferon therapy in MS'

COMPLAINT

Biogen stated that the UK Annual General Meeting of the Multiple Sclerosis Society, held in November 1998, was attended by approximately 500 patients and other members of the general public and approximately 7 health professionals. Schering Health Care had a stand at which many materials, including some that were product-specific and promotional, were

provided freely by personnel at the stand or left open and available when the stand was unmanned. Materials available included three reprints 'Treating and nursing patients with multiple sclerosis', 'Multiple Sclerosis: a new approach' (which included a Betaferon advertisement), and 'Placebo-controlled multicentre randomised trial of interferon ß-1b in treatment of secondary progressive multiple sclerosis'. There was also a leaflet, 'Handling and Storing Betaferon – Information for Retail Pharmacists', a videotape: 'Introducing Betaferon – A guide for users', and an audiotape: 'Betaferon – A guide for users'. Biogen provided photographs of the Schering Health Care stand which the company considered showed Schering Health Care's apparent promotional intent.

In addition to the materials listed above, Biogen objected to one reprint as being of highest concern. 'Patients' views of interferon therapy in MS' was a reprint of an article from the June 1998 edition of Professional Nurse which was purportedly written by a source independent of Schering Health Care. The reprint did not indicate that Schering Health Care sponsored any aspect of the reprint, the article or the study on which it was based; however, the circumstances of the study and the fact that the reprint was handed out by Schering Health Care representatives suggested that Schering Health Care had provided some sort of sponsorship related to this item. Biogen noted that the reprint had been used by Schering Health Care to imply very strongly that Betaferon could delay the progression of disability. The disclaimers in the article could not cure the fact that the article was misleading and inconsistent with the product's SPC and contravened the ruling in Case AUTH/569/6/97. Biogen noted in particular the following statements:

'In this study people using interferon beta-1b reported fewer relapses, less use of their primary healthcare services and an overall improvement in their condition.'

'Some debate has arisen … as to whether any improvement in disability or condition can be predicted or should be expected. (Markovitz *et al* (1994); Arnason (1993)). It is also mentioned in these papers that the effects of interferon beta-1b may not become apparent for 12 months. However, patients and their families do tend to report improvements in their overall condition before this time and the significance of this to individuals is illustrated in Figure 1.'

Figure 1 (a pie chart) was entitled 'Change in disease state as reported by patients since starting interferon therapy', which reported that a total of 56.5% of patients felt their 'disease state' had improved.

'Examples of some patient comments: 'After only a few weeks on the Betaferon, I became more upright in my walking with a lot more stamina.' …; 'My stamina has returned to near normal. Previously affected limbs have regained their strength.'; 'If there is a chance of halting the effects of MS, a few red blotches are worth putting up with.'

'…the majority of people report an improvement in their general condition.'

'The results suggest that individuals on interferon therapy experienced a reduced number of relapses and over half reported an improvement in their condition.'

Furthermore Biogen stated that the reprint, which was provided to members of the general public, included a journal-style advertisement for Betaferon.

Biogen alleged breaches of Clauses 3.2, 7 and 20; in light of the ruling in Case AUTH/569/6/97 it was alleged that the reprint was also in breach of Clauses 2, 9.1 and 21.

RESPONSE

Schering Health Care stated that in common with all companies working in the MS field (including Biogen) it had liaised closely with the MS Society and other MS charities in the UK in order to provide them with the technical information they required. The MS Society AGM was not open to the general public and was attended by many health professionals (particularly specialist nurses) with an interest in MS. Schering Health Care believed that the materials on offer at its stand were appropriate for this specialised and restricted audience.

Schering Health Care stated that its impression of the attendees had been based on its experience of such meetings over a number of years. In an attempt to clarify numbers the company had contacted the MS Society conference organiser and was informed that the Society did not keep records of the breakdown of attendees by profession. The Society was thus unable to confirm the numbers quoted by Biogen.

The article in question was made available at the stand amongst many others which would have been of interest to MS specialist nurses. It was not intended to be used as promotional material. The author had no connection with Schering Health Care and the article was neither sponsored nor suggested by it. The article concentrated on Betaferon because interferon beta-1a [Avonex] was not licensed for MS at the time of the study. Biogen's interferon beta-1a was, nevertheless, referred to by its trade and generic names and its benefits were stated in the opening paragraph. The advertisement for Betaferon was placed in the journal only after Schering Health Care was notified that the article was being published.

PANEL RULING

The Panel noted that Clause 20.1 of the Code prohibited the advertising of prescription only medicines and certain other medicines to the general public. Clause 20.2 of the Code permitted information to be made available to the public provided it was factual, balanced and did not raise unfounded hopes of successful treatment or mislead with respect to the safety of the product.

The Panel examined the article, entitled 'Patients' views of interferon therapy in MS' and noted that it discussed the management of relapsing/remitting MS. The article was very positive for Betaferon and referred to patients reporting an improvement in their condition. The back page of the reprint included an advertisement for Betaferon.

The Panel considered that the Annual General Meeting of the Multiple Sclerosis Society would be attended by its members, which would include not only healthcare professionals but also patients, carers and relatives. Companies exhibiting at meetings at which non-health professionals would be expected to be present had to ensure that the materials on their stands were appropriate for the general public.

The Panel considered that the reprint had been clearly associated with the promotion of Betaferon. It included an advertisement for the product and had been supplied by Schering Health Care. The article was misleading with regard to the licensed indication of the product as it implied that Betaferon improved patients' condition whereas the SPC stated that there was no evidence of an effect on disability. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel did not consider that the reprint constituted promotion of Betaferon outside its marketing authorization. No breach of Clause 3.2 was ruled.

The Panel noted that promotional literature for a prescription only medicine, which might give rise to unfounded hopes of successful treatment, had been made available to the general public. Breaches of Clauses 20.1 and 20.2 of the Code were ruled.

The Panel noted that the reprint had been used to imply that Betaferon had a positive effect on disability in MS. Although the previous case had concerned a company-produced press release the Panel considered that the use of the reprint still represented a failure to comply with the undertaking given in Case AUTH/569/6/97. A breach of Clause 21 was ruled. Given the changed circumstances the Panel ruled no breach of Clauses 9.1 and 2.

C Statement to the lay press – article in Mid Sussex Times

COMPLAINT

Biogen stated that a recent article in the Mid Sussex Times regarding the availability of interferon beta-1b quoted a Schering Health Care spokesman as follows:

'[Betaferon] is not a cure but it makes MS less frightening. Patients don't have as many relapses and research has shown that it actually delays the progress of the disease.'

In the open forum of the general press, the Schering Health Care spokesman had made the unqualified statement that Betaferon delayed the progression of disability, which had not been established and, in any event, was not consistent with the SPC. This statement was not factual or presented in a balanced way, and raised unfounded hopes of successful treatment.

Biogen alleged a breach of Clauses 2, 9.1, 20 and 21.

RESPONSE

Schering Health Care stated that this was not a quote from a Schering Health Care spokesperson but appeared to be an interpretation by a journalist of its spokeswoman's comments (during a telephone interview with the journalist) and the data from Schering Health Care's most recent trial which demonstrated that Betaferon slowed disability progression. These data had previously been presented at international scientific meetings and discussed in the medical press, and had therefore been in the public domain (including the lay press eg Daily Mail, February and June 1998, and The Daily Telegraph, February 1998) for several months before the interview. The Mid Sussex Times journalist was already aware of them, probably from other lay media reports and because Schering Health Care was a major local employer. It was certainly not Schering Health Care's intention to broadcast its data in the Mid Sussex Times.

Schering Health Care stated that the telephone call from the Mid Sussex Times journalist to its spokesperson was completely unsolicited. It was not company policy to record all external calls, and so no transcript of the conversation was available. The company spokeswoman remained adamant that she did not make any comments during the telephone call which could be misconstrued as advertising to the public. It therefore followed that the journalist must have created a composite from various other sources. These pre-dated the Mid Sussex Times articles by several months. Schering Health Care stated that as it had never sent any company press release to the Mid Sussex Times, it would not seem relevant to submit its press releases in response to this complaint.

PANEL RULING

The Panel noted that the article in question which had appeared in the Mid-Sussex Times of 15 October 1998 discussed funding the cost of treating multiple sclerosis with Betaferon. The Panel noted that the claim '…it actually delays the progress of the disease' was similar to those at issue in 1A and 1B above. Although the article did not define what type of MS was being discussed it did state that 'Betaferon is not considered suitable for MS patients with the progressive form of the disease or for those who are already disabled'. By default, the Panel assumed that the article was thus discussing relapsing/remitting MS.

The Panel noted that items in the media were judged on the information provided by the company. Clause 20.2 of the Code required that such information was factual and balanced. The Panel noted that no press release had been issued to the Mid Sussex Times although a journalist had contacted a spokeswoman from Schering Health Care. The Panel was concerned that no note had been kept of the conversation; it was difficult in such circumstances to determine what had transpired between the two parties. The Panel noted Schering Health Care's submission that the article had, in all probability, been created as a composite from various other sources such as the Daily Mail and The Daily Telegraph. The Panel noted that those articles clearly discussed positive findings in the treatment of the progressive form of MS with Betaferon. The Panel noted that the product had recently been licensed for secondary progressive MS to slow progression of disease and reduce the frequency of relapses; this was in contrast to its licence for relapsing/remitting MS in which there was no evidence of an effect of Betaferon on the progression of the disease or on disability. The Panel

considered that, given that Betaferon could slow the progression of secondary progressive MS but not of relapsing/remitting MS, it was important that the form of MS being discussed was always clearly defined. In that regard the Panel noted that Schering Health Care's response had not differentiated between the two forms of MS.

On balance the Panel considered that there was insufficient evidence to determine exactly what had been said to the journalist of the Mid Sussex Times and in the circumstances ruled no breach of Clauses 2, 9.1, 20 and 21 of the Code.

2 Statements that made misleading comparisons between Betaferon and Avonex

COMPLAINT

Biogen stated that the detail aid included a chart that showed the relapse rate for all patients for studies of Betaferon, Avonex and another interferon therapy (sc 1a). Schering Health Care had presented a relapse rate of –30% for Betaferon and –18% for Avonex.

The Avonex SPC stated that the medicine demonstrated a 'one third reduction in annual relapse rate' and the Betaferon SPC stated that it showed a 'reduction in frequency (30%) … of clinical relapses'. Furthermore, this section of the detail aid did not compare patients treated for the same period of time. A direct comparison of patients treated for two years would demonstrate a 32.2% reduction for Avonex and a 33.8% reduction for Betaferon. The chart might be viewed as all the more misleading in light of the fact that Schering Health Care had chosen to present two-year data in another section of the chart, which concerned the 'moderate/severe relapse rate'.

Biogen noted that the data as presented in the detail aid were extremely similar to a matter in Case AUTH/569/6/97 in which a breach of Clause 7.2 of the Code had been ruled in relation to the statement: 'In the clinical trials, the reduction in the relapse rate was far greater with Betaferon than with 1a – 30% compared to 18% in all patients studied'.

Biogen alleged a breach of Clauses 3.2 and 7. In the light of the ruling in Case AUTH/569/6/97 the company also alleged breaches of Clauses 2, 9.1 and 21.

RESPONSE

Schering Health Care said that the detail aid stated, correctly, that the relapse rate reductions for all patients in the Schering Health Care and Biogen studies were –30% and –18% respectively. Schering Health Care noted that Biogen did not seek to disagree with these figures, which were quoted accurately from published data. The previous decision in Case AUTH/569/6/97 also did not rule against the correctness of the 'all patient' figures but stated that the comparison had not been put into the context of patient type or treatment duration. The detail aid, in contrast, presented full details of study design, size and duration for all products specifically in order to comply with the previous ruling.

Schering Health Care stated that although Biogen was entitled to quote a relapse rate reduction of 32.2% in its own promotional literature, provided it was clear about how it was calculated, independent opinion leaders argued that use of the 18% reduction was most appropriate as this was the result of the 'intention-to-treat' analysis in Biogen's pivotal trial. Most recently, this point was made very persuasively by Professor Ebers in The Lancet, 6 February 1999. The relapse rate reduction of 32.2% for Biogen's interferon beta-1a was not equivalent to Schering Health Care's 2-year figure of 33.8% because the former was a highly selective analysis including only those patients completing 2 years on treatment. In contrast, the 2-year data in Schering Health Care's study was based upon an intention to treat analysis of data from the first 338 patients entered to the study, prior to the extension of the study beyond 2 years. Not all of these 338 patients would have completed 2 years on treatment at the time of the '2-year' analysis. Comparison of Schering Health Care's analysis with the selective '2-year' Biogen analysis was therefore not comparing like with like. The only valid comparison was the 'all patient' analysis for both studies ie 18% v 30%, as quoted and referenced in the detail aid.

PANEL RULING

The Panel noted that the claim at issue was closely similar to a statement considered in Case AUTH/569/6/97, namely 'In the clinical trials, the reduction in the relapse rate was far greater with Betaferon than with 1a - 30% compared to 18% in all patients studied. This represented an increased likelihood of remaining relapse free at two years of 94% with Betaferon compared to 46% with 1a and an increased time to first relapse of 93% and 31% respectively.'

The Panel had noted that the statement was very brief and it seemed to infer that patients on Betaferon were almost twice as likely to be relapse free at two years compared to patients on Avonex. The statement had not been put into context with regard to the types of patient studied or the length of time they had received treatment whereas according to the SPCs the reduction in relapse rates for Betaferon and Avonex were very similar (30% v one third after one year's treatment respectively).

The Panel had considered that the brevity of the statement gave a misleading impression of the reduction in relapse rates of the two products and had ruled a breach of Clause 7.2 of the Code.

Turning to the present case, the Panel noted that details of the study design were presented on page 3 of the detail aid whereas the chart, headed 'Summary of relapse data' appeared on page 5. The Panel considered that the chart in question gave a misleading impression about the reduction in relapse rates with Betaferon and Avonex. The basis of the data had not been explained. In this regard the Panel noted the statement in the Avonex SPC that it demonstrated a one third reduction in annual relapse rate. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that the reduction in relapse rate stated for Betaferon was consistent with that given in the product's SPC; no breach of Clause 3.2 was ruled.

The Panel considered that the claim at issue was sufficiently similar to that in Case AUTH/569/6/97 such that the company was in breach of its undertaking and ruled a breach of Clause 21 of the Code.

The Panel noted that Schering Health Care had amended the statement at issue in Case AUTH/569/6/97 but the amendments had not been adequate. In the circumstances the Panel ruled no breach of Clauses 9.1 and 2.

APPEAL BY SCHERING HEALTH CARE

Schering Health Care stated that the detail aid contained a chart on page 3 summarising the relapse rate data for the three types of interferon beta. The Panel had ruled that the presentation of a relapse rate of –30% for Betaferon and –18% for Biogen's interferon beta-1a was misleading. The Panel's reasoning was that the basis of the data had not been explained and the figure of 18% was not in line with the SPC for Biogen's product.

Schering Health Care submitted that the basis of the data had been explained clearly by the table ie that these figures related to the 'all patient' data for each study quoted. The one third reduction in relapse rate appearing on Biogen's SPC was based on a subset analysis of only those patients completing two years of treatment in the interferon beta-1a pivotal trial. This analysis involved only 172 of the 301 patients enrolled. It should be noted that it was the 'all patient' figure of 301 which was presented on page 3. The Code required that companies promoted their own products in concordance with the relevant SPC. It also demanded that all claims were accurate, fair and capable of substantiation and based on an up-to-date evaluation of all the evidence. It did not require competitor products to be discussed only in line with their SPCs, providing the former conditions were also met. Indeed, in this instance, Schering Health Care believed that the use of the 18% figure was in line with the most up-to-date scientific opinion and this could be supported by a wealth of independent evidence. At the time of Schering Health Care's original response, it had submitted a recent letter which had appeared in The Lancet which had explained its reasoning most succinctly (Ebers (1999)). In addition, it now submitted publications by Paty *et al* (1998), Green (1999), and The Wessex Institute (1997). All these publications quoted only the 18% figure (0.67 v 0.82 relapses year, p = 0.04). Indeed the Wessex Institute report specifically criticised the interferon beta-1a publication for failing to account for all patients and for concentrating instead on a subgroup The Drug and Therapeutics Bulletin (January 1998) review of interferon beta-1a also gave prominence to the 0.67 v 0.82 comparison as this included all randomised patients. Schering Health Care therefore maintained that the comparison was fair, accurate and supported by the data. Use of 'all patient' data was the only scientifically valid means of comparing data from unrelated studies with differing patient numbers, analytical methods and duration of follow-up. Indeed, to have presented anything other than an 'all patient' comparison of the relapse rate data from the three studies would have been a failure to compare like with like, and hence would have been in breach of Clause 7.2 of the Code.

Concerning the ruling of a breach of Clause 21, Schering Health Care's appeal against this followed directly from its arguments above. In addition, it wished to appeal against the Panel's implied criticism that the study design summary on page 3 of the detail aid was too far from the comparison on page 5. There was considerable detail in the design summary on page 3, much of which was included in order to comply with the Panel's original ruling in Case AUTH/569/6/97. The summary was given a prominent position inside the front cover of the detail aid. Further information on study duration and patient numbers was presented in bar charts on page 4, opposite the summary of relapse data. It would not have been possible to present this level of detail on the same page and still make it comprehensible to the reader.

In conclusion, Schering Health Care believed that the comparative relapse rate data presented in the detail aid were accurate, fair and supported by the weight of independent expert opinion.

In addition to the above, the Authority received a letter on the matter from a consultant neurologist and Schering Health Care asked that this be included in the papers to go before the Appeal Board.

The consultant neurologist was surprised by the ruling. The Avonex expedited publication (Jacobs *et al* (1996)) stated that the study had an intent-to-treat design and that randomisation was by bias coin method. It did not state the bias parameters. After the trial was started it was claimed that the expected drop-out rate was much lower than anticipated and therefore the sample size could be reduced. This was a most unusual procedure and it was not an *a priori* decision. This rendered the intent-to-treat analysis the only valid one. The number of patients recruited at the time of the decision to reduce the size of the trial on the basis of power calculation was 301, a number in excess of those required to give sufficient power to account for the lower drop-out rate. No further patients were therefore recruited.

The consultant neurologist stated that it was clear from the only valid analysis done in this trial that the relapse rate reduction was 18%. There were many reasons why the two-year subset might demonstrate a greater reduction but subset analysis on a cohort was a statistically dangerous thing to do. The fact that the SPC stated that approximately 32% relapse rate reduction was obtained by Avonex was not correct and should be amended as it was unfair to patients falsely to raise their hopes by statements that were not supported by the literature.

APPEAL BOARD RULING

The Appeal Board noted Schering Health Care's views about references to competitor products and whether such material needed to comply with Clause 3 of the Code ie not be inconsistent with the SPC. The Appeal Board's view was that each case should be considered on its own merits and that the requirements of other clauses of the Code, particularly Clause 7.2, would be relevant.

Turning to the case now before it, the Appeal Board noted that the relapse rate reduction for all patients

was 18% for Avonex. It noted Schering Health Care's submission regarding the use of 'all patient' data and that independent publications referred to the 18% reduction. The Appeal Board nevertheless noted that the SPC for Avonex stated that there was a one third reduction in annual relapse rate. The SPC represented the agreed information about a medicine. The Appeal Board considered that by not referring to the data in the SPC and only referring to the 'all patient' data the company had failed to present all the information and the detail aid was misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The Appeal Board considered that the claim at issue was sufficiently similar to that in Case AUTH/569/6/97 to mean that Schering Health Care was in breach of its undertaking. The Appeal Board upheld the Panel's ruling of a breach of Clause 21 of the Code.

The appeals were thus unsuccessful.

Complaint received **29 January 1999**

Case completed **21 July 1999**

CASES AUTH/850/3/99 to AUTH/855/3/99

UNIVERSITY PROFESSOR v BRISTOL-MYERS SQUIBB, NAPP, NOVARTIS, PHARMACIA & UPJOHN, SANOFI WINTHROP and SMITHKLINE BEECHAM

Articles in NHS Doctor and Commissioning GP

A university professor complained about five articles which had appeared in the journal NHS Doctor and Commissioning GP, Winter 1998/99. Four of these appeared adjacent to advertisements for associated products. The complainant alleged that the articles were advertising supplements for the medicines but that this was not stated.

In Case AUTH/850/3/99, an article on hydromorphone was followed by an advertisement for Napp's product Palladone (hydromorphone hydrochloride). At the end of the article the authors were identified as Napp employees. The Panel considered that it had to be regarded as promotional, taking into account its content, origin and format. The Panel considered that a reader would not necessarily be aware at the outset that it was a promotional item. The Panel considered that it constituted disguised promotion and ruled it in breach in that regard. It was also ruled in breach because of the lack of prescribing information and because Napp's involvement had not been made sufficiently clear.

In Case AUTH/851/3/99, a two page article on hepatitis A and B was immediately followed by a page bearing the prescribing information for Havrix, Engerix B and Twinrix, all SmithKline Beecham hepatitis vaccines. The Panel considered that the article and the page bearing the prescribing information amounted to a three page advertisement. No journal advertisement could exceed two pages in length and the Panel ruled a breach in that regard.

In Case AUTH/852/3/99, a two page article on Alzheimer's disease which referred to rivastigmine appeared on the page preceding and the page following a one page advertisement for Novartis' product Exelon (rivastigmine). The Panel considered that the position was similar to that in Case AUTH/850/3/99 as regards the nature and origin of the article. That had not been made clear and breaches of the Code were ruled. Each page of the two page article should have borne prescribing information as it amounted to a two page advertisement separated by a one page advertisement and as the two pages were not consecutive they had to be regarded as two separate advertisements. A breach of the Code was ruled in that regard.

In Case AUTH/853/3/99, a two page article on unstable coronary artery disease which described dalteparin concluded by stating that the advertisement which followed should be referred to for prescribing information. That advertisement was for Pharmacia & Upjohn's product Fragmin (dalteparin sodium). The article was by a Pharmacia & Upjohn employee and the Panel considered that the position was similar to that in Case AUTH/850/3/99 as regards the nature and origin of the article. Breaches were ruled because the article was disguised promotion, it lacked prescribing information and Pharmacia & Upjohn's involvement had not been made clear.

In Cases AUTH/854/3/99 and AUTH/855/3/99, an article on unstable coronary artery disease which described irbesartan was followed by a one page advertisement for Aprovel (irbesartan) placed by Bristol-Myers Squibb and Sanofi Winthrop. The Panel considered that the position was similar to that in Case AUTH/850/3/99 and breaches were ruled because the article was disguised promotion, it lacked prescribing information and the companies' involvement had not been made clear.

A university professor complained about five articles which had appeared in the journal NHS Doctor and Commissioning GP, Winter 1998/99. Four of these articles appeared adjacent to advertisements for associated products. The attention of the companies concerned was drawn to Clauses 4.1, 9.9 and 10.1 of the Code, in addition to Clause 6 which had been referred to by the complainant.

CASE AUTH/850/3/99

This complaint related to an article on hydromorphone which was followed by an advertisement for Palladone (hydromorphone hydrochloride) placed by Napp Laboratories Limited.

COMPLAINT

The complainant stated that a two page article written by employees of Napp Laboratories on hydromorphone was followed immediately by a full page advertisement for Palladone. There was no comment which mentioned that this was an advertising supplement on this medicine, in a company sponsored article which appeared in the middle of this journal. This appeared to be a clear breach of Clause 6 of the Code.

RESPONSE

Napp stated that NHS Doctor and Commissioning GP was published by Medical Information Systems Limited (MIS). It was a relatively new publication with which Napp had not had any dealings prior to the discussions relating to the Winter 1998/99 edition. MIS made an unsolicited approach to Napp to advertise in the journal and also invited Napp to submit a scientific paper for publication.

The paper in question was written by two of Napp's doctors. Editorial control, however, rested with MIS. The paper was not published in the form in which it had been submitted as it went through three proofs during which MIS made a number of editorial changes. These included the omission of text on side-effects and opioid substitution.

Neither Napp nor the authors who wrote the paper received any payment. The only payment that Napp made was in respect of the advertisement, not the publication of the paper. A copy of the invoice was supplied.

Napp appreciated that the juxtaposition of the paper and the advertisement might have raised the question in the reader's mind as to whether the paper was part of the advertisement. In the course of pre-publication discussions with MIS, Napp specifically asked for the advertisement and the paper to be kept separate. Clearly that request was not implemented.

In any event, the paper was not promotional for a number of reasons.

1 It was a very factual and balanced scientific paper.

2 No brand names appeared in the paper.

3 Alternative products were mentioned, ie morphine, fentanyl transdermal patch and methadone. Indeed it was made clear that morphine was the World Health Organisation's strong opioid of choice and that hydromorphone should be used in those patients for whom morphine was unsuitable.

4 The side effects, including abuse potential, of hydromorphone were clearly stated, along with contra-indications and interactions.

5 The authors pointed out limitations in certain of the data used.

Napp could confirm that because the paper was not promotional it had not been circulated to its sales force or used in any other promotional context.

Given that the paper was not promotional and was therefore not an advertisement, Napp did not believe that it was in breach of Clause 6 of the Code. For the same reason, there was no breach of Clause 4.1. With regard to Clause 9.9 of the Code, it was clearly stated at the end of the paper that the authors were from Napp Laboratories Limited. This distinguished the case from an earlier one as the company involved then did not make any statement that the paper in question had been written by its employees (Case AUTH/655/12/97). The present case was also distinguished from that earlier case on the grounds that no brand names had been used in the Napp paper and that other treatment options were mentioned.

With regard to Clause 10.1 of the Code, Napp did not see how there could have been disguised promotion, given that the paper was not promotional and that there was no element of disguise as the paper was clearly attributed to employees of Napp.

Napp noted that a number of other companies had contributed papers and advertisements. In contrast to Napp's paper, some of the other papers used brand names and might well have a more promotional focus.

As indicated earlier, Napp was not satisfied with the way in which the paper and advertisement were positioned together, contrary to its express instructions. Napp placed the advertisement and submitted the scientific paper in good faith and was disappointed both with MIS' actions and with the general format and content of the journal. Napp would not be contributing any papers or advertisements to this publication in the future.

PANEL RULING

General Comments

The Panel noted that the journal was divided into six main sections; Primary Care, The New NHS, Finance, Formulary, Technology and Endpieces. The Formulary section featured a series of articles on different disease areas and various aspects of their treatment. Each of the items at issue appeared within the Formulary section.

The Panel noted that there were important differences between the articles complained of and the other articles which appeared in the Formulary section. The articles at issue were not listed on the contents page of the journal and their typeface and layout were different to that of the editorial. In addition the articles were all printed on white pages whereas editorial appeared on pages which were slightly coloured.

The Panel noted that the whole area of company sponsored articles in publications and reports of symposia etc was not at all clear cut under the Code. Each case had to be considered on its own merits. The Panel referred to two previous complaints which were relevant. Cases AUTH/343/10/95 to AUTH/357/10/95 related to articles sponsored by pharmaceutical companies. The articles, which were reports of discussions with opinion leaders, had not been written by the companies although they had seen the articles prior to publication. The Panel had decided that the articles were not promotional as the

companies had no direct editorial input and the discussants and publishers had final editorial control. Sponsorship had been declared. No breach of the Code had been ruled. The subject of Case AUTH/655/12/97 was an article written by two pharmaceutical company employees which had been published in a journal. There had been no declaration that the authors were employed by the pharmaceutical company. The article had referred to two of the company's products. The article had been ruled to be disguised promotion. The failure to include prescribing information and to declare the sponsorship had also been ruled to be in breach of the Code.

CASE AUTH/850/3/99

The Panel examined the article and advertisement produced by Napp. The article was entitled 'Hydromorphone: A new choice in the treatment of cancer pain' and discussed the use of hydromorphone as an alternative to morphine in the treatment of cancer pain. The article did not mention brand names. At the end of the article the authors were identified as employees of Napp. The two page article was immediately followed by the one page advertisement for Palladone (hydromorphone hydrochloride).

Firstly the Panel had to decide whether the article was promotional. The company had been invited to submit the article for publication and it had been written by company employees. Napp had submitted that editorial control rested with the publishers who had made a number of changes. There was no reference to the article in the contents page of the journal. On balance the Panel considered that taking into account the content, origin and format, it had to be considered as promotional. It was immaterial that no brand names were included in the article; it was about hydromorphone and had been written by employees of the company which had a commercial interest in the medicine. The Panel considered that a reader would not necessarily be aware at the outset that this was a promotional item. The Panel considered that the article constituted disguised promotion and ruled a breach of Clause 10.1 of the Code.

The Panel noted that the promotional nature of the article meant that prescribing information for hydromorphone was needed. This had not been included and the Panel therefore ruled a breach of Clause 4.1 of the Code.

The identities of the authors of the article had been stated. The Panel noted that the supplementary information to Clause 9.9 of the Code stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The Panel considered that Napp's involvement in the article had not been made sufficiently clear and a breach of Clause 9.9 of the Code was ruled.

Clause 6.1 of the Code stated that no single advertisement included in a journal could consist of more than two consecutive pages. The Panel considered that the article was a two page advertisement which needed prescribing information and the Palladone advertisement was a one page advertisement which had the requisite prescribing information. The Code did not prohibit three consecutive pages of advertising provided that this was made up of a two page advertisement and a one page advertisement or of three one page advertisements. The Panel noted that while both pages of the article were headed 'Formulary' this heading was not carried on into the advertisement. The Panel thus considered that the two page article and the advertisement were separate items. The Panel ruled no breach of Clause 6.1 of the Code.

CASE AUTH/851/3/99

This complaint related to a two page article on hepatitis A and B which was immediately followed by one page bearing the prescribing information for Havrix, Engerix B and Twinrix, all SmithKline Beecham Pharmaceuticals' hepatitis vaccines.

COMPLAINT

The complainant said that under a section entitled Hepatitis was a two page unauthored sub-section 'A closer look at Hepatitis A and B' which referred exclusively to SmithKline Beecham vaccination products. Immediately following this in the same black and white style type face was an advertisement for the vaccines mentioned in the article. There was no comment which mentioned that this was an advertising supplement on this medicine, in a company sponsored article which appeared in the middle of this journal. This appeared to be a clear breach of Clause 6 of the Code.

RESPONSE

SmithKline Beecham stated that the article about hepatitis A and B, the risk factors for transmission, treatment and prophylaxis, was factually correct and valid as regards content.

In terms of the alleged breach of Clause 6, SmithKline Beecham's primary defence was that while the piece was promotional material, it was not an advertisement as such: the first page described the hepatitides, clinical features, treatment, transmission and risk groups; the only mention of the prophylactic vaccines available for these conditions was made on the second page. The information contained in these paragraphs was essentially factual. The piece went on to discuss the issue of universal immunisation of hepatitis B. There was no actual advertisement for SmithKline Beecham vaccines, as alleged by the complainant, and prescribing information was included only to support the trade-named products mentioned in the article. The company submitted that the prescribing information was clear and legible, formed part of the promotional material and was not separate from it. SmithKline Beecham did not believe the layout breached this clause.

SmithKline Beecham accepted that the piece did not clearly indicate that it had been sponsored by SmithKline Beecham.

SmithKline Beecham believed it was clear from the layout and typeface used in the piece that it was distinct and separate from the 'editorial' (non-

promotional) sections of the journal. Also the piece was not listed in the contents page. A number of other companies had included promotional pieces in the journal that were similarly distinct from the main journal. In this context SmithKline Beecham believed there was no breach of Clause 10.1.

SmithKline Beecham stated that it had no relationship with the publishers of NHS Doctor and Commissioning GP. The article came to be written when the publishers of the journal contacted SmithKline Beecham's public relations agency. The article was written by the agency and approved in accordance with Clause 14 of the Code. The agency paid the publishers for placement of the piece. SmithKline Beecham had no influence on the layout of the journal with respect to the positioning of the promotional piece. SmithKline Beecham understood that the journal was published four times a year and was distributed to approximately 12,000 doctors. SmithKline Beecham received copies of the journal which were distributed to its sales representatives for their information and private use only.

PANEL RULING

The Panel considered that its general comments made in Case AUTH/850/3/99 also applied here.

The Panel noted that the two page article discussed the symptoms of hepatitis A and B infection, clinical sequelae, treatment and vaccines available. All of the available vaccines mentioned were SmithKline Beecham products. They were referred to by brand name. Facing the second page of the article was a full page containing prescribing information for each SmithKline Beecham product mentioned. Although both in black and white, the article and the prescribing information used slightly different type faces.

The Panel noted that both pages of the article were headed 'Hepatitis' and that this heading was carried on to the page which bore the prescribing information for Havrix, Engerix and Twinrix. The Panel thus considered that the article and the page of prescribing information were a single item ie a three page advertisement. Clause 6.1 of the Code stated that no single advertisement included in a journal could consist of more than two consecutive pages. A breach of Clause 6.1 was therefore ruled.

The Panel considered that given its ruling of a breach of Clause 6.1, Clauses 4.1, 9.9 and 10.1 were not relevant and no breach of those clauses was ruled.

CASE AUTH/852/3/99

This complaint related to a two page article on Alzheimer's disease which appeared on the page immediately preceding and the page immediately following a one page advertisement for Exelon (rivastigmine) placed by Novartis Pharmaceuticals UK Ltd.

COMPLAINT

The complainant stated that an article on Alzheimer's disease, written by a doctor from Novartis, which referred to rivastigmine, appeared on either side of a full page advertisement for Exelon (rivastigmine). There was no comment which mentioned that this was an advertising supplement on this medicine, in an article which appeared in the middle of this journal. This appeared to be a clear breach of Clause 6 of the Code.

RESPONSE

Novartis stated that it was not the company's intention to create an advertorial or promotional supplement to the journal, through the combination of this article and advertisement as the complainant suggested.

The article in question was commissioned from Novartis by the editor of the NHS Doctor and Commissioning GP in July 1998, who was keen to obtain suitable articles for inclusion in the pages of this new journal. It was not the intention of the company to disguise the fact that a Novartis employee had written this article and this fact was therefore clearly included at the end of the article in the author's affiliation.

The company did not consider that this article could be viewed as a promotional item for Exelon and thus it did not include prescribing information. The article itself dealt with clinical data from the ADENA trials programme with which the author from the company's medical department was understandably very familiar. Its scientific purpose was to explain the potential of acetylcholinesterase inhibitors as a new therapeutic option in the management of Alzheimer's disease to readers of the journal.

Appropriate prescribing information did, of course, appear as an integral part of the promotional advertisement for Exelon that appeared in the journal.

The publishers of the journal had no special relationship with Novartis compared to that of any other publisher working in the healthcare sector. NHS Doctor and Commissioning GP was, Novartis understood, published four times a year and was available only on a postal subscription basis to UK health professionals.

Novartis was not responsible for the final layout of this publication, which was entirely created by the journal editorial team. The company was of course aware that the journal would contain the disease area article and that an advertisement for Exelon, the space for which had been purchased by the company, would also be included, but Novartis was not aware and did not intend that the two would appear together.

No copies of this journal had been circulated to company representatives or distributed by them. The company had not in fact used the item in question in any promotional context.

PANEL RULING

The Panel considered that its general comments made in Case AUTH/850/3/99 also applied here.

The Panel noted that the two page article discussed new options for the management of Alzheimer's

disease, disease aetiology, clinical trials, the impact on carers and society and cost implications. In particular the article featured the results of the phase 3 trials leading to the launch of rivastigmine. The Panel considered that its ruling at Case AUTH/850/3/99 was relevant with regard to the nature and origin of the article. The Panel considered that the article was promotional, the nature and origin of the article had not been made clear and ruled breaches of Clauses 10.1 and 9.9 of the Code.

Clause 6.1 of the Code stated that no single advertisement included in a journal could consist of more than two consecutive pages. The supplementary information to Clause 6 stated that a two page advertisement was one where the pages followed continuously without interruption by intervening editorial text or other copy. The Panel noted that while each page of the two page article was headed 'Formulary' this heading was not on the intervening advertisement. The Panel thus considered that the two page article and the advertisement were separate items. Under the Code each page of the material at issue was therefore a separate one page advertisement and no breach of Clause 6.1 was ruled. As separate advertisements, however, each page of the article ought to have contained prescribing information which neither did. A breach of Clause 4.1 was ruled.

CASE AUTH/853/3/99

This case concerned a two page article on unstable coronary artery disease under the heading Unstable Angina which concluded by stating 'For prescribing information please see advert on page 55'. Page 55 was a one page advertisement for Pharmacia & Upjohn Limited's product Fragmin (dalteparin sodium) which was indicated for the treatment of unstable coronary artery disease.

COMPLAINT

The complainant said that in a section headed Unstable Angina 'Unstable Coronary Artery Disease', clearly sponsored by Pharmacia & Upjohn, was an article describing dalteparin which referred to the following full page advertisement for Fragmin (dalteparin sodium). There was no comment which mentioned that this was an advertising supplement on this medicine, in an article which appeared in the middle of this journal. This appeared to be a clear breach of Clause 6 of the Code.

RESPONSE

Pharmacia & Upjohn said that it accepted that the piece in question was in breach of the Code. This was due to an internal error and the company apologised for this inadvertent breach.

PANEL RULING

The Panel noted that its general comments made in Case AUTH/850/3/99 also applied here.

The Panel noted that the article in question was written by an employee of Pharmacia & Upjohn. The article included sections on the burden of disease, clinical presentation, risk stratification and treatment options. Antiplatelet drugs, anti-ischaemic agents, antithrombotics and surgery were the treatment options mentioned. The Panel noted that there was discussion of dalteparin sodium which was referred to by both its brand and generic name. The final section discussed management options developed by Pharmacia and Upjohn. The Panel considered that its ruling at Case AUTH/850/3/99 was relevant with regard to both the nature, format and origin of the article and the failure to include prescribing information. The Panel ruled breaches of Clauses 10.1, 9.9 and 4.1 of the Code.

The Panel considered that its ruling in Case AUTH/850/3/99 with regard to the requirements of Clause 6 applied here and ruled no breach of Clause 6.1 of the Code.

CASES AUTH/854/3/99 and AUTH/855/3/99

This complaint concerned a two page article on unstable coronary artery disease under the heading Hypertension which was followed by a one page advertisement for Aprovel (irbesartan) which had been placed by Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi Winthrop Limited. The companies submitted a joint response. The article was written by a general practitioner and a consultant diabetologist and was subtitled 'A focus on irbesartan in primary and secondary care'.

COMPLAINT

The complainant stated that an unauthored article entitled 'Unstable Coronary Artery Disease' under the heading of 'Hypertension' described the pharmacological properties of irbesartan This followed on directly to a full page advertisement for Aprovel. There was no comment which mentioned that this was an advertising supplement on this medicine, in an article which appeared in the middle of this journal. This appeared to be a clear breach of Clause 6 of the Code.

RESPONSE

Bristol-Myers Squibb responded on behalf of both companies and addressed the issues in the order in which they appeared in the complainant's letter.

'Unauthored article' The article had two authors and their names were clearly written on the top of the article. In addition, their job titles and addresses were also stated underneath the names. Both were practising physicians with particular interests in hypertension within their clinical practice.

'Article entitled 'Unstable Coronary Artery Disease' under the heading of 'Hypertension' described the pharmacological properties of irbesartan' The article was written in the journal's section on Hypertension under the sub-heading 'Unstable Coronary Artery Disease'. It was entitled 'Efficacy, tolerability and cost in anti-hypertensive therapy; can the sartans help? A focus on irbesartan in primary and secondary care'. This article did not just describe the pharmacological

properties of irbesartan. Other aspects of hypertension were described.

The article began by describing the HOT Study, and the implications for clinical practice in reducing blood pressure appropriately. In the next section on 'Treatment Aims', issues such as achieving target blood pressure, compliance and requirements of an ideal medicine were discussed. This was followed by a section on 'Angiotensin II receptor Antagonists' (AIIRAs or sartans) – here all of the agents currently available in the UK were discussed in terms of their efficacy and tolerability profiles.

Next, the article discussed the individual pharmacokinetic differences within the class. All four sartans were included in a table, not just irbesartan. In outlining the differences in pharmacokinetic profiles of these agents, the authors went on to describe the clinical relevance of the pharmacokinetic profiles with reference to a study which compared the efficacy of irbesartan with losartan. They went on to discuss how the difference in efficacy could have a cost implication from a primary care perspective. In their conclusion, the authors wrote about how the AIIRAs as a class could be beneficial for patients who experienced adverse effects.

The article was not solely about the pharmacological properties of the medicine, which formed only a section of the article. The companies believed that the article, when viewed as a whole, expressed the views of two physicians on hypertension treatment and the benefits of the AIIRA class, and referred occasionally to the differences observed within the class. The article was balanced and fair and could not be construed as an advertisement for Aprovel.

'There was no comment which mentioned that this was an advertising supplement on this medicine, in an article which appeared in the middle of this journal.' This article was not an advertising supplement for Aprovel, neither was it an advertisement. It was commissioned for the journal by Bristol-Myers Squibb and Sanofi Winthrop, but the companies did not specify where either the article or the separate Aprovel advertisement should be placed in the journal or in relation to each other. This was the decision of the editor. Therefore the fact that the article was adjacent to a one page Aprovel advertisement was not relevant to Clause 6 of the Code.

The companies provided some relevant data on irbesartan to the authors, but did not write the article nor provide any guidance on the text. The finished article represented the views of the two authors. It was not promotional and did not therefore require prescribing information under Clause 4.1. The two physicians who wrote the article had a particular interest in the field of hypertension, and this was expressed in the article. It was not a form of disguised promotion and did not breach Clause 10.1 of the Code.

Although a nominal fee was paid to the authors for their time, the article represented their personal views, and not that of the companies. It was clear from reading the journal that many of the articles were commissioned (in fact, some were written by in-house medical advisers).

The journal had not been circulated by the companies' sales forces. The companies were intending to provide it to customers who specifically requested it. However to date no such activity had taken place.

In conclusion, the companies emphasised that the article was neither an advertisement nor an 'advertising supplement' on irbesartan. The article represented the views of the authors and was not a form of disguised promotion. As the article was non-promotional, there was no need to insert prescribing information next to it and it could be placed next to an Aprovel advertisement. The article and advertisement did not breach Clauses 6, 4.1 and 10.1 of the Code.

PANEL RULING

The Panel considered that its general comments made in Case AUTH/850/3/99 also applied here.

The Panel noted that the article discussed treatment aims, angiotensin II receptor antagonists (AIIRAs) and pharmacokinetic differences between AIIRAs. The article discussed the results of several studies and made favourable comparative clinical and cost claims in favour of irbesartan. In a table which featured the comparative pharmacokinetics of AIIRAs the brand name of irbesartan and each competitor product was mentioned. The Panel noted that the article had been commissioned by the companies which had provided some relevant data on irbesartan to the authors.

The Panel noted that the content of the article represented the independent views of the authors. However in the opinion of the Panel it would not be clear to the reader that the article had been commissioned by the companies who had arranged to place the article in the journal. The Panel considered that given the origin and content of the article it was promotional. The role of the companies had not been made clear. The Panel considered that the article was disguised promotion and ruled a breach of Clause 10.1 of the Code.

The Panel considered that its rulings at Case AUTH/850/3/99 applied here with reference to Clauses 4.1, 6 and 9.9. The Panel accordingly ruled breaches of Clauses 4.1 and 9.9 and no breach of Clause 6.1.

Complaint received	**15 March 1999**
Cases completed	
AUTH/850/3/99	**8 July 1999**
AUTH/851/3/99	**2 July 1999**
AUTH/852/3/99	**1 July 1999**
AUTH/853/3/99	**23 July 1999**
AUTH/854/3/99	**2 July 1999**
AUTH/855/3/99	**2 July 1999**

CASE AUTH/858/3/99

LILLY v JANSSEN-CILAG

Promotion of Risperdal

Lilly complained about the promotion of Risperdal (risperidone) by Janssen-Cilag. Lilly produced olanzapine (Zyprexa). The complaint concerned data presented in a booklet and at educational meetings. The booklet was a summary of a study by Conley *et al* and had been used by Janssen-Cilag's representatives to present the results of the study to clinicians.

A page of the booklet headed 'Efficacy' featured two graphs which compared Risperdal and olanzapine at weeks 2, 4, 6 and 8. One depicted the mean change from baseline positive and negative syndrome scale (PANSS) for positive symptoms of schizophrenia. Week 8 showed a statistically significant difference between the products. The second graph depicted the mean changes from baseline PANSS for negative symptoms. There was no statistically significant difference between the products. The Panel noted that one graph was not a precise reproduction of that in the study as the y-axis read from -2 to -5, rather than from -1 to -5. Neither had a zero axis and the Panel considered that because of that the visual impact of the graphs was to underrate the effect of olanzapine. A breach of the Code was ruled because of this and inadequate labelling. The Panel considered that it was misleading not to have stated the patient population and the numbers of patients at each time point. Data points had been linked by a continuous line suggesting that the population had been constant throughout but this was not so. A breach of the Code was ruled.

A page of the booklet headed 'Safety Results' summarised the safety results obtained in the study. The upper table featured data which compared the extrapyramidal syndrome (EPS) profile from baseline to week 8 and the lower table compared the number of patients with nonpuerperal lactation/breast discharge and gynaecomastia in each patient group. The Panel noted that the data in the lower table was based on the intention-to-treat (ITT) population whilst the data in the upper table was based on the change from baseline at week 8 of those patients recording an EPS assessment at week 8. The Panel considered that the omission of patients who had dropped out of the study at other time points could have influenced the data. The Panel noted Lilly's view that those patients might have dropped out due to EPS symptoms. The scores of those patients would normally be included in an ITT analysis. The Panel considered the page was misleading and ruled a breach of the Code.

The back cover of the booklet featured four claims: 'Significantly more effective than olanzapine in positive and affective symptoms', 'Comparable to olanzapine in negative symptoms', 'No significant differences in EPS profile or other side effects' and 'Significantly less weight gain than olanzapine patients'. The Panel noted that the back cover did not expressly refer to Conley *et al* and considered that the claims might be read as general comparative claims rather than limited to the results of the study. The Panel noted its previous rulings regarding the use of the data from Conley *et al*. If the claims were limited to the results of the study they were unacceptable. If the claims were general claims they did not reflect the totality of the comparative data. The Panel therefore ruled a breach of the Code.

A number of other aspects of the booklet were the subject of allegations by Lilly but the Panel considered that the rulings above covered these points also. It was also alleged by Lilly that the information with which it took issue was being used at meetings. The Panel noted that a series of meetings had been arranged and sponsored by Janssen-Cilag. The Panel considered that whilst the chairman and speakers were independent, the company was nonetheless responsible under the Code for the information presented at such meetings. The Panel did not know the exact content of the presentations but noted Janssen-Cilag's submission that information from Conley *et al* was presented at most of these meetings. The Panel therefore considered that its rulings above also applied here.

Eli Lilly and Company Limited complained about the promotion of Risperdal (risperidone) by Janssen-Cilag Ltd. The complaint concerned data presented in a booklet (ref 00185) and at educational meetings. Lilly produced olanzapine (Zyprexa).

A Risperdal Booklet (00185)

The booklet, entitled 'NEW STUDY: Double blind comparison of Risperdal and olanzapine in schizophrenia and schizoaffective disorder' was a 12 page summary of a study by Conley *et al* (1998) which had been presented as a poster at an international congress in November 1998. The original poster was reproduced on the inside back cover of the booklet. Janssen-Cilag stated that the booklet was used by its representatives to present the results of the study to clinicians.

Janssen-Cilag advised on 27 April that it had ceased using the item and all other promotional items which used the results from the trial and was no longer supporting presentations of the Conley *et al* poster.

1 Graphical presentation

Page four of the booklet was headed 'Efficacy' and featured two graphs which compared Risperdal and olanzapine at weeks 2, 4, 6 and 8. One graph depicted the mean changes from baseline Positive and Negative Syndrome Scale (PANSS) for positive symptoms of schizophrenia. Week 8 showed a statistically significant difference between the products. The second graph depicted the mean changes from baseline PANSS for negative symptoms. There was no statistically significant difference between the products. The graphs were adapted from the paper by Conley *et al*.

COMPLAINT

Lilly pointed out that the graphs were not exact reproductions of those in the poster in that the y-axis legend of each graph differed slightly.

Lilly alleged that Clause 7.6 was breached in numerous ways by both of the graphs which were highly misleading as a result. Neither of the graphs carried sufficient information for the reader to make sense of it on its own; the scales were exaggerated and unusual, no zero was present on either of the y-axes, the nature of the error bars was not defined, the patient numbers were not stated, the nature of population studied was omitted (last observation carried forward (LOCF) or completer?). It was possible to determine that the data must be from the completer analysis on the basis of the information presented in the poster. This meant that the lines in the graph joined data points which represented different populations of patients because different numbers of cases remained in the study at different time points. Linking data points of this type by lines implied that the data were continuous which they were not. This form of graph was not compatible with correct statistical practice.

A breach of Clause 7.2 was alleged because the data presented did not reflect all of the evidence fairly – the failure of the endpoint (primary) analysis to show a significant difference as reported in the poster on page 10/11 of the booklet was not consistent with the claims of superior efficacy made on this page.

RESPONSE

Janssen-Cilag stated that these graphs were faithful reproductions of the authors' poster. With regard to the allegation that the y-axis differed slightly from the poster, Janssen-Cilag noted that the y-axis range started at –2 instead of –1 but it did not see why this was a problem.

Janssen-Cilag noted the allegation that neither of the graphs carried sufficient information, but stated that it was not clear what additional information Lilly considered necessary. Hence it was unable to address this specifically. Janssen-Cilag noted that the scales represented the range of the mean changes and were in unit intervals as was the original measurement. It did not agree that this was exaggerated. Janssen-Cilag noted that whilst it was often useful to include zero when talking about change, it was not mandatory.

Janssen-Cilag noted the allegation that the nature of the error bars was not defined and accepted that this was a fair comment. From the poster, all references were to standard error, therefore it would be a reasonable assumption that this was what was shown on the graph – it was however an assumption and in retrospect probably should have been clarified on the graphs.

Patient numbers and population were not stated, but it was clear from the poster that week 8 and endpoint were labelled separately, and the number of patients could be approximated from the poster (assuming few patients failed to record the efficacy assessments if they returned at week 8).

Janssen-Cilag accepted that the use of lines to link data points implied continuous data but the data (mean changes) were measured on a continuous scale and this was the way such data would normally be represented. The fact that different patients contributed to the various timepoints did not affect the continuity of the data distribution illustrated in the graph. Also, the patients still came from the same population – it was the sample which changed in that the later samples were effectively sub-sets of the original sample. It believed that most people would consider it reasonable to graph the data as it existed at the various weeks. It could be argued that an additional timepoint 'Endpoint' could be added, or that the number of patients at each point should be clearly stated, but Janssen-Cilag believed this was a subjective opinion. Janssen-Cilag refuted the allegations of two breaches of Clause 7.6.

Janssen-Cilag referred to the allegation that the two efficacy graphs were in breach of Clause 7.2. and noted that Lilly considered the data misleading by virtue of having presented the results of the 'completer' analysis. It was generally accepted that endpoint analyses (LOCF) and completer analyses were perfectly legitimate standards for the presentation of data. Both were widely used in the industry to support promotional claims. One type of analysis did not exclude or negate the other and both were acceptable to clinicians, although, as stated above, the endpoint analysis was less intuitive than the completer one. There was no one 'correct' statistical way as Lilly alleged.

Accordingly, it refuted Lilly's allegation that each of these graphs was in breach of Clause 7.2.

PANEL RULING

The Panel noted that the lower graph was not a precise reproduction of that in Conley *et al* as the y-axis read from –2 to –5, rather than from –1 to –5. There was no indication of the baseline in either graph. In both graphs the mean change from baseline seen with olanzapine was less than that seen with Risperdal. The Panel considered that by failing to include a zero axis the visual impact of the graphs was to underrate the effect of olanzapine. The supplementary information to Clause 7.6 provided that particular care should be taken with graphs and tables to ensure that they did not mislead by the use of suppressed zeros or unusual scales.

The Panel noted the nature of the error bars was not defined and noted Janssen-Cilag's submission that this probably should have been clarified on the graphs. The Panel considered that it would have been helpful to have done so but did not consider that the omission rendered the graphs misleading. The Panel further noted that patient numbers and population were not stated and noted the submissions of both parties in this regard. Pages 2 and 3 of the booklet gave details of the study design and stated that 202 patients received Risperdal and 205 received olanzapine. The original poster which was reproduced on pages 10 and 11 stated that PANSS scores had been taken at weeks 2, 4, 6 and 8 or endpoint. The results section stated that 149

Risperdal patients and 160 olanzapine patients completed the study. The safety section stated that 145 Risperdal patients and 157 olanzapine patients provided data at week 8. The Panel considered that it was misleading not to state the patient population and the numbers of patients at each time point. Data points had been linked by a continuous line suggesting that the population was constant throughout. The Panel considered that it would have been helpful if the method of analysis had been clearly stated.

The Panel ruled a breach of Clause 7.6 of the Code due to the failure to include a zero axis and the inadequate labelling. A breach of Clause 7.2 of the Code was also ruled in relation to the failure to give details of the patient population.

The study evaluated patients using PANSS and the extrapyramidal symptom rating scale (ESRS). The study showed that the severity of extrapyramidal symptoms was reduced in both treatment groups with no statistically significant between group differences. A reduction in total PANSS scales was seen in both treatment groups although endpoint analysis revealed no significant between group differences in total PANSS or PANSS factors. The Panel considered that the failure to provided this information on the page in question meant that a misleading impression was given about the overall differences between the products. The Panel ruled a breach of Clause 7.2 of the Code.

2 Graphical presentation

Page 5 of the booklet headed 'Efficacy' featured two graphs adapted from Conley *et al*. The first depicted the reduction from baseline of symptoms of anxiety and depression beneath the text 'Risperdal was significantly more effective than olanzapine in reducing affective symptoms.' The second graph depicted the mean change in total PANSS beneath the text 'There was no significant difference between Risperdal and olanzapine in total pathophysiology'. Beneath the second graph was the claim 'Significantly more Risperdal patients experienced a 30% symptom reduction in total PANSS than did olanzapine patients ($p<0.05$).'

COMPLAINT

Lilly noted that the y-axis legend on each graph differed slightly from figures 1 and 3 of the poster.

Lilly alleged that Clause 7.6 was breached in numerous ways by both of the graphs which were highly misleading as a result. Neither of the graphs carried sufficient information for the reader to make sense of it on its own, the scales were exaggerated and unusual, no zero was present on either of the y-axes, the nature of the error bars was not defined the patient numbers were not stated, the nature of population studies was omitted (LOCF or completer?). In fact it was possible to determine that the data must be from the completer analysis on the basis of the information presented in the poster. This meant that the lines in the graphs joined data points which represented different populations of patients because different numbers of cases remained in the study at different time points. Linking data points of this type by lines implied that that the data were continuous which they were not. This form of graph was not compatible with correct statistical practice.

Lilly alleged a breach of Clause 7.2 because the data presented did not reflect all of the evidence fairly – the failure of the endpoint (primary) analysis to show a significant difference was not consistent with the claims of superior efficacy made on this page.

RESPONSE

Janssen-Cilag referred to its response at point A1 above and refuted the allegations of breaches of Clauses 7.2 and 7.6 of the Code.

PANEL RULING

The Panel considered that it rulings in A1 above in relation to the graphs and the failure to describe the patient population also applied here. The Panel therefore ruled breaches of Clauses 7.6 and 7.2 of the Code.

The Panel also considered that its ruling regarding the misleading impression of the overall differences between the two products in A1 above also applied here. The Panel therefore ruled a breach of Clause 7.2 of the Code.

3 Page 6 Safety results

Page 6 of the booklet, headed 'Safety Results' summarised the safety results obtained in Conley *et al*; the extrapyramidal syndrome (EPS) profile, spontaneously reported Parkinsonism symptoms, prolactin-related adverse events and safety profile. Two tables were featured. The upper table featured data which compared the change in the EPS profile from baseline to week 8 of Risperdal and olanzapine. The lower table presented safety data which compared the number of patients with nonpuerperal lactation/breast discharge and gynaecomastia in each patient group.

COMPLAINT

Lilly alleged that the lower of the two tables on this page presented prolactin related safety data from the whole patient population (Risperdal n=202, olanzapine n=205). This was statistically valid and complied with the standards expected by regulatory authorities in presenting safety data from clinical trials. The table in the top half of the page presented safety data related to extrapyramidal syndrome (EPS) based on completers only (Risperdal n=145, olanzapine n=157). This was highly misleading since the number of drop-outs was different in the two treatment groups (Risperdal n=57, olanzapine n=48) and patients might have dropped out due to EPS. The data table was misleading and the analysis was not statistically valid. A breach of Clauses 7.2 and 7.6 of the Code was alleged.

RESPONSE

Janssen-Cilag stated that the EPS table was not based on completers but on patients recording EPS assessment at week 8. (Completers: Risperdal 149, olanzapine 160, EPS scored at week 8: Risperdal 145, olanzapine 157).

Both week 8 and endpoint were analysed, as reported in the poster, with very similar differences between the groups, for mean change. As the rest of the graphs represented data recorded at week 8, it was reasonable to consistently quote the week 8 information, as the results were no different from the endpoint analysis.

Janssen-Cilag refuted allegations that this table breached Clauses 7.2 and 7.6.

PANEL RULING

The Panel noted that the data in the lower table was based on the intention-to-treat (ITT) population whilst the data in the upper table was based on the change from baseline at week 8 of those patients recording an EPS assessment at week 8. The Panel considered that the omission of patients who had dropped out of the study at other time points could have influenced the data. The Panel noted the view that these patients might have dropped out due to EPS symptoms. The scores of these patients would normally be included in an ITT analysis. The Panel considered the page was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel did not consider that Clause 7.6 was relevant.

4 Page 7 Safety results

Page 7 of the brochure featured two bar charts, based on figures 7 and 8 of the poster. The first bar chart featured the percentage weight change from baseline at week 8 beneath text which stated that 'olanzapine patients experienced significantly more weight gain than did Risperdal patients…'. The lower bar chart featured the weight gain from baseline of patients with a medium or high body mass index.

COMPLAINT

Lilly alleged that the graphs did not have any information on the number of patients included in the analysis presented and were thus potentially misleading in breach of Clause 7.6.

The upper graph (weight change at 8 weeks) presumably presented results based on completers only. The graph was inadequately labelled. Presenting safety data on completers did not take account of drop-outs which were more numerous on Risperdal (57) than on olanzapine (48). Since drop-outs might have occurred because of problems with safety, presenting data on the completer population was misleading and the potential for bias was in favour of Risperdal. The information presented was alleged to be in breach of Clauses 7.2 and 7.6.

The lower graph (change from baseline) was inadequately labelled. It was not clear which study population (completers or intention-to-treat) the data referred to. Drop outs were more numerous on Risperdal (57) than on olanzapine (48) and might have occurred because of problems with safety. In order to present the data in a fair manner the information on the population studied was needed and the fact that it was not presented left the data open to misrepresentation given that the number of drop-outs had potential for bias in favour of Risperdal. The information presented was alleged to be in breach of Clauses 7.2 and 7.6.

RESPONSE

Janssen-Cilag noted that the patient numbers were not stated: true, but it could be argued that the number of patients could be approximated from the poster (assuming few patients failed to record weight if they returned at week 8). Janssen-Cilag refuted the allegations of breaches of Clause 7.6 for each graph.

Janssen-Cilag stated that the upper graph was not necessarily based on completers, it was presumably based on patients recording weight at both baseline and week 8. It could not be judged whether excluding drop-outs was potentially biased in favour of Risperdal without knowing reasons for drop-out, time of drop-out and last recorded value. From figure 6 on the poster, weight change had been analysed at both week 8 and endpoint, with both analyses similar. From figure 6 of the poster it could be seen that weight gain in the Risperdal group was higher when drop-outs were excluded, which was not consistent with the suggestion that people dropped out due to weight gain.

Janssen-Cilag refuted the additional allegation that this graph was in breach of Clause 7.6 and the allegation that it was in breach of Clause 7.2.

Janssen-Cilag referred to the lower graph. It was true that the lower graph was not clear if this was completers or intention-to-treat. Technically it would be reasonable to assume this referred to the same patients as the other graph since it was a sub-grouping by body mass index strata.

Janssen-Cilag refuted the allegation that this graph was in breach of Clauses 7.2 and 7.6.

PANEL RULING

The Panel noted that neither graph presented data from the ITT population. The Panel considered that its ruling at A3 above was relevant. The patient numbers and population were undefined. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel did not consider that Clause 7.6 was relevant.

5 Page 8

Pages 8 and 9 discussed the conclusions of Conley *et al*. Page 8 stated that this 8 week double-blind comparative study had demonstrated that 'Risperdal is significantly more effective than olanzapine in treating the positive symptoms of schizophrenia ($p<0.05$); Risperdal is significantly more effective than

olanzapine in treating the affective symptoms of schizophrenia ($p<0.05$)' and 'Risperdal is comparable to olanzapine in treating negative symptoms (p=n.s.).'

COMPLAINT

Lilly alleged that Clause 7.2 was breached because the data presented on page 8 did not reflect all of the evidence clearly – the failure of the endpoint (primary) analysis to show a significant difference was not consistent with the claims of superior efficacy made on this page. Lilly referred to the results of the study on page 10 and 11 of the booklet.

RESPONSE

Since the poster clearly stated the non-significant findings, Janssen-Cilag did not think that the introductory line on this page 'This 8-week … demonstrated that:' would mislead readers, especially if they had followed the story from page 1 of the item.

Janssen-Cilag refuted the allegation of a breach of Clause 7.2.

PANEL RULING

The Panel noted that the p value was clearly stated alongside each claim. The claims referred to both statistically significant and non-significant results. The Panel noted that the claims regarding the advantages of Risperdal were based on week 8 data whereas endpoint analyses showed no significant between group differences in total PANSS or PANSS factors. The Panel considered that its ruling in point A1 above in this regard was relevant. The Panel considered that the page gave a misleading impression of the overall differences between the products. A breach of Clause 7.2 was ruled.

6 Page 9

Page 9 featured four stab points relating to side effects and dose.

COMPLAINT

Lilly stated that the first three stab points referred to the misleading safety data presented earlier in the document on page 7 (A4 above) The conclusions did not report findings based on a fair representation of the data and a breach of Clause 7.2 was alleged.

RESPONSE

Janssen-Cilag stated that EPS was not misleading as both week 8 and endpoint analyses were not significant. With regard to side effects Janssen-Cilag was not sure why Lilly deemed this misleading. The company had not queried other side effect data anywhere else. Janssen-Cilag stated that weight gain was not misleading as both week 8 and endpoint analyses were significant. Janssen-Cilag refuted the allegation of a breach of Clause 7.2.

PANEL RULING

The Panel considered that its ruling at point A3 above was relevant with regard to the nature of the patient population. The Panel ruled a breach of Clause 7.2 of the Code.

7 Reproduction of the poster by Conley *et al* (1998)

COMPLAINT

Lilly alleged that the poster was in breach of the Clauses 7.2 and 7.6 of the Code in a number of respects. Because the poster itself did not comply with the Code it should not be reproduced in full or in part in marketing material – that it had been reproduced in marketing material was in breach of Clause 7.6. Given that the poster had been included in marketing material, and given that it had not been subjected to peer review in the sense intended by the Code, it should comply with the Code in terms of the presentation of data. This was not the case as detailed below.

The majority of the problems with the poster related to the erroneous use of statistics, the inappropriate reporting of data and the misleading presentation of data in graphs. It should be noted that the primary endpoint analysis of the study showed no advantage of Risperdal over olanzapine on the PANSS score or on any of its sub-scores.

The statistics section gave no details of how the data were actually analysed. Indeed there was a rather prominent blank space where the information on the statistical methods might have been expected to be found in a poster as large and detailed as this. It was usual practice for primary endpoint data from clinical trials to be analysed on an intention-to-treat basis using the last observation carried forward method (LOCF). This constituted the primary endpoint analysis required by regulatory authorities and recommended by statisticians as being the fairest way to analyse data. In studies where there was a substantial problem with compliance or a large number of drop-outs (as there were in this case) it was usual to carry out a secondary analysis on the per-protocol or completer population to see if the study results were robust. If the results of the primary and secondary analyses did not agree the validity of the study was called in question.

Despite the paucity of information on the statistical methods employed it transpired that an intention-to-treat or endpoint analysis was carried out on the data (no doubt using the LOCF method). This analysis was alluded to in the small print of the third stab point under efficacy but the only way the results from this analysis which were presented was in a short statement (also in the small print of the third stab point under efficacy). The statement reported that no significant differences were found between the treatments for the PANSS score or any of the PANSS sub-scores. The presentation of the results in the rest of the poster did not reflect these findings and effectively ignored them. By playing down the findings of the primary endpoint analysis the

presentation and interpretation of data was not fair and was highly misleading. A breach of Clause 7.2 was alleged.

The results displayed so prominently in the first four figures at the bottom of the first page of the poster (page 10) turned out to come from a secondary or completer analysis (all patients who had not dropped out by week 8). The graphs depicting the results had serious short comings from a statistical construction and supporting legends. As a result the graphs were highly misleading: none of the graphs carried sufficient information for the reader to make sense of it on its own, the scales were exaggerated and unusual, no zero was present on any of the y-axes, the nature of the error bars was not defined, the patient numbers were not stated, the nature of population studied was omitted. In fact it was possible to determine that the data must be from the completer analysis on the basis of the information presented elsewhere in the poster. This meant that the lines in the graphs joined data points which represented different populations of patients because different numbers of cases remained in the study at different time points due to the drop-outs. Linking data points of this type by lines implied that the data was continuous which they were not. This form of graph was not compatible with correct statistical practice and was misleading.

Lilly alleged that the reporting of efficacy in the text sections of the poster breached Clause 7.2 because the data presented did not reflect all of the evidence fairly – the failure of the endpoint (primary) analysis to show a significant difference was not consistent with the claims of superior efficacy made on the second page of the poster no doubt on the basis of the conflicting secondary analysis.

The four graphs at the bottom of page 2 of the poster had a number of the shortcomings in common with the other graphs in the poster (none of these graphs carried sufficient information for the reader to make sense of it on its own, the patient numbers were not stated, the nature of population studies were omitted. Lilly alleged that these graphs were all in breach of Clauses 7.2 and 7.6.

The data tables were generally acceptable, however the table listing QTc values were misleading since no indication was given as to the patient numbers or population studied – material facts regarding safety data from studies with substantial numbers of drop-outs. Lilly alleged breaches of Clauses 7.2 and 7.6.

There were a number of questionable statements in the conclusions. These read like marketing copy rather than comments on the study results. The findings were not reported in the context of the known (published) data from similar clinical trials and were based on positive secondary analyses where the primary analysis was negative. As such the conclusions were grossly misleading as to the overall significance of the data. A breach of Clause 7.2 was alleged.

RESPONSE

Firstly, Janssen-Cilag considered the allegation of a breach of Clause 7.6 and noted that the allegations made about the poster largely repeated allegations made about earlier pages of the brochure.

Janssen-Cilag considered that the presentation of graphs and tables in the poster was not misleading and referred to its submission under points A1, 2, 3 and 4 above and refuted the allegation of a breach of Clause 7.6 as claimed.

Janssen-Cilag referred to the presentation in the poster of 'completer' analyses alleged to be in breach of Clause 7.2. The poster clearly stated the results of both the endpoint analyses and the completer analyses and therefore Janssen-Cilag did not see how it was misleading. Janssen-Cilag stated that the poster was the responsibility of the authors. Janssen-Cilag presumed that the authors did not give precise detail of the statistical methodology firstly, because of space constraints on the poster, secondly, because they, presumably, judged that the precise detail of statistical methodology would not have been of interest to their clinician audience at the international congress where the poster was presented and, thirdly, because the key elements of the statistical methods could be deduced anyway from the rest of the content of the poster. Janssen-Cilag thought there was some confusion over intention-to-treat and LOCF. Intention-to-treat was indeed the primary analysis. This required broadly that all randomised patients were included regardless of their compliance with the protocol. Although not specifically stated, the fact that all 407 patients were included in the demographics data demonstrated that this was done. Last observation carried forward (LOCF) was only one possible method of handling non-completers, but was by no means the only one (eg 'best case', 'worst case', 'missing' etc) and to the best of the company's knowledge there were no requirements to adopt this policy. It could in fact be a misleading approach eg if patients were deliberately overdosed to ensure they got a good response and they then dropped out due to intolerable side effects – using LOCF, the efficacy results would be excellent, even though most of the patients would have withdrawn because of intolerable side effects! The analysis of primary endpoint data from clinical trials on intention-to-treat basis using the last observation carried forward method was not specifically recommended by the SPI (Statisticians in the Pharmaceutical Industry). The highly respected statistician, Professor Stuart Pocock (in his book Clinical Trials: A Practical Approach stated that 'In some trials it is not easy to include withdrawals in the main analysis since a quantitative measurement forms the basis of patient evaluation. ……One could argue for including the last recorded respiration rate for withdrawals as a substitute for their missing rates at later times, but I am rather against this because the quoted mean respiration would then lack reality'. Since both an endpoint and a week 8 analysis were carried out and reported in the poster, Janssen-Cilag could not see the issue. Readers could make their own judgement as to which they believed was more relevant.

The proposition that if the primary and secondary analyses did not agree, the validity of the study was called into question was nonsense. If the analyses did not agree, the important thing was to investigate

possible causes of the conflict. This really needed an assessment of the reasons for drop-out.

Janssen-Cilag noted that it was interesting that the graphs suggested a deterioration in the olanzapine group at week 8. This might be due to losing good responders, or might indicate the development of resistance which was one possible explanation for the significance in the week 8 completer analysis.

In relation to the allegation that each of the 4 figures on page 10 were in breach of Clauses 7.2 and 7.6 Janssen-Cilag referred to its response at parts A1 and 2 above and refuted the allegation.

In relation to the allegation that the reporting of efficacy in the text sections of the poster was in breach of Clause 7.2, Janssen-Cilag refuted this allegation.

In relation to the allegation that each of the 4 figures on page 11 were in breach of Clauses 7.2 and 7.6, Janssen-Cilag referred to its previous arguments and refuted the allegations.

Janssen-Cilag referred to the allegation regarding the conclusions of the study. The poster reported the results of one study only. In the context of a poster at an international meeting it was unusual for a poster displaying the results of one study to refer at any length to other studies. Be that as it may, there was no other study which used olanzapine and Risperdal as per their licences and in which the doses given equated to those used in routine clinical practice which the authors could have referred to. The Tran *et al* paper referred to by Lilly included use of Risperdal in a way that led to most patients being given more Risperdal than they would in routine clinical use in the UK. The conclusion of the study were those of the authors, not Janssen-Cilag.

PANEL RULING

The Panel noted that as the poster had been reproduced in a promotional item it was therefore subject to the Code. The Panel considered that the allegations regarding the graphs and tables in the poster were covered by its rulings at points A1, 2, 3 and 4 above.

8 Back cover

The back cover of the booklet, page 12 featured four claims: 'Significantly more effective than olanzapine in positive and affective symptoms'; 'Comparable to olanzapine in negative symptoms'; 'No significant differences in EPS profile or other side effects' and 'Significantly less weight gain than olanzapine patients'.

COMPLAINT

Lilly alleged that if they were read as general statements, the first two claims were both in breach of Clauses 7.2 and 11.2. This was because they did not represent a balanced or fair view of the available published data (ie they were at odds with the findings reported by Tran *et al* 1997) and because they misled as to the significance of the results of the secondary analyses presented in the poster.

Alternatively, if all four claims were held to relate only to the results claimed in the poster and reproduced in the rest of the material, all four claims were alleged to be in breach of Clauses 7.2 and 7.6. This was because they did not represent a balanced or fair view of the data since they were based upon inappropriate analysis and presentation of the data from the study. As such the conclusions were grossly misleading as to the overall significance of the data.

RESPONSE

With reference to the allegation that all four claims should be read as general statements Janssen-Cilag referred to its response at point A7 in relation to the allegations concerning the conclusions of the study and denied a breach of the Code.

With reference to the interpretation that all four claims related only to the results claimed in the poster, Janssen-Cilag referred to its arguments above and refuted the allegations that the four claims were each in breach of Clauses 7.2 and 7.6.

PANEL RULING

The Panel noted that the back cover of the brochure did not expressly refer to Conley *et al* and considered that they might be read as general comparative claims rather than limited to the results of the study. The Panel noted its previous rulings regarding the use of the data from Conley *et al*. If the claims were limited to the results of the study they were unacceptable. If the claims were general claims they did not reflect the totality of the comparative data. The Panel therefore ruled a breach of Clause 7.2 of the Code. The Panel considered that this ruling covered the allegation of a breach of Clauses 7.6 and 11.2 of the Code.

B Educational meetings

Lilly complained about data presented at a series of regional educational meetings entitled 'Management Issues in Schizophrenia' sponsored by Janssen-Cilag.

COMPLAINT

Lilly understood that the information with which it took issue was being used in a promotional sense through 'educational' meetings and had asked Janssen-Cilag to stop using these data in such a way. No such assurances had been given and it alleged that these meetings were also in breach of Clause 7.2.

RESPONSE

Janssen-Cilag stated that if Lilly's allegations that the meetings breached Clause 7.2 related to the data presented in the booklet then it refuted the allegations.

The meetings referred to in Lilly's letter of complaint were part of a series of educational meetings. A copy of the agenda for these meetings was provided. Janssen-Cilag was the sponsor of the meetings and paid for the venue, the hospitality on the evening (generally a buffet supper) and honoraria and travelling expenses for the presenters, who were all

respected members of the psychiatry academic world. Between 700 and 750 members of the healthcare professions attended these meetings.

Information from the Conley *et al* study was presented at most of these meetings. The presentations on the Conley *et al* study were those of independent experts. They used the analyses of the data from this study as presented in the poster as the substance of their presentation and, hence, to the extent that Janssen-Cilag understood Lilly's complaint, it considered that the same points ('endpoint' versus 'completer' and 'not being state of the art') formed the basis for Lilly's allegations that the meetings were in breach of Clause 7.2. Janssen-Cilag referred to its detailed refutation of the allegations about the booklet and stated that these covered the possible concerns that Lilly had about the meetings, since Lilly had not complained about any other aspect of the meetings or their arrangements.

PANEL RULING

The Panel noted that the series of meetings had been arranged and sponsored by Janssen-Cilag. The Panel considered that whilst the chairmen and speakers were independent the company was nonetheless responsible under the Code for the information presented at such meetings.

The Panel did not know the exact content of the presentation but noted Janssen-Cilag's submission that information from Conley *et al* was presented at most of these meetings. The Panel therefore considered that its rulings at A1 to A8 above also applied here.

Complaint received **17 March 1999**

Case completed **15 July 1999**

CASE AUTH/863/4/99

MEDICINES CONTROL AGENCY v BRISTOL-MYERS SQUIBB

Internet site

The Medicines Control Agency (MCA) complained about an Internet website entitled the d4T FactSite established by Bristol-Myers Squibb which featured the brand name Zerit (stavudine-d4T), together with a product logo, on every page. The MCA was concerned that the material might potentially be in breach of the Advertising Regulations but Bristol-Myers Squibb had advised that it was within the guidance given under the Code for Internet sites. The MCA sought confirmation of this.

The Panel noted that a page headed 'who are you?' stated that the site was provided by Bristol-Myers Squibb to provide UK residents with information about d4T. It was therefore subject to the UK Code. There was no password or registration procedure, etc, before the home page, which also included the brand name and logo, could be accessed. The home page stated that it provided relevant information to health professionals and persons prescribed d4T and that the d4T FactSite was produced by Bristol-Myers Squibb, one of the leading manufacturers of HIV-related treatments, as part of its commitment to support all those associated with, and affected by, HIV. On entering the site enquirers were informed that it provided UK residents with information about d4T. Enquirers were then asked to click on one of four boxes. The descriptions on the boxes were 'I am a healthcare professional working in the UK', 'I have been prescribed d4T and am a UK resident', 'I am a UK resident but have not been prescribed d4T' and 'I am not a UK resident but I would like further information'. By selecting the box for health professionals an enquirer was presented with an electronic form to fill in by way of self-declaration. The Panel noted, however, that leaving the form blank and choosing the 'submit' box took an enquirer to the healthcare professionals' home page from which he/she could access pages of technical data on Zerit. The first page of data, entitled 'Introduction', contained the statement 'This clearly supports the use of d4T as a foundation of anti-HIV therapy'.

In the Panel's view, the fact that enquirers did not require a password meant that the site was an open access site which therefore needed to meet the requirements for information to the general public. The Panel considered that the layout and content meant that the site promoted a prescription only medicine to the general public. In this regard the Panel noted that the brand name, black triangle and a product logo appeared on each page. The description of d4T as a 'foundation of anti-HIV therapy' was a claim for the product. Prescribing information was accessible.

The Panel noted the submission that the site had only been advertised to healthcare professionals. It did not consider that this was an adequate method of restricting access to healthcare professionals only, given the Guidance issued by the Authority in 1999 which stated that promotional material for prescription only medicines had to have access restricted to healthcare professionals and appropriate administrative staff by way of a secure closed system. The Panel considered that the material did not meet the requirements of the Code and breaches were ruled.

Upon appeal by Bristol-Myers Squibb, the Appeal Board noted the comments made by Bristol-Myers Squibb regarding security of sites and possible mechanisms to restrict access. The Appeal Board

did not accept that access could be regarded as restricted by virtue of only promoting the site to healthcare professionals. The site in question had a section for healthcare professionals which, as acknowledged by Bristol-Myers Squibb, was available as open access. Such sites must not advertise prescription only medicines. In the Appeal Board's view the site constituted advertising. The combination of the product name and what amounted to claims for the product were unacceptable given that the site was an open access site. In this regard the Appeal Board noted phrases such as 'd4T has the attractive characteristics …', supporting the use of d4T '… as a foundation of anti-HIV therapy'. In the Appeal Board's view the description of Bristol-Myers Squibb as a leading manufacturer of HIV-related treatments implied that d4T was a leading product. The Appeal Board considered that the site constituted an advertisement for a prescription only medicine to the general public and upheld the Panel's ruling of a breach of the Code in that regard. In the Appeal Board's view the site would raise unfounded hopes of successful treatment and it therefore ruled a breach of the Code in that regard also.

The Medicines Control Agency (MCA) complained about an Internet website entitled the d4T FactSite established by Bristol-Myers Squibb Pharmaceuticals Limited which featured the brand name Zerit (stavudine-d4T), together with a product logo, on every page.

COMPLAINT

The MCA stated that it had received a telephone call querying the existence of the site and alleging that it was actually direct to consumer advertising. The MCA had reviewed the site and was concerned that the material might potentially be in breach of the Advertising Regulations. In its defence, Bristol-Myers Squibb had advised that it was within the guidance given under the Code for such Internet sites. The MCA asked for confirmation or otherwise that the material was in compliance with the Code.

In an earlier letter sent to Bristol-Myers Squibb, the MCA had said that although the company had stated that the site was aimed mainly at health professionals, a user was able to access pages such as 'efficacy and tolerability' and 'd4T factfile'. The site featured the brand name Zerit (stavudine d4T), together with a product logo, on every page. The MCA was concerned that the inclusion of the brand name in the corner of all pages of a website dedicated to AIDS/HIV could be viewed as promotional, particularly where the indications for use and phrases such as '… support its position as a foundation of anti-HIV therapy' were given. In some instances, the link between the brand name and 'product claims' could mean that the material could fall within the definition of an advertisement, as defined by the Medicines Act 1968 and supporting Regulations. Accordingly, all product names should be removed from the corner of the website. Alternatively, the site could be secured with password protection for use by health professionals only.

The MCA had also noted that the site was to be used for patients who had been prescribed d4T, although this was currently under construction. The MCA had asked what safeguards would be made to ensure that the patients had in fact been prescribed d4T.

RESPONSE

Bristol-Myers Squibb said that the decision had been taken to develop a website for stavudine when it was noted that there were well over 4000 other sites with information about the compound already on the Internet. There was considerable concern that there were no safeguards at all to ensure that the information provided by these sites was reliable, correct or, most importantly, safe. As a result, it was decided to develop a site that could be used as a verified source of factual and balanced information.

The Bristol-Myers Squibb UK virology team, with representation from the medical department, marketing, medical services and regulatory affairs, had been responsible for the development of the website. All materials had been reviewed and certified according to the Code. In recognition of the speed of change in this particular therapeutic area, and of the company's obligation to ensure that information provided was up-to-date, it had instituted a standard operating procedure for the timely incorporation of any relevant new information following scientific meetings and conferences. Bristol-Myers Squibb used a widely recognised UK opinion leader to validate this process.

Planned structure of the website The website was being developed in a modular fashion. An organogram of the planned structure was provided.

The content of each module was designed to be appropriate for its intended target audience, providing information relevant to the needs of those individuals accessing the site. To date, only the modules developed for healthcare professionals and 'other enquirers' had been completed and released.

'Other enquirers' module There was currently only one part of the website that was provided for members of the general public (the 'other enquirers' who were neither healthcare professionals, nor patients prescribed stavudine). This part did not carry any product-specific or promotional material, and thus contained no advertising. It was not, therefore, in breach of Clauses 20.1 or 20.2 of the Code.

Enquiries from the general public about personal medical matters generated via the website were always refused, and the enquirer referred back to his or her own doctor. There was, therefore, no breach of Clause 20.3 of the Code.

'Patients prescribed stavudine' module The part of the website that was being developed for patients prescribed stavudine was not yet complete, and had not been released. It was not available for use and was therefore not in breach of Clauses 20.1, 20.2 or 20.3 of the Code.

'Healthcare professional' module Bristol-Myers Squibb believed that the part of the website designed for healthcare professionals was adequately protected

from access by members of the general public, and was not, therefore, in breach of Clause 20.1 of the Code.

Bristol-Myers Squibb had given much thought to how best to restrict this part of the site from non-healthcare professionals, in order to comply with its legal and Code of Practice obligations.

There were currently several different approaches to protecting promotional material on the Internet.

- Some companies in this therapeutic field had chosen to base their websites on servers outside the UK and therefore outside the jurisdiction of the Authority and the MCA, and had installed no means of protection at all. Bristol-Myers Squibb considered this to be neither desirable, wishing to respect the spirit of the Code, nor acceptable, in the light of the guidance note previously issued by the Authority.
- Some companies had installed a password-protection system. This entailed the individual declaring him/herself to be a healthcare professional in order to receive a password for access to restricted parts of the site. Some sites included an electronic entrance form that offered the individual the opportunity to provide personal details in return for such a password. However, Bristol-Myers Squibb had studied these systems closely and all the sites it looked at with this system in place had no further checks on authenticity beyond that initial self-declaration. In fact, those Bristol-Myers Squibb looked at with entrance forms could easily be bypassed by entering either nonsensical text, or even by entering no text at all, thereby rendering the password system meaningless.
- Bristol-Myers Squibb had chosen to adopt a more practical and pragmatic approach to restricting access to the healthcare professional part of the site to those entitled to do so. At this time, the site had only been advertised to healthcare professionals and had not been advertised to the general public. Once accessed, the site invited self-declaration by the healthcare professional before access was granted to that part of the site, but without an intermediate password stage. If the enquirers did not declare themselves to be healthcare professionals, they were immediately directed away from this part of the site.

Bristol-Myers Squibb did not believe that the technology currently existed to produce an effective password system that would in practice provide any more protection than self-declaration alone. It was currently impossible to validate the credentials of those attempting to access the site, beyond their own self-declaration. Even by introducing mandatory fields in an entrance form, there was no feasible way to which to ensure the authenticity of the person attempting access.

Bristol-Myers Squibb was conscious of the fact that there might be a temptation for non-healthcare professionals to attempt to dishonestly gain access to the product-specific information it had provided. By deliberately and specifically designing a part of the site to provide information for members of the general public about HIV itself, Bristol-Myers Squibb believed that it would significantly reduce the temptation for them to falsely self-declare in order to gain access to promotional material. As mentioned before, Bristol-Myers Squibb was also developing a part of the website devoted to those patients who had been prescribed stavudine, which once released would provide a similar disincentive. By taking these practical steps, Bristol-Myers Squibb believed that it had taken measures to restrict and discourage access by non-healthcare professionals that would prove to be more effective than using an unenforceable password-system.

Summary The website was currently available to healthcare professionals, and to those who were neither healthcare professionals nor those who had been prescribed stavudine ('other enquirers').

- The part of the site provided for 'other enquirers' contained only links to other general sites relevant to the therapeutic area, and contained no company-produced promotional material.
- The area of the site devoted to patients prescribed stavudine was under construction and its release would be deferred until after the publication of guidelines from the MCA. It was not currently accessible.
- The healthcare professional site was adequately protected from access by non-healthcare professionals. Password-protection offered no additional protection to self-declaration alone with the technology available at the present time. By producing other parts of the site devoted to non-healthcare professionals, Bristol-Myers Squibb created a disincentive to seek access to the healthcare professional part of the site.

In conclusion, therefore, Bristol-Myers Squibb did not believe that the website was in any way in breach of Clause 20 of the Code.

In an earlier letter sent to the MCA, Bristol-Myers Squibb had stated that the first section of the site had been launched to an audience of physicians, nurses and pharmacists involved in HIV healthcare. It contained factual information about stavudine, with details of the pharmacology, safety profile and efficacy and tolerability data. There were no advertisements within the site. Access to this part of the website required explicit confirmation from the user that they were a healthcare professional. Bristol-Myers Squibb had plans to develop a separate part of the site for access by the general public, but this would contain solely factual and non-promotional material together with links to other educational and disease-specific information sites. There would be no promotional or product-specific information, and there would be no direct link to the restricted healthcare professional area.

In a later letter to the MCA, Bristol-Myers Squibb had stated that it believed that password systems were flawed in that in order to gain access to the password itself for access to the restricted area, self-declaration was still required from the user. Some existing sites did appear to require a password for entry to

restricted areas, but in fact absolutely no extra safeguards were in place beyond the initial self-declaration, and it was frequently possible to obtain the necessary password even if no extra information about the user was entered. Indeed, even if Bristol-Myers Squibb was to insist on healthcare professionals contacting it directly in order to get a password, it would still in effect be relying on their honesty in self-declaration. Even if it were possible in some way to check the credentials of applicants for a password (which was currently not technically feasible online), the company would still ultimately be relying on the honesty of the user.

Bristol-Myers Squibb had therefore, taken a different approach. At this time, the Website address had only been advertised to healthcare professionals. Therefore, there was no easy way for members of the general public to access the site, unless they had received this information from a healthcare professional beforehand. In addition, by having plans to develop a site devoted solely to patients, it was in fact reducing the temptation for members of the general public to falsely self-declare in order that they might access the (potentially more interesting) healthcare professional area of the site.

PANEL RULING

The Panel noted that it had received very few complaints about the Internet. Guidance on the subject had been published in the May 1996 Review. The Guidance stated, *inter alia*, that materials available on open access had to comply with Clause 20 of the Code as the materials would be accessible to the general public. Clause 20.1 of the Code prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code stated that information made available to the general public either directly or indirectly had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of a product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Guidance stated that where access was restricted to healthcare professionals and appropriate administrative staff, by way of a secure closed system, then companies could include promotional material provided that the relevant requirements in the Code were met.

The Panel noted that the website in question had been developed by the UK company. A page headed 'who are you?' stated that the site was provided by Bristol-Myers Squibb to provide UK residents with information about d4T. It was therefore subject to the UK Code. There was no password or registration procedure, etc, before the home page, which also included the brand name and logo, could be accessed. The home page stated that it provided relevant information to health professionals and persons prescribed d4T and that the d4T FactSite was produced by Bristol-Myers Squibb, one of the leading manufacturers of HIV-related treatments as part of its commitment to support all those associated with, and affected by, HIV. On entering the site enquirers were informed that the site provided UK residents with information about d4T. Enquirers were then asked to click on one of four boxes. The descriptions on the boxes were 'I am a healthcare professional working in the UK', 'I have been prescribed d4T and am a UK resident', 'I am a UK resident but have not been prescribed d4T' and 'I am not a UK resident but I would like further information'. By selecting the box for health professionals an enquirer was presented with an electronic form to fill in by way of self-declaration The Panel noted, however, that leaving the form blank and choosing the 'submit' box took an enquirer to the healthcare professionals' home page from which he/she could access pages of technical data on Zerit. The first page of data, entitled 'Introduction', contained the statement 'This clearly supports the use of d4T as a foundation of anti-HIV therapy'.

In the Panel's view, the fact that enquirers did not require a password meant that the site was an open access site which therefore needed to meet the requirements for information to the general public. The Panel considered that the layout and content meant that the site promoted a prescription only medicine to the general public. In this regard the Panel noted that the brand name, generic name, black triangle and a product logo appeared on each page. The description of d4T as a 'foundation of anti-HIV therapy' was a claim for the product. Prescribing information was accessible.

The Panel noted the submission that the site had only been advertised to healthcare professionals. It did not consider that this was an adequate method of restricting access to healthcare professionals only given the Guidance issued by the Authority. The Panel considered that the material did not meet the requirements of Clauses 20.1 and 20.2 of the Code and breaches of those clauses were ruled.

During its consideration of this case the Panel noted the comment that some companies had chosen to base their websites on servers outside the UK and therefore outside the jurisdiction of the Authority. The Panel noted that the Guidance stated that if information was put on the Internet in a country outside the UK and it referred specifically to the UK use of a product, then the UK Code would apply.

APPEAL BY BRISTOL-MYERS SQUIBB

Bristol-Myers Squibb appealed against the rulings of breaches of Clauses 20.1 and 20.2 of the Code.

The company stated that it understood that Clause 20.1 was included in the Code to satisfy the UK and EU legal requirements concerning prohibition of advertising prescription only medicines (POMS) to the general public.

However, it also understood that Clause 20.1 was developed to prohibit the active process of advertising such medicines. It was Bristol-Myers Squibb's understanding that 'inadvertent' (or passive) advertising was not covered within the scope of this clause. It understood that this clause did not apply, for example, to POM advertisements carried in (paper) medical journals kept in public libraries, even

though members of the general public could quite easily view such advertisements whilst reading the journal.

It also understood that this clause did not cover cases where a member of the general public actively sought out POM advertisements for themselves, whether by obtaining journals carrying such advertisements for personal use, or by deliberately providing false information in order to gain access to otherwise privileged material.

Mindful of its legal and Code responsibilities, Bristol-Myers Squibb required visitors to the website to declare whether or not they were healthcare professionals, so as to ensure that it did not 'actively' advertise to the general public. Bristol-Myers Squibb's research into the various methods of restricting certain areas of the website from non-healthcare professionals convinced it that the technology was not yet available to ensure complete protection, and that the password systems used by other companies in effect provided no additional security at all. As had been seen in several celebrated instances in the past, there was sufficient information available in the public domain for someone determined enough to dishonestly pose as a healthcare professional. As Bristol-Myers Squibb outlined in its original comments, it therefore adopted a different strategy to reduce the chances of inadvertently providing promotional material to a non-healthcare professional, or for it to be obtained dishonestly. By providing alternative areas within the website specifically designed for use by non-healthcare professionals, containing balanced, factual and non-promotional information about d4T and HIV, the company had taken steps to actively discourage dishonest self-declaration.

In summary, Bristol-Myers Squibb contended that it was not actively advertising to the general public through this website, and thus was not in breach of Clause 20.1 (and hence Clause 20.2) of the Code. The only means of access by a member of the general public was by a dishonest declaration of their healthcare professional status, and Bristol-Myers Squibb contended that companies could not be held responsible for every possibility for third parties to behave dishonestly. By recognising that the currently available means of securing website information were flawed, and by developing specific areas in the website for non-healthcare professionals, the company had taken a responsible and pragmatic approach to discourage members of the general public from accessing promotional material held elsewhere in the website.

APPEAL BOARD RULING

The Appeal Board noted that the Internet was a difficult area as far as the Code of Practice was concerned. The Internet was not mentioned in the Code and the Guidance had been produced over three years ago. The area was developing rapidly and to date there had been very few complaints under the Code.

The Appeal Board noted that patients were demanding more information about medicines. Pharmaceutical companies were obvious sources of information. It was perfectly acceptable for companies to provide information about their products as long as that such information complied with the Code. If the material was available for open access then it needed to comply with Clause 20 of the Code.

The Appeal Board noted the comments from the company about the layout and design of the site. Further work on developing the site had ceased until the current case had been completed.

The Appeal Board noted that Bristol-Myers Squibb had not placed the site on any search engines. The site had only been advertised to healthcare professionals who were presented with an electronic form to fill in by way of self-declaration, although it was possible to access the site by leaving the form blank. The Appeal Board noted the submission from the company that non-healthcare professionals were directed away from the site. Non-UK residents and UK residents who had not been prescribed d4T were also directed away from the site, although information on other sites which provided useful information on HIV and AIDS was given. The section for UK residents who had been prescribed d4T was referred to but it was stated that this section was still under construction.

The Appeal Board noted that as the site was available on open access all the material had to be in accordance with Clause 20 of the Code. This had been fully acknowledged by Bristol-Myers Squibb. The Appeal Board did not agree with Bristol-Myers Squibb's views regarding what it saw as the difference between active and passive advertising. Clause 20.1 of the Code did not distinguish between the two.

The Appeal Board noted the comments made by Bristol-Myers Squibb regarding security of sites and possible mechanisms to restrict access. The Appeal Board did not accept that access could be regarded as restricted by virtue of only promoting the site to healthcare professionals. The site in question had a section for healthcare professionals which, as acknowledged by Bristol-Myers Squibb, was available as open access and therefore needed to comply with Clauses 20.1 and 20.2 of the Code. Such sites must not advertise prescription only medicines.

The Appeal Board examined the printed copy of the content of the site and noted that each page included the brand name, generic name, black triangle and product logo. The Appeal Board did not accept that this necessarily meant that the site was an advertisement to the general public. Its view was that it was not unacceptable to make such information available to the public per se. The context and content of the material were factors in deciding whether or not material was acceptable.

In the Appeal Board's view the site constituted advertising. The combination of the product name and what amounted to claims for the product were unacceptable given that the site was an open access site. In this regard the Appeal Board noted phrases such as 'd4T has the attractive characteristics …', supporting the use of d4T '… as a foundation of anti-HIV therapy'. In the Appeal Board's view the

description of Bristol-Myers Squibb as a leading manufacturer of HIV-related treatments implied that d4T was a leading product.

The Appeal Board considered that the site constituted an advertisement for a prescription only medicine to the general public and upheld the Panel's ruling of a breach of Clause 20.1 of the Code. The appeal on this point was thus unsuccessful.

In the Appeal Board's view the site would raise unfounded hopes of successful treatment and it therefore ruled a breach of Clause 20.2 of the Code. The appeal on this point was thus unsuccessful.

Complaint received **1 April 1999**

Case completed **11 August 1999**

CASE AUTH/869/4/99

MERCK SHARP & DOHME v GLAXO WELLCOME

Naramig leavepiece

Merck Sharp & Dohme complained about a leaflet for Naramig (naratriptan) issued by Glaxo Wellcome. Merck Sharp & Dohme produced Maxalt (rizatriptan).

The claim 'Naramig has a half life three times longer than that of rizatriptan, which may account for Naramig's long duration of action' appeared as a bullet point beneath a bar chart which showed that the half life, in hours, of Naramig was 6 whilst that of rizatriptan 10mg was 2-3. Merck Sharp & Dohme stated that as the relative half life for naratriptan was two to three times that for rizatriptan in the bar chart, quoting 'three times' in the claim emphasised the larger figure. The Panel noted that the Naramig summary of product characteristics (SPC) stated that its mean elimination half life was six hours. The Maxalt SPC stated that its plasma half life averaged 2-3 hours. Whilst the Panel noted that the correct half life for each product was stated in the bar chart, it considered that the claim that Naramig's half life was three times longer than that of Maxalt was misleading given the plasma half life range given in the Maxalt SPC. The Panel further noted that the association between half life and duration of action had not been proven. The Panel considered the claim misleading in this regard as it linked pharmacokinetic data to a clinical advantage when there was no evidence to show that this was the case. The Panel did not consider that the use of the word 'may' negated this impression. The Panel considered that the claim was not capable of substantiation and ruled a breach of the Code.

The claim 'Headache symptoms appear less likely to return' appeared as a heading above the claim 'Low rate of return of headache symptoms' beneath which was a bar chart which featured the headache recurrence rates of Naramig and rizatriptan 10mg from different placebo controlled studies. Naramig was shown to have minimum and maximum recurrence rates of 17 and 28%. The minimum and maximum recurrence rates for rizatriptan were shown to be 33 and 47%. Merck Sharp & Dohme stated that recurrence rates for naratriptan and rizatriptan were quoted alongside each other implying a direct comparison could easily be made. However, recurrence was defined differently in the naratriptan and rizatriptan studies making a direct comparison impossible. The Panel considered that the presentation of the bar chart invited direct comparison of the results obtained from different studies. Readers would be left with the impression that headache symptoms were less likely to return in Naramig treated patients than in those treated with rizatriptan 10mg. There was no direct comparative data to support this. The Panel did not consider that the word 'appear' in the claim 'Headache symptoms appear less likely to return' negated this impression. Further the Panel was concerned about the differences between the studies used. For example the determination of recurrence at 4 hours for naratriptan but at 2 hours for rizatriptan was a factor that had not been referred to or taken into account. The Panel considered that the comparison was misleading and a breach of the Code was ruled.

The claim '… so the majority of attacks can be treated with just one tablet' appeared in a bullet point beneath the bar chart at issue above which stated 'In a range of placebo controlled studies, Naramig has demonstrated a low rate of return of headache symptoms, so the majority of attacks can be treated with just one tablet.' Merck Sharp & Dohme stated that this claim seemed to imply that the vast majority of migraine attacks would be effectively treated with just one 2.5mg naratriptan tablet. It was referenced to Bomhof *et al* (1996). In two other major studies of naratriptan the proportions taking only one tablet were 53% (Klassen *et al* (1997) and 49% (Mathew *et al* (1997)). Since there were only small majorities in two studies, one of which might be biased, Merck Sharp &Dohme alleged that this claim misled to the extent of the majority, and did not reflect the balance of the available data. Whilst the Panel noted that the studies cited supported the use of the term majority in a mathematical sense, there were studies with results around or below 50%. It considered that without stating the size of the majority and linking the claim to the recurrence rate bar chart, the claim gave a misleading impression as to the size of the majority and therefore the clinical significance of the studies' findings. A breach of the Code was ruled.

The claim 'Appears to have a low incidence of side effects' appeared beneath a heading 'Extremely well tolerated' and above a bar chart entitled 'Incidence of commonly expressed side effects' which favourably compared the side effect profile of Naramig with that of rizatriptan 10mg. A bullet point beneath the chart stated that 'Naramig is the only available 5-HT1 agonist with a side effect

profile similar to placebo'. Merck Sharp & Dohme stated that again comparisons were made between naratriptan and rizatriptan on the basis of different studies. Such comparisons could only be valid in the setting of a head to head study. No attempt had been made to clarify that the data for rizatriptan came from a number of studies. Data for naratriptan was selectively quoted for only one study. The statement and the bar chart were therefore misleading, did not reflect the balance of the data and were in breach of the Code. The Panel noted that the data featured in the bar chart was a review of the tolerability of naratriptan tablets across clinical trials (a total of over 4000 patients), seven placebo controlled and one open label. In the Panel's view the data would be representative of the body of data for naratriptan. In this regard one incidence figure was quoted for each side effect listed eg nausea 5%. Conversely, the data for rizatriptan had been taken from three studies and the figures quoted represented the range of incidences as reported in each trial eg nausea 3-5%. In the Panel's view the two sets of data, one representing the balance of the evidence, the other representing a range, were not comparable. The Panel considered, however, that the layout invited readers to make direct comparisons of the figures which was unfair and misleading. The use of the term 'appears' was insufficient in this regard. The Panel ruled a breach of the Code.

The claims 'Highly effective' and 'Works in most patients' appeared in a series of bullet points beneath the heading 'Naramig – a favourable first line profile' adjacent to columns headed Naramig and rizatriptan which featured ticks or crosses alongside each claim. Both claims featured a tick for both Naramig and rizatriptan. Merck Sharp & Dohme stated that this implied that naratriptan was at least equal to rizatriptan in terms of efficacy. Merck Sharp & Dohme alleged that the table misled the reader regarding the relative efficacy of the two products. The Panel noted that the data referred to by Merck Sharp & Dohme was an unpublished study which favourably compared rizatriptan 10mg with naratriptan 2.5mg. This unpublished data was not available to Glaxo Wellcome when the detail aid was created and whilst in use. The Panel noted that Goadsby (1998) presented data upon headache response based on a meta-analysis of the Phase II/III clinical trial programme for naratriptan. The Panel noted that it was difficult to draw valid comparisons between a meta-analysis of one medicine and three separate studies of another. In the opinion of the Panel the claims at issue gave the general impression that naratriptan and rizatriptan were of similar efficacy. On balance the Panel considered that the claims were a fair reflection of the evidence available to Glaxo Wellcome at the relevant time and no breach was ruled.

Merck Sharp & Dohme Limited complained about a leavepiece (ref: 20135588) for Naramig (naratriptan) produced by Glaxo Wellcome UK Limited. Merck Sharp & Dohme marketed Maxalt (rizatriptan). Glaxo Wellcome stated that the leavepiece was no longer in circulation and had not been printed after another claim had been ruled in breach in December 1998.

1 Claim 'Naramig has a half life three times longer than that of rizatriptan, which may account for Naramig's long duration of action'

This claim appeared as a bullet point beneath a bar chart which showed that the half life, in hours, of Naramig 2.5mg was 6 while that of rizatriptan 10mg was 2-3.

COMPLAINT

Merck Sharp & Dohme stated that the relative half life for naratriptan was 2-3 times that for rizatriptan in the bar chart. Quoting 'three times' in the bullet point below then emphasised the larger value. The claim clearly implied that naratriptan had a long duration of action whereas rizatriptan did not, and that this was likely to be because of differences in half life. In correspondence with Merck Sharp & Dohme, Glaxo Wellcome had stated 'It is currently unknown why some 5-HT_1 agonists appear to be associated with higher ranges of recurrence than others' and 'Although this theory (that half life is linked to recurrence) has not yet been proven, it has also not been disproven.' Merck Sharp & Dohme alleged that Glaxo Wellcome could not substantiate the claim and it was in breach of Clause 7.3.

RESPONSE

Glaxo Wellcome stated that the difference in half lives between Naramig and rizatriptan was substantiated by their respective summaries of product characteristics (SPCs).

The SPC for Naramig described a half life of 6 hours and that for Maxalt of 2-3 hours. These data were illustrated prominently in the bar chart above the claim. The bullet point below the bar chart suggested that the long half life of Naramig might account for the long duration of action of Naramig. It did not imply that rizatriptan did not have a long duration of action, but suggested that if it did, it was unlikely to be due to its half life.

The link between half life and duration of action had yet to be proven, hence Glaxo Wellcome had stated that the term '<u>may</u> account for Naramig's long duration of action'. The data available suggested that there was a positive correlation between half life and duration of action. Of the currently available triptans, Naramig had the longest half life, and was associated with the lowest rates of return of migraine headache. It was the only 5-HT_1 agonist proven to be associated with less recurrence than Imigran (sumatriptan), the first 5-HT_1 agonist, which was used as a yardstick for other triptans. Further weight was provided by frovatriptan (a 5-HT_1 agonist in development) which had the longest half life to date – 25 hours. Indeed, frovatriptan was associated with even lower rates of recurrence than those seen with Naramig (10-17%). Such evidence was reflected in reviews on 5-HT_1 agonists which similarly proposed that half life and duration of action might be linked.

PANEL RULING

The Panel noted that the Naramig SPC stated that its mean elimination half life was six hours. The Maxalt

SPC stated that its plasma half life averaged 2-3 hours.

Whilst the Panel noted that the correct half life for each product was stated in the bar chart, it considered that the claim that Naramig's half life was three times longer than that of Maxalt was misleading given the plasma half life range stated in the Maxalt SPC. The Panel further noted that the association between half life and duration of action had not been proven. The Panel considered the claim misleading in this regard as it linked pharmacokinetic data to a clinical advantage when there was no evidence to show that this was so. The Panel did not consider that the use of the word 'may' negated this impression. The Panel considered that the claim was not capable of substantiation and ruled a breach of Clause 7.3 of the Code as alleged.

2 Claim 'Headache symptoms appear less likely to return'

This claim appeared as a heading above the claim 'Low rate of return of headache symptoms', beneath which was a bar chart which featured the headache recurrence rates for Naramig and rizatriptan 10mg from different placebo controlled studies. Naramig was shown to have minimum and maximum recurrence rates of 17 and 28% respectively. The minimum and maximum recurrence rates for rizatriptan were shown to be 33 and 47% respectively.

COMPLAINT

Merck Sharp & Dohme stated that recurrence rates for naratriptan and rizatriptan were quoted alongside each other implying a direct comparison could easily be made. However, recurrence was defined differently in the naratriptan studies versus the rizatriptan studies making a direct comparison impossible. Both defined recurrence in migraine studies as a return of migraine headache of 2/3 severity after initial relief. But there were a number of issues with the comparison made:

- Whilst it was made clear that the data came from different studies the implication was clear that a simple comparison could be made. Any such comparison between different studies required extreme care.
- To suffer a recurrence patients must first have responded to begin with. In the naratriptan studies this response was at 4 hours and with rizatriptan studies 2 hours, so this introduced a confounding factor into the interpretation.
- Assessment of recurrence at two different time points, as above, allowed patients who received rizatriptan to be monitored for recurrence during a 22 hour period whereas patients receiving naratriptan were only monitored for a 20 hour period thus creating a bias in favour of naratriptan.
- In the majority of studies patients were allowed rescue medication for inadequate headache relief at 2 hours. Therefore if recurrence was measured at 4 hours, as in the naratriptan studies, the use of rescue medication needed to be taken into account as an additional confounding factor.
- Data from the 3002 study recently presented at the 3rd Congress of the European Federation of Neurological Societies seemed to have been omitted. In this study higher recurrence rates of 32 and 30% were recorded for naratriptan 2.5mg but these had not been included in the bar chart.

This claim was also alluded to in the table that appeared on the page headed 'Naramig – a favourable first line profile' and similar criticisms applied. Merck Sharp & Dohme believed that the comparison made was far too simplistic, did not take account of differences in definitions, did not include all the relevant data, and was therefore misleading in breach of Clause 7.2 of the Code.

RESPONSE

Glaxo Wellcome stated that it understood the concerns about making comparisons across studies. Therefore, in order that the reader was not misled, it had made it clear in the graph that the recurrence rates shown were taken from 'different placebo-controlled studies'. It also stated that 'headache symptoms appear less likely to return'. In the absence of any published direct comparative data, Glaxo Wellcome submitted that the use of comparisons across studies, with the appropriate caveats, was justified.

Whilst Merck Sharp & Dohme suggested that there was a difference in the definition of recurrence used throughout the Naramig and rizatriptan studies, recurrence was consistently defined as the percentage of patients who experienced a return of their headache (usually graded as moderate or severe) after initial relief. It was assessed from the responding population. Consequently, any differences in initial response rates were largely irrelevant, as it was interested in those patients who got a return of their headache once they had gained relief. However, response rates for Naramig and rizatriptan were very similar (60-76% and 66-77% respectively). It was also irrelevant whether one was measuring the initial response at 2 or 4 hours, as the average time to recurrence to migraine headache was about 10-12 hours.

The ranges of recurrence quoted in the figure were from first attacks. In order to make the data comparable, when studies over more than one attack were used, the data from only the first attack had been taken. When more than one attack was treated, the intention-to-treat populations in the second and third attacks were usually smaller than in the first attack, making the data less robust, as in the 3002 study presented by Bates *et al*.

Overall, across the studies the maximum recurrence rate seen after Naramig was lower than the minimum recurrence rate seen after rizatriptan.

In summary, therefore, Glaxo Wellcome submitted that the comparison did include all the relevant data, and that the difficulties in comparing across studies were reflected in the claim that symptoms appeared less likely to return. Consequently it did not believe that this claim was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the bar chart was labelled 'Recurrence rates from different placebo-controlled studies' and different references were cited for the recurrence rates for Naramig and rizatriptan.

The Panel examined the studies in question. Two references, Bomhof *et al* (1996) and Goadsby (1998) were cited in support of Naramig. Bomhof *et al* (1996) was an abstract presentation but the Panel noted that it had been supplied with what it assumed was the full paper published two years later. Bomhof *et al* (1998) was an open-label study designed to examine the long-term tolerability and efficacy of Naramig 2.5mg to treat all migraine attacks for 6 months. Headache recurrence occurred in a mean of 13% of attacks per patient treated with Naramig 2.5mg and was defined as return of moderate/severe pain within 24 hours of initial dosing where such pain had previously been reduced to mild or none 4 hours after initial dosing. The study authors noted that the percentage figures quoted for recurrence did not represent a rate of or incidence of recurrence.

Goadsby was a review of data from four parallel group, placebo controlled trials which were pooled and two additional trials, one in a recurrence-prone population comparing naratriptan tablets with sumatriptan tablets and the second comparing naratriptan injection 5mg with sumatriptan injection 6mg. Overall, in four of the studies sumatriptan was the comparator. The percentage of patients reporting headache recurrence in naratriptan parallel group clinical trials was 17%, 28%, 19% and 27%. The figure for sumatriptan was 38%. Headache recurrence was not defined. Goadsby *et al* concluded that data from the clinical trials program consistently showed that naratriptan tablets were associated with a low incidence of headache recurrence.

In addition, Glaxo Wellcome referred to Bates *et al* (1998), which was designed to compare the efficacy and tolerability of Naramig at 0.1, 0.25, 1 and 2.5mg with sumatriptan 100mg. Measurements for headache relief were taken 4 and 2 hours post dose across three migraine attacks. Headache recurrence was not defined. The percentage of patients with headache recurrence on Naramig 2.5mg was 19% (first attack), 32% (second attack) and 30% (third attack). The Panel noted that the total patient population included in the efficacy analysis across the three attacks decreased from 1219 to 940 to 864. Rescue medication was used. Rescue medication was used by 38% to 42% of patients on naratriptan 2.5mg over three attacks. It appeared that the rescue medication could be used within 24 hours post initial dose.

Three studies were cited in support of rizatriptan. Teall *et al* (1998), Visser (1996) [The Panel noted that this should have been Visser (1997)] and Visser *et al* (1996). Teall *et al* (1998) examined the efficacy and tolerability of rizatriptan (5 and 10mg) in the treatment of migraine recurrences. Migraine recurrence was defined as a return to grade 2 (moderate) or grade 3 (severe) within 24 hours of the initial dose and after initial headache relief to grade 0 or 1 at 2 hours. Recurrence rates of 44%, 47% and 40% were reported for rizatriptan 5mg, 10mg and placebo groups respectively. With regard to comparing the headache recurrence rates of 5-HT_1 agonists obtained in different non-comparative studies, the study authors stated that direct comparisons were required before any conclusions could be drawn on the relative merits with regard to this parameter.

In Visser *et al* (1996) 41% of patients receiving rizatriptan 10mg reported headache recurrence which was defined as the return of moderate or severe headache within 22 hours after previous relief to mild or no headache at 2 hours after the initial study medication. Patients could use certain escape medication from 4 hours and sumatriptan or ergot derivatives from 24 hours following initial study medication.

Visser (1997) was an article which discussed the pharmacologic profile and clinical efficacy of rizatriptan and stated that headache recurrence was reported in approximately one third of patients within 24 hours after administration of initial dose.

The Panel considered that the presentation of the bar chart invited direct comparison of the results obtained from different studies. Readers would be left with the impression that headache symptoms were less likely to return in Naramig treated patients than in those treated with rizatriptan 10mg. There was no direct comparative data to support this. The Panel did not consider that the word 'appear' in the claim 'Headache symptoms appear less likely to return' negated this impression. Further the Panel was concerned about the differences between the different studies used. For example the determination of recurrence at 4 hours for naratriptan but at 2 hours for rizatriptan was a factor that had not been referred to or taken into account. The Panel considered that the comparison was misleading and a breach of Clause 7.2 was ruled.

3 Claim '...so the majority of attacks can be treated with just one tablet'

This claim appeared in a bullet point beneath the bar chart at issue in point 2. The bullet point stated 'In a range of placebo controlled studies, Naramig has demonstrated a low rate of return of headache symptoms, so the majority of attacks can be treated with just one tablet.'

COMPLAINT

Merck Sharp & Dohme stated that this claim seemed to imply that the vast majority of migraine attacks would be effectively treated with just one 2.5mg naratriptan tablet. This was referenced to Bomhof *et al* (1996). With such long-term studies responders tended to treat more attacks than non-responders biasing the average number of tablets downwards (median response rate at 4 hours was 63% in those treating = 18 attacks and 76% in those treating > 18 attacks). 44% of attacks were treated with further medication (either another naratriptan tablet or rescue medication). The median value was not of much value in this context as patients could only treat their

attack with either one or two tablets. In two other major studies of naratriptan the proportions taking only one tablet were 53% (Klassen *et al* (1997)) and 49% (Mathew *et al* (1997)). Since there were only small majorities in two studies, one of which might be biased, Merck Sharp & Dohme believed this claim was in breach of Clause 7.2 since it misled to the extent of the majority, and did not reflect the balance of the available data.

RESPONSE

Glaxo Wellcome outlined the different ways of looking at these data.

Attacks over long-term

Glaxo Wellcome had referenced this claim to the long-term study by Bomhof as this study treated the largest number of attacks of any of the published Naramig clinical studies and hence was the most representative study to use to support a claim about attacks (rather than patients). In addition, migraine was a chronic condition and patients were likely to be taking their migraine treatment for many years. Long-term data looking at tablet usage was therefore more relevant than single attack studies.

Bomhof *et al* stated that a second dose of Naramig was taken for 2472 attacks (out of a possible 7709 attacks that were treated). This equated to a second dose of Naramig being taken for 32%, and therefore the majority of attacks did not require a second dose. Data from this study had now been collected over 12 months and 12,930 attacks. Of these attacks, a second dose was required in 31%, clearly demonstrating that the majority of attacks did not require a second dose.

Attacks with response only – long-term study

Glaxo Wellcome stated that an alternative way of looking at this data was to consider just those patients who had a response, and how many of these required a single dose of Naramig. In the long-term study, of the 12,930 attacks treated, 9016 attacks had a response at 4 hours. Of the successfully treated attacks, 2324 required a second dose for treatment of recurrence.

Therefore from the entire attack population, 6,692 attacks responded and only required a single tablet of Naramig. This gave a percentage of 52% which was the majority of attacks.

Attacks with response only – controlled studies

A further way of looking at the data, as described by Merck Sharp & Dohme, was to consider just the controlled clinical studies. Merck Sharp & Dohme quoted data from two single attack studies, giving the proportions requiring one tablet as 53% and 49%. However, Merck Sharp & Dohme had omitted a third, three attack study which contained over 500 migraine attacks. Data from this study were as follows: number of attacks treated with Naramig, 535; number of attacks responding, 357; number of attacks requiring a second dose for recurrence, 70; number of attacks with response and needing a single tablet, 287; percentage of attacks with response and requiring a single tablet, 54.

These data showed that the majority of attacks were treated with a single Naramig tablet.

In summary, the weight of the clinical evidence, irrespective of how the data were analysed, showed that the majority of attacks required one Naramig tablet. Therefore Glaxo Wellcome believed that this statement was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim in question was referenced to an abstract by Bomhof *et al* (1996) although what it assumed was the full paper was supplied (Bomhof *et al* (1998)). The work by Bomhof *et al* was a 6 month study wherein 68% of attacks required only one dose. If only attacks which had shown a response at 4 hours were considered, 52% required only one dose. The median and mean number of tablets taken per attack for 414 patients treating 9014 attacks was 1.0 and 1.25 respectively.

The Panel noted the submission that in Klassen *et al* 53% of patients took only 1 tablet. The Panel noted that Klassen *et al* showed that approximately 50% of patients receiving naratriptan 2.5mg reported relief 8,12 and 24 hours after the dose of study medication. Matthew *et al* referred to by Merck Sharp & Dohme stated that headache relief 4 hours post dose was maintained with no significant worsening and no use of rescue medication for 8 and 12 hours post dose in the majority of patients treated with naratriptan 2.5mg and for at least 24 hours post dose in nearly 50% of patients after treatment with naratriptan 2.5mg.

The Panel noted Merck Sharp & Dohme's submission that long-term studies could be biased by responders tending to treat more attacks than non-responders. The Bomhof study stated that headache relief analysis was not affected by the number of attacks treated with naratriptan tablets.

Whilst the Panel noted that those studies cited supported the use of the term majority in a mathematical sense, there were studies with results around or below 50%. It considered that without stating the size of the majority and linking the claim to the recurrence rate bar chart the claim gave a misleading impression as to the size of the majority and therefore the clinical significance of the studies' findings. A breach of Clause 7.2 was ruled.

4 Claim 'Appears to have a lower incidence of side effects'

This claim appeared beneath a heading 'Extremely well tolerated' and above a bar chart entitled 'Incidence of commonly expressed side effects' which favourably compared the side effect profile of Naramig with that of rizatriptan 10mg. A bullet point beneath the chart stated that 'Naramig is the only available 5-HT_1 agonist with a side effect profile similar to placebo'.

COMPLAINT

Merck Sharp & Dohme stated that again comparisons were made between naratriptan and rizatriptan on the basis of different studies. Such comparisons could only be valid in the setting of a head to head study. Rates for placebo groups were not quoted. Unlike in the preceding bar chart, no attempt was made to clarify that the data for rizatriptan came from a number of studies. Data for naratriptan was selectively quoted for only one study. Nausea for example had been noted at higher rates in at least 2 studies compared with the one quoted (7% and 9%). The statement and the bar chart were therefore misleading, did not reflect the balance of the data and were in breach of Clause 7.2.

RESPONSE

Glaxo Wellcome stated that in the absence of any direct head to head comparative studies, data from different studies had been compared, and the term 'appears' had been used to reflect this. Unfortunately an error had been made in the referencing of the data for Naramig. It should have been referenced to the review of the tolerability of Naramig by Mathew *et al* (1997) and it was this review that was represented in the figure. This review was chosen as it summarised the data from seven Naramig studies conducted world wide.

In addition, the adverse event profile of Naramig in clinical trials was similar to placebo, a fact supported by the individual clinical studies, and the Naramig SPC. Glaxo Wellcome was not aware of any studies of rizatriptan 10mg where the adverse event profile was similar to placebo.

Glaxo Wellcome believed that these data did represent the balance of evidence and that the statement was not misleading and not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the data featured in the bar chart was incorrectly referenced to Bomhof (1996) in relation to Naramig. The Panel noted that the paper by Mathew *et al* to which the data should have been referenced, was a review of the tolerability of naratriptan tablets across clinical trials (a total of over 4000 patients), seven placebo controlled and one open label. In the Panel's view the Mathew data would be representative of the body of data for naratriptan . In this regard one incidence figure was quoted for each side-effect listed ie nausea 5%. Conversely, the data for rizatriptan had been taken from three studies and the figures quoted represented the range of incidences as reported in each trial ie nausea 3-5%. In the Panel's view the two sets of data, one representing the balance of the evidence the other representing a range, were not comparable. The Panel considered, however, that the layout invited readers to make direct comparisons of the figures which was unfair and misleading. The use of the term 'appears' was insufficient in this regard. The Panel ruled a breach of Clause 7.2 of the Code.

5 Claims 'Highly effective' and 'Works in most patients'

On the final page beneath the heading 'Naramig – a favourable first line profile' a series of bullet points, including the claims in question, appeared, adjacent to which were columns, headed Naramig and rizatriptan, which featured ticks or crosses alongside each claim. The claims 'Highly effective' and 'Works in most patients' each featured a tick with regard to both Naramig and rizatriptan.

COMPLAINT

The appearance of these two statements in the table with ticks implied that naratriptan was at least equal to rizatriptan in terms of efficacy. Merck Sharp & Dohme had recently completed a head to head study of rizatriptan 10mg and naratriptan 2.5mg which showed clear superiority of rizatriptan over naratriptan in terms of headache relief at two hours (69% vs 48%, $p<0.001$) and pain free at 2 hours (45% vs 21%, $p<0.001$). Therapeutic gain for headache relief at 2 hours in a meta-analysis of phase II/III data for naratriptan was 20% and for pain free 15%. Whilst no meta-analysis for rizatriptan was included in the article therapeutic gain for rizatriptan 10mg had been found to be higher: the majority in the range of 27-40% for headache relief and 31-37% for pain free. Merck Sharp & Dohme believed the table clearly misled the reader regarding the relative efficacy of the two products and was therefore in breach of Clause 7.2.

RESPONSE

Glaxo Wellcome stated that this leavepiece was in circulation up until the end of 1998. Prior to its receipt of the letter of complaint from Merck Sharp & Dohme, it was unaware of any data from a direct comparison of rizatriptan and Naramig. It should be noted that the study quoted by Merck Sharp & Dohme (data on file), which it had requested but was yet to receive, had selected 2 hours as the study end-point. Similarly, whilst it was aware of the meta-analysis by Goadsby, it did not consider rizatriptan. It was not clear whether meta-analysis methods had been applied to the data supplied by Merck Sharp & Dohme on rizatriptan.

However, the published data clearly reflected that both treatments were highly effective in the treatment of migraine, with up to three-quarters of patients responding to both treatments. Therefore, Glaxo Wellcome believed that this table was not misleading and not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the data on file referred to by Merck Sharp & Dohme comprised an unpublished study which favourably compared rizatriptan 10mg with naratriptan 2.5mg in the treatment of migraine. The Panel noted that this unpublished data was not available to Glaxo Wellcome when the detail aid was created and whilst in use. The Panel noted that Goadsby (1998) presented data upon headache response based on a meta-analysis of the Phase II/III

clinical trial programme for naratriptan. The Panel noted that it was difficult to draw valid comparisons between a meta-analysis of one medicine and three separate studies of another.

In the opinion of the Panel the claims at issue gave the general impression that naratriptan and rizatriptan were of similar efficacy. On balance the Panel considered that the claims were a fair reflection of the evidence available to Glaxo Wellcome at the relevant time. The Panel ruled no breach of Clause 7.2 of the Code.

Complaint received **21 April 1999**

Case completed **10 August 1999**

CASE AUTH/870/4/99

LOREX SYNTHÉLABO v TRINITY

Promotion of Angitil

Lorex Synthélabo complained about the promotion of Angitil (diltiazem) by Trinity. Angitil was available as a twice daily, slow release preparation (Angitil SR) and a once daily extended release preparation (Angitil XL). Lorex Synthélabo marketed modified release preparations of diltiazem for twice daily and once daily administration (Tildiem Retard and Tildiem LA respectively).

A booklet 'Improving Rational Prescribing' was ruled in breach of the Code because although it was more than four pages in length it bore no reference as to where the prescribing information could be found. A breach was also ruled because the stated date of preparation could not be correct because it predated one of the references quoted. The booklet contained a claim that Angitil SR was bioequivalent to the leading brand of diltiazem. Lorex Synthélabo stated that this was Tildiem Retard. Substantiation had been requested but not received and it was alleged that the claim might not be capable of substantiation. The Panel considered that the Code had not been breached because Trinity had supplied data from a study comparing Angitil with Cardizem. The latter was not available in the UK but was otherwise the same product as Tildiem Retard. Lorex Synthélabo alleged that the booklet referred to data relating to once daily use of Angitil SR but the product was not licensed for once daily use. In the Panel's view, the page in question promoted the use of Angitil SR once daily. This was not in accordance with its marketing authorization and a breach of the Code was ruled.

A breach of the Code was also ruled because Trinity had taken over seven working weeks to supply substantiating data requested by Lorex Synthélabo. This fell short of the requirement that substantiation had to be provided without delay.

Lorex Synthélabo alleged that a document entitled 'Angitil XL 240 and Angitil XL 300…' did not contain prescribing information for all of the products to which it referred and nor did it contain a reference as to where to find the prescribing information. Trinity stated that it was not a promotional item but designed to be issued in response to requests for specific information. The Panel considered that the nature and tone of the document, together with the style of presentation, meant that it was promotional and subject to the Code, a breach of which was ruled because of the absence of prescribing information for Angitil SR. The document was only four pages long and thus did not need a reference as to where to find prescribing information. No breach of the Code was ruled in that regard.

Lorex Synthélabo also alleged that it had asked for substantiation of a number of claims within the document. It might be that these were not capable of substantiation. The Panel noted that the Code required substantiation for any information, claim or comparison to be provided without delay. It need not be provided, however, in relation to the validity of indications approved in the marketing authorization. The Panel considered, therefore, that Trinity did not have to provide substantiation in relation to simple claims that Angitil could be used in hypertension and/or angina. For claims which went further than this, such as 'Long term efficacy has been demonstrated in trials lasting for up to 6 and 12 months', substantiation would have to be provided if requested. In addition the Panel noted that cost comparison claims were not related to the validity of the product's indications approved in the marketing authorization and would also have to be substantiated to a third party. The Panel considered that Lorex Synthélabo had not received substantiation of all of the thirteen claims it had brought to Trinity's attention and breaches of the Code were ruled.

Lorex Synthélabo Ltd complained about the promotion of Angitil (diltiazem) by Trinity Pharmaceuticals Limited. Angitil was available as a twice daily, slow release preparation (Angitil SR) and a once daily, extended release preparation (Angitil XL). Lorex Synthélabo similarly marketed modified release preparations of diltiazem for twice daily and once daily administration (Tildiem Retard and Tildiem LA respectively).

A Document entitled 'Improving Rational Prescribing'

This 16 page booklet gave clinical and pharmacoeconomic information about Angitil SR in the management of hypertension and/or angina. Trinity had advised Lorex Synthélabo by a letter dated 11 January 1999 of a number of errors in the booklet and that the booklet had been withdrawn.

1 Reference to prescribing information

COMPLAINT

Lorex Synthélabo alleged a breach of Clause 4.6 of the Code as the booklet did not contain a reference to where prescribing information could be found.

RESPONSE

Trinity agreed that the item was in breach of the Code as it did not state where the prescribing information could be found.

PANEL RULING

The Panel noted that Clause 4.6 of the Code required promotional material consisting of more than four pages to give a clear reference as to where the prescribing information could be found. The booklet did contain the prescribing information for Angitil SR on page 15 but no reference as to its location. A breach of Clause 4.6 was ruled.

2 Date of preparation

COMPLAINT

Lorex Synthélabo noted that the booklet bore the statement 'Date of Preparation: September 1995' below the prescribing information. This date presumably referred to the date of preparation of the prescribing information since the booklet itself contained a reference to the 1996 Drug Tariff. A breach of Clause 4.7 was alleged.

RESPONSE

Trinity agreed that the booklet was in breach of the Code. The September 1995 date referred to the prescribing information and not the booklet.

PANEL RULING

The Panel noted that Clause 4.7 of the Code required promotional material, other than advertisements appearing in professional publications, to include the date on which the material was drawn up or last revised. The Panel noted that References 51 and 52 given in the booklet referred to June 1996 publications. The booklet could not have been prepared in September 1995. The date given in the booklet referred to the prescribing information and not the booklet itself as acknowledged by Trinity. A breach of Clause 4.7 was ruled.

3 Substantiation of a claim

COMPLAINT

Lorex Synthélabo noted that the booklet contained a claim that Angitil SR was bioequivalent to the leading brand of twice daily (bd) diltiazem. Tildiem Retard was the leading brand of bd diltiazem in the UK. Substantiation of the claim had been requested but had not been provided. A breach of Clause 7.4 was alleged.

Lorex Synthélabo stated that the claim might not be capable of substantiation in breach of Clause 7.3.

In addition Lorex Synthélabo stated that this unsubstantiated claim had misled prescribers. In one area a circular was distributed, in July 1998, by the regional health authority containing the claim that Angitil SR was bioequivalent to the leading brand (Tildiem Retard). Lorex Synthélabo alleged a breach of Clause 7.2 of the Code.

RESPONSE

Trinity stated that it was not required to inform Lorex Synthélabo regarding the origins of its product. The company stated that it could substantiate the claim and had provided data to the Authority. This data had been submitted to the Medicines Control Agency and resulted in the issuance of the licences. Trinity stated that it had not misled prescribers as it could substantiate the claim.

PANEL RULING

The Panel noted that pages 6 and 9 of the booklet contained the claim that 'The key conclusion from this important pharmacokinetic study is that Angitil SR 120mg is bioequivalent to the brand leader'. Similar claims appeared on pages 8 and 12. The regional health authority circular stated 'Angitil SR is equivalent to the leading brand (Tildiem Retard)'. The Panel noted that Lorex Synthélabo had misquoted the claim in the circular as 'Angitil SR is bioequivalent ……..'.

The Panel noted that in intercompany correspondence provided by Lorex Synthélabo, the company had referred to data supplied by Trinity The letter stated that with one exception all of the 14 data on file references were drawn from the clinical expert report submitted for product registration. Lorex Synthélabo had expressed concern that the data supporting the claim of bioequivalence with the brand leader was from a study comparing Angitil with Cardizem and not Tildiem. Cardizem was not available in the UK.

The Panel noted that Trinity had explained in its original response that the Tildiem Retard product range sold on the UK market was developed by Gacell and the rights to this acquired by various companies for specific territories and specifically by Lorex Synthélabo in the UK. The product range was marketed worldwide under the trade marks of Tildiem, Cardizem or Bi-Tildiem.

The Panel noted, therefore, that Lorex Synthélabo had been provided with data by Trinity and this had been acknowledged in intercompany correspondence. The Panel noted that the data referred to Cardizem not Tildiem and considered that it would have been helpful, and necessary if such a request for substantiation had come from an independent health professional, if the relationship between the two products had been made clear. The Panel considered that material had been provided to substantiate the claim. It appeared from a letter to Lorex Synthélabo from Trinity that the expert report had been provided. Lorex Synthélabo questioned the data on the basis that it referred to Cardizem and not Tildiem. This had been answered by Trinity which had explained that the trade marks Tildiem and Cardizem were used

for the same product. The Panel noted that there was no other comment on the data itself. In the circumstances the Panel ruled no breach of Clause 7.4 of the Code as data had been provided. It was possible that the data could substantiate the claims. In the absence of any specific allegations other than the use of different trade names the Panel ruled no breach of Clause 7.3 of the Code. It also ruled no breach of Clause 7.2 of the Code in relation to the allegation that prescribers would be misled.

The Panel considered that if Lorex Synthélabo wished to make specific allegations about the data then this would have to be dealt with as a new case as the Panel had not ruled on the data itself only on the issue of the use of different trade names in the data.

4 Promotion of unlicensed dosage schedule

COMPLAINT

Lorex Synthélabo noted that the booklet referred to data relating to once daily use of Angitil SR. Angitil SR was not licensed for once daily use; a breach of Clause 3.2 was alleged. Alternatively Lorex Synthélabo considered that the data might be referring to the once daily use of Angitil XL 300 for which the booklet did not contain the prescribing information, in which case a breach of Clause 4.1 was alleged.

RESPONSE

Trinity stated, that amongst numerous other studies, the booklet referred to three comparing Angitil SR 180mg with 3 x 60mg immediate release tablets (page 6). The conclusion on page 8 which read '…….. Angitil SR can provide 24 hour cover for most patients with angina and hypertension' should have read '……. Angitil SR given twice daily does provide 24 hours of cover for most patients with angina and hypertension'.

Trinity agreed that the booklet had breached Clause 3.2. However the representatives and any other advertising material never promoted Angitil SR as a once daily product.

Trinity stated that the booklet referred to the 300mg Angitil XL 300 which was licensed at the time but not marketed.

PANEL RULING

The Panel noted that Angitil was available in two sustained release preparations; as a slow release preparation (Angitil SR 90mg, 120mg and 180mg) and an extended release formulation (Angitil XL 240mg and 300mg). The Panel noted the booklet's subtitle 'Clinical and Pharmacoeconomic Information Angitil SR (Diltiazem)'. The introduction stated that the publication would address the pharmacokinetics, clinical and cost effectiveness of the SR formulation and show how Angitil SR could significantly improve the rational prescribing of diltiazem. The Panel considered that in the absence of a suffix readers would therefore assume that any mention of the brand name Angitil referred to Angitil SR. Some readers might not have known of the existence of an alternative Angitil preparation. The Panel noted that in the booklet Angitil was sometimes used with no suffix but could find no specific mention of Angitil XL.

The Panel noted that page 8 of the booklet referred to the use of Angitil SR 300mg once daily. (This dose would have been achievable by the combined use of a 120mg and a 180mg capsule). A table of results on the same page contained a heading 'Angitil 300mg (od)'. The recommended dose of Angitil SR for the treatment of angina and/or hypertension was 90mg twice daily which might be increased gradually to 120mg twice daily or 180mg twice daily if required. The Panel considered that this page was confusing. In the Panel's view the page promoted the use of Angitil SR once daily which was not in accordance with the terms of its marketing authorization. A breach of Clause 3.2 was ruled.

The Panel considered that given its ruling that the page promoted Angitil SR once daily in breach of Clause 3.2 of the Code, there was no breach of Clause 4.1.

5 Time to respond to request for substantiation

COMPLAINT

Lorex Synthélabo stated that its first request for substantiation of claims made in the booklet was on 18 November 1998. Trinity did not reply until 11 January 1999. Clearly this was not a timely response in breach of Clause 7.4 of the Code.

RESPONSE

Trinity did not respond specifically to this allegation.

PANEL RULING

The Panel noted that in its original response Trinity had said that at the time of Lorex Synthélabo's letter [assumed to be 18 November 1998] the Director of Trinity was out of the country. Despite this the Director did telephone and confirm that she would respond soonest upon her return. A letter from Trinity to Lorex Synthélabo, dated 11 January 1999 began, 'I am writing further to your letters of 18 November and 16 December 1998 and our conversation …'.

The Panel noted that Lorex Synthélabo did not receive the information it had requested in its letter of 18 November 1998 until 11 January 1999, an interval of over seven working weeks. The Panel considered that such a time span fell short of the requirement of Clause 7.4 of the Code that substantiation for any claim must be provided without delay. A breach of that clause was ruled.

B Document entitled 'Angitil XL 240 and Angitil XL 300 (diltiazem hydrochloride)' (Ref: TR142 10 June 1998)

This four page document introduced the reader to the Angitil range (SR and XL) and while the document referred mainly to Angitil XL the SR preparation was

mentioned in the section on pharmacokinetics and in boxed text giving a summary of clinical efficacy and safety. The final page of the document gave the prescribing information for Angitil XL 240 and Angitil XL 300.

1 Prescribing information

COMPLAINT

Lorex Synthélabo stated that the item did not contain full and complete prescribing information for Angitil XL 90,120, or 180, which were referred to in the text. In particular, the item did not include the cost of Angitil XL 90,120 and 180 products. A breach of Clauses 4.2 and 4.1 was alleged.

RESPONSE

Trinity stated that the document was not a promotional item; it had been designed to be issued in response to requests for specific information from the medical profession. Trinity confirmed that only five had been sent out.

Trinity stated it did not have Angitil XL 90,120 and 180.

PANEL RULING

The Panel noted that the Angitil range consisted of Angitil SR 90mg, 120mg and 180mg and Angitil XL 240mg and 300mg. In the Panel's view the complaint from Lorex Synthélabo had mistakenly referred to Angitil XL when it should have referred to Angitil SR.

The Panel noted that Clause 1.2 of the Code excluded from the definition of promotion replies made in response to individual enquiries from members of the health professions or in response to specific communications but only if they related solely to the subject matter of the letter of enquiry, were accurate and not misleading and were not promotional in nature.

The Panel noted that the document gave a brief resumé of the pharmacokinetics, clinical use and pharmacoeconomics of Angitil XL although Angitil SR was mentioned in places. The Panel considered that the scope of the document was broad. The document made use of emboldened headings and boxed text. The final boxed text stated 'Summary – Conclusions and Recommendations Use of Angitil XL improves rational prescribing'. The Panel considered that the nature and tone of the document together with the style of presentation meant that it was promotional and therefore subject to the Code.

The Panel noted that the document contained the prescribing information for Angitil XL. The Panel considered that the references to Angitil SR meant that prescribing information for that product was also required. Clause 4.2 of the Code listed the component parts of the prescribing information. Clause 4.1 stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of Clause 4.1 and not Clause 4.2. Trinity had not provided the prescribing information for Angitil SR. The Panel therefore ruled a breach of Clause 4.1 of the Code.

2 Reference to prescribing information

COMPLAINT

Lorex Synthélabo stated that the document did not contain a reference as to where prescribing information could be found. A breach of Clause 4.6 was alleged.

RESPONSE

Trinity stated that the document was only three pages and was thus not required to contain references to where prescribing information might be found.

PANEL RULING

The Panel noted that the document consisted of three pages of promotional copy with the fourth page bearing prescribing information for Angitil XL. The document as a whole accordingly consisted of four pages and thus did not need a reference as to where the prescribing information could be found. No breach of Clause 4.6 was ruled.

3 Requests for substantiation

COMPLAINT

Lorex Synthélabo stated that it had asked for substantiation of a number of claims made within the document. It might be that these claims were not capable of substantiation. A breach of Clauses 7.1, 7.3 and 7.4 were alleged.

RESPONSE

Trinity stated that the claims in the document did not go beyond the summary of product characteristics and were substantiated by the clinical expert report of which Lorex Synthélabo had had a copy since January 1999. The particular statement in the report was highlighted in the original response to the complaint.

PANEL RULING

The Panel noted that intercompany correspondence provided by Lorex Synthélabo showed that the company had asked for substantiation of thirteen claims such as 'Pharmacokinetic parameters are not affected by food', 'Clinical equivalence of Angitil XL to brand leading reference product in angina', 'confirmation of efficacy of Angitil XL 300mg over 12 months' and 'Angitil XL offers the lowest overall costs for once daily diltiazem hydrochloride dosing'. No reply to the letter from Lorex Synthélabo to Trinity had been supplied by either party. Lorex Synthélabo had been sent a copy of the clinical expert report on 11 January 1999 although the covering letter sent with it referred only to claims in the 'Improved Rational Prescribing' booklet (point A above). The Panel noted that the report was a long, complex document. The copy supplied to the Authority had not been highlighted and the Panel noted that it could find no reference in the report to such data as would be needed to substantiate the claim 'Angitil XL offers the lowest overall costs for once daily diltiazem hydrochloride dosing'.

The Panel noted that Clause 7.4 of the Code stated that substantiation for any information, claim or comparison must be provided without delay; it need not be provided, however, in relation to the validity of indications approved in the marketing authorization. The Panel considered, therefore, that Trinity did not have to provide substantiation in relation to simple claims that Angitil could be used in hypertension and/or angina. For claims which went further than this ie 'Long term efficacy has been demonstrated in trials lasting for up to 6 and 12 months' substantiation would have to be provided if requested. In addition the Panel noted that cost comparison claims were not related to the validity of the product's indications approved in the marketing authorization and would also have to be substantiated to a third party.

The Panel considered that Lorex Synthélabo had not received substantiation of all of the thirteen claims it had brought to Trinity's attention. Breaches of Clauses 7.3 and 7.4 were ruled. The Panel considered that this ruling covered the allegation of a breach of Clause 7.1 and so no ruling upon that allegation was made.

During its consideration of this case the Panel noted its concern that a complex, regulatory document had been supplied in request for substantiation of claims for Angitil. While such a document might be suitable to send to another pharmaceutical company, its content and format would, in the Panel's view, make it unsuitable for an independent health professional. Substantiation should be provided in a readily understandable format. The Panel requested that Trinity be advised of its views on this matter.

Complaint received **22 April 1999**

Case completed **5 August 1999**

CASE AUTH/874/5/99

LUNDBECK v LILLY

Prozac leavepiece

Lundbeck complained about a Prozac (fluoxetine) leavepiece issued by Lilly. Lundbeck alleged that the claim 'compared to newer antidepressants Prozac delivers a cost effective alternative' implied that the cost effectiveness of Prozac was superior when compared to the new antidepressants listed (paroxetine, citalopram and venlafaxine). It was alleged that Lilly had failed to substantiate the claim.

The Panel considered that overall there was not sufficient data to substantiate the claim and a breach of the Code was ruled.

Lundbeck Limited complained about a Prozac (fluoxetine) leavepiece (ref PZ 1102) issued by Eli Lilly and Company Limited. The leavepiece compared Prozac 20mg in terms of comparative doses and cost efficacy with other antidepressants. Under a heading of 'Prozac delivers efficacy' a table of data listed comparative doses to Prozac 20mg of six antidepressants three of which were tricyclic antidepressants and the other three were paroxetine (20mg), citalopram (20 or 40mg) and venlafaxine (75-150mg). Two bullet points followed; '91% of Prozac prescriptions in depressed patients were for 20mg' and 'Compared to newer antidepressants Prozac delivers a cost effective alternative'. The second bullet point was immediately followed by another table of data which compared the cost of Prozac 20mg with four other antidepressants three of which had featured in the first table of data although the stated doses now differed ie paroxetine (20-50mg), citalopram (20-60mg) and venlafaxine (75-375mg). The stated doses were referenced to the British National Formulary (BNF) recommended dose range for the treatment of depression. Only the lowest dose of citalopram was shown to be less expensive than Prozac 20mg with all other medicines being either the same cost (paroxetine 20mg) or more expensive. A strapline at the bottom of the leavepiece read 'Fixed Dose = No Titration = Fixed Cost'.

Lundbeck produced citalopram (Cipramil).

COMPLAINT

Lundbeck alleged that the claim 'Compared to newer antidepressants Prozac delivers a cost effective alternative' clearly implied that the cost effectiveness of Prozac was superior when compared to the 'newer antidepressants' listed. As was Lundbeck's practice it had attempted to resolve this issue directly with the other party. Lilly, however, had contended that at no stage did it assert that Prozac was more cost effective than the other treatments.

Lundbeck stated that it had requested pharmacoeconomic data to substantiate the above claim on two occasions and none was forthcoming. Failure to provide data to substantiate a claim was a breach of Clause 7.3 of the Code and Lundbeck therefore had no option but to complain to the Authority.

RESPONSE

Lilly stated that the implication of the complaint from Lundbeck was that Lilly did not respond to its request for information and referred to its letter sent on 31 March 1999 to Lundbeck's medical director a copy of which was provided to the Panel. Discussions had been ongoing around this item but had not been resolved before Lundbeck filed the above complaint.

Lilly's letter to Lundbeck referred to papers by Donaghue (1998) and Paton (1997) which confirmed

that Prozac was used almost entirely at the 20mg dose in both general practice and hospital. The pharmacoeconomic benefits of fluoxetine had been reviewed by Wilde and Benfield (1998) who found it generally to have a favourable pharmacoeconomic profile. Lilly stated that it had not claimed that Prozac was more cost effective than the other treatments. The effectiveness of the medicines listed was not in dispute. The monthly cost for Prozac was clear and this was not the case for other antidepressants. Lilly had also stated that citalopram which was already being marketed in 1989 could not be considered to be one of the newer antidepressants.

Lilly presented additional information not contained in the original correspondence with Lundbeck.

Data from the paper by Wilde and Benfield (1998) showed that fluoxetine's tolerability and safety advantages over tricyclic antidepressants were obtained without additional overall cost to healthcare providers, ie compared with tricyclic antidepressants, fluoxetine was cost effective. The same authors also demonstrated cost advantages for fluoxetine over other selective serotonin re-uptake inhibitors (SSRIs) (sertraline and paroxetine). This was because patients who started therapy with fluoxetine were more likely to achieve patterns of antidepressant use consistent with recommended standards of care than patients who started therapy with other SSRIs. The review highlighted that the percentage of patients treated with fluoxetine that required upward dosage titration from starting doses appeared to be lower than that for patients receiving other SSRIs. Also, fluoxetine-treated patients appeared to be less likely to switch or augment therapy and more were likely to refill their prescriptions.

Lilly stated that upward dosage titration of the other SSRIs must be considered and this was reflected in the doses listed in the BNF (Number 37, March 1999). The dosage range for citalopram listed in the BNF was that presented in the bar chart in the leavepiece: 20mg to 60mg daily.

The BNF dose for fluoxetine in depressive illness was 20mg daily. That upward dosage titration for fluoxetine was rarely required had been confirmed by data from the MediPlus UK Primary Care Database (IMS UK and Ireland) in which 91% of prescriptions in depressed patients were for 20mg. This datum was highlighted in the leavepiece.

Lilly submitted that published data showed that fluoxetine was cost effective when compared to the tricyclic antidepressants and also the other SSRIs sertraline and paroxetine. For a treatment to be considered cost effective it should meet one of the following conditions:

- It was no more expensive and at least as effective as its comparator,
- Although more expensive than its comparator, it provided additional benefit that was worth the additional cost, or
- It was less expensive and less effective in those cases where the extra benefit was not worth the extra cost.

Citalopram was a relatively recent addition to the pharmacological arsenal in the UK, having been introduced as recently as 1995. Fluoxetine was the yardstick against which all new antidepressants must be measured. Citalopram was not a more effective treatment than fluoxetine for the treatment of depressive illness. For it to be cost effective compared to fluoxetine it would therefore have to be cheaper than fluoxetine. Citalopram was cheaper than fluoxetine at the bottom of its dosage range. However, this advantage was lost with any dosage titration.

With fluoxetine, a prescriber could be confident that 20mg would be an effective dose in the majority of patients. This afforded clinicians the clinical effectiveness they desired for their patients plus confidence that they could control their prescribing costs.

PANEL RULING

The Panel noted that the claim in question 'Compared to newer antidepressants Prozac delivers a cost effective alternative' appeared immediately above a table comparing the acquisition costs of Prozac 20mg with four other antidepressants. The Panel considered that most readers would associate the claim with the table of data and assume that the 'newer antidepressants' were those listed therein. In the Panel's view 'cost effective' implied more than a simple comparison of the acquisition cost of products. Other factors such as relative efficacy, incidence of side-effects, etc, had to be taken into account.

Wilde and Benfield had stated that the SSRIs had similar efficacy and generally similar tolerability profiles and although there was some evidence that fluoxetine had cost advantages over other SSRIs, confirmatory evidence was required. The Panel considered that in these particular circumstances it was not unreasonable for the cost effectiveness of the SSRIs to be based solely on their acquisition costs. The Panel considered, however, that the acquisition costs stated should be those of clinically equivalent doses. In this regard the Panel noted that the first table of data in the leavepiece had stated that, compared to Prozac 20mg, the comparative dose of citalopram was 20 or 40mg; the table comparing costs, however, had shown the costs of citalopram 20mg and 60mg. Similarly it had been stated in the first table that paroxetine 20mg was comparable to Prozac 20mg but the cost data showed the cost of paroxetine 20mg and 50mg. The Panel noted that Prozac was more expensive than the lowest dose of citalopram and the same price as the 20mg dose of paroxetine.

The Panel noted that the leavepiece had included a comparison of Prozac 20mg with venlafaxine 75-150mg in the table comparing doses and 75-375mg in the table comparing costs. Venlafaxine was not an SSRI and the review by Wilde and Benfield stated that the pharmacoeconomics of Prozac had not been compared with venlafaxine. In the Panel's view there was no data to show that a cost effective comparison of Prozac with venlafaxine could reasonably be based only on the acquisition costs of the two medicines.

The Panel considered that, overall, there was not

sufficient data to substantiate the claim that Prozac 20mg delivered a cost effective alternative. The Panel, therefore, ruled a breach of Clause 7.3 of the Code.

Complaint received **17 May 1999**

Case completed **30 July 1999**

CASE AUTH/877/5/99 *NO BREACH OF THE CODE*

GLAXO WELLCOME v MERCK SHARP & DOHME

Maxalt leavepiece

Glaxo Wellcome complained about a leavepiece for Maxalt (rizatriptan) issued by Merck Sharp & Dohme. The leavepiece compared Maxalt with sumatriptan, Glaxo Wellcome's product Imigran.

In relation to the claim 'Within 2 hours Maxalt 10mg tablets provided headache relief sooner than sumatriptan 100mg (p<0.05, age adjusted time to headache relief analysis)', Glaxo Wellcome noted that the same claim but with 'faster' instead of 'sooner' had previously been ruled in breach of the Code in Case AUTH/759/8/98 and Glaxo Wellcome did not consider that the change in wording changed the meaning of the claim as both implied that patients on rizatriptan would experience relief earlier than those on Imigran – a fact that was not represented by the clinical data.

The Panel noted that the claim appeared above a graph depicting the results from Tfelt-Hansen *et al* (1998). The graph plotted cumulative % of patients against time post dosing and showed a consistent advantage for Maxalt at the individual time points. The graph included an arrow which ran from zero to two hours post dosing. The arrow included the statement 'hazard ratio 1.21, p<0.05'. The Panel noted that the claim was slightly different to that in Case AUTH/759/8/98 and overall it was presented in the case now at issue with much more detail about the study and its results than it had been in the previous case. Some explanation of the data had been given by the use of the arrow on the graph and by two bullet points below the graph, 'A patient is 21% more likely to achieve headache relief sooner with Maxalt 10mg than with sumatriptan 100mg' and 'Over 30% more patients taking Maxalt 10mg tablets reported headache relief at 1 hour compared with those taking sumatriptan 100mg'. Given its context the Panel did not accept that the claim was misleading as alleged and no breach of the Code was ruled. Given its ruling of no breach of the Code there could be no breach of the undertaking given in Case AUTH/759/8/98.

Glaxo Wellcome noted that the claim 'Faster pain relief than sumatriptan 100mg' was ruled in breach in Case AUTH/780/10/98 because the unqualified use of the claim was misleading as there was only a statistically significant difference between the products at one hour. Glaxo Wellcome considered that the graphical representation of data under the claim did not support it and, in addition, considered that the graph was misleading. The Panel considered that the claim at issue was essentially the same as that at issue in Case AUTH/780/10/98 ('Faster headache relief than sumatriptan 100mg') although the context was different. In the previous case it headed a chart comparing the data at the one hour time point whereas in this case the claim was the sub-heading on the 'Fast' page of the leavepiece which introduced the reader to the results of the Tfelt-Hansen study. The Panel noted its ruling above regarding the context of the page in question. The Panel considered that the claim 'Faster pain relief than sumatriptan 100mg' had been sufficiently qualified by the data on the page in question. No breach of the Code was ruled. Given its ruling of no breach of the Code there could be no breach of the undertaking given in Case AUTH/780/10/98.

Glaxo Wellcome UK Limited complained about an 8 page leavepiece for Maxalt (rizatriptan) 10mg issued by Merck Sharp & Dohme Limited (ref 02-00 MXT.98.GB.45138.B.5m.CW.0299). The leavepiece promoted Maxalt 10mg as fast, effective and convenient. Page 3 of the leavepiece was headed 'Fast'. Beneath the heading was the claim 'Faster pain relief than sumatriptan 100mg' and the explanation that in a placebo-controlled, double-blind comparative study 'Within 2 hours Maxalt 10mg tablets provided headache relief sooner than sumatriptan 100mg (p<0.05, age adjusted time to headache relief analysis).' There then followed a graph which showed, in stepwise fashion, the cumulative percentage of patients experiencing headache relief at 0.5, 1, 1.5 and 2 hours. At all time points the Maxalt results were more favourable than those for sumatriptan. Glaxo Wellcome marketed Imigran (sumatriptan).

The Authority noted that, although not specifically alleged, Glaxo Wellcome implied that the undertakings given by Merck Sharp & Dohme in Cases AUTH/759/8/98 and AUTH/780/10/98 had been breached. In accordance with advice given by the Appeal Board, breaches of undertakings were taken up as complaints by the Director as the Authority itself was responsible for ensuring compliance with undertakings. The situation in this case was not clear. The Authority asked Merck Sharp & Dohme to consider the requirements of Clause 21 and the company was told that a judgement with regard to a breach of undertaking would be reserved until its response had been received. In the interim it would be dealt with as a complaint from Glaxo Wellcome but it might later become a complaint from the Director.

1 Claim 'Within 2 hours Maxalt 10mg tablets provided headache relief sooner than sumatriptan 100mg (p<0.05, age adjusted time to headache relief analysis)'

COMPLAINT

Glaxo Wellcome noted that the claim, '…Maxalt 10mg tablets provided faster headache relief within two

hours than sumatriptan 100mg', had previously been considered in Case AUTH/759/8/98. The Panel's ruling was that, given the data, the claim was misleading and in breach of Clause 7.2 of the Code.

Glaxo Wellcome did not consider that changing the term 'faster' to 'sooner' in any way changed the meaning of this claim as both phrases implied that patients on rizatriptan would experience relief earlier than those on Imigran – a fact that was not represented by the clinical data.

Glaxo Wellcome considered that the only way to determine if one treatment was faster than another was by asking patients to note down the time it took for them to first experience relief of their migraine. To date this had not been done in the rizatriptan and Imigran (sumatriptan) clinical studies. Instead, the percentages of patients responding to each treatment had been measured at set time points. Like rizatriptan, Imigran demonstrated significant relief of headache compared with placebo at 30 minutes. In direct comparative studies of both Imigran 100mg and Imigran 50mg against rizatriptan 10mg, no significant difference in efficacy had been established at this 30 minute time point.

Glaxo Wellcome stated that the 'time to headache relief analysis' was a comparison of the cumulative percentage of patients who had experienced relief at the set time points of 30, 60, 90 and 120 minutes on each treatment. It did not allow for when patients first experienced relief within these time points. It was therefore not a measure of speed of onset. For example, if treatment A, a fast but relatively ineffective treatment, was compared with treatment B, a slower but much more effective treatment, the cumulative percentage of patients who responded to treatment B within 2 hours might be more than responded to treatment A, but of course this did not make treatment B the faster treatment.

RESPONSE

Merck Sharp & Dohme noted that the essence of the claim and that at issue in point 2 below, was identical and it was the company's understanding that it was the unqualified use and the mode of presentation of these claims, which was found to be misleading and consequently in breach of Clause 7.2 in Cases AUTH/759/8/98 and AUTH/780/10/98 respectively. Clarification on this matter was subsequently sought from the Authority and the company understood that the use of the claim might well be justified by the data available, but the lack of a clear explanation of the nature and interpretation of the analysis had led to a breach of Clause 7.2. In this case, therefore, Kaplan-Meier curves, a straightforward and commonly used method for presenting time-to-event data was employed together with additional text to add further clarification on the analysis. It was clear that the company had made considerable efforts to make the presentation of this data as straightforward as possible rather than simply substituting the term 'faster' for 'sooner' as implied by Glaxo Wellcome.

Merck Sharp & Dohme stated that it would appear Glaxo Wellcome was continuing to dispute the use of the time-to-event analysis rather than the way in which the data was presented. As the company had highlighted in the past, this concept (although a different statistical test) had been utilised by Glaxo Wellcome in some migraine studies with sumatriptan. Based on this analysis, the multinational oral sumatriptan and Cafergot comparative study group concluded that 'headache improvement started significantly earlier in those patients treated with sumatriptan compared with those receiving Cafergot' and 'the onset of headache resolution was more rapid with sumatriptan'. It seemed that Glaxo Wellcome's views and interpretation of this form of analysis changed as to whether it or a competitor was presenting the data in this fashion.

Merck Sharp & Dohme considered that it had adequately addressed the use of this analysis in its response to Case AUTH/759/8/98 regarding the above claim. In summary, the claim was based on the primary end-point of the rizatriptan vs sumatriptan comparison study (030 study) which showed a statistically significant difference ($p < 0.05$) in terms of the age adjusted time to headache relief analysis. (These results had now been published in the November/December 1998 issue of the peer reviewed journal Headache). As previously stated, this type of analysis was commonly used in clinical trials, and was also known as survival analysis or life table analysis. The concept and methods of such analyses were discussed in medical statistical textbooks (eg D G Altman, Practical Statistics for Medical Research) and were currently the subject of an ongoing series in the BMJ, Statistics Notes (first in series published 15 August 98).

In the 030 study the analysis compared the time that patients first reported headache relief at time points up to 2 hours for rizatriptan vs sumatriptan 100mg. The analysis was considered more than simply a number of comparisons at different time points for several reasons:

1 Used all the available data up to 2 hours.

2 Avoided the statistical problem of making a number of comparisons within the same study at different time points ('multiplicity'). Such multiple comparisons increased the chance of finding $p<0.05$ merely by chance. A number of statistical methods existed to allow for multiplicity when making such multiple comparisons. However, survival analysis (ie time to headache relief analysis) was a perfectly valid alternative.

3 Accommodated 'censoring'. The analysis included all the data available. Data from early time points were included even when those from later time points were not available.

4 Increased the statistical power.

Merck Sharp & Dohme stated that the method used for the analysis produced a summary statistic, the 'hazard ratio', which quantified the treatment comparison. The hazard ratio for rizatriptan vs sumatriptan 100mg was 1.21 ($p=0.032$). This meant that for any patient with a headache at a particular time point they were approximately 21% more likely to get relief of their headache within the next unit of time (second, minute) with rizatriptan than with

sumatriptan 100mg. Merck Sharp & Dohme noted that the arrow above the graph regarding the hazard ratio and p value stretched from 0-2 hours clearly indicating that the graph did not relate to individual time points.

As further support for the use of this analysis in this context Merck Sharp & Dohme included a review by Professor John Whitehead, Director of Medical and Pharmaceutical Statistics Research Unit, University of Reading. The comments in this review related to the non-age adjusted figures.

PANEL RULING

The Panel noted that the study cited in support of the claim, Tfelt-Hansen *et al* (1998) was the published version of the 030 study. The Panel noted that the primary efficacy endpoint, time to pain relief through two hours, demonstrated that after adjustment of age imbalance Maxalt 10mg had a significantly faster time to pain relief than sumatriptan 100mg (hazard ratio 1.21 p=0.032). Similar results were obtained in the non-age adjusted 'per protocol' analysis (hazard ratio 1.20 p=0.04). Furthermore Maxalt showed a numerically greater response rate over sumatriptan at each time point 0.5, 1, 1.5 and 2 hours. It was only at one hour that this reached statistical significance.

The Panel noted that the study stated that the time to pain relief analysis used data from all gathered time points (0.5 to 2 hours) rather than just a single 2-hour time point to calculate a hazard ratio comparing treatments. The hazard ratio expressed whether a patient would respond more rapidly to one treatment compared to another and therefore whether one treatment was superior to another treatment with respect to time to pain relief. The hazard ratio generally had more power than a specific time point analysis. The study concluded that rizatriptan 10mg had a fast onset of action and relieved migraine more effectively than sumatriptan 100mg with both products having an acceptable safety and tolerability profile.

The Panel noted that in Case AUTH/759/8/98 the claim '… Maxalt 10mg tablets provided faster headache relief within two hours than sumatriptan 100mg' had appeared in a letter which had been sent to hospital and retail pharmacists announcing the launch of Maxalt 10mg. The Panel had noted that while there was data to show a trend in favour of Maxalt 10mg compared with sumatriptan 100mg, study 030, to which the claim was referenced, had only recorded a statistically significant advantage for Maxalt at 1 hour. The Panel had considered that given the data the claim was misleading and ruled a breach of Clause 7.2 of the Code.

Turning to the case now before it the Panel noted that the claim 'Within 2 hours Maxalt 10mg tablets provided headache relief sooner than sumatriptan 100mg (p<0.05, age adjusted time to headache relief analysis)' appeared above a graph depicting the results from Tfelt-Hansen *et al* (1998). The graph plotted cumulative % of patients against time post dosing and showed a consistent advantage for Maxalt at the individual time points. The graph included an arrow which ran from zero to two hours post dosing. The arrow included the statement 'hazard ratio 1.21, p<0.05'.

The Panel noted that the claim was slightly different to that in Case AUTH/759/8/98 and overall it was presented in the case now at issue with much more detail about the study and its results than it had been in the previous case. The Panel questioned whether readers would be familiar with hazard ratios. Some explanation of the data had been given by the use of the arrow on the graph and by two bullets points below the graph, 'A patient is 21% more likely to achieve headache relief sooner with Maxalt 10mg than with sumatriptan 100mg' and 'Over 30% more patients taking Maxalt 10mg tablets reported headache relief at 1 hour compared with those taking sumatriptan 100mg'. Given its context the Panel did not accept that the claim was misleading as alleged and no breach of Clause 7.2 of the Code was ruled.

Given its ruling of no breach of Clause 7.2 of the Code there could be no breach of the undertaking given in Case AUTH/759/8/98. The Panel therefore ruled no breach of Clause 21 of the Code.

2 Claim 'Faster pain relief than sumatriptan 100mg'

COMPLAINT

Glaxo Wellcome noted that this claim was one of those considered in Case AUTH/780/10/98. The Panel's ruling in Case AUTH/780/10/98 was that the unqualified use of this claim was misleading, as there was only a statistically significant difference between the products at 1 hour. A breach of Clause 7.2 was ruled.

Glaxo Wellcome alleged that the graphical representation of data under this claim did not support the claim that patients on rizatriptan would experience headache relief earlier than those on Imigran.

In addition, Glaxo Wellcome alleged that the graph was misleading because, although the cumulative percentage of patients responding within the two hours was slightly greater on rizatriptan than on sumatriptan (as indicated by the graph), there was in fact no significant difference between the treatments at 30, 90 or 120 minutes. This was not shown within the graph, misleading readers into believing that rizatriptan was more effective than Imigran at each individual time point studied.

Glaxo Wellcome alleged that the claim and the graph used to substantiate it were misleading and in breach of Clause 7.2 of the Code of Practice.

RESPONSE

Merck Sharp & Dohme did not agree that the graph might mislead readers to believe that rizatriptan was significantly different to sumatriptan at all the individual time points. Survival curves were commonly presented in the medical press and it would be reasonable to assume that the majority of doctors would recognise this form of survival analysis. In the context of the above leavepiece the company considered that the claim had now been

clearly explained, in an easy to understand manner, and that the presentation of the data in this manner was not misleading and consequently not in breach of Clause 7.2.

PANEL RULING

The Panel noted that in Case AUTH/780/10/98 the claim 'Faster headache relief than sumatriptan 100mg' had appeared as a page heading in a detail aid and was followed by the claim 'Maxalt 10mg tablets provided faster headache relief within two hours than sumatriptan 100mg ($p<0.05$).' A bar chart beneath the two claims showed that at 1 hour 37% of patients reported headache relief on Maxalt 10mg compared with 28% in the sumatriptan group ($p=0.01$). The claims and the graph were based upon the results of study 030.

In its ruling in Case AUTH/780/10/98 the Panel had noted its comments in Case AUTH/759/8/98 regarding the results of the 030 study ie that at all time points (0.5, 1, 1.5 and 2 hours) more patients reported pain relief in the Maxalt 10mg group than in the sumatriptan 100mg group. The difference between the two groups was statistically significant only at 1 hour. In Case AUTH/780/10/98 the Panel had considered that the unqualified claim 'Faster headache relief than sumatriptan 100mg' was misleading as there was only a statistically significant difference between the products at 1 hour. A breach of Clause 7.2 was ruled.

Turning to the case now before it the Panel considered that the claim at issue 'Faster pain relief than sumatriptan 100mg' was essentially the same as that at issue in Case AUTH/780/10/98 ('Faster headache relief than sumatriptan 100mg') although the context was different. In the previous case it headed a chart comparing the data at the one hour time point whereas in this case the claim was the sub-heading on the 'Fast' page of the leavepiece which introduced the reader to the results of the Tfelt-Hansen study.

The Panel noted its ruling in point 1 above regarding the context of the page in question. The Panel considered that the claim 'Faster pain relief than sumatriptan 100mg' had been sufficiently qualified by the data on the page in question. No breach of Clause 7.2 of the Code was ruled.

Given its ruling of no breach of Clause 7.2 of the Code there could be no breach of the undertaking given in Case AUTH/780/10/98. The Panel therefore ruled no breach of Clause 21 of the Code.

Complaint received **19 May 1999**

Case completed **10 August 1999**

CASE AUTH/878/5/99

ZENECA v SCHERING HEALTH CARE

Cyprostat detail aid

Zeneca Pharma complained about a detail aid for Cyprostat (cyproterone acetate) issued by Schering Health Care.

It was alleged that the claim that Cyprostat was '… an effective monotherapy for the long-term palliative care of prostate cancer patients' was inconsistent with the summary of product characteristics (SPC). In the Panel's view the claim implied that Cyprostat could be used in all prostate cancer patients which was not so. It was to be used in patients when LHRH analogues or surgery were contraindicated, not tolerated or where oral therapy was preferred. A breach of the Code was ruled.

The claim 'A Gold Standard in Prostate Cancer Therapy' was alleged to be exaggerated given that the product could only be used in certain patients. The Panel ruled a breach of the Code.

References in the detail aid to the use of Zeneca's product bicalutamide (Casodex) at an unlicensed dosage regimen were alleged to be misleading and unfair. There was no mention of the licensed dose and indication nor of the efficacy results for the licensed use. The data had not been put in the context of the Casodex SPC. The Panel ruled a breach of the Code.

Zeneca Pharma complained about a detail aid (ref 97002085) for Cyprostat (cyproterone acetate) which had been issued by Schering Health Care Limited.

The twelve page, A5 detail aid was entitled 'Cyprostat vs bicalutamide' and directly compared the two products in the treatment of prostate cancer in terms of mode of action, efficacy, tolerability, quality of life and cost. Zeneca marketed Casodex (bicalutamide). There were three allegations which were considered as follows.

1 Claim 'Cyprostat is an effective monotherapy for the long-term palliative care of prostate cancer patients'

This claim appeared prominently on page 5.

COMPLAINT

Zeneca pointed out that according to the summary of product characteristics (SPC), the licensed indication for Cyprostat was more restricted, namely '… long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred'. The claim appeared prominently, in a boxed section for emphasis, and without any additional text adjacent or elsewhere to qualify it. Zeneca, therefore, alleged a breach of Clause 3.2 insofar as it promoted Cyprostat in a manner inconsistent with its SPC.

RESPONSE

Schering Health Care submitted that the SPC for Cyprostat stated clearly that the product was licensed as monotherapy for the long-term treatment of prostatic cancer, and there was ample published evidence to support this claim. It was not a requirement of the Code that the entire wording of the SPC was included in every claim, simply that all claims were in accordance with the licensed indications and the SPC. It was for this reason that companies were required to include prescribing information as an integral part of each promotional piece. The prescribing information for Cyprostat, on the inside back cover of the detail aid, stated the licensed indications in full.

PANEL RULING

The Panel noted that the therapeutic indications for Cyprostat given in the SPC were the 'Management of patients with prostatic cancer (1) to suppress 'flare' with initial LHRH analogue therapy, (2) in long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred, and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had orchidectomy'.

In the Panel's view the claim 'Cyprostat is an effective monotherapy for the long-term palliative care of prostate cancer patients' implied that the product could be used in all prostate cancer patients which was not so. The SPC stated that the product could be used in these patients only when LHRH analogues or surgery were contraindicated, not tolerated or where oral therapy was preferred. The claim was too general given the licensed indication. It was immaterial that full details were given in the prescribing information; it was an accepted principle under the Code that misleading claims could not be qualified by the small print.

The Panel considered that the claim at issue was not a fair reflection of the information given in the SPC regarding the use of Cyprostat. The long-term palliative care of prostate cancer patients, provided that they satisfied the criteria set out in the SPC, was a licensed indication for Cyprostat. The Panel considered that the claim was inconsistent with the SPC and ruled a breach of Clause 3.2 of the Code.

2 Claim 'A Gold Standard in Prostate Cancer Therapy'

This claim appeared as the heading on the back cover of the detail aid.

COMPLAINT

Zeneca stated that it was widely accepted that the gold standard for treatment of advanced prostate cancer was medical or surgical castration. This was

reflected in the Cyprostat SPC which indicated Cyprostat for long-term palliative treatment where LHRH analogues (which produced medical castration) or surgical castration were contraindicated or not tolerated. Furthermore, because of serious hepatic toxicity, the Committee on Safety of Medicines (CSM) had recommended that the use of cyproterone acetate was restricted to:

(i) short courses to cover the testosterone flare associated with LHRH agonists

(ii) treatment of hot flushes after orchidectomy or LHRH agonists.

(iii) patients who had not responded to, or were intolerant of other treatments.

(ref Current Problems in Pharmacovigilance, Volume 21, February 1995)

Zeneca, therefore, alleged that to claim Cyprostat to be a 'gold standard' in the treatment of prostate cancer was an exaggerated claim in breach of Clause 7.8.

RESPONSE

Schering Health Care stated that Cyprostat was the highest selling and longest established of the antiandrogens. The wording on the Cyprostat SPC was agreed by the CSM and the Medicines Control Agency following their review into possible hepatotoxicity. Since then cyproterone acetate had maintained its position as market leader within this therapeutic group. It was therefore reasonable to refer to it as 'a' gold standard in the treatment of prostatic cancer.

PANEL RULING

The Panel noted that prior to 1995, when the CSM had issued its advice regarding the use of cyproterone acetate in prostatic cancer, the licensed indication for Cyprostat had been 'Palliative treatment of prostatic carcinoma' (ref ABPI Data Sheet Compendium 1993-94). It appeared that the original, broad indication in prostate cancer had been qualified in line with the CSM advice.

With regard to the management of prostate cancer the Panel noted that the standard treatment for metastatic disease was bilateral subcapsular orchidectomy. Alternatively a gonadorelin analogue might be given (ref BNF 37 March 1999).

The Panel considered that the claim 'A Gold Standard in Prostate Cancer Therapy' was a broad claim. Cyprostat might be a gold standard treatment where LHRH analogues or surgery were contraindicated, not tolerated, or where oral therapy was preferred but this was not what the claim stated. The Panel considered that the claim was exaggerated and ruled a breach of Clause 7.8 of the Code.

3 Reference to unlicensed doses

Three sections of the detail aid, efficacy, tolerability and quality of life, quoted data relating to the use of bicalutamide 150mg daily as monotherapy.

COMPLAINT

Zeneca stated that its product Casodex (bicalutamide) was licensed at a dosage of 50mg for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration. The detail aid directly compared Cyprostat with bicalutamide but did so using bicalutamide in an unlicensed indication at an unlicensed dosage. Cyprostat was compared with bicalutamide used as monotherapy in the treatment of prostate cancer. Furthermore, the comparison was made using bicalutamide at a dosage of 150mg daily whereas the licensed dosage was 50mg daily.

Zeneca regarded a comparison with its product in an unlicensed indication or an unlicensed dosage to be unfair and the claims derived from that comparison with regard to efficacy and tolerability to be grossly misleading. Zeneca alleged a breach of Clause 7.2.

RESPONSE

Schering Health Care stated that the Code placed a clear requirement on companies to promote their own products in concordance with the relevant SPC. It also demanded that all claims were accurate, fair and capable of substantiation and based on an up-to-date evaluation of all the evidence. It did not require competitor products to be discussed only in line with their SPCs, providing the former conditions were also met. This was a particular issue in oncology, where many products were widely used by clinicians in indications, or at dosages, for which they had no product licence. It would severely limit the information available to such prescribers if companies were unable to provide fair and accurate comparative data between all available clinical options. Schering Health Care noted that Zeneca did not allege that the data presented were either inaccurate or unfair. Bicalutamide was used as monotherapy at a dose of 150mg daily and Zeneca had sponsored trials with this dose which had been published with prominent use of the Casodex trade name. Indeed, Zeneca sponsored a satellite symposium at the 1998 European Association of Urology Congress at which the use of bicalutamide 150mg monotherapy featured prominently.

Schering Health Care added that the detail aid was produced to enable its representatives to handle the increasing number of questions on bicalutamide monotherapy and its comparison with cyproterone acetate. Bicalutamide trial results had been widely publicised (in journals and at scientific meetings). The piece was used only when prompted by a question from the clinician since it would not be in Schering Health Care's interest to generally raise awareness of bicalutamide monotherapy with its customers.

PANEL RULING

The Panel noted Schering Health Care's views about references to competitor products in promotional material and whether such material needed to comply with Clause 3 of the Code, ie not be inconsistent with the SPC. The Panel considered that this was a difficult matter. Clause 3 of the Code was clear that the promotion of a medicine must be in accordance

with the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not be promoting the competitor medicine and therefore the Panel considered that Clause 3 would not apply. Clause 7.2 of the Code required that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect the evidence clearly. They must not mislead either directly or by implication. The Panel questioned whether comparing products using only unlicensed doses and/or indications of a competitor product met the requirements of Clause 7.2. Readers might be misled as to the approved use of competitor products and the company with the competitor product could not counter the arguments as it would be open to accusations of promoting an unlicensed indication and/or dose.

Turning to the case before it the Panel noted that the detail aid referred to Zeneca's product bicalutamide at an unlicensed dose (150mg/day) and as monotherapy whereas the SPC stated that the dose was 50mg/day in combination with LHRH analogue therapy or surgical castration. Readers were not told that the dosage regimen discussed was unlicensed. There was no mention of the licensed dose and indication for bicalutamide nor of the efficacy results for the licensed use of the product. The efficacy section also referred to the cessation of bicalutamide treatment on the advice of the safety committee. The Panel considered that the sections in question were unfair and misleading as the data presented had not been put in the context of the Casodex SPC. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **20 May 1999**

Case completed **22 July 1999**

CASE AUTH/880/5/99

GLAXO WELLCOME v ASTRAZENECA

Zomig advertisements

Glaxo Wellcome alleged that the claim 'Time's up for migraine' used in the promotion of Zomig (zolmitriptan) by AstraZeneca was an exaggerated and all-embracing claim which could not be substantiated.

The claim appeared as the only claim in an abbreviated advertisement. It also appeared in a full advertisement as the final claim. The full advertisement referred to the patient responding to Zomig and that the product worked quickly.

The Panel considered that the claim in the abbreviated advertisement could be read as Zomig prevented migraine in all patients. It was ruled to be an exaggerated claim in breach of the Code. The full advertisement provided further information and linked the claim to speed of onset of action and no breach of the Code was ruled.

COMPLAINT

Glaxo Wellcome UK Limited complained about the current promotion for Zomig (zolmitriptan) by AstraZeneca. Glaxo Wellcome alleged that the claim 'Time's up for migraine' was an exaggerated and all-embracing claim which could not be substantiated. A breach of Clause 7.8 of the Code was alleged. Glaxo Wellcome referred to abbreviated advertisements that appeared in Pulse, 6 March 1999.

Both of the abbreviated advertisements referred to by Glaxo Wellcome were headed with the claim 'Time's up for migraine'. One advertisement included a visual of part of a woman's face with a watch face set in the eye socket.

Glaxo Wellcome stated that the claim 'Time's up for migraine' implied that a cure had been found for migraine with the launch of zolmitriptan. This was clearly not so. Zolmitriptan, in common with the other available 5-HT1 agonists, provided acute relief of migraine headache. There was no evidence that it acted prophylactically to prevent migraines from occurring, and it was not licensed for use in this way.

In addition, the claim implied that the arrival of zolmitriptan had brought something new to the treatment of migraine which could abolish migraine, unlike other available treatments. However this was not so. Highly effective migraine treatments were available prior to the launch of zolmitriptan and indeed zolmitriptan did not appear to offer any benefit over Imigran (sumatriptan), which had been available since 1991.

RESPONSE

AstraZeneca explained that the theme 'Time's up for migraine' had been used since March 1998. Both full and abbreviated advertisements on this theme had appeared in the more popular medical journals and publications every week since that date. It was, therefore, surprised to receive a request from Glaxo Wellcome to support the statement 'Time's up for migraine'. This issue plus other matters had been discussed between the companies. Both parties reached an agreement on the various points at issue and that neither party would be taking further action. AstraZeneca was, therefore, very surprised that Glaxo Wellcome should now raise this matter as a formal complaint and state that it had been unable to resolve the matter with AstraZeneca.

As had previously been stated to Glaxo Wellcome in relation to the advertisement which appeared in the February edition of Pulse, 'Time's up for migraine' was not a stand alone claim for Zomig *per se*. The whole theme of the advertisement revolved around

the speed of onset of activity of Zomig. The advertisement had three elements relating to time, namely 'An hour ago a phone call would have split her skull', the watch face set in the model's eye and 'Time's up for migraine'. These elements were placed around the central text which contained the specific claim for Zomig '…Zomig acts quickly …'. The claim was referenced to the Zomig summary of product characteristics (SPC) and the relevant section of the SPC was quoted, namely 'In those patients who respond, significant efficacy is apparent within 1 hour of dosing'. 'Time's up for migraine' was not a specific claim for Zomig. It was a general conceptual statement of the type often seen in advertisements – somewhat akin to 'An MDI for today' and 'A good friend that the family values' which Glaxo Wellcome currently used in its Ventolin and Flixotide journal advertisements.

AstraZeneca pointed out that the advertisement which Glaxo Wellcome now used as the basis of its complaint was a different advertisement which appeared in the March edition of Pulse. It was unfortunate that Glaxo Wellcome had chosen not to raise its concern over this advertisement with AstraZeneca before taking the matter to the Authority.

The company noted that Glaxo Wellcome alleged that 'Time's up for migraine' implied that a cure had been found for migraine and that Zomig abolished migraine unlike other available treatments.

AstraZeneca did not believe that any such inference would be drawn and it would appear that Glaxo Wellcome was attempting to construe a meaning from the phrase that simply did not exist. It did not believe that readers would take 'Time's up for migraine' to mean that Zomig abolished migraine. In a similar vein, it was interested to note that Glaxo Wellcome had used the phrase 'say goodnight to asthma' in a Serevent advertisement. AstraZeneca assumed that Glaxo Wellcome did not intend this to mean that Serevent abolished night time asthma in children which, of course, it did not.

PANEL RULING

The Panel noted that Glaxo Wellcome complained about the current promotion of Zomig which included the claim 'Time's up for migraine' and had also referred to its appearance in an abbreviated advertisement as an example.

The Panel did not accept the submission that the claim 'Time's up for migraine' was not a claim for Zomig per se. In the abbreviated advertisement it was the only claim and would be seen as the indication for use as required in such advertising by Clause 5.4 of the Code. In the full advertisement the context was different to the abbreviated advertisement. The full advertisement stated that the patient responded to Zomig and that the product worked quickly with the claim 'Time's up for migraine' appearing at the bottom of the advertisement as the final claim.

The Panel noted the statement in the SPC that in those patients who responded to Zomig significant efficacy was apparent within 1 hour of dosing.

In the Panel's view it was difficult to judge how the intended audience would read the claim. The phrase 'Time's up' would usually be interpreted as something was finished, over or at an end. Context was a relevant factor. The claim when used without further qualification or explanation was a strong claim. The full advertisement provided further information and this, in the Panel's view, linked the claim to speed of onset of action. Overall the Panel considered that the claim in the abbreviated advertisement could be read as Zomig prevented migraine in all patients. The Panel considered that the claim was an exaggerated claim and therefore ruled a breach of Clause 7.8 of the Code. The Panel did not consider that its use in the full advertisement was unacceptable and no breach of Clause 7.8 of the Code was ruled.

Complaint received **24 May 1999**

Case completed **28 July 1999**

HEALTH AUTHORITY PRIMARY CARE MEDICAL ADVISER v SANOFI WINTHROP and BRISTOL-MYERS SQUIBB

Payment for meeting

A health authority primary care medical adviser complained about a letter which he had received from a senior product manager which was on paper headed Sanofi and Bristol-Myers Squibb with a reference to an agreement between the companies for the co-development and marketing of clopidogrel and irbesartan, two compounds from Sanofi Research. The letter asked if the writer could meet with the complainant to discuss changes in the NHS which would impact on patient care, including the development of PCG-based formularies. The letter offered an honorarium of £100 and the complainant took great exception to the health authority or its employees being offered a financial reward for taking part in business discussions.

The Panel noted that the companies were trying to establish an advisory panel which they could consult with regard to recent changes in the NHS. There was no mention of this in the letter to the complainant. The Panel considered that it was not unacceptable *per se* to establish an advisory panel with a limited number of members to advise the companies on specific issues. The Panel fully understood the concerns of the complainant, however, as the letter appeared to be asking for a meeting that would be a promotional meeting to talk about products as well as other issues.

The Panel considered that the nature of the meeting was not unacceptable; the companies were in effect intending to employ the health professional to act as a consultant. The Panel considered, however, that the failure to make the purpose of the meeting clear to the recipient of the letter meant that the impression was given that a payment was to be made for what appeared to be a promotional meeting. The Panel considered that this meant that the companies had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled.

COMPLAINT

A health authority primary care medical adviser complained about a letter from a senior product manager written on paper headed Sanofi and Bristol-Myers Squibb which referred to an agreement between the companies for the co-development and marketing of clopidogrel and irbesartan, two compounds from Sanofi Research. The letter was addressed to the complainant and asked if the senior product manager could meet the complainant to discuss key changes being implemented in the NHS and in particular those which affected him as a medical adviser. The letter explained that Sanofi/Bristol-Myers Squibb was working closely with doctors and pharmacists within primary care groups (PCGs) and hospitals to ensure that the development of communications programmes for products in different disease areas was appropriate and relevant. The senior product manager asked if the complainant could spare about an hour to talk to her and one of her colleagues about the issues arising from the current changes, which the complainant considered would impact on patient care. Views about the development of PCG-based formularies, and new trends in the management of patients across the primary/secondary care interface were of interest. The letter offered an honorarium of £100.

The complainant took great exception to either the health authority or its employees being offered a financial reward for taking part in business discussions. A breach of Clause 15.3 of the Code was alleged.

RESPONSE

Sanofi Winthrop Limited and Bristol-Myers Squibb Pharmaceuticals Limited submitted a joint response. They firstly apologised for any distress caused to the complainant by the letter. However, they submitted that the letter had been unfortunately misconstrued. It was quite clear that no specific product was to be discussed at the proposed meeting. On the contrary, the sole aim was to discuss the issues arising from the current changes in the NHS, which would impact on patient care. In particular, the areas of PCG-based formularies and the primary/secondary care interface were highlighted as being of relevance. The motive for arranging this meeting was to form an advisory panel that the companies could consult, and which could advise on the recent changes in the NHS. A copy of a briefing document developed by the companies' communications agency, outlining the proposed format of the meeting, was provided. It was not intended to discuss individual products for the purpose of promotion. The companies, however, were aware that the current NHS changes would impact dramatically on the environment in which the pharmaceutical industry operated, and wished to ensure that advice was received from appropriate personnel within the NHS on these changes.

The companies referred to the definition of a 'representative' given in Clause 1.6 of the Code as being 'a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines'. The promotion of a product was not the aim of the suggested meeting, and was not in any way implied by the letter. Although the letter was signed by a senior product manger, in so far as she was responsible for following PCG-based changes, the product for which she was responsible was specifically omitted, so as not to mislead or infer that a specific product was to be discussed. The other company member was not determined at the time the letter was sent.

The letterhead referred to two products, clopidogrel and irbesartan. It was important to note that those were not the trade names. The names and addresses of both Sanofi and Bristol-Myers Squibb were given because of legal requirements for European Union (EU) -wide partnerships. It was required under English law (Partnership Act, 1980) to give the business name and address of either all, or no partners of a partnership. In addition, under EU law, any companies forming joint ventures throughout Europe require a European Commission (EC) approval. Thus an application was submitted in 1998 to the EC to form a joint venture between Sanofi and Bristol-Myers Squibb solely for the purpose of an agreement for co-development and marketing, in its widest sense, of the two products in question in Europe. In the UK, a partnership was formed. The EC gave its approval for this specific purpose. The letterhead, therefore, served clear notification of the purpose of the partnership and reflected the limited approval given by the EC in respect of the molecules cited. Copies of Halsbury's laws and the public EC approval notice were provided.

The purpose of the meeting was not sales promotion. As far as Clause 15.3 was concerned, therefore, firstly, the senior product manager was not fulfilling the Code's definition of a 'representative', in so far as the meeting was not intended to be related to the promotion of medicines. Secondly, the supplementary information to Clause 15.3 stated that '… any financial inducement for the purpose of sales promotion' was prohibited but since the purpose of the meeting was not sales promotion, the companies did not believe that they were in breach of this clause. Equally, Clause 18.1 covered 'inducement to prescribe, supply, administer or buy any medicine' and was therefore not relevant, as the purpose was clearly not to discuss a specific product but more general NHS issues. Partnership letterhead was used as Sanofi and Bristol-Myers Squibb shared some staff resources to address industry-wide changes such as those occurring currently within the NHS.

Finally, the letter was a business communication from one professional to another requesting the recipient's views and offering a reasonable fee – in line with BMA recommendations for fees for professional services – for the recipient's time. Therefore, high standards were maintained and Clause 9.1 had not been breached.

Overall, this activity was not intended to relate to promotion and did not refer to promotion, and in light of this and the above there was, by definition, no breach of Clause 2.

The companies stated that seven people, from different parts of the country, had been contacted regarding the meetings under discussion. All but one had been visited. As a result of the meetings the companies would develop an advisory panel that it could consult with twice a year. The meetings were therefore one-off meetings which would not be repeated.

PANEL RULING

The Panel noted a previous case, Case AUTH/686/3/98, where it had been established that in principle it was acceptable for companies to pay healthcare professionals and others for advice as to how their products should be promoted. There was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. The case, however, had been ruled in breach of the Code as the Panel considered that ten focus group meetings, to which a relatively large number of doctors had been invited on a first come first served basis, constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The ruling was upheld on appeal by the respondent.

Turning to the case now before it, the Panel noted Sanofi and Bristol-Myers Squibb's submission that the companies were trying to establish an advisory panel that they could consult with regard to recent changes in the NHS. There was no mention of this in the letter to the complainant. The Panel considered that it was not unacceptable *per se* to establish an advisory panel with a limited number of members who could advise the companies on specific issues. The Panel fully understood the concerns of the complainant, however, as it appeared that the letter was asking for a meeting that would be a promotional meeting to talk about products as well as other issues. In this regard the Panel noted that the names of products were given on the letterhead.

The Panel considered that given the extra information supplied by the companies, the nature of the meeting was not unacceptable; the companies were in effect intending to employ the health professional to act as a consultant to them. The Panel ruled no breach of Clauses 15.3 and 18.1 of the Code. The Panel considered, however, that the failure to make the purpose of the meeting clear to the recipient of the letter meant that the impression was given that a payment was to be made for what appeared to be a promotional meeting. The Panel considered that this meant that the companies had failed to maintain a high standard of ethical conduct and a breach of Clause 9.1 of the Code was ruled.

Complaint received **1 June 1999**

Case completed **12 August 1999**

CASE AUTH/883/6/99

GENERAL PRACTITIONER v SCHERING-PLOUGH

Nasonex detail aid

A general practitioner complained about a detail aid for Nasonex (mometasone) issued by Schering-Plough.

The complainant took exception to claims regarding the safety profile of Nasonex and alleged that the claim 'The absolute bioavailability of intranasally administered Nasonex is negligible and has been estimated at ≤0.1% with studies showing a complete absence of systemic effects' was very misleading. This was contrary to the prescribing information for all intranasal steroids. The Panel accepted that the bioavailability of mometasone was low and that in studies no systemic effects had been attributed to Nasonex. Nevertheless Nasonex was a corticosteroid and the BNF referred to certain precautions regarding side-effects of systemic corticosteroids and stated that systemic absorption might follow nasal administration particularly if high doses were used or treatment was prolonged. The Panel did not consider that the claim was acceptable and a breach of the Code was ruled.

The complainant stated that the cost of treatment exceeded 18 pence per day which was in contrast to a claim in the detail aid that the product cost less than 17 pence per day. The Panel noted that the usual recommended dose cost 32.6 pence per day. The cost in the detail aid was linked by an asterisk to the cost of the maintenance dose. The Panel was concerned that readers would assume that the cost referred to the usual recommended dose and not the dose that might be effective for maintenance therapy. The Panel ruled that the cost calculation was misleading in breach of the Code.

A general practitioner complained about a detail aid for Nasonex (mometasone furoate) issued by Schering-Plough Ltd (ref NSX/99-168). The complainant had seen the detail aid at a medical symposium and stated that the complaint in no way reflected any contact with Schering-Plough medical representatives. The origin of the misleading statements stemmed from the company, and the representatives were somewhat handicapped by this seemingly inaccurate information which it produced. However, behaviour of this sort might undermine a prescriber's confidence in the reliability of information provided by pharmaceutical companies.

1 Page headed 'The blessing of reassurance'

Beneath the page heading there were two bullet points 'Nasal steroids with different levels of bioavailability can promote differing systemic effects and growth rate retardation' and that 'About 80% of an intranasal dose is swallowed and thus available for GI uptake'. The bullet points were followed by a table comparing the percentage oral bioavailability of Nasonex with fluticasone, budesonide, beclomethasone and triamcinolone. Nasonex had the lowest percentage oral bioavailability.

A final bullet point beneath the table read 'The absolute bioavailability of intranasally administered Nasonex is negligible and has been estimated at ≤0.1%, with studies showing a complete absence of systemic effects'.

COMPLAINT

The complainant took exception to claims regarding the safety profile of Nasonex. The complainant alleged that the claim '… complete absence of systemic effects' was very misleading. As far as the complainant was aware, this was contrary to prescribing information for all intranasal steroids ie as a prescriber one must be aware of such effects.

RESPONSE

Schering-Plough submitted that the claim was fully in line with the summary of product characteristics (SPC). For example, under 'Undesirable Effects' a list of local adverse events was reported, namely: headache, epistaxis, pharyngitis, nasal burning, nasal irritation and nasal ulceration. The statement was made: 'The incidence of all other effects was comparable to that of placebo'. Schering-Plough submitted that it might therefore be assumed that the incidence of systemic side effects was equivalent to placebo.

Under 'Special Warnings and Precautions for Use' the statement was made: 'There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with Nasonex aqueous nasal spray.'

In the section entitled 'Pharmacokinetic Properties' there was another supportive statement. The first sentence of this section stated: 'Mometasone furoate, administered as an aqueous nasal spray has negligible (≤0.1%) systemic bioavailability and is generally undetectable in plasma, despite the use of a sensitive assay with a lower quantitation limit of 50pg/ml; thus there are no relevant pharmacokinetic data for this dosage form'.

Similarly, under 'Pregnancy and Lactation' the statement was made: 'Following intranasal administration of the maximal recommended clinical dose, mometasone plasma concentrations are not measurable'.

Finally the company referred to the section entitled 'Overdose'. This stated: 'Because of the negligible (≤0.1%) systemic bioavailability of Nasonex, overdose is unlikely to require any therapy other than observation'.

Schering-Plough submitted that all these statements confirmed the accuracy of the claim that 'The absolute bioavailability of intranasally administered Nasonex is negligible and has been estimated at ≤0.1% with studies showing a complete absence of systemic effects'.

PANEL RULING

The Panel noted that Clause 7.7 of the Code stated that claims about side effects must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product had no side-effects, toxic hazards or risks of addiction.

The Panel considered that the claim '… studies showing a complete absence of systemic effects' gave the impression that it had been shown that there were not, and never would be, any systemic side-effects attributable to Nasonex. The Panel did not accept Schering-Plough's assumption that, as the SPC listed local adverse effects and stated that the incidence of other effects was comparable to placebo, this necessarily included systemic effects.

The Panel accepted that the bioavailability of mometasone was low and that in studies to date no systemic effects had been attributed to Nasonex. Nevertheless, Nasonex was a corticosteroid and the BNF referred to certain precautions regarding side-effects of systemic corticosteroids and stated that systemic absorption might follow nasal administration particularly if high doses were used or treatment was prolonged.

The Panel did not consider that the claim '… studies showing a complete absence of systemic effects' was acceptable given that the Code prohibited the use of statements such as 'no side-effects'. A breach of Clause 7.7 was ruled.

2 Page headed 'Nasonex – a real blessing for continuous or periodic relief'

The page listed six properties of Nasonex nasal spray such as time to onset of action, duration of action, indications etc. The final claim read '140 metered sprays, costing less than 17 pence per day'.

COMPLAINT

The complainant alleged that a simple calculation for two months, 62 days' treatment, showed that the cost exceeded 18 pence per day. The calculation was based on MIMS. This was in stark contrast to the claim that the product cost less than 17 pence per day. The complainant stated that this point might seem trivial, however he was currently investigating issues around what the GP believed the cost to be (usually with the help of the medical representative) and the actual cost to the Government.

RESPONSE

Schering-Plough stated that the claim '140 metered sprays, costing less than 17 pence per day*', was followed by an asterisk which was linked to the statement 'maintenance dose'.

The company explained how they arrived at this calculation. The NHS price of Nasonex was £11.43. There were 140 individual doses in each container. Therefore each individual dose would cost £11.43/140 or 8.16 pence per dose. With a general maintenance dose of one spray in each nostril a day, a total maintenance daily dose of two sprays, the cost per day would be 16.3 pence per day.

Schering-Plough submitted that most individuals would start by using Nasonex at two sprays per day in each nostril for 10 or more days and then move to a maintenance dose of one spray in each nostril a day. For the 50 or less days on maintenance the cost will be 16.3 pence per day, therefore less than 17 pence per day.

Schering-Plough was pleased that the doctor's concerns did not reflect any contact with Schering-Plough medical representatives. The company regretted any impression given that Schering-Plough had any intention of producing 'misleading statements' or 'inaccurate information'. It certainly hoped to maintain prescribers' confidence in the reliability of information provided by pharmaceutical companies.

PANEL RULING

The Panel noted that the usual recommended dose of Nasonex given in the SPC was two sprays in each nostril once daily. Once symptoms were controlled dose reduction to one spray in each nostril might be effective for maintenance. From the size and cost of a Nasonex nasal spray the Panel calculated that the usual recommended dose cost 32.6 pence per day.

The Panel noted that the claim that the daily cost of Nasonex was less than 17 pence per day appeared immediately beneath the statement '2 simple sprays of 50mcg to each nostril, once daily'. The Panel was concerned that readers would assume that the stated cost referred to the usual recommended dose and not the dose which might be effective for maintenance therapy.

The Panel was concerned about calculating the cost on the maintenance dose given that the SPC stated that the lower dose might be effective for maintenance.

The Panel considered that the cost calculation was misleading and a breach of Clause 7.2 of the Code was ruled.

Complaint received **10 June 1999**

Case completed **4 August 1999**

PHARMACIA & UPJOHN v MERCK SHARP & DOHME

Cosopt detail aid

Pharmacia & Upjohn complained about a Cosopt detail aid issued by Merck Sharp & Dohme.

Pharmacia & Upjohn alleged that the claim '43% more IOP [intraocular pressure] – lowering than timolol' was inaccurately referenced to data on file as a paper by Boyle had been supplied by Merck Sharp & Dohme in response to a request for the reference. It was alleged that the extrapolation of the results in the Boyle paper to give the figure 43% was misleading and exaggerated. It was not a calculation that accorded with the statistical analysis presented in the paper. The claim related to peak effect although this was not stated. The Panel ruled no breach with regard to the referencing of the claim. It was not one that required referencing. With regard to the claim itself the Panel noted that the paper expressed the same results in a different way to the detail aid. The data on file was supplied to explain the calculation. The Panel did not consider that the claim was either misleading or exaggerated. No breach of the Code was ruled.

Pharmacia & Upjohn alleged that the claim 'Power of two ease of one' was misleading as it implied that Cosopt had double the efficacy of each of its components used singly. This was not accepted by the Panel. The claim only appeared in conjunction with the product logo which included details of the two active ingredients. No breach of the Code was ruled.

Pharmacia & Upjohn alleged that the claim 'A tolerability profile you can trust' was in breach as it implied that Cosopt had some special merit or quality in terms of safety. This could not be substantiated using current data on the products used singly. The Panel noted that the claim was immediately followed by two prominent statements justifying the claim. Further the Cosopt summary of product characteristics stated that in clinical studies no adverse experiences specific to Cosopt had been observed. No breach of the Code was ruled.

Pharmacia & Upjohn Limited complained about a Cosopt detail aid (ref 09-99 CST.98.GB (W6009) 55008.DA 3.5c.HO.998) issued by Merck Sharp & Dohme Limited. Cosopt was a fixed combination eye drop containing dorzolamide (a carbonic anhydrase inhibitor) and timolol (a beta-blocker) indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when beta-blocker monotherapy was not sufficient. In response to a previous complaint about the same detail aid (Case AUTH/831/1/99) Merck Sharp & Dohme had explained that it was used by representatives when discussing Cosopt with ophthalmology specialists.

Claim '43% more IOP-lowering than timolol'.

This claim appeared on the front cover of the detail aid referenced to Data on file, Merck Sharp & Dohme Limited.

COMPLAINT

Pharmacia & Upjohn stated that on requesting the supporting reference for the claim, a paper (Boyle *et al* (1998)) was supplied. Pharmacia & Upjohn stated that although the detail aid was thus inaccurately referenced, in breach of Clause 7.5 of the Code, it was on the paper supplied that it based its complaint.

Pharmacia & Upjohn stated that it was clear from Boyle *et al* that the extrapolated '43% more IOP-lowering than timolol' was not a calculation that accorded with the statistical analysis presented in the paper, but was a simple mathematical calculation based on the absolute values of lowered IOP (mmHg). This completely ignored the statistical method of calculation presented in the paper in which the drop in IOP of each component was expressed as a percentage of the original baseline value and then the percentage values were compared. A table of data in the paper gave the 'estimated differences between treatments in mean percent change in IOP from baseline', and the percentage point difference between Cosopt and timolol at month 3 hour 2 (peak) was, according to the authors' calculation, given as –9.9%, not 43%. Pharmacia & Upjohn alleged, therefore, that as this claim stood it was misleading and was in breach of Clauses 7.2 and 7.8 of the Code.

Pharmacia & Upjohn stated that Merck Sharp & Dohme, in intercompany correspondence, had accepted that the claim on the front cover represented peak data but had contended that this was not misleading as peak effect was mentioned on page 4 of the detail aid. Pharmacia & Upjohn did not accept this contention for the following reasons:

- The 43% quoted was inaccurate for the reasons given above.
- On the graph on page 4 of the detail aid there was only one mention of peak effect – bracketed – in the heading on the graph, and nothing to relate this graph to the disputed statement made on the front cover. Furthermore, on the lower half of the page the 43% claim was reiterated, again making no reference to the fact that this was peak effect, in a layout that was much more apparent than the bracketed 'peak effect' in the heading of the graph.
- The use of a detail aid by representatives varied widely and was dependent on many factors, not the least of which was the call time. It was naïve to think that in all cases a representative would be afforded the time to take the doctor through a full detail, drawing attention to the graph on page 4 and explaining the claim on the cover in relation to it. On a practical level the front cover might be all the customer saw in many cases and therefore the claim should not mislead either directly or by implication.

RESPONSE

Merck Sharp & Dohme stated that the reference to data on file was correct at the date of publication of the detail aid. Clearly at the time of renewing the material it would be appropriate to add full references. However, providing the material remained an up-to-date evaluation of all the evidence the company considered that it remained appropriate for references to remain as data on file and to be updated in the normal course of the renewal procedure. Merck Sharp & Dohme did not accept that a breach of Clause 7.5 had occurred.

Merck Sharp & Dohme noted that it had been suggested that it had inaccurately referenced the statement '43% more IOP-lowering than timolol' to date on file, which the company also disputed. In a letter to Pharmacia & Upjohn the relevant data on file to support the figure 43% was supplied. Additional information in the form of the paper by Boyle *et al* from the peer reviewed journal Ophthalmology was also included. Merck Sharp & Dohme stated that in its view it would have been inappropriate not to have included the published work relating to the data on file. As Pharmacia & Upjohn had acknowledged, the Boyle paper did not quote the actual figure 43%, which was the precise reason why the data on file was provided in order to demonstrate the data from which the figure of 43% was derived. Merck Sharp & Dohme noted that despite the fact that it had referenced the claim to data on file and provided the data on file to support the claim, Pharmacia & Upjohn had disregarded this and based its complaint on the paper by Boyle *et al*. On this basis Merck Sharp & Dohme did not consider that there was any basis on which to claim a breach of Clause 7.5.

Merck Sharp & Dohme stated that it had acknowledged that the data presented were the peak data results. The company considered that this was straightforward data, on a common condition in ophthalmology, which was being presented to an informed audience which had plenty of experience in measuring IOP and would have a good understanding of peak and trough IOP levels. The data presented on the front cover was a summary of the detail presented on page 4. In the heading of the graph at the top of page 4 it was clearly stated that results reflected peak effect data. Once this point had been established the company did not consider that it needed to continue to state this fact. In addition to this, the total mean reduction in IOP from baseline (33%) for Cosopt was presented with equal prominence. Merck Sharp & Dohme did not consider that there could be any confusion over the data presented.

Merck Sharp & Dohme noted that it was also suggested that the 43% quoted on the above pages was an extrapolated comparison of the peak effect. This was incorrect. The 43% represented the additional relative reduction in IOP (at peak) for patients treated with Cosopt compared with those receiving timolol. At month three, two hours after dosing, the IOP reduction from baseline for patients treated with timolol was 6.3mmHg with an additional 2.7mmHg achieved by patients treated with Cosopt: these absolute changes in mean IOP were presented in the graph. By convention the difference between treatments could be expressed in either absolute terms, ie 2.7mmHg or in terms of relative reduction ie 43% [(2.7 ÷ 6.3) x 100].

Merck Sharp & Dohme stated that as outlined in its response above, '43% more IOP-lowering than timolol' was referenced to data on file not the Boyle paper and this data on file had been supplied to Pharmacia & Upjohn to support this result. The company therefore did not consider there was a basis for complaint.

Merck Sharp & Dohme noted that the two companies still appeared to be contesting the issue of how the claim '43% more IOP-lowering that timolol' was referenced. Importantly the claim itself was accurate and, as stated previously, data on file was provided to Pharmacia & Upjohn to support the claim. Whether the statistical analysis presented in the paper actually presented this figure was irrelevant. It would seem that the legitimacy of the claim had been called into question on the basis that the data from the paper was at odds with the data on file supplied. The fundamental principle of the study was to compare the efficacy of the treatments and the statistical analysis in the paper evaluated the differences in IOP achieved for Cosopt compared with the monotherapy groups (timolol and dorzolamide). As outlined previously, the comparison between treatments could be expressed in two equally useful ways either in absolute figures or as a percentage of the difference. Merck Sharp & Dohme noted that it had chosen the latter as the main comparison, but with absolute figures given in mmHg as well. As further clarification, the reference to –9.9% related to the absolute percentage point difference ie –32.7% –22.6%, not the relative additional IOP reduction achieved with Cosopt expressed as a percent of the total IOP achieved with timolol (which the authors had not calculated in the paper). Presentation of data in this way as relative risk reduction was commonly used to compare treatments. Thus the company could show that the data on file were completely compatible with data from the paper.

With regard to the data presented being that of peak effect, Merck Sharp & Dohme noted that peak effect had been clearly stated at the top of page 4 and was more than just mentioned as had been suggested. The company considered 43% to be an accurate reflection of the data on file and a true and balanced representation of the effect of Cosopt compared with timolol as discussed previously.

Merck Sharp & Dohme noted the allegation that there was only one mention of peak effect on page 4 and that this was not related to the front cover. The company stated that peak effect had been clearly stated at the top of page 4 in association with the graph. The company considered that the audience to which the detail aid was presented understood that the data represented peak effect without having to continually repeat this fact. The arrows at the bottom of page 4 were clearly summaries of the data presented in the graph. 43% more IOP lowering was juxtaposed with the 33% reduction [in IOP] from baseline. Merck Sharp & Dohme did not consider that physicians could fail to appreciate that '43% more

IOP-lowering than timolol' as stated on the front cover related to the identical wording in the graph on page 4 that stated '43% more IOP-lowering than timolol' and the summary arrow at the bottom of the page that stated '43% more IOP-lowering than timolol'. It could not be clearer that '43% more IOP-lowering than timolol' on the front cover was related to the data on page 4.

With regard to a representative's time with a doctor, Merck Sharp & Dohme agreed that a physician might not be taken through the whole detail aid. Ophthalmologists treated glaucoma every day and were only too familiar with peak and trough data. Merck Sharp & Dohme said that it was not delivering a complicated message, Cosopt offered 43% more IOP-lowering than timolol and to the audience in question the company did not consider that the front cover could be construed to be misleading.

Merck Sharp & Dohme noted that the claim was also referenced on front cover.

PANEL RULING

The Panel noted that Clause 7.5 of the Code stated that when promotional material referred to published studies clear references must be given. The Panel considered that Clause 7.5 meant that if promotional material used the phrase 'in a published study' or similar, then references needed to be given. The Panel further considered that if promotional material referred to the author or authors of published studies by name, then this amounted to referring to a published study and references should be given. The Panel noted that the claim '43% more IOP-lowering than timolol' only referred to results from a study but gave no further detail of the study itself. The Panel decided that in the circumstances there was no need to give a reference and ruled no breach of Clause 7.5 of the Code.

The claim had been referenced to data on file. The Panel noted Merck Sharp & Dohme's submission that the Boyle data did not quote the actual figure 43% and the data on file was supplied to demonstrate how the figure of 43% was derived from the Boyle study. The Boyle study had also been supplied. In the Panel's view it would have been helpful if the detail aid had referred to both the published study and the data on file. This might not have been possible at the time the piece was produced. The detail aid was dated October 1998 and the Boyle study was not published until October 1998.

The Panel considered that the claim '43% more IOP-lowering than timolol' would be read in absolute terms and convey to most readers that if timolol lowered IOP by xmmHg, Cosopt lowered it by almost half as much again. Figures quoted in the Boyle paper showed that peak IOP reduction from baseline for timolol monotherapy was 6.3mmHg while that for Cosopt was 9mmHg – a difference of 43% in absolute terms. The Panel considered that whilst Boyle *et al* expressed the same results in a different way, the way the results had been expressed in the detail aid was not misleading. The figures were in the paper to allow the reader to make the same calculation and, in addition, the alternative way of expressing the Boyle data had been explained by Merck Sharp & Dohme in a letter to Pharmacia & Upjohn. The Panel did not consider that claim was either misleading or exaggerated. No breach of Clauses 7.2 and 7.8 was ruled.

The Panel noted that the claim related to the peak effect of both Cosopt and timolol. Pages 4 and 5 gave more details of the study and graphs depicting peak effects of the two medicines were labelled as such. The Panel did not accept the submission that because page 4 referred to the peak effects the intended audience would appreciate that the front page referred to peak effects. The Panel noted, however, that only peak effects of both medicines were discussed in the detail aid. The Panel did not consider that readers would be misled by the presentation of the data on the front page and ruled no breach of Clause 7.2 in that regard.

Strapline 'Power of two ease of one'

This strapline appeared throughout the detail aid beneath each product logo.

COMPLAINT

Pharmacia & Upjohn stated that this strapline implied that Cosopt had double the efficacy of each of its components used singly. This was not borne out by the available data and as such the strapline was misleading in breach of Clause 7.2.

RESPONSE

Merck Sharp & Dohme noted that ophthalmologists already widely prescribed timolol and dorzolamide both as monotherapy and in combination. In addition, they had considerable experience prescribing other combinations of two therapies. The company, therefore, did not consider that ophthalmologists would be misled to believe that the fixed combination of Cosopt had double the efficacy of the single components given concomitantly.

PANEL RULING

The Panel noted that page 2 of the detail aid was headed 'The power of two proven therapies in a single bottle' beneath which was the product logo followed by the strapline 'Power of two, ease of one'. The Panel noted the submission that the audience had considerable experience in prescribing combination therapy. In the Panel's view the claim did not imply that Cosopt had double the efficacy of each of the components. The strapline only appeared in conjunction with the product logo which included the non-proprietary names of the two active ingredients. Given the context in which it was used the Panel did not consider that the strapline was misleading. No breach of Clause 7.2 was ruled.

Claim 'A tolerability profile you can trust'

This claim appeared as a sub-heading on page seven of the detail aid. Immediately below the claim were the statements 'Well-established tolerability profile of the individual components' and 'Adverse experiences

have been limited to those reported previously with dorzolamide hydrochloride and/or timolol maleate'.

COMPLAINT

Pharmacia & Upjohn alleged that this claim was in breach of Clause 7.8 of the Code as it implied that Cosopt had some special merit or quality in terms of safety. This could not be substantiated using current data on the products used singly – the only claim which could be considered valid being that the safety profile for the products used singly was 'known'.

RESPONSE

Merck Sharp & Dohme did not consider that it was appropriate to extract a summary point from a page which was entirely dedicated to tolerability. Page 7 initially provided information on discontinuations due to adverse reactions and detailed information on frequently reported drug related adverse effects. The claim 'A tolerability profile you can trust' was quite obviously qualified with the immediately adjacent statements. The company did not consider that the claim, when taken in context, implied some special merit or quality in terms of safety and consequently it was not in breach of Clause 7.8 of the Code.

PANEL RULING

The Panel noted that the claim was immediately followed by two prominent statements justifying why Cosopt had 'A tolerability profile you can trust'. Furthermore the Cosopt summary of product characteristics (SPC) stated that in clinical studies, no adverse experiences specific to Cosopt had been observed. Given its context, the Panel did not accept that the claim implied some special merit or quality in terms of safety as alleged. No breach of Clause 7.8 was ruled.

Complaint received **14 June 1999**

Case completed **10 August 1999**

CASE AUTH/886/6/99

GENERAL PRACTITIONER v GOLDSHIELD

Marevan 'Dear Doctor' letter

A general practitioner complained about a 'Dear Doctor' letter relating to Marevan which he had received from Goldshield. The complainant stated that the letter did not give the non-proprietary name, warfarin, adjacent to the brand name or, indeed, anywhere on the front of the letter. The Panel noted that the only reference to the non-proprietary name was in the prescribing information on the back of the letter. It did not appear adjacent to the most prominent display of the brand name, which was on the front of the letter, and a breach of the Code was ruled.

A general practitioner complained about a 'Dear Doctor' letter he had received from Goldshield Pharmaceuticals (ref 99/05 LVM02). The letter announced a line extension to the Marevan range – Marevan 0.5mg. The product name and strength appeared in very large italic type in the middle of the letter such that it occupied the whole central area. Prescribing information was printed overleaf.

COMPLAINT

The complainant alleged a breach of Clause 4.2 of the Code as Goldshield had failed to include the non-proprietary name adjacent to the brand name, or indeed anywhere on the front of the letter.

RESPONSE

Goldshield agreed that it did not include the non-proprietary name on the front of the letter, however the abbreviated prescribing information was clearly present on the reverse. The company did not consider that it had breached the Code.

Goldshield stated that it was totally committed to adhering to the Code at all times and considered that the promotion of Marevan 0.5mg was in adherence to the spirit of the Code.

PANEL RULING

The Panel noted that the text of the 'Dear Doctor' letter contained two references to Marevan 0.5mg and that, in addition, the brand name and strength appeared in large type in the centre of the letter. The only reference to warfarin, the non-proprietary name, was in the prescribing information printed on the back of the letter. The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information and, in addition, stated that the non-proprietary name or a list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in not less than 10 point bold or in type size which occupied a total area no less than that taken by the brand name. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of this clause and not of Clause 4.2. The failure to include the non-proprietary name immediately adjacent to the most prominent display of the brand name, which was in the centre of the letter, meant that Goldshield had not complied with Clause 4.1 and the Panel therefore ruled a breach of that clause.

Complaint received **17 June 1999**

Case completed **30 July 1999**

CASE AUTH/887/6/99

SCHERING HEALTH CARE v ROCHE

Promotion of MabThera

Schering Health Care complained about the promotion of MabThera (rituximab) by Roche.

A document entitled 'Rituximab Clinical, Patient and Cost Justification for the Management of Low Grade NHL', which was described inside as a purchaser pack, featured claims for the efficacy of rituximab in non-Hodgkin's lymphoma (NHL). Schering Health Care alleged that it should have included prescribing information. Roche stated that the document was a non-promotional item designed to provide health professionals involved in the budgetary process of oncology/haematology with the relevant information for budgetary decisions. The reviews and analyses included in the document were independent reviews and had been published in abstract form and in peer reviewed journals. In the Panel's view the document was a product monograph, albeit one aimed specifically at purchasers. Although there was limited use of colour and emboldening etc, the Panel considered that the nature of the document meant that it was promotional and therefore subject to the Code. Prescribing information for MabThera had not been included in the document and the Panel ruled a breach of the Code.

A patient information booklet entitled 'Important information for patients being treated with MabThera (rituximab)… Your questions answered' provided the answers to such questions as 'What is MabThera and how does it work?', 'How will MabThera make me feel?' and 'Can I still lead a normal life?' The inside back cover gave the names and addresses of patient support groups. Schering Health Care alleged that the information on side effects was neither balanced nor in line with the summary of product characteristics (SPC).

The Panel noted that in answer to the question 'What can I expect during treatment with MabThera?', there was no mention that, as stated in the SPC, premedication with a pain-reliever and an antihistamine would be required and premedication with corticosteroids might also be necessary. In answer to the question 'How will MabThera make me feel?', the booklet stated that there were relatively few side effects and that if they did occur it was likely to be only during the first infusion when patients might experience fevers, chills/shivering and headache, dizziness/feeling faint. The SPC stated that patients treated with MabThera should be closely monitored for the onset of cytokine release syndrome which occurred in more than 50% of patients, usually during the first one or two hours of the first infusion. While such an event was characterised by the symptoms listed above there were other symptoms associated with it and these included flushing, angiodema, nausea, urticaria/rash, throat irritation, rhinitis, vomiting and tumour pain. In 10% of cases these symptoms were accompanied by hypotension and bronchospasm. The Panel considered that the omission of information regarding premedication and the incomplete list of side effects associated with MabThera meant that the patient booklet had not been presented in a balanced way and a breach of the Code was ruled.

Schering Health Care Limited complained about the promotion of MabThera (rituximab) by Roche Products Limited.

A Document entitled 'Rituximab Clinical, Patient & Cost Justification for the Management of Low Grade NHL [non-Hodgkin's lymphoma]'

Page ii of this large, spiral bound, glossy A4 document described it as a 'Purchaser Pack'. In intercompany correspondence Roche had stated that the document had been provided only on request to personnel involved in the budgetary process and that it was a confidential document.

COMPLAINT

Schering Health Care stated that this document was clearly promotional in content and had been made available to NHS personnel involved in the budgetary process. It featured numerous claims for the efficacy of rituximab in non-Hodgkin's lymphoma (NHL), prominent use of the MabThera trade name in the abstract and introduction, and a comparison with Schering Health Care's product fludarabine which was not licensed for treatment of NHL but which was widely used in this indication. Despite its promotional nature, Schering Health Care noted that the document did not contain the prescribing information for MabThera and was therefore in breach of Clause 4.1 of the Code. The fact that it was allegedly confidential did not exclude it from the Code. Furthermore, Schering Health Care stated that, according to its information, the document was being used much more generally with haematologists by Roche personnel.

RESPONSE

Roche stated that the document was a non-promotional item designed to provide health professionals involved in the budgetary process of oncology/haematology with the relevant information for budgetary decisions. The reviews and analyses included in the document were independent reviews and had been published in abstract form and in peer reviewed journals.

Roche noted that in Schering Health Care's letter of complaint it was claimed that there were numerous claims of the efficacy of MabThera and that there was prominent use of the MabThera trade name in the document. In all there were only three mentions of the MabThera trade name in the entire document, all of which were in the independent reviews and appeared in brackets after the generic name. Roche submitted that the widespread use of the generic name supported its position that this was a non-promotional item. Any efficacy claims were made in the independent reviews, which had been accepted

for publication by peer reviewed journals. The company considered that it was appropriate to include fludarabine in these cost analyses as it was widely used in the treatment of non-Hodgkin's lymphoma, despite not having a licence in this disease area. As this was a non-promotional item, intended for budgetary uses only, and provided to clinical directors, oncology pharmacists, business managers and purchasing pharmacists, Roche considered that prescribing information was not required and that the item was not covered by Clause 4.1.

PANEL RULING

The Panel noted that the document began by briefly introducing the reader to rituximab and then stated that the objective was to address the three main justifications in the use of rituximab for low grade relapsing NHL patients. The section dealing with the clinical justification reviewed the development, preclinical and clinical pharmacology and toxicity of rituximab and its place in treatment. The aim of the patient justification section was to identify which patients should receive rituximab, the evidence, the methods of evaluation and future uses for the product. The section entitled cost justification gave a number of examples of cost implications for given scenarios for the use of rituximab. There were four appendices, 'Incidence of adverse effects', 'Explanation of costs', 'Breakdown of costs' and 'Progression free survival'. In the Panel's view the document was a product monograph albeit one aimed specifically at purchasers. Although there was limited use of colour and emboldening, etc, the Panel considered that the nature of the document meant that it was promotional and therefore subject to the Code. Prescribing information for MabThera had not been included in the document. The Panel therefore ruled a breach of Clause 4.1 of the Code.

B Patient Information Booklet (ref P510065/898)

This booklet was entitled 'Important information for patients being treated with MabThera (rituximab) …Your questions answered'. This 8 page, A5 booklet provided the answers to such questions as 'What is MabThera and how does it work?', 'How will MabThera make me feel?' and 'Can I still lead a normal life?' The inside back cover gave the names and addresses of some patient support groups.

COMPLAINT

Schering Health Care stated that the booklet was available to haematologists on the Roche stand at the British Society of Haematology (BSH) meeting held in Brighton, 12 - 15 April 1999. It was in breach of Clause 20.2 of the Code in that the information on the side effect profile of MabThera was not balanced nor in line with the summary of product characteristics (SPC). In particular, on pages 4 and 5 of the booklet ('What can I expect during treatment with MabThera?' and 'How will MabThera make me feel?') there was no mention of either the need for premedication (analgesic and antihistamine, probably with the addition of corticosteroids) nor the risk of serious infusion-related reactions secondary to cytokine release syndrome. These had a reported incidence of 1 in 160 to 190 patients, and might be fatal in at least 10% of those affected. Not only did the booklet fail to discuss these problems but the information on page 5 suggested that any side effects with MabThera were rare and likely to be mild (limited to tiredness, 'flu symptoms and headache).

RESPONSE

Roche confirmed that the patient booklet was available on its stand at the BSH meeting to those haematologists who requested a copy. Following an intercompany letter of complaint from Schering Health Care, dated 21 April 1999, Roche stated that it replied on 5 May 1999 with an offer to revise the booklet once Schering Health Care had provided the company with its specific issues. Roche regretted that it now found itself before the Authority on this matter since Schering Health Care unfortunately had not yet responded to the letter of 5 May 1999. Roche submitted that the symptoms included in the booklet of fever, chills, shivering, headache and dizziness were indeed the symptoms of cytokine release syndrome as could be expressed in patient-friendly language. The company did not consider that the item breached Clause 20.2 of the Code as the side effect profile was balanced, but was communicated in lay terms which the average patient would understand; it would confuse patients to include the term 'cytokine release syndrome'. Roche stated that in fact there was no clear definition for this condition throughout the medical community. Following Schering Health Care's original letter Roche had suspended the distribution of this booklet, whilst awaiting Schering Health Care's reply to Roche's correspondence. Roche stated that it had already asked the two independent experts who had helped the company with the previous version to review the text of the booklet.

PANEL RULING

The Panel noted that in answer to the question 'What can I expect during treatment with MabThera?' the booklet gave information about the practical issues connected with each infusion ie how long it would last, brief details of the pre-infusion examination and what would happen during the infusion. There was no mention that, as stated in the product SPC, premedication with a pain-reliever and an antihistamine would be required and premedication with corticosteroids might also be necessary.

In answer to the question 'How will MabThera make me feel?' the booklet stated that there were relatively few side effects and that if they did occur it was likely to be only during the first infusion when patients might experience fevers, chills/shivering and headache, dizziness/feeling faint. The Panel noted that the SPC stated that patients treated with MabThera should be closely monitored for the onset of cytokine release syndrome which occurred in more than 50% of patients, usually during the first one or two hours of the first infusion. While such an event was characterised by the symptoms listed above there were other symptoms associated with it and these included flushing, angiodema, nausea, urticaria/rash,

throat irritation, rhinitis, vomiting and tumour pain. In 10% of cases these symptoms were accompanied by hypotension and bronchospasm.

The Panel considered that the omission of information regarding premedication and the incomplete list of side effects associated with MabThera meant that the patient booklet had not been presented in a balanced way. A breach of Clause 20.2 was ruled.

Complaint received	**21 June 1999**
Case completed	**5 August 1999**

CASES AUTH/888/6/99 & AUTH/897/7/99

DIRECTOR v AMGEN and ROCHE

Failure to comply with undertaking – Neupogen dosage booklet

An allegation from Chugai Pharma that a dosage booklet for Neupogen (filgrastim) used at a conference contained claims previously ruled in breach of the Code was taken up as a complaint by the Director. It was the responsibility of the Authority itself to ensure compliance with undertakings. The booklet was produced jointly by Amgen and Roche.

The Panel considered that the claims 'Efficacy has been demonstrated across the range 4-8.4µg/kg/day' in association with 'For patients ≤75kg 1 x Neupogen 30 For patients >75kg 1 x Neupogen 48' were sufficiently similar to the claims at issue in the previous cases for the present cases to be covered by the undertakings given in the previous cases. The Panel considered that Amgen and Roche had failed to comply with their undertakings and a breach of the Code was ruled, as acknowledged by the companies. Whilst noting the circumstances which had led to the breach of undertaking, the Panel considered that the failure to comply with the undertakings brought discredit upon and reduced confidence in the pharmaceutical industry and ruled a breach of Clause 2. Both companies appealed this ruling.

The Appeal Board noted that in March 1998 Neupogen promotional materials had been transferred from one distributor to another. Amgen ordered any materials remaining at the original distributor after 5 March 1998 to be destroyed. In April 1998 Amgen contacted the new distributor and arranged for the destruction of the dosage booklet now at issue as it had been superseded by a revised edition. In May 1998 a complaint was received about a Neupogen detail aid and, as a result of the undertaking given in the ensuing cases, the detail aid and the revised Neupogen dosage booklet were destroyed. In November 1998 Amgen physically checked the premises of the new distributor and found no stocks of either the detail aid or the two versions of the dosage booklet. In April 1999, unbeknown to Amgen, the original distributor sent two boxes of the original dosage booklet to the new distributor. Contrary to procedures agreed with Amgen the new distributor did not send the company copies of the material it had received and just added it to a list of materials approved for representatives' use. Amgen did not spot this error. The original dosage booklet was then subsequently ordered, unseen, by a representative who arranged for it to be sent direct to meeting organisers for inclusion in delegates' bags.

The Appeal Board noted that Amgen did have procedures in place to ensure compliance with undertakings and had made genuine and expeditious efforts to comply. The Appeal Board noted that the dosage booklet at issue had been put back into circulation by a third party some 12 months after Amgen had ordered its destruction; nonetheless the company had to bear responsibility under the Code. The parties had accepted the Panel's ruling of a breach of Clause 21 of the Code. Noting the steps taken by the company to comply with the undertaking the Appeal Board did not consider that the circumstances in these cases constituted a breach of Clause 2 and ruled accordingly.

Chugai Pharma UK Limited submitted a complaint about a dosage booklet (ref P593271/197) for Neupogen (filgrastim) produced jointly by Amgen Limited and Roche Products Limited.

COMPLAINT

Chugai alleged that the dosage booklet produced by Amgen appeared to contain statements that had previously been ruled in breach of the Code. The item had been used for promotional purposes by Amgen at a conference called 'Advances in Haematology' held at a London hospital in June 1999. The organisers of the conference offered pharmaceutical companies, which were supporting the meeting, the option to place promotional items in conference delegate bags which were given to the 250 doctors and nurses attending. Amgen placed the item in the conference delegate bags which were given to all attendees.

The dosage booklet contained claims which appeared to have already been ruled in breach of the Code. These breaches were ruled in Cases AUTH/714/5/98 and AUTH/725/6/98. The claims appeared on pages 3 and 4 of the booklet and were as follows:

'Efficacy has been demonstrated across the range 4–8.4µg/kg/day'

'For patients ≤75kg 1 x Neupogen 30

For patients >75kg 1 x Neupogen 48'

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

RESPONSE

Amgen noted that the allegation concerned the use of two claims which had previously been found in breach of the Code (Cases AUTH/714/5/98 and

AUTH/725/6/98). These breaches referred to a promotional item which was no longer in use by Amgen at the time of the complaint.

Following the ruling, Amgen had actively removed and destroyed all items considered to contain these claims, including a dosage booklet (P593287/7/97) which had subsequently replaced item P593271/197.

Amgen accepted that the dosage booklet P593271/197 now at issue should not have been distributed, in accordance with the previous breaches of the Code. Amgen, therefore, investigated how this particular item, which was not current to Amgen's promotional materials, could have been provided to the conference organisers.

Amgen distributed promotional material to its sales representatives using a third party. Amgen recently changed the appointed company. Unbeknown to Amgen, materials thought to have been destroyed were sent from its previous distributor to the new distributor. Included was the dosage booklet at issue and this found its way on to the list of available Neupogen promotional materials in May 1999.

A stock check list of promotional items dated 24 August 1998 did not include the dosage booklet at issue whereas the version dated 17 May 1999 did.

A representative ordered the dosage booklet for the specific purpose of placing it in the conference bag; again not knowing that this was a discontinued item.

Amgen had ensured the return and destruction of further copies of the dosage booklet from the representative, and the destruction of all further stocks at the distributor warehouse. Furthermore, to ensure that this occurrence was never repeated, its distributor had been instructed to ensure that no item was made available to sales representatives without the express instruction of Amgen. Amgen provided a copy of its letter to the distributor in this regard.

In summary, Amgen was extremely frustrated that this oversight had occurred, but could reassure the Authority that it was accidental and unintentional. All possible actions had been taken to avoid this situation happening again.

Amgen accepted that it had inadvertently breached Clause 21, but strongly refuted any breach of Clause 2. Since its establishment, Amgen had been a member of the ABPI and had striven to uphold the highest of industry operating standards. Amgen was committed to regular staff training courses on the Code. This activity would now be broadened to include key suppliers and distributors.

Roche confirmed its agreement with the response submitted by Amgen.

PANEL RULING

The Panel noted that Cases AUTH/714/5/98 and AUTH/725/6/98 concerned a number of claims which appeared in a Neupogen detail aid. The claim 'efficacy has been demonstrated across the range 4-8.4µg/kg/day' had appeared beneath the claim '2 syringe sizes for convenient dosing in neutropenic patients'. The summary of product characteristics (SPC) stated that the recommended dose was 5µg/kg/day and gave further information regarding the route of administration of this dose before stating that in randomised clinical trials a subcutaneous dose of 4-8.4µg/kg/day was used. The Panel had considered that the claim referring to 4-8.4µg/kg/day was not a fair reflection of the information given in the SPC regarding the recommended dose of Neupogen and ruled a breach of Clause 7.2 of the Code. The claims 'For patients <75kg 1 x Neupogen 30MU' and 'For patients >75kg 1 x Neupogen 48MU' had been ruled to be misleading in breach of Clause 7.2 of the Code as the doses had been calculated from the claim that efficacy had been demonstrated in the range 4-8.4µg/kg/day and not from the recommended dose of 5µg/kg/day given in the SPC. At the recommended dose the 30MU syringe would be suitable for patients up to 60kg. The next size of syringe would have to be used for patients heavier than 60kg. The companies had provided the requisite form of undertaking to withdraw the promotional item in question and provided an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future.

Turning to the present case, the Panel noted that the recommended daily dose of Neupogen was given in the dosage booklet and the layout was slightly different to that at issue in Cases AUTH/714/5/98 and AUTH/725/6/98. The Panel's view was that the differences were not sufficient as the doses had not been calculated from the recommended dose of 5µg/kg/day. The Panel considered that the claims 'Efficacy has been demonstrated across the range 4-8.4µg/kg/day' in association with 'For patients ≤75kg 1 x Neupogen 30 For patients >75kg 1 x Neupogen 48' were sufficiently similar to the claims at issue in the previous cases for the present cases to be covered by the undertakings given in the previous cases. The Panel considered Amgen and Roche had failed to comply with their undertakings given in Cases AUTH/714/5/98 and AUTH/725/6/98. A breach of Clause 21 of the Code was ruled as acknowledged by the companies.

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 Amgen had attempted to organise the withdrawal of the dosage booklet from circulation and its destruction pursuant to its undertaking. Unbeknown to Amgen stocks of the item had however been held by a previous distributor and passed to its successor. The dosage booklet subsequently appeared on the new distributor's stock check list headed 'Amgen General Delivery Instructions' dated 17 May 1999 which recorded a total stock of 2,348. After the company had provided the requisite undertaking the item had been requested

(and received) by a representative for distribution in the conference delegate bags.

The Panel noted that Amgen had made efforts to comply with the original undertaking. The Panel considered that Amgen's efforts in this regard were insufficient. Companies should have procedures in place to prevent the distribution of promotional material which had been withdrawn from circulation. The Panel expressed concern that such a large number of dosage booklets had been retained by the distributor company without Amgen's knowledge. The Panel noted that Amgen had taken steps to ensure that in future the distribution company would not put items onto the representatives' list without the express agreement of Amgen. In a letter to its distributor Amgen had stated that it would visit the warehouse to check the stock and it would also provide the staff with training on the Code. Nevertheless the Panel considered that the companies' failure to comply with the undertakings brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

APPEAL BY AMGEN AND ROCHE

Amgen stated that it accepted the ruling of breach of Clause 21, due to the use of materials containing statements similar to those that had previously been found in breach of Clause 7.2. Amgen appealed, however, against the ruling of breach of Clause 2. Roche endorsed Amgen's appeal.

Amgen fully supported both the letter and the spirit of the Code and recognised the importance of the undertaking given in relation to Cases AUTH/714/5/98 and AUTH/725/6/98. Amgen believed that it made every effort to retrieve and destroy all relevant materials and to ensure that they could not be used again. That they were made available, and subsequently used by one representative, was due to exceptional circumstances and human error, rather than either a failure of the systems or a deliberate act by an Amgen employee. Amgen therefore did not believe that this case merited the particular censure that was associated with the ruling of breach of Clause 2.

Amgen noted the Panel's observation that previous cases involving breaches of Clause 21 had also been ruled to be in breach of Clause 2. However, Amgen drew attention to Case AUTH/185/7/94 where human error and exceptional circumstance were the basis of a successful appeal. Amgen believed that that case had marked similarities with its own.

Background

It was important background to state that during 1998 Amgen was finalising the transfer of Neupogen promotion from Roche. This included a change of distributor for promotional materials. The final transfer was ordered on 5 March 1998 after which time any remaining materials at the Roche distributor were to be destroyed.

The dosage booklet that was the subject of this ruling (ref P593271/197) was not in use at the time of the original complaint in May 1998, having been superseded by a new piece (ref P593287/7/97). Amgen had written to its distributor and arranged destruction of remaining stock of P593271/197 on 6 April 1998.

Specific Issues

With regard to the specific issues highlighted by the Panel in reaching its decision, Amgen addressed each in turn:

'The Panel noted that Amgen had made efforts to comply with the original undertaking. The Panel considered that Amgen's efforts in this regard were insufficient.'

Following the original complaint, Amgen decided to voluntarily withdraw the material that was the subject of that complaint (Neupogen detail aid – ref P593290/797) until the outcome of the Panel's consideration was known. Immediately after the ruling, Amgen also withdrew the Neupogen dosage booklet (ref P593287/7/97).

On 29 May Amgen ordered the destruction of all remaining items at its warehouse, including those returned by the field force, with the exception of 20 copies to be held at the office, in line with Clause 14.4 of the Code. Records were maintained for each representative to ensure compliance.

As Amgen had already ordered the destruction of the piece at the centre of this ruling on 6 April 1998, and any stock at the previous Roche distributor was ordered to be destroyed after 5 March, Amgen did not send any further instruction regarding this piece.

Amgen's distributor was visited regularly to ensure that it was fully conversant with the company's procedures, and to check inventory. Such a visit was made in November 1998, and, at this visit, there were no stocks of either the materials that had been withdrawn (P593290/797) and P593287/7/97) or the dosage booklet at the centre of this ruling (P593271/197). The distributor's stock listing of 17 November 1998 did not contain any of the aforementioned materials.

Amgen believed that the process for withdrawing and destroying the materials was rapid and effective. A visit made to the distributor confirmed that there were no further stocks of any of the material in November 1998. Amgen did not believe that any additional practicable steps could have been taken to ensure that the materials were destroyed.

'The Panel expressed concern that such a large number of dosage booklets had been retained by the distributor company without Amgen's knowledge'.

Although the actual number of pieces was 2348, these were particularly small items, and when packed would take up only two A4 size boxes. It appeared that these were originally mislaid at Roche's distributor and neither sent to Amgen's distributors as requested or subsequently destroyed. It was these pieces that were eventually discovered by Roche's distributor and forwarded to Amgen's distributor during April 1999 and made available in May 1999.

'The Panel noted that companies should have procedures in place to prevent the distribution of promotional materials which had been withdrawn from circulation'.

Amgen believed that the best way to avoid circulation of withdrawn materials was to destroy them. This was ordered in this instance, and a physical check was made to ensure that this had been done.

Furthermore, in order to ensure that there could be no mistake about the items being made available to the field force, Amgen insisted that its distributor send five pieces of all promotional items it received to Amgen for checking, prior to inclusion on the medical representatives' list of available materials. This was an additional step taken to ensure that the correct items were available, as all items that were sent by Amgen had already been certified by the company.

In this instance, the two boxes of P593271/197 were sent by Roche's distributor direct to Amgen's distributor, and were added to the medical representatives' list without five pieces being sent to Amgen. Had they been sent, in line with procedure, then they would have been identified as old items, and would have been immediately destroyed.

This was an exceptional circumstance, in that there should never be materials sent to Amgen's distributor for Amgen products from any source other than Amgen's designated printer. Roche's distributor had sent all items that it had to Amgen's distributor on 6 March 1998, and Amgen had subsequently destroyed all stocks of item P593271/197 that were held. It was over a year later that Roche's distributor subsequently found these two boxes and sent them to Amgen's distributor. Moreover, even at this stage, had Amgen's procedures been followed at its distributor, then the material would still have been identified and would not have been made available.

Conclusions

Amgen believed that it made every effort to comply with the undertaking made in relation to Cases AUTH/714/5/98 and AUTH/725/6/98. The withdrawal and destruction of the materials in question was rapid and effective. Amgen reasonably and genuinely believed that it had therefore complied with its undertaking. In these circumstances a finding of a breach of Clause 2 was unwarranted, given that this was a 'sign of particular censure'.

The piece at the centre of this case was an old item that had been ordered destroyed in March 1998, and a subsequent check on the distributor in November 1998 had confirmed that this had been done. That two small boxes of this item were subsequently discovered at the previous distributor and sent to its distributor some 12 months later was exceptional. Even so, had Amgen's procedure been followed at its distributor, then this item would still have been identified and would not have been distributed. It was the combination of circumstance and human error that led to this issue, and not a failure of the systems.

APPEAL BOARD RULING

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 the materials ruled in breach. Companies must have procedures in place to ensure compliance with undertakings.

The Appeal Board noted that in March 1998, Neupogen promotional materials had been transferred from one distributor to another. Amgen ordered that any materials remaining at the original distributor after 5 March 1998 were to be destroyed. In April 1998 Amgen contacted the new distributor and arranged for the destruction of the dosage booklet now at issue as it had been superseded by a revised edition. In May 1998 a complaint was received about a Neupogen detail aid and as a result of the undertaking given in the ensuing cases, Cases AUTH/714/5/98 and AUTH/725/6/98, the detail aid and the revised Neupogen dosage booklet were destroyed. In response to a question the company representatives stated that the medical representatives were each provided with a copy of the relevant case report so that they would understand the matters at issue. In November 1998 Amgen had physically checked the premises of the new distributor and had found no stocks of either the detail aid or the two versions of the dosage booklet.

In April 1999, unbeknown to Amgen, the original distributor had sent two boxes of the original dosage booklet to the new distributor. Contrary to procedures agreed with Amgen the new distributor did not send the company copies of the material it had received and just added it to a list of materials approved for representatives' use. Amgen did not spot this error. The original dosage booklet was then subsequently ordered, unseen, by a representative who arranged for it to be sent direct to meeting organisers for inclusion into delegates' bags for a conference held in June 1999.

The Appeal Board noted that Amgen did have procedures in place to ensure compliance with undertakings and had made genuine and expeditious efforts to comply with the undertaking given in Cases AUTH/714/5/98 and AUTH/725/6/98. The Appeal Board noted that the dosage booklet at issue had been put back into circulation by a third party some 12 months after Amgen had ordered its destruction; nonetheless the company had to bear responsibility under the Code. The parties had accepted the Panel's ruling of a breach of Clause 21 of the Code. Noting the steps taken by the company to comply with the undertaking the Appeal Board did not consider that the circumstances in these cases constituted a breach of Clause 2 and no breach of Clause 2 was ruled.

The appeal was thus successful.

Complaint received	**21 June 1999**
Cases completed	
AUTH/888/6/99	**11 October 1999**
AUTH/897/7/99	**8 September 1999**

BOEHRINGER INGELHEIM v SANOFI WINTHROP and BRISTOL-MYERS SQUIBB

Promotion of Plavix

Boehringer Ingelheim complained about the promotion of Plavix (clopidogrel) by Sanofi Winthrop and Bristol-Myers Squibb. It was alleged that the claim that Plavix was 'significantly more effective at reducing MI [myocardial infarction], stroke and vascular death' than aspirin, with which it was compared in the CAPRIE study, was misleading and exaggerated.

The Panel noted that the licensed indication for Plavix was the reduction of atherosclerotic events (MI, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined as ischaemic stroke (from 7 days until less than six months), MI (from a few days until less than 35 days) or established peripheral arterial disease. The product was thus licensed to prevent a composite end point in a composite patient population. The 'Pharmacodynamic properties' section of the Plavix summary of product characteristics (SPC) stated that in patients who were enrolled in the trial on the sole basis of a recent MI, clopidogrel was numerically inferior, but not statistically different from aspirin. The indication section of the SPC stated that the slight but significant difference in favour of clopidrogel with reference to the primary endpoint was mainly related to patients enrolled due to peripheral arterial disease.

The Panel noted that the primary analysis of efficacy in the CAPRIE study was based on a composite end point ie first occurrence of ischaemic stroke, myocardial infarction or vascular death. The section of the SPC detailing pharmacodynamic properties stated that clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of MI, stroke and vascular death) compared to aspirin. No reference was made to a combined end point in either the advertisement or the page of the detail aid provided. In the Panel's view both pieces implied that, compared to aspirin, Plavix was significantly more effective at reducing MI, reducing stroke and reducing vascular death, which was not so. The Panel noted that beneath the product logo on the advertisement the strapline 'Preventing Vascular Events' appeared but did not consider this was sufficient to prevent readers assuming that the significant result in favour of Plavix was applicable to each outcome. The Panel considered that the claims were misleading and exaggerated as alleged and ruled breaches of the Code.

Boehringer Ingelheim Limited complained about the advertising of Plavix (clopidogrel) by Sanofi Winthrop Limited and Bristol-Myers Squibb Pharmaceuticals Limited. There was an agreement between the two companies for the co-development and marketing of Plavix.

COMPLAINT

Boehringer Ingelheim noted that Sanofi Winthrop and Bristol-Myers Squibb were using the claim that Plavix was 'significantly more effective at reducing MI [myocardial infarction], stroke and vascular death' than aspirin with which it was compared in the CAPRIE study. Boehringer Ingelheim alleged that this claim was misleading and exaggerated and thus in breach of Clauses 7.2 and 7.8 of the Code.

Boehringer Ingelheim stated that CAPRIE, whilst being a very large-scale study, adopted as a primary end-point for the purposes of comparison with aspirin a composite or cluster end-point including myocardial infarction, stroke and vascular death in a population of patients who had sustained as an entry criterion either a very recent MI or a relatively recent stroke or had established peripheral arterial disease (PAD). For the composite end-point of 'MI, stroke and vascular death' clopidogrel was shown to be more effective than aspirin alone with a difference in relative risk reduction of 8.4%, absolute annual risks being 5.83% for aspirin and 5.32% for clopidogrel. The confidence intervals for the 8.4% difference were just inside unity, ie the difference was statistically significant, but only for the composite end-point.

Boehringer Ingelheim noted, however, that when the study population was broken down into the various populations ie those with entry criterion of prior MI or prior stroke or prior PAD and then the composite end-point was broken-down to end-point MI, end-point stroke or end-point vascular death a very different picture emerged. CAPRIE was not powered to do this and it became evident that the difference over aspirin was driven solely by the outcome in patients with PAD.

Clopidogrel was clearly not superior to aspirin in preventing myocardial infarction or stroke, the point values being not statistically significantly different from those achieved with aspirin and the confidence intervals including unity as shown in figure 4 of the paper.

Boehringer Ingelheim stated that in achieving the product licence for clopidogrel both in the USA and in Europe, Sanofi Winthrop and Bristol-Myers Squibb were restricted in any claim or promotion of superiority of clopidogrel over aspirin. The Plavix summary of product characteristics (SPC)/ product information, as well as the advice given in the report of the Food and Drugs Administration (FDA) advisory committee and the European Public Assessment Report (EPAR), all confirmed that such a claim would have to be treated with caution. The supporting evidence adduced derived from only one comparative trial which had not been corroborated and in any case was not consistent across the differing vascular end-points in the different populations. Sanofi Winthrop and Bristol-Myers Squibb had asserted a claim which might certainly be interpreted as universal superiority over aspirin. In the light of the data and the regulatory commentary, the claim

could not be substantiated as written and required considerable qualification to be understood. In this respect Boehringer Ingelheim submitted that the claim of superiority over aspirin with respect to 'MI, stroke and vascular death' would be read by a majority of the audience as implying superiority in each of the three separate indications and not with respect to the primary composite end-point of the study.

In support of its allegations Boehringer Ingelheim referred to the relevant pages of the FDA advisory committee meeting minutes, and enforcement letter from the FDA, the EPAR and the validity of the claim for superiority over aspirin.

RESPONSE

Sanofi Winthrop and Bristol-Myers Squibb noted that to substantiate its allegations Boehringer Ingelheim had referred to two FDA documents, the EPAR and the SPC for Plavix. It was Sanofi Winthrop's and Bristol-Myers Squibb's opinion that references relating to the FDA were entirely irrelevant to Europe, and therefore these would not be considered further in response to this complaint. Additionally, the companies contended that Boehringer Ingelheim's letter was factually inaccurate with respect to the statement about restriction of promotional claims in Europe. This was simply untrue; no such restriction existed in the EPAR.

Sanofi Winthrop and Bristol-Myers Squibb stated that the licence for Plavix was granted on the basis of the CAPRIE study for the indication 'Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular disease) in patients with a history of symptomatic atherosclerosis defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days to less than 35 days) or established peripheral arterial disease.' Furthermore, the statistical superiority of Plavix over aspirin was stated in Section 5.1 of the SPC 'Pharmacodynamic properties', 'Clopidogrel significantly reduced the incidence of new ischaemic events (combined end-point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA [aspirin]'.

Thus, Sanofi Winthrop and Bristol-Myers Squibb contended that the claim that Plavix was 'significantly more effective at reducing MI, stroke and vascular death' than aspirin was neither misleading nor exaggerated, but accurately reflected the licensed indication, and the significant benefit over aspirin documented in the SPC.

The companies maintained that in the UK their claims for Plavix were an accurate reflection of the product licence, and therefore were not in breach of either Clause 7.2 or 7.8 of the Code.

PANEL RULING

The Panel noted that the relevant page of the Plavix detail aid was headed 'The Plavix Advantage: efficacy that surpasses aspirin'. A series of bullet points discussed the design of the CAPRIE trial above a claim which stated 'CAPRIE demonstrated that Plavix was significantly more effective than aspirin in preventing MI, ischaemic stroke and vascular death'. The claim was referenced to a footnote which read 'In patients with ischaemic stroke (from 7 days to less than 6 months), MI (less than 35 days) or established peripheral vascular disease'. A similar claim 'In a trial against aspirin in over 19,000 recent MI, recent ischaemic stroke and atherosclerotic PVD [peripheral vascular disease] patients, Plavix was proven to be significantly more effective at reducing MI, stroke and vascular death,' appeared in the advertisement provided.

The licensed indication for Plavix was the reduction of atherosclerotic events (MI, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined as ischaemic stroke (from 7 days until less than six months), MI (from a few days until less than 35 days) or established peripheral arterial disease. The product was thus licensed to prevent a composite end point in a composite patient population.

The Panel noted that CAPRIE was a randomised blinded trial designed to assess the relative efficacy of clopidogrel (75mg once daily) and aspirin (325mg once daily) in reducing the risk of a composite outcome cluster of ischaemic stroke, MI or vascular death. The population studied comprised subgroups of patients with atherosclerotic vascular disease namely recent ischaemic stroke, recent MI or symptomatic peripheral arterial disease. The study was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups. The primary endpoint showed a statistically significant relative risk reduction in favour of clopidogrel. Analyses of the stroke, MI and PAD subgroups showed a relative risk reduction of 7.3%, –3.7% and 23.8% respectively. The study authors stated that a test for heterogeneity suggested that the observed differences in these relative treatment effects were greater than might be due to chance. The 'Pharmacodynamic properties' section of the Plavix SPC stated that in patients who were enrolled in the trial on the sole basis of a recent MI, clopidogrel was numerically inferior, but not statistically different from aspirin. The indication section of the SPC stated that the slight but significant difference in favour of clopidrogel with reference to the primary endpoint was mainly related to patients enrolled due to peripheral arterial disease.

The Panel noted that the primary analysis of efficacy in the CAPRIE study was based on a composite end point ie first occurrence of ischaemic stroke, myocardial infarction or vascular death. The section of the SPC detailing pharmacodynamic properties stated that clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of MI, stroke and vascular death) compared to aspirin. No reference was made to a combined end point in either the advertisement or the page of the detail aid provided. In the Panel's view both pieces implied that, compared to aspirin, Plavix was significantly more effective at reducing MI, reducing stroke and reducing vascular death, which was not so. The Panel noted that beneath the product logo on the advertisement the strapline 'Preventing Vascular Events' appeared but did not consider this was

sufficient to prevent readers assuming that the significant result in favour of Plavix was applicable to each outcome. The Panel considered that the claims were misleading and exaggerated as alleged and ruled breaches of Clauses 7.2 and 7.8 of the Code.

Complaint received **23 June 1999**

Case completed **18 August 1999**

CASE AUTH/891/6/99

DIRECTOR v LILLY

Failure to comply with an undertaking – Evista exhibition panel

An allegation from Wyeth that Lilly was continuing to use claims which had previously been ruled to be in breach of the Code was taken up as a complaint by the Director. It was the responsibility of the Authority itself to ensure compliance with undertakings. The claim 'Non-hormonal protection for post-menopausal women' had been ruled to be misleading and not consistent with the indications in the Evista summary of product characteristics.

The Panel noted that the claims 'Non-hormonal protection for post-menopausal women' and 'Non-hormonal protection' appeared on an exhibition panel used at a scientific meeting. On notification of the complaint Lilly had taken action immediately to completely cover the offending advertising. The company had failed to comply with its undertaking and a breach was ruled. The Panel noted that the wrong exhibition panel had been used by a third party. A new exhibition panel had been made. Lilly had reviewed its procedures for destroying materials ruled in breach. The Panel decided that the company's failure to comply with the undertaking brought discredit on and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Wyeth complained about an Evista exhibition panel used by Eli Lilly and Company which featured the claim 'Non-hormonal protection for post-menopausal women'. The complaint was received while the exhibition panel was in use at a scientific meeting.

COMPLAINT

Wyeth referred to a previous case it had brought to the Authority, Case AUTH/836/1/99, in which the Panel ruled that the use of the broad claim 'Non-hormonal protection for post-menopausal women' was misleading as it was not consistent with the indications in the Evista summary of product characteristics (SPC) which limited the use of the product to post-menopausal women at increased risk of osteoporosis. Breaches of Clauses 3.2 and 7.2 of the Code had been ruled.

Wyeth noted that it had come to its attention that Lilly was exhibiting at the British Menopause Society Meeting in Manchester 23-25 June 1999 and that the exhibition panels it was using there contained the following statements:

'Viva Evista'
'Non-hormonal protection'
'Non-hormonal protection for post-menopausal women'

There was no further clarification of these statements; use of the latter was clearly in breach of the previous ruling on this issue.

Given the flagrant breach of a previous Panel ruling Wyeth requested that Lilly be required to remove the relevant panels from display immediately. Wyeth alleged a breach of Clause 2.

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

RESPONSE

Lilly stated that the exhibition panels were part of the stand at the meeting on 24 and 25 June 1999 in Manchester, having been assembled the previous day. The stand was one that was made available to European affiliates of Lilly and used wording that was similar to that found to be in breach of the Code, Case AUTH/836/1/99, relating to an Evista journal advertisement (EV100). This stand was set up by a third party instead of the new approved stand which was in line with the undertaking the company had previously given. However Lilly recognised that it was responsible for the actions of third parties working on its behalf.

Lilly submitted that on having this breach pointed out, action was immediately taken to completely cover the offending advertisements.

In order to be certain that this type of mistake did not happen again, Lilly stated that it had initiated a complete review of the processes involved in ensuring that all materials remained in compliance. It would also ensure that all materials, such as stand panels or films of advertisements, that had been found to be in breach were removed from any storage facilities or returned by advertising agencies for destruction.

In view of the fact that immediate action was taken to remove the offending panels and that it had initiated a review to ensure that this did no recur, Lilly did not consider that it had brought discredit on the pharmaceutical industry in breach of Clause 2.

PANEL RULING

The Panel noted that in Case AUTH/836/1/99 Wyeth had complained about the broad focus of the Evista campaign. The company had been particularly concerned about the claim 'Non-hormonal protection'. A journal advertisement (ref EV100) carried the heading 'Non-hormonal protection for post-menopausal women' and 'Non-hormonal protection' was its final claim. Wyeth had stated that the claims suggested that Evista could deliver the same range of therapeutic benefits as conventional hormone replacement therapy and alleged that this was highly misleading.

In its ruling in Case AUTH/836/1/99 the Panel had considered that the very broad claim 'Non-hormonal protection for post-menopausal women' was misleading. It was not consistent with the indications in the Evista SPC which limited the use of the product to post-menopausal women at increased risk of osteoporosis. Breaches of Clauses 3.2 and 7.2 had been ruled.

Turning to the case now before it the Panel noted that the exhibition panel was headed 'Viva Evista'. The claim 'Non-hormonal protection for post-menopausal women', appeared near the top of the exhibition panel and 'Non-hormonal protection' ran along its lower edge.

The Panel noted that the exhibition panel in question had been set up by a third party instead of the exhibition panel which had been revised in the light of the ruling in Case AUTH/836/1/99. Nevertheless, Lilly was responsible, under the Code, for the action of its agents. The use of the exhibition panel represented a failure to comply with the undertaking given in Case AUTH/836/1/99 and a breach of Clause 21 was ruled.

The Panel considered whether there had also been a breach of Clause 2 of the Code as a failure to comply with an undertaking was a serious matter. The Panel noted that Case AUTH/836/1/99 was completed on 13 May 1999 and that only six weeks later material which was covered by the relevant undertaking was being used again. The Panel noted that the wrong exhibition panel had been set up by a third party; a new exhibition panel had been made which was in keeping with the undertaking. Once Lilly had realised the situation immediate action had been taken to cover up the offending exhibition panels. The company acknowledged that it had to take responsibility for its agents and had reviewed its procedures for destroying materials ruled in breach. The Panel decided that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry and therefore ruled a breach of Clause 2 of the Code.

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 decided that the circumstances did not warrant reporting Lilly to the Appeal Board.

Proceedings commenced 25 June 1999

Case completed 1 August 1999

CASE AUTH/892/6/99

DERMAL v SEARLE

Powergel tissue box

Dermal complained about a box of tissues issued by Searle which promoted Powergel (ketoprofen), a topical non-steroidal anti-inflammatory drug (NSAID). Three sides of the box detailed results from a review of topical NSAIDs by Moore *et al*. Dermal marketed three topical formulations of the NSAID ibuprofen.

The side of the tissue box at issue was headed 'Ketoprofen, strong on pain relief'. A bar chart showed the percentage of patients achieving a successful outcome with five topical NSAIDs (ketoprofen 76.1%; felbinac 70.9%; ibuprofen 66.2%; piroxicam 61.4% and benzydamine 52.2%). A figure of 37.6% was recorded for placebo. Below the bar chart was the claim 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief'.

The Panel noted that the review had been undertaken to examine the evidence that topical NSAIDs were effective beyond their use as rubefacients and to determine whether there was any evidence for differences between the products available. In acute conditions it was shown that ketoprofen, felbinac, ibuprofen and piroxicam were significantly superior to placebo. The authors stated, however, that there was no clear message as to which one of them '… was best or indeed whether there was any difference in efficacy. They all worked'. The Panel noted that the ketoprofen bar was the tallest with the others arranged in descending order by height. The ketoprofen bar was blue while those for the other NSAIDs were pink. The Panel considered that the bar chart gave a visual impression that there was a difference between ketoprofen and all of the other topical NSAIDs shown which was not so; there was only a difference between it and benzydamine. The claim below the bar chart 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief' implied that at times ketoprofen might be more effective and added support to the visual impression of general superiority. Overall the Panel considered that the side of the tissue box at issue did not give a clear, fair or balanced view of the work by Moore *et al*. The bar chart was visually misleading and the overall impression with regard to the relative efficacy of ketoprofen was misleading and did not reflect the stated views of the authors. The Panel ruled breaches of the Code.

Although the matter was similar to that in a previous case, AUTH/713/5/78, the Panel considered that the material in the present case was sufficiently different for there not to have been a breach of the undertaking given in the previous case.

Dermal Laboratories Limited complained about a cube shaped box of tissues issued by Searle. The box promoted Powergel (ketoprofen), a topical non-steroidal anti-inflammatory drug (NSAID). Three sides of the box detailed results from a review of topical NSAIDs which had been published in the BMJ (Moore *et al* (1998)). A fourth side of the box bore a number of claims for Powergel while prescribing information was on the base of the box. Dermal marketed three topical formulations of the NSAID ibuprofen.

The side of the tissue box at issue was one of those detailing results from the BMJ review and was headed 'Ketoprofen, strong on pain relief'. A bar chart showed the percentage of patients achieving a successful outcome with five topical NSAIDs (ketoprofen 76.1%; felbinac 70.9%; ibuprofen 66.2%; piroxicam 61.4% and benzydamine 52.5%). A figure of 37.6% was recorded for placebo. The NNT (numbers needed to treat) figure was given below each bar these being ketoprofen 2.6; felbinac 3.0; ibuprofen 3.5; piroxicam 4.2 and benzydamine 6.7. Below the bar chart was the claim 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief'. No explanation of the abbreviation NNT was given on the tissue box.

The Authority noted that the complaint touched on allegations at issue in Case AUTH/713/5/98. Both companies were informed that, when information about a potential breach of undertaking was received, in accordance with established procedure the matter was taken up by the Director as a complaint under the Code. The Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

COMPLAINT

Dermal noted that the tissue box referred to the BMJ paper as a 'Quantitative, systemic review …' and not, as it should have been, a quantitative systematic review of topical NSAIDs. The company noted that the bar chart at issue compared ketoprofen (highlighted in blue) with felbinac, ibuprofen, piroxicam, benzydamine (in pink) and placebo (in white). Dermal considered that undue relative prominence was afforded to ketoprofen both visually and statistically, and that the data and conclusions from the BMJ paper were not adequately interpreted.

Dermal noted that the 'Discussion' section of the BMJ paper stated: 'There is no clear message as to which of ketoprofen, felbinac, ibuprofen or piroxicam was best or indeed whether there was any difference in efficacy. They all worked.'

Dermal stated that the bar chart relied selectively on data referring only to acute conditions (but did not say so). It therefore attempted to present a tenuous difference in a specific sub-category as a general endorsement of superiority, without appropriate qualification. Dermal did not consider that the claim 'Ketoprofen is at least as effective…' below the chart addressed that disparity, nor did it provide adequate balance to offset the overall misleading impression of general superiority.

Dermal noted that the supplementary information to Clause 7.6 of the Code required graphs and tables to

be 'adequately labelled so that the information can be readily understood', as well as 'clearly labelled as having been adapted from the paper'. Dermal stated that the use of initials like 'NNT' could only be readily understood by a clinician having the source reference to hand, to know that it stood for numbers needed to treat. The chart was not clearly labelled as adapted from the paper and did not refer to 'acute conditions' data.

In summary, Dermal considered that the overall impression conveyed to prescribers was one of general superiority for ketoprofen in both acute and chronic pain conditions – an impression that was not supported by the facts and one that was made difficult to scrutinise properly by inadequate explanation and labelling.

RESPONSE

Searle did not agree that it had not adequately interpreted the data and conclusions from the BMJ paper. The company stated that the bar chart presented a clear, fair and balanced view of the data presented in the BMJ paper; it did not afford undue relative prominence to ketoprofen other than by its representation in a contrasting colour.

Searle provided a rationale for the figures in the bar chart. The bars were clearly labelled to indicate that there was no significant difference between ketoprofen, felbinac, ibuprofen and piroxicam, although all were superior to placebo. In addition, ketoprofen was superior to both benzydamine and placebo. The 95% confidence intervals around the NNT values for ketoprofen did not overlap those of benzydamine, a point which was commented upon in the paper.

Searle stated that the claim below the bar chart 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief' supported the statement in the discussion section of the BMJ paper 'There is no clear message as to which of ketoprofen, felbinac, ibuprofen or piroxicam was best or indeed whether there was any difference in efficacy. They all worked'.

Searle submitted that the bar chart did not rely on selective use of data. It was based on a table of data in the BMJ paper (table 2) and reflected that data in its entirety. In the paper it was explained that medicines were included in that table if they had been studied in three or more trials. These were all studies in acute painful conditions. In chronic painful conditions no single topical NSAID was tested in three placebo controlled studies.

Searle stated that NNT was a commonly used term in evidence based medicine; it would be readily understood by clinicians.

In retrospect Searle accepted that, for clarity, the bar chart should have been labelled as 'adapted from…'. The company undertook to correct this error and the incorrect spelling of the word 'systemic' in all future items.

In summary, Searle considered that it had presented a fair and balanced view of the data and in no way had it given the misleading impression of superiority of ketoprofen. Therefore, the company did not consider that the tissue box breached Clause 7.2 of the Code. The company accepted that by omitting the words 'adapted from …' it had not complied with the letter of the Code with respect to Clause 7.6.

With regard to a possible breach of undertaking Searle stated that it had reviewed the previous case (Case AUTH/713/5/98) in detail before deciding to use the data from the BMJ review in further promotional items. The company ensured that the claims that had been found in breach were not used. In addition, the company had qualified the bar chart to ensure that it did not imply that ketoprofen was superior to felbinac, ibuprofen or piroxicam. The claim below the bar chart clearly stated 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief'. The bars were also labelled to indicate that there was no significant difference between the topical NSAID gels.

Searle considered that it had fully complied with its undertaking and was not in breach of Clause 21. It did not consider that its actions had either brought discredit to, or reduced confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted that the review featured on the sides of the tissue box (Moore *et al* (1998)) was undertaken to examine the evidence that topical NSAIDs were effective beyond their use as rubefacients and to determine whether there was any evidence for differences between the products available. The authors analysed the results of 86 trials involving 10,160 patients with acute (strains, sprains, sports injuries) or chronic conditions (arthritis, rheumatism). Data was pooled for individual medicines which had been studied in at least three randomised trials. In acute conditions it was shown that ketoprofen, felbinac, ibuprofen and piroxicam were significantly superior to placebo. The authors stated, however, that there was no clear message as to which one of them '… was best or indeed whether there was any difference in efficacy. They all worked'.

The side of the tissue box at issue featured a bar chart which depicted successful outcomes in terms of percentages of patients treated with five topical NSAIDs. Although ketoprofen achieved the highest percentage the results were not significantly different from those for felbinac, ibuprofen and piroxicam. The Panel noted that the bars for these three NSAIDs were labelled N.S. Conversely there was a statistically significant difference between ketoprofen and benzydamine; the bar for benzydamine was labelled $p<0.05$.

The Panel noted that the ketoprofen bar was the tallest with the others arranged in descending order by height. The ketoprofen bar was blue while those for the other NSAIDs were pink. The Panel considered that the bar chart gave a visual impression that there was a difference between ketoprofen and all of the other topical NSAIDs shown which was not so; there was only a difference between it and benzydamine. The Panel did not consider that the labelling of the other bars with N.S. negated this

impression. The claim below the bar chart 'Ketoprofen is at least as effective as a range of currently available topical NSAIDs at providing effective pain relief', referenced to the Moore paper, implied that at times ketoprofen might be more effective and added support to the visual impression of general superiority.

The bar chart depicted only those results for acute conditions but was not labelled as such. Given that acute and chronic conditions were referred to elsewhere on the tissue box the Panel considered that it was not unreasonable for readers to assume that the bar chart also referred to acute and chronic conditions particularly as some of the topical NSAIDs in the bar chart were indicated for such use.

The Panel noted that the bar chart had been derived from figures quoted in the review. The percentages of patients achieving a successful outcome had been obtained by standardising the response rate for placebo and then, for each treatment, adding to the placebo response rate a value of 100 divided by the relevant NNT as stated in the paper. This procedure was explained below the graph although, in the Panel's view, it was not entirely clear that the figures quoted in the bar chart had not been directly quoted from the paper. The abbreviation NNT had not been explained and the Panel queried whether all of the intended audience would have been familiar with its meaning.

Overall the Panel considered that the side of the tissue box at issue did not give a clear, fair or balanced view of the work by Moore *et al*. The bar chart was visually misleading and the overall impression with regard to the relative efficacy of ketoprofen was misleading and did not reflect the stated views of the authors. The Panel ruled breaches of Clauses 7.2 and 7.6.

With regard to the undertaking given in the previous case, Case AUTH/713/5/98 the Panel noted that there were differences between the material at issue in that case and the material at issue in the new case. The claims were different and some changes had been made to the bar chart. The previous case had focussed primarily on two claims which were ruled to be misleading. The Panel considered that the material in the new complaint was sufficiently different for there not to have been a breach of the undertaking given in Case AUTH/713/5/98. The Panel therefore ruled no breach of Clause 21 of the Code.

During its consideration of this case the Panel noted that the box included references to topical NSAIDs in both acute and chronic pain conditions. The Panel considered that such references might be misleading with respect to the licensed indications for Powergel which was only licensed for acute use. The Panel requested that Searle be advised of its concerns.

Complaint received **30 June 1999**

Case completed **20 August 1999**

GENERAL PRACTITIONER v RHÔNE-POULENC RORER and MERCK PHARMACEUTICALS

'Dear Colleagues' letter

A general practitioner complained about a letter which he had received from the doctor who was the secretary of the local medical committee. The letter followed on from a meeting on angina which that doctor had chaired and gave a very positive account of nicorandil. The complainant considered this was unfair promotional activity by the secretary of the local medical committee working on behalf of Rhône-Poulenc Rorer. Nicorandil was co-promoted as Ikorel by Rhône-Poulenc Rorer and Merck Pharmaceuticals.

The Panel noted that the letter summarized the main points raised at a meeting which had been sponsored by Rhône-Poulenc Rorer and Merck. The chairman of the meeting had agreed with an area business manager from Rhône-Poulenc Rorer to write the letter for the benefit of those unable to attend the meeting. The letter had been compiled from the chairman's own notes and those of a senior representative. Although the letter had been printed on the chairman's own notepaper, it had been distributed by local representatives. The Panel considered that as the companies had been involved in the compilation of the letter and were responsible for its distribution, it had to be regarded as promotional material subject to the Code. Certain requirements of the Code had not been met. Prescribing information should have been included. The letter should have been certified.

The role of the companies was not mentioned. The Panel considered that the letter constituted disguised promotion for Ikorel and a breach of the Code was ruled.

The complainant had noted that the letter advocated the use of nicorandil monotherapy to treat angina patients. He considered this quite contrary to standard procedure. In a subsequent letter, the complainant stated that his main point was that nicorandil was advised as second line treatment but the letter from the chairman had suggested that it should be used as first line treatment. The Panel noted that it had ruled no breach of the Code in a previous complaint in which identical concerns had been expressed. In Cases AUTH/812/12/98 and AUTH/813/12/98 the Panel had considered that the promotion of nicorandil as a first line treatment was not unacceptable and had ruled no breach of the Code. The Panel considered that its ruling in Cases AUTH/812/12/98 and AUTH/813/12/98 would also apply to the new complaint. The Panel therefore ruled no breach of the Code.

A general practitioner complained about a letter he had received from the doctor who was the secretary of the local medical committee. The letter began 'Dear Colleagues' and expressed regret that the reader had not been able to attend a meeting at a local hotel to hear two speakers talk on 'New Horizons in Angina Treatment' and introduce the concept of myocardial preconditioning. The main points of the meeting were summarised in the letter. The first point was that angina was a major problem. Secondly, treatment options were examined which included a very positive account of nicorandil including phrases such as '… very effective and easy to use therapy' and '…is considered 'eminently suitable as monotherapy', in place of nitrates …'. The final matter covered in the letter was ischaemic preconditioning where it was stated that 'nicorandil may be the first anti-anginal which has the ability to both vasodilate, relieve symptoms, and also protect the cells and improve prognosis'. The letter ended with the following 'With PCGs rapidly approaching and the need to assess value against costs, nicorandil, as a monotherapy, provides us with effective 24 hour anti-anginal control and the potential to protect our patients like no other agent at a similar price to most other popular agents. With just under $^1/_2$ of all patients still reporting pain, maybe we should all re-assess our current treatment of our angina patients'. Nicorandil was co-promoted as Ikorel by Rhône-Poulenc Rorer Limited and Merck Pharmaceuticals.

COMPLAINT

The complainant noted that the letter advocated the use of nicorandil monotherapy to treat angina patients. He considered this was quite contrary to standard procedure and that it was unfair promotional activity by the secretary of the local medical committee working on behalf of Rhône-Poulenc Rorer. The complainant had written to the secretary of the local medical committee expressing his disquiet.

RESPONSE

Rhône-Poulenc Rorer and Merck submitted similar responses and explained that they had sponsored a scientific meeting on 21 January entitled 'Short Term Pain, Long Term Gain. The Importance of Myocardial Preconditioning'. The secretary of the local medical committee had chaired the meeting. The agenda was designed to be informative and also to stimulate discussion and debate around the important subject of the treatment of angina pectoris. The companies had developed the programme in conjunction with the two main speakers, one a professor of cellular cardiology and the other a consultant cardiologist and clinical director. A copy of the invitation letter sent to local GPs was provided; 300 GPs were sent invitations to the meeting and 120 attended on the night. The meeting started with registration at 6.30pm followed by introductory remarks from the chairman. The consultant cardiologist then gave his presentation entitled 'New Horizons in the Treatment of Angina'

followed by the professor's presentation entitled 'Myocardial Preconditioning'. Both speakers used their own slide sets to illustrate key points. A copy of the agenda was provided.

The companies stated that during the two days before the meeting the local Rhône-Poulenc Rorer representative, co-ordinating the logistics for the meeting, checked with the doctors who had accepted the invitation to the meeting. During these conversations several doctors said that they would now be unable to attend and spontaneously asked for information on the meeting's content to be forwarded to them after it had taken place. Regrettably no records now existed of these requests. The chairman of the meeting was informed of the last minute difficulties that some invitees had in attending the meeting. The Rhône-Poulenc Rorer area business manager and the chairman agreed it would be valuable for the doctors who had accepted the invitation to the meeting, but could not attend on the night, to receive a synopsis of the key points presented and discussed. After discussion it was decided that the best way of doing this was if the chairman wrote to the doctors personally.

The companies stated that it was important for the Authority to note that the chairman of the meeting wrote the letter referred to by the complainant only in his capacity as chairman; he did not, as implied by the complainant, write the letter in his capacity as the secretary of the local medical committee, which would clearly have been an inappropriate abuse of the office. An outline of the chairman's letter was drafted from his own notes taken during the meeting and those of a senior company representative. The chairman used these notes to produce and then sign the letters on his personal notepaper.

The companies submitted that with the benefit of hindsight, it might have been wiser for the area business manager to have been more forthright in his advice to the chairman that he should reiterate the companies' sponsorship of the meeting in his opening paragraph. However, in the original letter of invitation to the meeting, which all recipients of the chairman's summary letter received, it was clearly stated that Rhône-Poulenc Rorer and Merck sponsored the meeting. The companies did not consider that any recipients of the letter could have been in doubt that they had sponsored the meeting. The companies denied any allegation that at their request, or unwittingly, the chairman had promoted the content of the meeting in a disguised manner.

The companies stated that no more than 25 copies of the letter were distributed to the doctors who had accepted an invitation but did not turn up on the night. The letters were produced by the chairman and then collected and distributed, as a courtesy, by the local representatives who had been responsible for collating responses from the invitees. As far as the companies knew, the chairman did not include anything other than his letter. The representatives distributed no other materials or documents with the letter. The companies explained that they could not supply the Panel with an original of the chairman's letter as they did not produce it.

In conclusion, the companies regretted that the complainant did not appreciate the genuine attempt by the chairman of the meeting to inform the small number of doctors who had previously accepted the invitation to attend the meeting but were unable to be present on the night about the content of the presentations. The companies considered that they had clearly pointed out to the recipients of the chairman's letter that the meeting was sponsored by them when they were first invited to attend.

Rhône-Poulenc Rorer and Merck did not consider that they had either acted against the spirit of the Code or breached it.

PANEL RULING

The Panel noted that the letter received by the complainant had provided a summary of the main points raised at a meeting which had been sponsored by Rhône-Poulenc Rorer and Merck. The chairman of the meeting had agreed, with an area business manager from Rhône-Poulenc Rorer, to write the letter for the benefit of those doctors who had not been able to attend the meeting. The letter had been compiled from the chairman's own notes and those of a senior representative. Although the letter had been printed on the chairman's own notepaper it had been distributed by local representatives. The Panel considered that as the companies had been involved in the compilation of the letter and were responsible for its distribution, it had to be regarded as promotional material subject to the Code. In consequence certain requirements of the Code had not been met. Prescribing information should have been included. The letter should have been certified.

The letter had been written on the chairman's own personal notepaper; it was his address which appeared in the top right-hand corner of the paper. The letter had been signed by the chairman and appeared to be an independent letter from him which was not so. The letter was a report of a meeting sponsored by Rhône-Poulenc Rorer and Merck and the companies had been involved in producing and distributing the letter which referred to their product nicorandil (Ikorel). This was not mentioned. The Panel considered that the letter constituted disguised promotion for Ikorel and a breach of Clause 10.1 was ruled.

The Panel noted that at the time the complaint was received the Authority was unaware of the involvement of the representatives in the preparation and distribution of the letter. If it had been so aware the companies would have been asked to bear in mind the requirements of Clause 15.2 of the Code. It appeared to the Panel that the representatives had failed to comply with the relevant requirements of the Code.

The Panel considered that although the letter had not been signed by the chairman in his official capacity as secretary of the local medical committee, given that it was distributed locally many of the recipients would have known him as such. This was not however relevant in this instance as far as the Code of Practice was concerned.

The complainant had noted that the letter advocated the use of nicorandil monotherapy to treat angina patients; he considered this quite contrary to standard procedure. The companies had not responded on this point. In a subsequent letter, received after the companies had responded to the complaint but before the Panel had considered it, the complainant stated that his main point was that nicorandil was advised as second line treatment but the letter from the chairman had suggested that it should be used as first line treatment. The Panel noted that it had ruled no breach of the Code in a previous complaint in which identical concerns had been expressed. In Cases AUTH/812/12/98 and AUTH/813/12/98 a hospital drug information pharmacist complained about the use of the phrase 'Think Ikorel first…'. The complainant had noted that national guidelines and general cardiology opinion was that beta-blockers should always be used as the medicines of first choice in angina. The Panel had noted that the indication for Ikorel in its summary of product characteristics (SPC) was for the prevention and long-term treatment of chronic stable angina pectoris. There was no statement in the SPC to suggest that Ikorel could only be used as a second line medicine, for instance if the use of a beta-blocker was otherwise contraindicated. The Panel had considered that the SPC did not preclude the use of Ikorel as a first line agent. The Panel had considered that the promotion of nicorandil as a first line treatment was not unacceptable and had ruled no breach of Clause 7.2. The ruling of no breach of Clause 7.2 of the Code had not been appealed by the complainant. In accordance with Paragraph 5.1 of the Constitution and Procedure for the Authority the Director had allowed the new complaint to proceed as the previous case had not been appealed.

The Panel considered that its ruling in Cases AUTH/812/12/98 and AUTH/813/12/98 would also apply to the new complaint. The Panel therefore ruled no breach of Clause 7.2 of the Code.

Complaint received **1 July 1999**

Case completed **23 August 1999**

CASE AUTH/896/7/99 *NO BREACH OF THE CODE*

DIRECTOR v GLAXO WELLCOME

Possible breach of undertaking

A university professor complained about a claim in a Seretide advertisement issued by Glaxo Wellcome which had appeared in the BMJ. The claim had previously been ruled in breach of the Code and this ruling had been accepted by Glaxo Wellcome.

Paragraph 5.1 of the Constitution and Procedure allowed the Director discretion in certain circumstances as to whether to proceed with a complaint that was closely similar to one that had been the subject of a previous adjudication. The Director decided that the complaint should not proceed.

The complaint had, however, raised a possible breach of undertaking and the matter was taken up as a complaint by the Director as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with advice previously given by the Appeal Board.

The Panel noted that the lead time for the journal was eleven days, the date that the undertaking had been returned was 22 June and the advertisement had appeared in the 26 June issue of the BMJ. In the circumstances the Panel did not accept that Glaxo Wellcome had failed to comply with its undertaking and no breach of the Code was ruled.

COMPLAINT

A university professor complained about an advertisement for Seretide (ref GEN 25942/February 1999) issued by Glaxo Wellcome UK Limited which appeared in the BMJ, 26 June 1999.

Attention was drawn to the claim 'Seretide is the first preventative medication to improve lung function on day one, which may aid compliance.'

The Authority noted that the claim at issue was similar to that considered in a previous case, Case AUTH/866/4/99, which concerned a Seretide leavepiece, wherein it was alleged that the claim was misleading and incapable of substantiation. Seretide was a combination of salmeterol and fluticasone, each of which had been available separately for a number of years. Glaxo Wellcome had accepted that Seretide might not be the first preventative medication to improve lung function on the first day of treatment. The Panel had ruled a breach of Clause 7.2 of the Code. This had been accepted by Glaxo Wellcome.

Paragraph 5.1 of the Constitution and Procedure allowed the Director discretion as to whether to proceed with a complaint that was closely similar to one which had been the subject of a previous adjudication if new evidence was provided or if the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint. The Director decided that the circumstances were such that the complaint about the claim should not proceed.

The complaint had, however, raised a possible breach of undertaking and the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with advice previously given by the Appeal Board.

RESPONSE

Glaxo Wellcome was particularly concerned that the Authority might consider that it had not fulfilled the undertaking given in Case AUTH/866/4/99.

Despite a typographical error in the form of undertaking, Glaxo Wellcome assured the Authority that it had clearly understood that the advertisement and all promotional material containing the claim 'Seretide is the first preventative medication …' should cease as from Friday, 25 June 1999, as noted in the letter from the Authority dated 10 June 1999.

The situation was that it was not possible to prevent publication of the advertisement in the BMJ following the decision to withdraw this claim.

Following discussions with the marketing department, the print buyers and the BMJ advertisement sales manager, the actual deadline for a copy change for the edition of the BMJ in question was 15 June 1999. A letter from the BMJ confirming this was provided. Under Paragraph 7.2 of the Constitution and Procedure, Glaxo Wellcome submitted that it had conformed to the undertaking in demanding that the offending advertisement was not placed with any publications after 25 June.

The company confirmed that it continued to abide by both the letter and the spirit of the Code. It strongly denied any breaches of the Code.

PANEL RULING

The Panel noted the timing of various letters etc in the previous case, Case AUTH/866/4/99. Glaxo Wellcome had stated in its response dated 28 April 1999 that it accepted that Seretide might not be the first preventative medication to improve lung function on the first day of treatment and that the claim represented an inadvertent breach of the Code. Glaxo Wellcome was advised on 10 June that the Panel had ruled the claim to be in breach of Clause 7.2 of the Code. Glaxo Wellcome stated in a letter dated 22 June that it accepted the Panel's ruling and the claim had already been changed in all new material. The undertaking stated that the date the material was last used was 21 June 1999.

Turning to the case now before it, Case AUTH/896 /7/99, the Panel noted that the minimum lead time for withdrawing an advertisement from the BMJ was 11 days prior to the publication date. To have stopped the advertisement at issue appearing in the BMJ dated 26 June 1999 it would have had to have been withdrawn by 15 June 1999.

The Panel noted that if Glaxo Wellcome had withdrawn the advertisement immediately on receiving details of the Panel's ruling which had confirmed the company's previous acceptance of a breach of the Code, the advertisement would not have appeared in the 26 June issue of the BMJ. This would have been the preferred course of action.

It was not the case, as Glaxo Wellcome had stated in its response, that the Authority had told it that use of the claim '… should cease as from Friday, 25 June …'. That was the day by which the undertaking and assurance had to be provided or an appeal lodged.

The Panel was concerned that Glaxo Wellcome stated in its response to the new case that the advertisement would not be placed in any publication after 25 June. In the Panel's view this was unacceptable. The undertaking given in the previous case required more than this in that advertisements already placed with a journal but ruled in breach should be actively withdrawn forthwith and not just cease to be placed. It was not the date an advertisement was placed that was at issue but the date on which it appeared. The lead times for journals etc were a factor that would be taken into account. With monthly journals for example this could mean that an advertisement ruled in breach appeared some time after it should have been withdrawn.

The Panel noted that the undertaking in Case AUTH/866/4/99 had been returned on 22 June and the advertisement had appeared in the BMJ on 26 June. The lead time for the journal was eleven days. In the circumstances the Panel did not accept that Glaxo Wellcome had failed to comply with its undertaking and therefore no breach of Clause 21 of the Code was ruled. The Panel also ruled no breach of Clause 2 of the Code.

The Panel noted that the Authority itself had raised the matter of a potential breach of undertaking. It had not been raised by the complainant. In the circumstances the complainant did not have the right to request that this ruling be appealed.

Proceedings commenced 6 July 1999

Case completed 28 July 1999

CASE AUTH/898/7/99

GENERAL PRACTITIONER v GOLDSHIELD

Fenbid Forte 10% Gel mailing

A general practitioner complained about a mailing introducing an extension to the Fenbid (ibuprofen) range, Fenbid Forte 10% Gel, which he had received from Goldshield. The mailing consisted of a 'Dear Doctor' letter with a tear-off competition entry form and a leaflet which compared Fenbid Forte 10% Gel with the market leading ibuprofen 5% gel.

The Panel noted that the competition consisted of three multiple choice questions. The answers to the questions could be found in the mailing. The competition had ten aerobic walkers as prizes each of which cost £100, excluding VAT. The Panel had a number of concerns. Firstly, it did not accept that the aerobic walkers were relevant to the practice of medicine. In the Panel's view they were items of personal exercise equipment. Secondly, the Panel queried whether ten prizes fell within the definition of 'few' as in the supplementary information to the Code. Thirdly, the Panel did not consider that the competition was a *bona fide* test of skill. The Panel ruled that the competition was in breach of the Code. This ruling was upheld by the Appeal Board upon appeal by Goldshield.

Fenbid Forte 10% Gel was described in the mailing as less than half the price of the market leading ibuprofen 5% gel. The Panel noted Goldshield's submission that this was based on the fact that, as Fenbid Forte was twice the strength of ibuprofen 5% gel, patients would use half as much. Thus a 100g tube of Fenbid Forte (£6.50) would last twice as long as a 100g tube of ibuprofen 5% gel (£6.53). The Panel considered that this argument was only valid if patients did use half as much of the gel and if at least 100g of Fenbid Forte was required to complete a course of treatment. Given the nature of topical products usage rates would be imprecise and likely to vary from patient to patient. It was difficult to imagine that a patient who used only enough 5% gel to thinly cover an area (as recommended in the summary of product characteristics) could, in practice, use half as much Fenbid Forte, assuming both products were to be used at their maximum dosage frequency. In the short term treatment of acute conditions such as sprains, strains and sports injuries the cost of a whole tube was a relevant factor given that one tube of either product was likely to be the usual prescription. The whole tube had to be paid for even if only part of it was used. The Panel considered that the description of Fenbid Forte 10% Gel being half the price of, or lasting twice as long as, the market leading ibuprofen 5% gel, was misleading and a breach of the Code was ruled. Upon appeal by Goldshield, the Appeal Board considered that it was not acceptable to state that one tube of Fenbid Forte 10% would last twice as long as one tube of ibuprofen 5% gel given the differences between the dosing schedules. It was not possible to categorically state that the dose of Fenbid Forte 10% was half that of ibuprofen 5% gel. The Appeal Board considered that the description of Fenbid Forte 10% Gel being half the cost of the market leading ibuprofen 5% gel was misleading and upheld the Panel's ruling of a breach of the Code.

The claim '… a new topical NSAID that lasts twice as long' appeared in the top right hand corner of the 'Dear Doctor' letter. It was not clear as to what aspect of the medicine it was referring and nor did it state that with which the medicine was being compared. The Panel considered that the claim was misleading and ruled a breach of the Code. This ruling was upheld by the Appeal Board on appeal by Goldshield.

A general practitioner complained about a mailing he had received from Goldshield Pharmaceuticals. The mailing consisted of a 'Dear Doctor' letter (ref LFG03) introducing the reader to a line extension to the Fenbid range – Fenbid Forte 10% Gel (ibuprofen 10%). A tear-off competition entry form (ref FG059M02) at the bottom of the letter gave details of a competition in which three multiple choice questions had to be answered for the chance to win one of ten aerobic walkers. There was also a leaflet sent with the mailing (ref MFG02) which compared Fenbid Forte 10% Gel with the market leading ibuprofen 5% gel; a 100g tube of each gel cost £6.50 and £6.53 respectively. It was stated that the average gel application of Fenbid Forte 10% Gel was 2 to 5cm and that of the market leading ibuprofen 5% gel was 4 to 10cm. A diagram of the nozzle end of two tubes showed half the length of gel extruding from a tube of Fenbid Forte 10% Gel compared with a tube of ibuprofen 5% gel. The leaflet featured the claims 'Double the strength', 'Less than half the cost'.

COMPLAINT

The complainant stated that apart from a certain uneasiness about the ethics of offering him the chance to win expensive exercise equipment, he had specific concerns about two of the claims which were made in the mailing.

In the complainant's view it was most unusual for the letter to describe as 'less than half the price' a product priced at £6.50 per 100g in direct comparison with another priced almost identically at £6.53 per 100g. 'Twice the strength' perhaps, but 'half the price'? Surely not.

Being an occasional prescriber of another topical NSAID, Ibugel, the complainant was surprised to note the cost-per-dosage comparison on the leavepiece. The leavepiece ascribed a '4 to 10cm' dosage to the 'market leading ibuprofen gel – £6.53' (which could only be Ibugel). However, as far as the complainant could tell from MIMS and the Data Sheet Compendium, there was no specific, quantitative dose recommendation for Ibugel. Its data sheet recommended applying 'only enough to thinly cover the affected area'.

Finally, the letter announced Fenbid Forte as a 'new topical NSAID that lasts twice as long'. Did this mean slow-release or prolonged analgesia? Doctors ought to be told.

RESPONSE

Goldshield noted that the complainant had suggested that the prizes offered in the mailing were expensive. According to Clause 18.2 of the Code the maximum acceptable cost to the donor of a prize in a promotional competition was £100, excluding VAT. Goldshield stated that the aerobic walkers in question fell within this guideline and a copy of the relevant invoice was enclosed.

Goldshield noted that the general practitioner also indicated that he did not understand why the company had stated that Fenbid Forte 10% was half the price of the market leading 5% gel. The reasoning behind this was based on information contained in the licence issued by the Medicines Control Agency (MCA) for Fenbid Forte and Fenbid 5%.

Goldshield stated that Fenbid 5% Gel had to be shown to be essentially similar to the market leader in order to obtain its licence, and dosage instructions were approved by the MCA accordingly (4-10cm (50-125mg) no more frequently than every four hours and only four times in 24 hours). Due to Fenbid 10% being double the strength of 5% gels the MCA indicated that a dosage of half that of 5% gels would be necessary (2-5cm (25-62.5mg) etc).

Applying half the normal dose from the same size tube should offer the patient twice the number of doses for the same price. If the tubes were the same price then the gel in the 10% tube would be half the price of that in the 5% tube. Goldshield stated that as the market leader was £6.53/100g of 5% gel it seemed logical that Fenbid Forte 10% was less than half the price of it at £6.50 with twice the number of doses contained within. The company noted that Clause 7.2 stated that claims of superior potency in relation to weight were relevant where there was 'a practical advantage, for example, reduction in side-effects or cost of effective dosage.'

Goldshield noted that the third point made by the complainant related to the fact that the data sheet for the market leader did not give a specific dose to be applied. This implied that the company should not be able to make a comparison of the cost-effectiveness of the two. There might be no stated dose, however, the doses approved for Fenbid by the MCA were based on the fact that Fenbid 5% Gel was considered by the MCA to be essentially similar to the market leader. A direct comparison in dose to Fenbid 5% Gel therefore should also apply to the market leader.

In stating that Fenbid Forte 'lasts twice as long' Goldshield stated that it was referring to the length of time one 100g tube would last a patient compared to a 100g tube of 5% ibuprofen gel if the dosage instructions were followed as explained earlier and as recommended by the MCA. The company considered that this was made clear by the diagram showing that half the amount of gel was required in comparison to 5% gels.

PANEL RULING

The supplementary information to Clause 18.2 (Competitions and Quizzes) stated, inter alia, that any competition must be a bona fide test of skill and must recognise the professional standing of the recipient. Prizes of a higher value than would ordinarily be acceptable for a promotional aid were only acceptable where the competition was a serious one and the prizes few in number, relevant to the potential recipient's work and not out of proportion to the skill required in the competition. The maximum acceptable cost to the donor of a prize in a promotional competition was £100, excluding VAT.

The Panel noted that the competition consisted of three multiple choice questions. The answers to the questions could be found in the mailing. The competition had ten aerobic walkers as prizes each of which cost £100, excluding VAT.

The Panel had a number of concerns about the competition. Firstly it did not accept that the aerobic walkers were relevant to the practice of medicine. In the Panel's view they were items of personal exercise equipment and in that regard noted that they were described as 'just the job for toning those hips and thighs!' on the competition entry form. The Panel queried whether ten prizes fell within the definition of 'few'. Thirdly the Panel did not consider that the competition was a bona fide test of skill. The Panel considered that the competition was in breach of Clause 18.1 of the Code and ruled accordingly.

The Panel noted that Goldshield had not identified the market leader ibuprofen 5% gel. The complainant had referred to Ibugel and the cost of Ibugel at £6.53 per 100g tube was the same as the cost for ibuprofen 5% gel given in the mailing.

Fenbid Forte 10% Gel was described in the mailing as less than half the price of the market leading ibuprofen 5% gel. The Panel noted Goldshield's submission that this was based on the fact that, as Fenbid Forte was twice the strength of ibuprofen 5% gel patients would use half as much. Thus a 100g tube of Fenbid Forte (£6.50) would last twice as long as a 100g tube of ibuprofen 5% gel (£6.53). The Panel considered that this argument was only valid if patients did use half as much of the gel and if at least 100g of Fenbid Forte was required to complete a course of treatment.

The Panel noted that the dose of Fenbid Forte was 25 to 62.5mg (2 to 5cm) of the gel up to four times daily. Treatment should be reviewed after two weeks, especially if the symptoms worsened or persisted. Ibugel was to be applied up to three times daily. On each occasion only enough gel to thinly cover the affected area was to be applied. Therapy should be reviewed after a few weeks particularly if symptoms worsened or persisted (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). The Panel noted Goldshield's submission regarding the dosage instructions for its ibuprofen 5% gel (Fenbid 5%; 100g, £5.25). The comparisons made in the mailing, however, were with the market leading ibuprofen 5% gel (Ibugel; 100g, £6.53) and its dosage instructions differed slightly from Fenbid 5%. The Panel noted, however, that a product's summary of product characteristics (SPC) or its data sheet represented the agreed information about a product and so the comparisons had to be made on the basis of the Ibugel SPC.

The Panel noted that given the nature of topical products usage rates would be imprecise and likely to vary from patient to patient. It was difficult to imagine that a patient who used only enough Ibugel, three times daily, to thinly cover an area could, in practice, use half as much Fenbid Forte when applied four times daily, assuming both products were to be used at their maximum dosage frequency. In the short term treatment of acute conditions such as sprains, strains and sports injuries the Panel considered that the cost of a whole tube was a relevant factor given that one tube of either product was likely to be the usual prescription. The whole tube had to be paid for even if only part of it was used.

The Panel considered that the description of Fenbid Forte 10% Gel being half the price of, or lasting twice as long as, the market leading ibuprofen 5% gel was misleading and a breach of Clause 7.2 was ruled.

The claim '… a new topical NSAID that lasts twice as long' appeared in the top right hand corner of the 'Dear Doctor' letter. It was not clear as to what aspect of the medicine it was referring nor did it state that with which the medicine was being compared. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2.

APPEAL BY GOLDSHIELD

Goldshield stated it would raise each point in turn, but firstly it wished to state that the campaign centred around Fenbid 10% being double the strength of 5% ibuprofen gels and that half the dose of these was therefore recommended. The key message that should come across in this mailing was how the cost-effectiveness of Fenbid Forte 10% was improved in comparison to 5% ibuprofen gels as a result of this difference in strength.

Goldshield took great care to adhere to the Code and the production of this mailing was no exception. Goldshield did not accept that it was in breach of the Code on this occasion for the following reasons:

1 The complainant had suggested that the prizes involved were 'expensive'. According to Clause 18.2 of the Code – 'The maximum acceptable cost to the donor of a prize in a promotional competition is £100, excluding VAT.' The aerobic walkers in question fell within this guideline and a copy of the relevant invoice was provided. Goldshield acknowledged that the cost of the individual prizes were £100, but they were within the limit allowed.

2 The general practitioner also indicated that he did not understand why Goldshield had stated that Fenbid Forte 10% was half the price of the market leading 5% gel. The reasoning behind this was based on information contained in the licence for Fenbid Forte and Fenbid 5%.

Fenbid 5% gel had to be shown to be 'essentially similar' to the market leader in order to obtain its licence, and dosage instructions were approved by the MCA accordingly (4-10cm) (50mg-125mg) no more frequently than every four hours and only four times in 24 hours. Due to Fenbid 10% being double the strength of 5% gels, the MCA indicated that a dosage of half that of 5% gels would be necessary (2-5cm) (25mg-62.5mg), etc.

Applying half the normal dose from the same size tube should offer the patient twice the number of doses for the same price. If the tubes were the same price, then the gel in the 10% tube would be half the price of that in the 5% tube. As the market leader was £6.53/100g of 5% gel it seemed logical that Fenbid Forte 10% was less than half the price of it at £6.50, with twice the number of doses contained within. Clause 7.2 stated that claims of superior potency in relation to weight were relevant where there was 'a practical advantage, for example, reduction in side-effects or cost of effective dosage.' Due to the licence granted by the MCA, a reduced amount equivalent to half that of 5% could be given.

3 The third point made related to the fact that the data sheet for the market leader did not give a specific dose to be applied. This implied that Goldshield should not be able to make a comparison of the cost-effectiveness of the two. There might be no stated dose, however, the doses approved for Fenbid were based on the fact that Fenbid 5% Gel was considered to be 'essentially similar' to the market leader. A direct comparison in dose to Fenbid 5% Gel therefore should also apply to the market leader.

4 Finally, Goldshield had adhered to the Code in stating that Fenbid Forte 10% was 'new', as there had never been a 10% ibuprofen gel available and Fenbid Forte had been on the market for less than 12 months (Clause 7.9).

In saying that Fenbid Forte 'lasts twice as long', Goldshield was referring to the length of time one 100g tube would last a patient, compared to a tube of 100g 5% ibuprofen gel if the dosage instructions were followed, as explained earlier and as recommended by the MCA. Goldshield considered that this was made clear by the diagram showing that half the amount of gel was required in comparison to 5% gels.

In conclusion, Goldshield had applied dosages as the licence indicated and compared them to 5% gels, which allowed the general practitioner to save considerable money from his practice budget.

APPEAL BOARD RULING

The Appeal Board considered that the competition was not a bona fide test of skill. It did not accept that the aerobic walkers offered as prizes were relevant to the practice of medicine. They were items of personal exercise equipment. The Appeal Board considered that the competition failed to meet the requirements of Clause 18.2 of the Code. It was not possible to breach Clause 18.2 which gave an exemption to the requirements of Clause 18.1. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 18.1 of the Code.

The appeal on this point was thus unsuccessful.

The Appeal Board examined the mailing which announced the launch of Fenbid Forte 10% Gel. The mailing compared the cost of Fenbid Forte 10% with

the market leading ibuprofen 5% gel. The cost comparisons were referenced to MIMS May 1999 which gave the cost of a 100g tube of Fenbid 5% as £5.25, a 100g tube of Fenbid Forte 10% as £6.50 and a 100g tube of Ibugel 5%, the market leader, as £6.53.

The Appeal Board noted Goldshield's submission that Fenbid 5% Gel had been shown to be essentially similar to the market leader, Ibugel, in order to obtain its licence. The products however had different dosing schedules which the Appeal Board considered unusual as Fenbid 5% had been licensed on the basis of its essential similarity to Ibugel. Fenbid 5% was to be used at 4-10cm (50-125mg) only four times in 24 hours. The dosing schedule for Ibugel was for it to be applied up to 3 times daily and on each occasion only enough gel to thinly cover the affected area was to be applied. Therapy should be reviewed after a few weeks particularly if symptoms worsened or persisted. The Appeal Board did not accept that it was appropriate to assume that the dose of Ibugel was the same as the dose of Fenbid 5% and thus half the licensed dose of Fenbid 10%.

The Appeal Board considered that the situation was more complicated than the impression given in the mailing. In order for savings to be made by the practice further qualification and explanation needed to be given. If the patient needed one 100g tube of ibuprofen 5% to treat the condition the difference in cost between Fenbid 10% and Ibugel was 3 pence (£6.50 v £6.53). It was accepted that it would be likely that there would be more gel left over in the Fenbid 10% tube than in the Ibugel tube. The whole tube nevertheless had to be paid for. It was not always the case that treatment with Fenbid 10% would cost less than half that of ibuprofen 5% gel.

If Fenbid 5% was used the difference was £1.25. For short term treatment Fenbid Forte 10% would be more expensive. There would perhaps be savings if the products were used long term and more than one tube of ibuprofen 5% was needed. Two tubes of Fenbid 5% would in theory last as long as one tube of Fenbid Forte 10%. In the Appeal Board's view it was not acceptable to state that one tube of Fenbid Forte 10% would last twice as long as one tube of Ibugel given the differences between the dosing schedules. It was not possible to categorically state that the dose of Fenbid Forte 10% was half that of Ibugel.

The Appeal Board considered that the description of Fenbid Forte 10% Gel being half the cost of the market leading ibuprofen 5% gel was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point was thus unsuccessful.

The Appeal Board considered that the claim '… a new topical NSAID that lasts twice as long' was not clear as to what aspect of the medicine it was referring nor did it state that with which the medicine was being compared. The claim was misleading and unqualified as there was no reference to dose. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point was thus unsuccessful.

Following its consideration of this case the Appeal Board was concerned that a claim 'Double the active ingredient to melt away pain' implied that the efficacy of Fenbid Forte 10% was an improvement on ibuprofen 5% gel. The Appeal Board noted Goldshield's submission that the data showed that the products had similar efficacy. In the Appeal Board's view the claim was misleading and potentially in breach of Clause 7.2 of the Code. The Appeal Board requested that its concerns be drawn to Goldshield's attention.

Complaint received **9 July 1999**

Case completed **13 October 1999**

CASE AUTH/899/7/99

NAPP v JANSSEN-CILAG

Promotion of Durogesic

Napp complained about the promotion of Durogesic (fentanyl transdermal patch) by Janssen-Cilag and alleged that claims that the product caused fewer unpleasant side effects than sustained release (SR) morphine were misleading and unsubstantiated. The Panel noted that the study referenced to a claim 'The strength of SR morphine with fewer unpleasant side effects' reported more adverse events with transdermal fentanyl treatment although significantly fewer patients considered that it caused side effects compared to morphine. The Panel considered that the claim was not a fair reflection of the study and a breach of the Code was ruled.

Napp alleged that claims that Durogesic caused less constipation than SR morphine were misleading. Napp referred to a recent audit which did not represent robust clinical data but supported anecdotal reports from clinical practice that Durogesic was not associated with less constipation than SR morphine. The Panel noted that the study to which the claims were referenced concluded that fentanyl treatment was associated with significantly less constipation than morphine. The claim 'Less constipation … than SR morphine' was a fair reflection of the study. No breach of the Code was ruled.

Napp Laboratories Limited submitted a complaint about promotional material for Durogesic (fentanyl transdermal patch) issued by Janssen-Cilag Ltd. Durogesic was indicated for the management of chronic intractable pain due to cancer. Napp produced MST Continus, a sustained release (SR) formulation of morphine sulphate for the prolonged relief of severe and intractable pain. The complaint concerned claims which appeared in two promotional items; a leavepiece (ref 603974) and an advertisement (ref 00262A).

COMPLAINT

Napp alleged that claims that Durogesic caused fewer unpleasant side effects than SR morphine and less constipation than SR morphine were misleading, unsubstantiated and in breach of Clauses 7.2 and 7.7 of the Code. The claims were supported with a paper by Ahmedzai and Brooks (1997). Napp considered that this study was inadequately designed to support these claims.

Napp stated that Ahmedzai and Brooks performed an open, two-part, crossover study comparing Durogesic with SR oral morphine. The study was sponsored by the Janssen Research Foundation. Although the study was used to support the claim that Durogesic was associated with fewer unpleasant side effects than SR morphine, it was noted that more adverse events were reported during fentanyl treatment. Indeed table 5 of the study (commonest adverse events) indicated that there were 148 reports in the Durogesic group and 92 in the SR morphine group. An event described as adverse implied that it was unpleasant. The data from this study therefore did not support the claim that Durogesic was associated with fewer unpleasant side effects than SR morphine.

The study was also used to support the claim that Durogesic was associated with significantly less constipation than SR morphine. Although this was a conclusion of the authors Napp considered that the study had two major flaws in its design and, as a result, did not support this claim.

1 The study was not blinded

The study was an open assessment and was therefore susceptible to bias in the assessment of pain control, the collection of adverse events and the assessment of acceptability of therapy. Until several double-blind, randomised, controlled trials were conducted Napp believed that no claim relating to superior efficacy or tolerability could be made in favour of Durogesic over SR morphine.

Patient and investigator bias, inherent in open studies, could clearly affect outcomes. The removal of this bias, by blinding both parties, could sometimes lead to unexpected results. This was seen clearly in a double-blind, randomised, placebo-controlled trial, sponsored by Janssen Pharmaceutica, in which Durogesic was compared with placebo in the treatment of cancer pain. The results showed that Durogesic was not superior to placebo in terms of analgesic efficacy.

2 The study did not compare equi-analgesic doses of opioids

It was clear on analysis of secondary efficacy measures that patients in both treatment groups did not receive equi-analgesic doses of opioids. Rescue medication was used on average for 53.9% of days during Durogesic treatment compared with 41.5% of days for SR morphine treatment ($p=0.0005$). The number of doses of rescue medication taken per day in both groups was 1.64 for fentanyl and 1.24 for morphine. Patients treated with SR morphine reported significantly less sleep disturbance than those treated with Durogesic. These findings supported the conclusion that comparison was not made of equi-analgesic doses.

Patients entering the trial had previously had their pain controlled with morphine. It was stated that two cases of withdrawal effects were reported in the study during Durogesic treatment and that other adverse experiences might have been associated with morphine withdrawal. Abdominal pain (18 with fentanyl v 0 with morphine) agitation or anxiety (10 v 5) sweating (12 v 5) and flu like symptoms (5 v 0) all might indicate opioid withdrawal. The emergence of withdrawal symptoms during treatment with Durogesic was strong evidence to suggest that

patients did not receive equi-analgesic doses of opioid.

The decreased incidence of constipation seen in the fentanyl treated patients could be a function of reduced opioid administration *per se* or might be a result of opioid withdrawal. The claim that Durogesic caused less constipation than SR morphine was therefore misleading and in breach of Clause 7.2 of the Code.

Evidence did exist to suggest that Durogesic had no advantages over morphine in terms of constipation. A recent audit performed by Davies and Prentice (1997) suggested that Durogesic was less efficacious than other opioids and had a similar adverse event profile. Although this audit did not represent robust clinical data and would not support a promotional claim, it supported anecdotal reports from clinical practice that Durogesic was not associated with less constipation than SR morphine.

RESPONSE

Janssen-Cilag noted that this complaint was very technical in nature. It related to the design and interpretation of complex clinical trials data in a very complex setting, namely the use of strong opioids in terminally ill patients with cancer pain. As a consequence the company considered it was necessary to provide some detailed background information to help put its response into the appropriate context.

Janssen-Cilag explained that in recognition of the need for better and more consistent treatment of cancer pain, the World Health Organisation (WHO) published an analgesic ladder which provided a clear guide to the choice of therapy. The WHO ladder consisted of three key steps for pain management: Step 1, simple analgesia such as aspirin or paracetamol; Step 2, a weak opioid such as codeine, if pain persisted and Step 3, strong opioid analgesia for pain persisting despite the use of weak opioids. This included immediate release morphine and sustained release morphine (MST) and fentanyl (Durogesic).

Not all strong opioids had the same basic molecular structure and consequently they varied in their physico-chemical, pharmacodynamic and pharmacokinetic properties. Morphine was the principal alkaloid with a relative potency of 1 while fentanyl was a chemically distinct 4-anilopiperidine with a relative potency of 50-100. The low molecular weight and high lipophilicity of fentanyl allowed it to permeate the skin easily which made it suitable for transdermal administration. In addition, the higher lipophilicity enabled fentanyl molecules to cross more readily the blood-brain barrier to enter the central nervous system, a property that in part explained why fentanyl (Durogesic) was less constipating than SR morphine.

Janssen-Cilag stated that it was also important to provide some details of the practical use of Durogesic and MST as these products were very different in nature and these differences were at the heart of the complaint.

Durogesic was licensed for the management of chronic intractable pain due to cancer. It was a transdermal strong opioid patch that contained fentanyl. The patch was designed to deliver fentanyl through the skin into the systemic circulation for up to 72 hours (three days) thus avoiding the direct action of opioids on the bowel wall nerve plexus, causing constipation. Like morphine, fentanyl had a high degree of affinity and selectivity for the μ opioid receptor, where it acted as a pure agonist. Analgesic fentanyl concentrations in the plasma could be expected within 6-12 hours of the first application. Fentanyl plasma concentrations rose steadily for the first 12-24 hours and once peak levels were reached they remained relatively constant for 72 hours and could be maintained by patch replacement every 72 hours thereafter. The Durogesic patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy was attained. If analgesia was insufficient at the end of the initial application period the dose might be increased. Dose adjustment, when necessary, should normally be performed in 25μg/h increments, although the supplementary analgesic requirements (oral morphine 90mg/day ≈ Durogesic 25μg/h) and pain status of the patient should be taken into account. Patients might require periodic supplemental doses of immediate release morphine (which provided pain relief for up to 4 hours) for 'breakthrough' pain. There was no immediate release fentanyl product available in the UK. One patch strength of Durogesic covered a wide range of SR morphine doses (eg a 50 μg/h patch covered 135-224mg morphine/day – this information was relevant when considering the difficulties in blinding studies).

Again, fundamental to this complaint was the issue of the issue of breakthrough pain relief. Breakthrough pain occurred for two reasons:

a) During dose titration

The correct dose of a sustained release strong opioid required to provide effective analgesia was determined by titrating the dose for an individual to achieve pain relief. During the titration phase, the dose of sustained release analgesia might not be sufficient and supplemental doses of immediate-release morphine were required until the dose of sustained release opioid could be optimised. Regular breakthrough pain indicated that the dose of sustained release opioid should be increased.

b) For incident pain

Incident pain was pain that was not controlled by the background sustained release opioid analgesia. It occurred as a result of an incident such as a procedure (eg dressing changes) or movement. Short acting breakthrough medication would usually be required but, unlike use during titration, this would be infrequent.

Janssen-Cilag stated that MST Continus Tablets (MST) were modified release, film-coated tablets containing morphine sulphate. MST was indicated for the prolonged relief of severe and intractable pain. MST should be used at 12 hourly intervals. A copy of the data sheet was provided. As with Durogesic, the dosage was dependent on the severity of the pain. A patient presenting with severe pain uncontrolled by a

weaker opioid (eg dihydrocodeine) should normally be started on 30mg 12 hourly. The correct dosage of MST for any individual patient was that which was sufficient to control pain with no, or tolerable, side effects for a full 12 hours. Patients were titrated to appropriate pain control using immediate release morphine to relieve pain until the correct dose was established.

With regard to the specific allegations made by Napp, Janssen-Cilag noted that they were based on four assertions.

Assertion 1 – the data in the Ahmedzai and Brooks paper did not support the claim that Durogesic had 'The strength of SR morphine with fewer unpleasant side effects'. Janssen-Cilag presumed that this related to Clause 7.7 of the Code.

Janssen-Cilag noted that it had sponsored the Ahmedzai and Brooks study which had been published in the Journal of Pain and Symptom Management which was a well respected, peer reviewed journal. As sponsors of the study Janssen-Cilag had access to the full clinical data which due to space limitations could often not be included in publications.

The data presented in table 5 of the paper showed the occurrence of adverse events and the complainant had misrepresented these as being synonymous with side effects. The International Conference on Harmonisation (ICH) had published definitions which helped explain the various terms used.

- adverse event: any untoward occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment.
- adverse drug reaction: a response to a drug which was noxious and unintended and which occurred at doses normally used in man for prophylaxis, diagnosis, or therapy or disease or for modification of physiological form.
- side effect: as per adverse drug reaction but this term had been used usually to describe not only negative (unfavourable) effects, but also positive (favourable) effects.

The data presented in the body of the Ahmedzai and Brooks paper stated that fewer patients considered that fentanyl caused side effects compared to morphine (40.4%, 51/126 patients for fentanyl v 82.5%, 104/126 for morphine, $p<0.001$). Furthermore, given the fact that the patients had all received morphine pre-study, then if bias was present it would tend to favour morphine (as patients might not have reported an already existing adverse reaction). Janssen-Cilag referred the Panel to the response to assertion 2 relating to the study design.

Janssen-Cilag therefore believed that the claim relating to side effects was accurate, balanced, fair, objective and unambiguous. The claim was also based on up-to-date data which was clearly reflected and was not misleading.

Assertion 2 – the Ahmedzai and Brooks study was not blinded and was therefore biased for assessment of pain control, the collection of adverse events and the acceptability of therapy. Several double-blind, randomised, controlled trials were required to make the claim. Janssen-Cilag presumed these formed the basis of the alleged breach of Clause 7.2 of the Code.

With regard to the unblinded study design, Janssen-Cilag explained that the Ahmedzai and Brooks study was carried out in 38 palliative care centres throughout the United Kingdom. Adult cancer patients who required strong opioid analgesia and were receiving a stable dose of morphine for at least 48 hours, and who had a life expectancy of more than 1 month were entered into the study. Immediate release oral morphine was made available throughout the study to treat 'breakthrough' pain but, apart from this, no other opioid analgesia was permitted.

Patients were randomised to receive either SR morphine or Durogesic for 15 days (period 1), followed by a further 15 days with the other medication (period 2). Dose conversion between morphine and fentanyl was as per the data sheet recommendations. Durogesic was replaced every 72 hours (3 days) and SR morphine administered every 12 hours. Immediate release morphine was used to relieve pain during titration at the start of the study and, as previously explained, for incident pain.

Patients underwent a medical examination and a baseline clinician's assessment of performance status and a self-rated assessment of quality of life at the beginning of the study using the WHO scale and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire respectively. Both scoring systems had been validated and extensively used in patients with advanced cancer. Patients reporting constipation or diarrhoea on the EORTC questionnaire were asked to provide further details of their bowel function. On the last day of each period, patients completed the EORTC questionnaire in which they answered questions on side effects, convenience of use, and effects on daily activities and on carers. Patients also kept diaries to record other parameters including the amount of rescue medication used. The Memorial Pain Assessment Card (MPAC) was used twice daily to record pain and mood. Investigators recorded adverse events.

Two hundred and two patients were entered into the study (101 per treatment group) which was analysed using acceptable statistical methodology.

Ideally, a comparative study of strong opioids would use a double-blind design but there were inherent problems. As Durogesic and SR morphine were different formulations, a blinded study could only be performed by using a double-dummy approach (ie where a patient received both patches and tablets, one of which was placebo). The main difficulty related to the correlation in dosing regimens which was dictated by the products' very different pharmacokinetics and the requirement for safe and effective use of immediate release morphine for breakthrough pain.

Janssen-Cilag outlined a hypothetical blinded study design to illustrate this particular point.

The two groups of patients were randomised to receive either active Durogesic and placebo SR

morphine, or placebo Durogesic and active SR morphine. A patient randomised to the group receiving active Durogesic and placebo SR morphine whose starting dose was insufficient to relieve pain, would require rescue medication for 3 days until a higher strength active patch could be applied (patches were titrated up every 3 days).

In contrast, a similar patient in the group receiving placebo Durogesic and active SR morphine whose starting dose was insufficient to relieve pain, would require rescue medication for less time as the shorter titration interval might lead to the establishment of an appropriate pain relieving dose more quickly (as the dose of SR morphine could be titrated every 12 hours).

The implications of this blinded design were manifold and were recognised by opinion leading palliative care clinicians who assisted in the design of this and other Janssen-Cilag clinical trials:

- In both groups of patients, no suitable advice could be given about the use of rescue medication which would need to vary depending on the treatment received to take into account the differing titration regimen.
- It was the patient who was best placed to decide whether to take breakthrough medication and it would be difficult for the patient to know whether it was appropriate.
- Patients would be potentially exposed to unnecessary pain and/or unacceptable risks with obvious ethical considerations.
- Patients who were not obtaining adequate pain relief were likely to withdraw from the study thus threatening the power of the study to detect differences.
- As explained above, the fact that one Durogesic patch covered a wide range of morphine doses meant that there would be differing titration of SR morphine between groups and this would unblind the study.

In conclusion, therefore, the normally accepted gold-standard of study design (double-blind randomised comparisons) could not, for a number of strong reasons, be applied for comparisons of Durogesic and SR morphine.

The question then arose as to whether bias was introduced which prevented use of the data in substantiation of the claim of superiority.

Janssen-Cilag stated that the open study design was carefully constructed to be a randomised, parallel, crossover study. It was accepted that bias could not be eliminated from the study but all measures to minimise its effect were taken. Ahmedzai and Brooks addressed this issue in their peer reviewed paper as follows: 'We acknowledge that the open design may have introduced bias in reporting of side effects, but the randomised design was used to ensure that this effect would have been present in both arms, and there was no a priori reason to expect this to have occurred with any one formulation.'

Janssen-Cilag concluded that interpretation of the data was not compromised by bias arising from the study design.

With regard to the assertion that several double-blind, randomised, controlled trials were required to make the claim, Janssen-Cilag noted that the Code did not require claims to be substantiated by one or more such trials.

In conclusion, the data published by Ahmedzai and Brooks was strong data given the complexities of controlled studies in this area, and therefore the claims based on this paper were accurate, balanced, fair, objective and unambiguous. Janssen-Cilag denied a breach of Clause 7.2.

Assertion 3 – the Ahmedzai and Brooks study did not compare equi-analgesic doses and therefore the decreased incidence of constipation was as a result of reduced opioid administration and opioid withdrawal. Janssen-Cilag presumed these related to the alleged breach of Clause 7.2 of the Code.

Janssen-Cilag noted that the complainant asserted that the difference in the amount of rescue medication administered between Durogesic treated and SR morphine treated patients demonstrated that the doses of Durogesic and SR morphine were not equi-analgesic (the dose being lower with Durogesic) and that this accounted for the difference in constipation. This assertion was based on the fact that rescue medication was used on significantly more days in the fentanyl treated group compared to the SR morphine treated group.

Equi-analgesia was measured by comparing two treatments in terms of the pain relief delivered. In this study pain control was assessed using various measures and no significant differences in any of these scales were detected between phases. By definition the two treatments compared, which were titrated according to the data sheet requirements (Durogesic ± immediate release morphine v SR morphine ± immediate release morphine), were equi-analgesic.

As discussed previously, differences in the amount of rescue medication were likely to be seen between the titration phase and stabilisation at a particular dose of sustained release product. In the Ahmedzai and Brooks study the difference in use of rescue medication between treatment groups declined over the last 7 days in each treatment phase (31.25% days with rescue medication for fentanyl v 27.8% for morphine, p=0.027). Moreover, the actual number of doses of rescue medication taken per day in both groups was small (in the last 7 days: 1.4 doses/day in fentanyl treated patients v 1.23 doses/day for morphine treated patients).

Ahmedzai and Brooks suggested that the use of morphine as a rescue medication in both arms of the study might have reduced the potential to reveal differences in side effects between the two treatments. In order to reduce the impact of rescue medication on constipation, the assessments of constipation were made at the end of each phase, when the number of patients undergoing titration was likely to be minimal, and consequently the use of immediate release morphine was minimised. Despite the

confounding effect of immediate release morphine, significantly fewer patients were constipated on transdermal fentanyl compared to SR morphine (27.2% v 44.5% respectively, p=0.002) in the last week. In addition, it should be noted that the data suggested that there was a lower tendency for painful/difficult and hard stools in those patients treated with fentanyl in the constipated patients.

In conclusion, the difference in use of breakthrough medication was not associated with differences in the level of analgesia and therefore this did not account for the lower incidence of constipation with Durogesic.

With regard to the assertion that the lower incidence of constipation was due to opioid withdrawal, Janssen-Cilag explained that it was accepted that up to 10% of patients would experience an opioid withdrawal when converted from morphine to Durogesic. There were two reasons, which might explain this phenomenon.

- Oral administration of opioids resulted in a direct effect on the bowel wall nerve plexus, causing constipation. Laxatives were administered to reduce the incidence of constipation. Transdermal administration, avoiding direct contact with the gut wall, eliminated this cause of constipation and thus the laxative dose was too high giving symptoms similar to opioid withdrawal. (Standard advice was to half the amount of laxatives when converting from morphine to Durogesic).
- Fentanyl crossed the blood-brain barrier more readily than morphine due to its higher lipophilicity. As a consequence, a lower concentration gradient, and thus lower plasma levels, were needed to enable sufficient fentanyl to enter the central nervous system to achieve adequate analgesia. A diagramatic representation was provided. The lower concentrations of fentanyl in the systemic circulation compared to morphine might therefore manifest as opioid withdrawal, which was primarily characterised by gastro-intestinal disturbance and predominately diarrhoea.

Both of the above reasons also explained why Durogesic was less constipating than SRM.

In the Ahmedzai and Brooks study, patients' constipation was assessed by using the EORTC QLQ-C30 questionnaire item on constipation and it was important to note that this assessment was made at the end of each study period. In addition, as stated previously, these findings were confirmed using the specific bowel questionnaire which showed a higher frequency of normal stool (p=0.002) in fentanyl treated patients compared to morphine. Furthermore, the data showed that there was no statistically significant difference in the incidence of diarrhoea. There was in fact no evidence of opioid withdrawal in this study.

In conclusion, the data from the Ahmedzai and Brooks study showed that Durogesic was less constipating than SR morphine and therefore the claims were accurate, balanced, fair, objective and unambiguous. Janssen-Cilag denied a breach of Clause 7.2.

Assertion 4 – that the Davies and Prentice audit was evidence that Durogesic was not less constipating than SR morphine. Janssen-Cilag presumed that this related to the alleged breach of Clause 7.7 of the Code.

Janssen-Cilag stated that the audit data, which were only published in abstract form, suggested that Durogesic was less efficacious than other strong opioids. These data were clearly at variance to the data presented by Ahmedzai and Brooks which were generated from a randomised controlled trial and showed that Durogesic had equivalent efficacy to SR morphine, and caused less constipation. Janssen-Cilag believed that the Davies and Prentice data represented early clinical use from launch of Durogesic in 1994 and the results might reflect a lack of experience with Durogesic which could be expected for a novel dosage form. In addition, in a published exchange of letters, the audit data showed that one month after conversion, 5 patients' laxatives had been decreased, 6 patients' laxatives had remained the same, and 8 patients' laxatives had been increased. There was no analysis of the distribution of the change, nor was there information on the doses of Durogesic used, and on the use of breakthrough pain medication and consequently the Davies and Prentice data did not convincingly argue against a body of evidence which showed that Durogesic was both effective and was associated with less constipation than SR morphine.

Janssen-Cilag stated that additional supportive data were available and reviewed some of the principal studies.

- **Megens *et al* (1998).** This was a proof of principle study. Comparative data on experimental pain in animals had demonstrated lower antidiarrhoeal activity in rats on fentanyl compared to morphine, given both subcutaneously and orally. The study compared the dose of either medicine required to produce analgesia with the dose needed to protect from castor-oil induced diarrhoea in rats. The required amount of naloxone, an opioid antagonist, to reverse opioid-induced antidiarrhoeal properties was thought to reflect the intensity of the intestinal effect. Considerably larger amounts of naloxone were needed to reverse the morphine (5.4mg/kg sc) than the fentanyl (0.19mg/kg sc) induced antidiarrhoeal effects.
- **The [Transdermal] – Fentanyl Multi-centre Study Group (1994).** Patients were entered into this study with malignant neoplastic disease requiring opioid analgesia and were stabilised on oral morphine for at least 48 hours prior to being switched to transdermal fentanyl according to a standard conversion. The dose of transdermal fentanyl was titrated according to clinical response. During the stabilisation phase (oral morphine) and fentanyl treatment phase, patients gave an assessment of their pain using 100mm visual analogue scales 3 times per day. Patient assessments of pain were expressed as percentages of the maximum possible area under the curve and were compared between phases using the

paired t-test. The incidence of nausea, vomiting and constipation during the two phases were compared using the Wilcoxon Matched-Pairs Signed-Ranks test. There was a statistically significant reduced mean incidence of constipation (0.33 in morphine stabilisation v 0.19 in fentanyl treatment phase, p=0.022) which supported the claim that Durogesic was associated with a lower level of constipation than SR morphine.

- **Donner *et al* (1996).** This study was an open label study in which patients were directly converted from oral morphine to transdermal fentanyl; 98 patients were entered into the study. Patients experienced fewer constipated days (35.1% fentanyl v 58.8% SR morphine) and severe constipated days (8.3% fentanyl v 18% SR morphine) and there was a statistically significant difference in the amount of laxatives used (62% SR morphine v 38% fentanyl, p<0.05). A higher conversion ratio of 100:1 v 150:1 (morphine to fentanyl) than in previous studies was used and therefore these data further supported the claim that Durogesic was associated with less constipation than SR morphine rather than due to lowered opioid use during fentanyl treatment.
- **Allan *et al* (1998).** Two hundred and fifty six chronic non-malignant pain patients were randomised to one of two crossover groups in which they were either converted from 4 weeks' transdermal fentanyl to 4 weeks' SR morphine (n=126) or 4 weeks' SR morphine to 4 weeks' transdermal fentanyl (n=130). The results showed 35% of patients considered their pain relief as good or very good after transdermal fentanyl compared to 23% after SR morphine (p=0.002) and average pain intensity was significantly lower (p<0.001). Constipation was experienced by 48% of patients during SR morphine treatment compared with 29% during fentanyl treatment (p<0.001). These data clearly demonstrated a lower incidence of constipation with transdermal fentanyl compared to SR morphine in association with an improved level of pain relief. While these data were in a different patient group, and the absolute incidence of constipation might vary in comparison to patients with cancer pain, it was argued that these data provided further support for the lower incidence of constipation in patients treated with Durogesic compared to sustained release morphine.

The Davies and Prentice abstract did not, therefore, throw sufficient doubt on the results of the Ahmedzai and Brooks study, and the other data available, and therefore the claims reflected the available evidence. Janssen-Cilag therefore denied any breach of Clause 7.7.

PANEL RULING

The Panel noted that the advertisement featured the claim 'The strength of SR morphine with fewer unpleasant side effects' whilst the detail aid featured the claim 'Less constipation and drowsiness than SR morphine'. Each claim was referenced to Ahmedzai and Brooks (1997).

The Ahmedzai and Brooks study was a randomised, open, two-period crossover study undertaken to compare transdermal fentanyl with sustained release oral morphine in cancer patients receiving palliative care with particular emphasis on patient preference, side effects and their effects on patients' quality of life. The Panel noted that in the study more adverse events were reported during the fentanyl treatment. The study featured a table of the commonest adverse events recorded during treatment; abdominal pain, constipation, diarrhoea, dyspnea, nausea, somnolence/drowsiness, sweating and vomiting. Patients on morphine recorded a greater number of adverse events in relation to constipation (15 v 6) and somnolence/drowsiness (19 v 17) while the incidence of vomiting in both groups was the same. With regard to the other adverse events more were recorded in the fentanyl group than in the morphine group. The authors noted that some adverse experiences, such as increased incidence of abdominal pain, might have been associated with, and were consistent with, morphine withdrawal rather than fentanyl treatment *per se*. It was further noted that despite the greater number of adverse events reported in the fentanyl group, the patient progress questionnaire indicated that fewer patients considered that fentanyl caused side effects compared with morphine (40.4% for fentanyl v 82.5% for morphine, p<0.001) and that this might be due to under-reporting of previously experienced events because all patients had received morphine before the study. The authors acknowledged that the open design might have introduced bias in the reporting of side effects but the randomised design was used to ensure that this effect would have been present in both arms and there was no *a priori* reason to expect such bias to occur with any one formulation. The authors also stated that the fact that morphine was used as rescue medication in both arms of the study might have reduced the potential to reveal differences in side effects between the two treatments. The Panel considered that given that more adverse events were reported during fentanyl treatment, although significantly fewer patients considered that fentanyl caused side effects compared to morphine, the claim '… with fewer unpleasant side effects' was not a fair reflection of the data in the study. The Panel ruled a breach of Clause 7.7 of the Code. The Panel considered that the allegation of a breach of Clause 7.2 was covered by this ruling.

The study concluded that fentanyl treatment was associated with significantly less constipation than morphine (p<0.001). The authors noted that different effects on constipation might be due to local drug effects on the gut, the reduction of first pass metabolism, the difference between a 12 hour and 72 hour sustained-release delivery system or a combination of all three. These effects required confirmation and further elucidation. The Panel considered that the claim 'Less constipation … than SR morphine' was a fair reflection of the study and ruled no breach of Clause 7.2 of the Code in that regard.

Complaint received **12 July 1999**

Case completed **3 September 1999**

CASE AUTH/900/7/99

NOVO NORDISK v HOECHST MARION ROUSSEL

Promotion of Amaryl

Novo Nordisk complained about the promotion of Amaryl (glimepiride) by Hoechst Marion Roussel. A claim in a technical supplement that 'Glimepiride appears to imitate the process of physiological insulin release' was alleged not to be balanced and to be potentially misleading. Novo Nordisk stated that it was based on a study by Sonnenberg *et al* which was designed to assess a once versus twice daily regimen of glimepiride and not specifically glimepiride's process of insulin release. In a study by van der Wal *et al*, specifically designed to assess beta cell response to oral glimepiride, the conclusions and observations made clearly showed that glimepiride did not appear to imitate the process of physiological insulin release.

The Panel noted that Sonnenberg *et al* investigated the metabolic effects of glimepiride 6mg daily, given either as a single dose or in two divided doses and demonstrated that both regimens were equally effective in promoting glycaemic control in patients with non-insulin dependent diabetes mellitus (NIDDM). The 24-hour insulin plasma concentration profile was enhanced by glimepiride treatment and mirrored that seen with placebo ie a sharp post-prandial rise followed by a decline until the next meal. The increases in C-peptide concentrations paralleled those seen with insulin. The authors concluded that glimepiride seemed to stimulate insulin production primarily after meals, when plasma glucose concentrations were highest, but controlled blood glucose throughout the day. The Panel noted that in other clinical studies in NIDDM patients treated with glimepiride, insulin release mirrored normal physiological patterns seen in response to meals or exercise. Only the study by van der Wal, which was conducted using an artificial model, at a dose outside the licence, had produced results to the contrary. The claim appeared in a sub-section of the Amaryl technical supplement which summarised the Sonnenberg study and reproduced the graph from the paper which depicted the insulin plasma concentration profiles over 24 hours. The Panel considered that in terms of the data from other clinical studies the data was not unrepresentative and the claim in question accurately reflected the study's findings. No breach of the Code was ruled.

A claim in a leavepiece 'Amaryl stimulates insulin production in response to meals' was referenced to Sonnenberg *et al*. Novo Nordisk stated that this was a statement of fact and not opinion and drew attention to the points raised above and, in addition, noted that the paper stated that 'Glimepiride seems to stimulate insulin production primarily after meals.' The claim could be misconstrued as implying that glimepiride only released insulin in response to meals which was misleading and exaggerated. Novo Nordisk also alleged that the claim was not balanced and might be liable to misinterpretation with potential consequences regarding safety ie hypoglycaemia.

In the Panel's view the claim in the leavepiece went further than the conclusion in the paper; it was more definite and positive about the effect of Amaryl on insulin production than the authors had been. It was possible that some readers might assume that Amaryl stimulated insulin production only in response to meals. The Panel considered that the claim was misleading and exaggerated as alleged and ruled a breach of the Code.

Novo Nordisk Pharmaceuticals Ltd complained about the promotion of Amaryl (glimepiride) by Hoechst Marion Roussel Ltd. An Amaryl technical supplement (ref AML159) contained the claim 'Glimepiride appears to imitate the process of physiological insulin release' and a leavepiece (ref AML151) contained the claim 'Amaryl stimulates insulin production in response to meals'.

COMPLAINT

Novo Nordisk noted that the claim 'Glimepiride appears to imitate the process of physiological insulin release' was referenced to a study by Sonnenberg *et al* (1997) which was designed to assess a once versus twice daily regimen of glimepiride and not specifically glimepiride's process of insulin release. Physiological release of insulin meant a rapid insulin response to a glucose load, with insulin secretion reducing with a reducing glucose load and a rapid return to baseline levels in the absence of a glucose load. In a study by van der Wal *et al* (1997), specifically designed to assess beta cell response to oral glimepiride, the conclusions and observations made clearly showed that glimepiride did not appear to imitate the process of physiological insulin release:

(i) '.... in glimepiride clamps the plasma insulin concentration remained at these high levels during 1.5h, despite declining blood glucose levels …'

(ii) '… the composition of the beta cell output is constant and is not affected by administration of glimepiride during the first hours after glucose stimulus.'

(iii) 'The lowering of blood glucose levels is not accompanied by a commensurate inhibition of insulin secretion (with glimepiride).'

(iv) The insulin graph showed continued insulin secretion despite declining blood glucose levels between points 'D' and 'E'.

Novo Nordisk alleged that the claim was therefore not balanced and potentially misleading in breach of Clause 7.2 of the Code.

Novo Nordisk noted that the first bullet point in the leavepiece stated that 'Amaryl stimulates insulin production in response to meals' (Sonnenberg *et al* (1997)). This was a statement of fact not opinion and the company drew attention to the points above, and in addition noted that the authors actually stated that 'Glimepiride seems to stimulate insulin production primarily after meals.' The claim could be misconstrued as implying that glimepiride only released insulin in response to meals which was

misleading and exaggerated and in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Hoechst Marion Roussel did not agree that the claims were in any way unbalanced or misleading. The supporting study (Sonnenberg *et al* (1997)) which was conducted in patients with non-insulin dependent diabetes mellitus (NIDDM), had, as a specific objective, the investigation of the metabolic effects of glimepiride. Subjects had insulin and C-peptide (a precursor of insulin) measurements performed at sixteen time points over a 24-hour period following either a twice daily or once daily regimen of glimepiride. Glucose measurements were performed at 20 time points throughout the same period. The groups were crossed over to the alternative regimen following a placebo washout period. Ninety-four patients completed the study. The authors concluded that 'glimepiride seems to stimulate insulin production primarily after meals, when glucose concentrations are highest, but controls blood glucose throughout the day'.

Hoechst Marion Roussel also noted the study by Schade *et al* (1998), conducted in patients with type 2 diabetes. Patients were randomised to receive Amaryl or placebo, once daily for a 10 week dose titration period, after which they were maintained on an individually optimised dose of either Amaryl or placebo for 12 weeks. Amaryl or placebo dosages were administered once daily to a maximum of 8mg. Amongst the variables measured during the study were fasting plasma glucose, 2 hour post-prandial glucose and fasting and 2 hour post-prandial C-peptide and insulin. Results showed that glimepiride improved post-prandial insulin and C-peptide response without producing clinically meaningful increases in fasting insulin or C-peptide levels.

In further support of its claim, Hoechst Marion Roussel also noted a review article by Campbell (1998) entitled 'Glimepiride Role of a New Sulphonylurea in the Treatment of Type 2 Diabetes Mellitus.' Two clinical studies in 161 and 416 NIDDM patients were reviewed (including the study of Sonnenberg referred to above) leading to the author's conclusions that 'These findings suggest that glimepiride enhances insulin and C-peptide secretion under physiological conditions (eg meal induced glucose bolus).' These studies provided data on insulin release collected under 'normal' clinical conditions which the company considered were reflective of the clinical situation.

With regard to the publication by van der Wal cited by Novo Nordisk, Hoechst Marion Roussel noted that the study, in contrast to those it had cited as supporting data, was conducted using an artificial model to investigate insulin release. The data presented were based on 14 NIDDM patients treated with an artificial glucose bolus and an Amaryl dose of 10mg prior to the glycaemic clamp. It was important to note that this dose was well in excess of the maximum licensed dose for Amaryl. Hoechst Marion Roussel therefore did not consider this data to be representative of the totality of the clinical evidence concerning Amaryl's effects on insulin secretion and did not consider it was appropriate if used to demonstrate the insulin profile to be expected in normal clinical use.

Hoechst Marion Roussel noted that a further aspect of normal physiological insulin release, which it was important to bear in mind in the treatment of diabetes, was the response to exercise. With regard to Amaryl, this issue was addressed in a multinational study investigating the effects of acute exercise on metabolic control in 167 type 2 diabetic patients treated with either Amaryl or glibenclamide (Massi-Benedetti *et al* (1996)). In their conclusion the authors stated 'In our well controlled type 2 diabetic patients treated with glimepiride, exercise produced significant decrease of both blood glucose and insulin secretion, restoring a nearly normal pattern of response to physical exercise. Under glibenclamide treatment the same physiological response to exercise was not present.' In further support of this evidence was the statement in the summary of product characteristics: 'The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride'.

In the light of this evidence, Hoechst Marion Roussel failed to understand Novo Nordisk's concern that the claims were unbalanced and as such might lead to potential adverse consequences ie hypoglycaemia.

Hoechst Marion Roussel noted that quite apart from any claims it made with respect to experimental data concerning Amaryl, it did not in any sense advocate any use of Amaryl outside the terms of its product license, which permitted its use as a once daily sulphonylurea. In conclusion, Hoechst Marion Roussel refuted any implication that it was in breach of the Code.

PANEL RULING

The Panel noted that the study by Sonnenberg *et al* was a crossover study to investigate the metabolic effects of glimepiride 6mg daily, given either as a single dose or in two divided doses. Each dosage regimen was administered for four weeks. The study demonstrated that both dosage regimens of glimepiride were equally effective in promoting glycaemic control in patients with NIDDM. Results showed that the 24-hour insulin plasma concentration profile was enhanced by glimepiride treatment and mirrored that seen with placebo ie a sharp post-prandial rise followed by a decline until the next meal. The increases in C-peptide concentrations paralleled those seen with insulin. The authors concluded that glimepiride seemed to stimulate insulin production primarily after meals, when plasma glucose concentrations were highest, but controlled blood glucose throughout the day.

The Panel noted that in other clinical studies in NIDDM patients treated with glimepiride, insulin release mirrored normal physiological patterns seen in response to meals (Schade *et al* (1998)) or exercise (Massi-Benedetti *et al* (1996)). Only the study by van der Wal, which was conducted using an artificial model, at a dose outside the licence, had produced results to the contrary.

The claim 'Glimepiride appears to imitate the process of physiological insulin release' was referenced to Sonnenberg *et al* and appeared in a sub-section of the Amaryl technical supplement which summarised the study and reproduced the graph from the paper which depicted the insulin plasma concentration profiles over 24 hours. The Panel considered that in terms of the data from other clinical studies the data from Sonnenberg was not unrepresentative and that the claim in question accurately reflected the study's findings. No breach of Clause 7.2 was ruled.

The claim 'Amaryl stimulates insulin production in response to meals' in the leavepiece was referenced to Sonnenberg *et al* which had in fact concluded that '[Amaryl] seems to stimulate insulin production primarily after meals…'. In the Panel's view the claim in the leavepiece went further than the conclusion in the paper; it was more definite and positive about the effect of Amaryl on insulin production than the authors had been. It was possible that some readers might assume that Amaryl stimulated insulin production only in response to meals. The Panel considered that the claim was misleading and exaggerated as alleged and ruled breaches of Clause 7.2 and 7.8 of the Code.

Complaint received **14 July 1999**

Case completed **6 September 1999**

CASE AUTH/901/7/99 *NO BREACH OF THE CODE*

PHARMACIST v ALLEN & HANBURYS

Promotion of Flixotide

A pharmacist complained about a 'Dear Pharmacist' letter produced by Allen & Hanburys which announced a reduction in the price of Flixotide 50mcg (fluticasone). The pharmacist alleged that the letter was misleading as it used the proprietary price of Becotide in a comparison rather than the cheaper generic version of beclomethasone. It might also imply that generic versions of beclomethasone were somehow inferior to the branded products.

The Panel considered that the clear intention of the letter was to announce the price reduction of Flixotide and compare the new price with that of Becotide. The basis of the comparison was clear and the failure to refer to generic presentations of beclomethasone did not render the comparison misleading. The Panel did not accept that the letter implied that generic beclomethasone was somehow inferior to the branded product. No breach of the Code was ruled.

A pharmacist, complained about a 'Dear Pharmacist' letter (ref HM5246 – ALP/June 1999) produced by Allen & Hanburys which announced a reduction in the price of Flixotide 50mcg (fluticasone propionate).

COMPLAINT

The complainant alleged that the 'Dear Pharmacist' letter contravened the spirit of the Code in respect of an unfair price comparison.

The letter compared the cost of two puffs twice a day of Flixotide 50mcg with two puffs twice a day of Becotide 100mcg. However, it used the proprietary price of Becotide rather than the cheaper generic version of beclomethasone.

The complainant stated that for 30 days' treatment the costs were as follows: Flixotide – £5.85; Becotide – £6.19; beclomethasone (Drug Tariff) – £5.11.

The complainant stated that as well as contravening Clause 7 of the Code, the letter might also mislead prescribers and undermine the advice given by many prescribing advisers in their attempts to ensure cost-effective use of NHS resources. In addition, it might also imply that generic versions of beclomethasone were somehow inferior to the branded products. There was of course no robust evidence to support such accusations.

RESPONSE

Glaxo Wellcome stated that the purpose of the mailing was to inform pharmacists of a reduction in the price of the Flixotide 50 microgram inhaler. The headline made a direct comparison with the price of Becotide (beclomethasone dipropionate) at a dosage that would be expected to achieve similar clinical results in patients with asthma. As was stated in the mailing, over 80% of the patients initiated on inhaled corticosteroids, in whom the dosage was known, were prescribed a dose equivalent to Becotide 100 micrograms, 2 puffs twice daily. Apart from the fact that Becotide was the natural comparator, as it was the long-established Allen & Hanburys formulation of beclomethasone dipropionate, it was also more likely to have a consistent price than the Drug Tariff price for a generic formulation, which might fluctuate from month to month, as indeed it had so far this year. In addition, the Allen & Hanburys presentations of beclomethasone dipropionate were also more widely used than any other – 62% of prescriptions for the 100 microgram inhaler of beclomethasone dipropionate were met with the Becotide 100 inhaler.

The price comparison with Becotide was fair, appropriate and explicit and Glaxo Wellcome did not believe that there was any breach of Clause 7.2 of the Code.

The mailing did not mention generic beclomethasone dipropionate and therefore there could be no implication that generic formulations were inferior to

Becotide. The comparison was only between Flixotide and the most widely used formulation of inhaled beclomethasone dipropionate, which was Becotide.

PANEL RULING

The Panel noted that the 'Dear Pharmacist' letter was headed 'Now Flixotide 50mcg MDI [metered dose inhaler] costs even less than Becotide 100mcg MDI'. The letter featured a bar chart which compared the monthly cost of treating a patient with Flixotide 50mcg MDI, 2 puffs bd at £5.85 and Becotide 100mcg MDI 2 puffs bd at £6.19. The letter discussed dosage and stated that 'Flixotide should be introduced at half the daily dose of beclomethasone dipropionate' and concluded by referring to the results of a comparative study between Flixotide and Becotide which demonstrated that Flixotide was more effective and overall was rated better by the patients themselves. A postscript referred to Flixotide as 'your first choice inhaled corticosteroid' after Ventolin.

The supplementary information to Clause 7.2 of the Code stated that price comparisons must be accurate, fair and must not mislead. In the opinion of the Panel the clear intention of the letter was to announce the price reduction of Flixotide 50mcg MDI and compare the new price of Flixotide 50mcg with that of Becotide 100mcg. Neither the text nor the bar chart sought to compare the cost of Flixotide with that of other preparations of beclomethasone dipropionate. In the opinion of the Panel the basis of the comparison was clear and the failure to refer to generic presentations of beclomethasone dipropionate did not in itself render the comparison misleading. The Panel did not accept that the letter implied that generic versions of beclomethasone were somehow inferior to the branded products. The Panel did not consider the price comparison misleading as alleged and ruled no breach of Clause 7.2 of the Code.

Complaint received **15 July 1999**

Case completed **23 August 1999**

CASE AUTH/903/7/99

NOVO NORDISK v LILLY

Promotion of Humalog Mix25

Novo Nordisk complained about a Humalog Mix25 (25% insulin lispro solution/75% insulin lispro protamine suspension) leavepiece issued by Lilly. Novo Nordisk alleged that a statement with regard to the timing of the human 30/70 insulin injections as '30-45 minutes before a meal' was contrary to the summary of product characteristics for its product Human Mixtard 30 ge which stated that it should be followed by a meal within 30 minutes of administration. The Panel ruled that the statement was misleading in breach of the Code.

Novo Nordisk was concerned that it was invalid to use references to support the use of Humalog Mix25 when the studies used a 50:50 mix formulation in the morning and a 25:75 mixture in the evening. The Panel ruled a breach of the Code as readers would assume that the section related to patients maintained on Humalog Mix25 and this was not so.

Novo Nordisk Pharmaceuticals Ltd. complained about a leavepiece for Humalog Mix25 (ref HM26) produced by Eli Lilly and Company Limited. The leavepiece was distributed by sales representatives to both diabetes specialist nurses and physicians, usually in a hospital setting. Humalog Mix25 was a premixed insulin containing 25% insulin lispro (fast acting human insulin analogue) and 75% insulin lispro protamine suspension (intermediate acting human insulin analogue).

Novo Nordisk marketed Human Mixtard 30 and Human Mixtard 30 ge both of which were mixtures of 30% human soluble insulin (fast acting) and 70% human isophane insulin (intermediate acting).

1 Statement regarding timing of injections before a meal

A table compared injection timing and insulin activity of Humalog Mix25 and human 30/70 insulins. With regard to the timing of the human 30/70 insulin injections the table stated '30-45 minutes before a meal'.

COMPLAINT

Novo Nordisk noted that the statement regarding injection timing of human 30/70 insulin was in direct contradiction to its summary of product characteristics (SPC) for Human Mixtard 30 ge. The SPC stated under the headline 'Precautions' that 'Owing to their strong early effect, injections of Human Actrapid or Human Mixtard 30 ge should be followed by a meal within 30 minutes of administration'.

Novo Nordisk considered that there was an increased risk of hypoglycaemia if patients were advised to inject Human Mixtard forty five minutes before a meal and that this was not in keeping with current UK clinical practice. Furthermore it did not convey the fact that patients could inject Human Mixtard within the 30 minute period. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Lilly stated that there was a broad spectrum of opinion in clinical practice about the optimum timing of human premixed insulin. Although the company was aware that Novo Nordisk's SPC recommended that its 30/70 premixed insulin preparation, Mixtard 30 ge, was followed by a meal within 30 minutes of administration, Lilly did not have specific instructions with reference to injection timings on its SPC for Humulin M3 because healthcare professionals had differing views. While it was clear in clinical practice that patients could, and indeed did, inject their insulin within 30 minutes, the company did not consider that that was an accurate reflection of the published recommendations. As most diabetologists viewed regular premixed insulins as having very similar pharmacokinetic properties, Lilly considered that it would be inappropriate to artificially separate premixed insulins made by different manufacturers. There was published data demonstrating the equivalence of Lilly's and Novo Nordisk's isophane insulins.

Lilly submitted that to resolve the discrepancy between Novo Nordisk's and its own SPCs, and to comply with Clause 7.2 to ensure a fair and accurate representation of the data, it had reviewed the published literature. There was a great deal of variability in the published recommended times for the injection prior to meal times. In the accepted reference textbook for diabetes in the UK (Pickup and Williams, Textbook of Diabetes) there were three different recommendations, ranging from 20-40 minutes to 30-60 minutes. A literature search gave similarly variable results, but the following frequently quoted papers suggested that approximately 30-45 minutes should be the recommended pre-prandial injection interval (Dimitriadis and Gerich (1983), Lean and Tennison (1985) and Hildebrant (1991)). More recent work suggested that even longer injection intervals might be appropriate (Howey *et al* (1995)).

Lilly stated that the only original research data it was able to find, which supported Novo Nordisk's SPC, was a small study (Heinemann *et al* (1992)) which demonstrated that an increased glucose infusion was required in 8 healthy volunteers (previously clamped to normoglycaemia) given large doses of insulin 30 minutes pre-prandially. The discussion speculated about a possible increase in early hypoglycaemia in diabetic patients who were normoglycaemic pre-prandially associated with a pre-prandial injection period of 30 minutes. This study had not been reproduced in diabetic patients.

There was data demonstrating that, in real clinical practice, the risk of both mild hypoglycaemia (Anderson *et al* (1997)), and severe hypoglycaemia (Brunelle *et al* (1998)) associated with giving insulin 30-45 minutes pre-prandially was no higher than that seen in the conventional treatment groups of the Diabetes Control and Complications Trial or the UK Prospective Diabetes Study. These studies had large numbers and did not support the argument of an increased risk associated with giving insulin at this time interval.

Lilly stated that a later work (Heinemann (1995)) discussed the broad range of recommendations from a number of publications about optimal timing of injections, which ranged as stated from 0 to 90 minutes and discussed the dangers of injecting insulin too soon, specifically poor post-prandial control and late post-prandial hypoglycaemia.

Optimal injection time was an individual compromise between the risk of early hypoglycaemia, post-prandial hyperglycaemia and late post-prandial hypoglycaemia. In this respect Lilly stated that it had presented the current recommendations of the American Diabetes Association, which recommended an interval of at least 30 minutes. The company was not aware that the British Diabetic Association had produced any similar guidelines.

In summary Lilly considered that the data was a fair and accurate representation of the published data in this area, consistent with Clause 7.2 of the Code, and in no way compromised patient safety.

PANEL RULING

The Panel noted that the SPC for Novo Nordisk's human 30/70 insulins (Human Mixtard 30 and Human Mixtard 30 ge) clearly stated that an injection should be followed by a meal within 30 minutes. The table of data in question referred to human 30/70 insulin and so the statement that it should be injected 30-45 minutes before a meal would be taken to apply to all presentations of the product including Novo Nordisk's.

The Panel noted that while there was published data to support the statement in the table an SPC nevertheless represented the agreed information about a product. The Panel considered that by not, in addition, referring to the information in Novo Nordisk's SPCs, or conversely making it clear that the statement in the table did not apply to that company's human 30/70 insulins, the table was misleading with regard to the recommended timing of Human Mixtard 30 injections. A breach of Clause 7.2 was ruled.

2 Citation of studies using Humalog Mix50

Two of the studies cited in the leavepiece were Roach *et al* (1998) and Malone *et al* (1998). In both of these studies patients had been treated with Humalog Mix50 and Humalog Mix25. Both studies were cited in support of the claim 'Significantly less nocturnal hypoglycaemia than with human insulin mixtures'.

COMPLAINT

Novo Nordisk was concerned that Roach *et al* and Malone *et al* used an unlicensed formulation of lispro in a 50:50 mix with neutral protamine lispro (NPL). This 50:50 formulation was administered in the morning with the marketed 25:75 mixture being used in the evening.

Novo Nordisk alleged that it was invalid to use these references supporting the use of Humalog Mix25 when only half of the injections in patients on the analogue mixtures were actually Humalog Mix25. The argument that only the evening doses were affecting the post-dinner, bedtime and nocturnal readings was unsafe since glycaemic control both in

the evening and overnight was, in part, dependent on the glycaemic control prior to dinner. Additionally the NPL would still exert an effect into the evening and could not be excluded from the analysis. A breach of Clause 7.2 was alleged.

RESPONSE

Lilly stated that while it was true that Humalog Mix50 was used in the referenced studies, it was not true that the formulation was unlicensed. The licence numbers for the various preparations of Humalog Mix50 were provided.

Lilly submitted that the studies were perfectly valid to support Humalog Mix25.

Lilly accepted that glycaemic control prior to dinner would be one of many influences on control over the next 12 hours. The glycaemic control in both treatment and control groups in both studies, before dinner, was not significantly different.

With any study of a twice-daily insulin regime containing isophane type insulin, there would be some overlap between the treatment effect of the two isophane injections. Of course, both Humalog Mix25 and Mix50 had the same compound, neutral protamine lispro (NPL) as their long-acting component. Pharmacokinetic studies had shown that the time of action of NPL was similar to isophane insulins, at 12-14 hours. The pharmacokinetic data showed that NPL would only be present in small quantities after 12 hours (relative to the amount of insulin present from the evening injection of Humalog Mix25). The differences in the amount of NPL present following Mix50 or Mix25 injection 12 hours earlier would be very small. After 12 hours, it was unlikely that NPL would have any significant effect on glycaemic control, or that the minute differences in the amount of NPL present in Mix50 and Mix25 at this time, would have a disparate effect on glycaemic control.

Lilly stated that any difference in glycaemic control which occurred during the 12 hours following administration were reasonably assumed to be a consequence of the action of Humalog Mix25. The company considered the data to be clinically and statistically valid.

PANEL RULING

The leavepiece dealt exclusively with Humalog Mix25. (To the Panel's knowledge Humalog Mix50 was not available in the UK.) The Panel noted that some of the claims made for the product were referenced to Roach *et al* and Malone *et al*. In both of these studies diabetic patients received Humalog Mix50 before breakfast and Humalog Mix25 before dinner. In the Panel's view, however, readers would assume that the claims related to patients maintained exclusively on Humalog Mix25 which was not so. The Panel considered that the claims were thus misleading and a breach of Clause 7.2 was ruled.

Complaint received **19 July 1999**

Case completed **26 August 1999**

CASE AUTH/906/7/99

SCHERING HEALTH CARE v ROCHE

Promotion of MabThera

Schering Health Care complained about a promotional item entitled 'Rituximab: Clinical patient and cost justification for the management of low grade NHL' produced by Roche. Schering Health Care alleged that the item was being used to compare rituximab (MabThera) with Schering Health Care's product fludarabine (Fludara) in the treatment of non-Hodgkin's lymphoma (NHL), an indication for which Fludara was not licensed in Europe.

The Panel noted that according to its summary of product characteristics (SPC) Fludara was indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia with significant bone marrow reserve who had not responded to or whose disease had progressed during or after treatment with at least one standard alkylating agent containing regimen. The promotional item in question sought to address three main justifications for the use of rituximab for low grade relapsing NHL patients and featured comparisons with fludarabine. The cost justification section featured a direct comparison of the costs associated with the administration and side effects of a combination chemotherapy or monotherapy with either fludarabine or rituximab. The estimated incidence of adverse effects associated with fludarabine was given. The change in the additional annual expenditure incurred by using rituximab instead of fludarabine in second relapse low grade NHL patients was calculated. The patient justification section referred to the response rate seen with fludarabine as monotherapy, in combination therapy and its toxicity.

The Panel considered that the references to fludarabine were unfair and misleading as they had not been placed in the context of the product's SPC. There was no mention that the use of fludarabine in NHL was unlicensed. It had been established in previous cases that the position had to be made clear in such circumstances. The Panel accordingly ruled a breach of the Code.

Schering Health Care Limited submitted a complaint about a promotional item entitled 'Rituximab: Clinical patient & cost justification for the management of low grade NHL' produced by Roche Products Limited.

COMPLAINT

Schering Health Care alleged that this item was being used by Roche to compare rituximab (MabThera) with Schering Health Care's product fludarabine (Fludara) in the treatment of non-Hodgkin's lymphoma (NHL), an indication for which Fludara was not licensed in Europe. Schering Health Care referred to Cases AUTH/837/1/99 and AUTH/878/5/99 and submitted that these rulings made it clear that this item was also in breach of Clause 7.2 for discussing Schering Health Care's product in an unlicensed indication.

RESPONSE

Roche pointed out that fludarabine was widely used in the treatment of low grade NHL, presumably, at least, in part due to Schering Health Care's activities highlighting fludarabine usage for the treatment of NHL. In fact, the Disease Management Database from Medicare showed that 35% of fludarabine sales were due to use in low grade NHL. Also a review of published clinical data showed extensive use of fludarabine in this setting as well as a number of ongoing trials.

Roche did not accept that its comparisons with fludarabine contravened Clause 7.2. The cost comparison was based on a peer reviewed published clinical paper. Secondly, routine and widespread use of fludarabine among clinicians in low grade NHL preceding the introduction of MabThera onto the market clearly demonstrated that the item in question would not be responsible for misleading any clinicians. Fludarabine was so routinely used that Roche understood that certain hospitals were applying for funding of fludarabine in low grade NHL.

Roche referred to the supplementary information to Clause 8.1 which stated that 'comparison with other products was acceptable under the Code provided the information was accurate, balanced, fair, etc and could be substantiated'. Again as the comparisons were based on peer reviewed published clinical papers, Roche submitted that the Code was not contravened.

Roche noted that Clause 3 did not apply when considering a competitor medicine since that product was not actually being promoted. This situation clearly applied to this complaint.

Roche considered that the comparison of MabThera with fludarabine was not in breach of the Code for the following reasons:

- It was not in breach of Clause 3
- The comparison complied with Clauses 7.2 and 8.1
- The routine and widespread use of fludarabine in low grade NHL which preceded the introduction of MabThera clearly demonstrated that Roche's comparison would not mislead clinicians in any way.

PANEL RULING

The Panel noted that Case AUTH/837/1/99: Biogen/Director v Schering Health Care concerned, *inter alia*, a chart in a Betaferon detail aid which compared the relapse rate for all patients for studies of Betaferon (–30%), Avonex (–18%) and another interferon therapy (sc1a). The Panel had considered the data misleading, in breach of Clause 7.2 of the Code, as the basis of the Avonex data had not been explained. In this regard the Panel had noted the statement in the Avonex summary of product characteristics (SPC) that it demonstrated a one third reduction in annual relapse

rate. On appeal, the Appeal Board's view about references to competitor products was that each case should be considered on its own merits and the requirements of other clauses of the Code, particularly Clause 7.2 would be relevant. The SPC represented the agreed information about a medicine. The Appeal Board considered that by not referring to the data in the SPC (a one third reduction) and only referring to the 'all patient' data (-18%) the company had failed to present all the information and the detail aid was misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The Panel noted that Case AUTH/878/5/99 concerned a detail aid for Cyprostat issued by Schering Health Care. Zeneca alleged that three sections of the detail aid which quoted data relating to the use of bicalutamide (Zeneca's product) at an unlicensed dosage or indication were misleading and alleged a breach of Clause 7.2 of the Code. The Panel considered whether references to competitor products in promotional material needed to comply with Clause 3 of the Code. Clause 3 of the Code was clear that the promotion of a medicine must be in accordance with the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. A company would not be promoting the competitor medicine and therefore the Panel considered that Clause 3 would not apply. Clause 7.2 of the Code required that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead directly or by implication. The Panel questioned whether comparing products using only unlicensed doses and/or indications of a competitor product met the requirements of Clause 7.2. Readers might be misled as to the approved use of competitor products and the company with the competitor product could not counter the arguments as it would be open to accusations of promoting an unlicensed indication and/or dose. The Panel noted that the detail aid referred to Zeneca's product at an unlicensed dose of 150mg per day and as monotherapy whereas the SPC stated that the dose was 50mg per day in combination with LHRH analogue therapy or surgical castration. Readers were not told that the regimen was unlicensed. There was no mention of the licensed dose and indication for Zeneca's product and nor of the efficiency results for the licensed use of the product. The Panel considered that the sections in question were unfair and misleading as the data presented had not been put in the context of the bicaltumide SPC. A breach of Clause 7.2 was ruled.

Turning to the present case, the Panel noted that according to the SPC Fludara was indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia with significant bone marrow reserve and who had not responded to or whose disease had progressed during or after treatment with at least one standard alkylating agent containing regimen.

The promotional item in question sought to address three main justifications in the use of rituximab for low grade relapsing NHL patients and featured comparisons with fludarabine. The cost justification section featured a direct comparison of the cost/patient/course associated with the administration and side effects of a combination chemotherapy or monotherapy with fludarabine or rituximab. The estimated incidence of adverse effects associated with fludarabine was given. The change in the additional annual expenditure incurred by using rituximab instead of fludarabine in second relapse low grade NHL patients was calculated. The patient justifications section referred to the response rate seen with fludarabine as monotherapy, in combination therapy and its toxicity.

The Panel considered that the principle set out in Cases AUTH/837/1/99 and AUTH/878/5/99 applied here. The Panel considered that the references to fludarabine were unfair and misleading as they had not been placed in the context of the product's SPC. There was no mention that the use of fludarabine in NHL was unlicensed. The Panel accordingly ruled a breach of Clause 7.2 of the Code.

Complaint received **21 July 1999**

Case completed **10 September 1999**

CASE AUTH/907/7/99

ROCHE v GLAXO WELLCOME

'Choose life' advertisement in Axiom magazine

Roche complained about an advertisement headed 'Choose life' which had been placed by Glaxo Wellcome in Axiom, a gay men's health and lifestyle magazine on sale in retail outlets. The advertisement discussed the use of triple nucleoside therapy in the treatment of HIV. Roche alleged that it was covert promotion to patients of a regimen unique to Glaxo Wellcome. The claim that one triple regimen involved taking only two tablets twice a day could apply only to a regimen using Glaxo Wellcome's product Combivir.

The Panel noted that in combination with another nucleoside analogue the only regimen which could involve taking only two tablets twice a day would necessarily include Combivir. The Panel considered the reference to a dosage regimen which was solely associated with Combivir meant that the advertisement in question constituted an advertisement to the general public for a prescription only medicine and ruled a breach of the Code. The Panel considered that the advertisement encouraged patients to discuss treatment options with their physician. The nature of the advertisement was such that it would encourage patients to ask their doctors to prescribe the regimen referred to which would in effect lead to a prescription for Combivir. A further breach of the Code was ruled.

Roche also alleged that the bullet points 'generally well tolerated' and 'By starting with triple nucleoside therapy, it is possible to reserve other treatment options for future use' were unsubstantiated. The Panel examined the draft of the British HIV Association guidelines for the treatment of HIV disease. These stated that a major advantage of triple nucleoside therapy was 'good tolerability … and relative freedom from side effects'. The guidelines also stated that a potential advantage was that virological failure would not be associated with the development of resistance to the other two classes of medicines which were currently available. The Panel did not accept that the bullet points were unsubstantiated as alleged and ruled no breach of the Code in that regard.

Roche Products Limited submitted a complaint about an advertisement (ref 26098/B) headed 'Choose life' which appeared in Axiom, a gay men's health and lifestyle magazine on sale in retail outlets. The advertisement discussed the use of triple nucleoside therapy in the treatment of HIV and had been issued by Glaxo Wellcome UK Limited.

COMPLAINT

Roche noted that the advertisement promoted a specific regimen for the treatment of HIV. Although the advertisement did not mention a product by name, it was covert promotion to patients of a therapeutic regimen unique to Glaxo Wellcome (Clause 20).

The statement that one regime (ie three nucleosides) involved taking only two tablets twice a day was applicable only to a regimen of the Glaxo Wellcome product 'Combivir' (which contained two nucleosides in one pill) plus one other nucleoside. The other nucleoside could be from another company but many of the triple combination regimens studied were with abacavir, another Glaxo Wellcome product. If a patient asked for the regimen referred to in the advertisement the prescriber was likely to infer that the advertisement referred to Combivir plus abacavir. Roche alleged that the advertisement was a serious breach of the Code and of the Medicines Act in that it was covert promotion of a Glaxo Wellcome medicine regimen to patients and the general public.

Roche stated that it was also serious because triple nucleoside regimens for first line treatment of HIV were controversial and by no means generally accepted by expert consensus within the HIV speciality as standard of care. Some physicians might agree, others did not, and Glaxo Wellcome by this type of promotion would stimulate patient demand to put pressure on prescribers who might not normally advise this treatment regimen. Indeed a large MRC clinical end-point trial was about to begin in the UK to compare different types of initial treatment regimens in treatment naïve patients (INITIO). This trial did not contain a triple nucleoside regimen.

Debate was by no means over on this issue and Roche believed that promotion of one type of regimen directly to patients was not justified. In addition the second stab point of the advertisement stated that the regimen was generally well tolerated. No attempt had been made to substantiate this statement or to indicate what was meant by well tolerated. Whereas the healthcare professional was able to check statements by reading the prescribing information on the advertisement, the patient did not have the opportunity. Thus the statement was entirely a subjective view of Glaxo Wellcome. The final stab point was also unsubstantiated. There was no data to show whether patients initially treated with triple nucleoside therapy reserving 'other treatment options' for later had a better or even equivalent prognosis to patients starting with a protease inhibitor containing regimen. This was another reason why studies like INITIO were being carried out.

Roche stated that to promote one of these regimens directly to the patients was reprehensible and set a very worrying precedent.

RESPONSE

Glaxo Wellcome strongly refuted the allegation as it did not believe the piece to be product promotion.

Glaxo Wellcome gave a brief overview of current HIV therapy, including the issue of triple nucleoside therapy. Significant advances had been made in the management of HIV infection over the last decade. The first medicine to act directly against the HIV virus was the nucleoside analogue, zidovudine, in 1987.

Zidovudine was initially used as monotherapy. However, advances in the understanding of HIV, and the availability of new antiretroviral drugs, led to its use in combination therapy and dual nucleoside combinations had become widely used.

The most recent milestones had been the development of two new classes of antiretroviral agents – the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The use of a protease inhibitor and two nucleoside analogues produced dramatic results, and this triple therapy approach had become the treatment of convention.

However, the limitations of this new therapeutic strategy had become clearer over the past couple of years. There had been an increased awareness of the potential long-term adverse effects of protease inhibitors, including effects on lipids and lipodystrophy. This had established the need for other therapeutic options, which offered the same high level of potency as PI-containing regimens.

There were now two 'PI-sparing' treatment options available to patients starting therapy for the first time:

- 2 nucleoside analogues + 1 NNRTI
- 3 nucleoside analogues (triple nucleoside therapy)

Head-to-head studies demonstrating at least equivalent potency of these regimens with a gold-standard PI-containing triple combination had been presented within the last year, and the quality of clinical evidence to support their use was increasing. For example, long-term data had demonstrated the potency and durability of a triple nucleoside combination through 96 weeks. In addition, both of these PI-sparing regimens were recognised as treatment options in the draft revision of the British HIV Association (BHIVA) treatment guidelines.

Turning to the substance of the complaint, Glaxo Wellcome did not believe that the piece in question represented covert promotion, but that it fulfilled a legitimate function in keeping the HIV-positive community aware and informed of new therapeutic options.

Glaxo Wellcome referred to the specific elements in the complaint:

1 Although the advertisement did not mention a product by name it was covert promotion to patients of a therapeutic regimen unique to Glaxo Wellcome…

This statement was untrue. The copy related to the relatively recent availability, and potential advantages, of feasible triple nucleoside regimens for the treatment of HIV, and it was quite possible to construct such a regimen without using Combivir and abacavir. As evidence for this, GlaxoWellcome enclosed details of a large-scale study (the 'Atlantic' study), in which different anti HIV treatment regimens were compared. The study was presented at the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999 and included a triple nucleosides arm, consisting of the agents d4T, ddI and 3TC. Only one of these agents (3TC, Epivir) was marketed by Glaxo Wellcome.

It was true that, currently, the only regimen that could involve taking two tablets twice a day would necessarily include Combivir. However, this regimen was only mentioned in passing as an example of the lifestyle benefits of the triple nucleoside therapy option and the copy was quite evidently concerned with triple nucleoside therapy as a whole, rather than any one example of it. The 'two tablets twice a day' regimen was clearly identified as one example, and there was an unambiguous statement at the bottom of the piece recommending discussion between patient and doctor to identify the best treatment option for the individual.

Glaxo Wellcome submitted that the piece could not realistically be interpreted as covert promotion of a specific Glaxo Wellcome product, but rather sought to inform, and motivate discussion, on a significant new therapy option in HIV, involving several possible combinations of different products.

2 Triple nucleoside regimens for first line treatment of HIV were controversial and by no means generally accepted by expert consensus within HIV speciality as standard of care.

Glaxo Wellcome stated that the piece did not suggest that triple nucleoside therapy was in any way the 'standard of care', merely that it was an interesting new treatment option, that might be worth discussing with the individual's treating physician. Triple nucleoside therapy was included as a therapy option within the publicly accessible draft revision of the BHIVA treatment guidelines, and thus had been accepted by the medical community as an appropriate treatment choice.

3 A large MRC clinical end-point trial was about to begin in the UK to compare different types of initial treatment regimens in treatment naïve patients (INITIO). This trial did not contain a triple nucleoside regimen.

Glaxo Wellcome stated that it was inappropriate to imply, as this statement seemed to do, that triple nucleoside therapy was 'omitted' from the INITIO trial because of concerns about the viability of this regimen. The reality was simply that large scale trials of this type took a very long time to plan and design, and that triple nucleoside therapy did not exist as a tested option whilst the INITIO trial was being designed. Although not provable either way, it was highly probable that, were the trial to be designed today, a triple nucleoside arm would be included.

4 Debate was by no means over on this issue and Roche believed that promotion of one type of regimen directly to patients was not justified.

Glaxo Wellcome stated that there was room for debate in every area of medicine, but this did not mean that it was inappropriate to keep patients informed of the options available to them, provided that this is done ethically and responsibly. As far as the Code was concerned, Clause 20.2 stated 'Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine'. As noted, the piece in question referred to a polytherapeutic treatment regimen rather than a

specific medicine, and thus fell outside the scope of the Code.

5 The second stab point of this advertisement stated that the regimen was generally well tolerated. No attempt was made to substantiate this statement or to indicate what was meant by well tolerated. Thus the statement was entirely a subjective view of Glaxo Wellcome.

Glaxo Wellcome stated that no attempt was made to substantiate the statement, as it was evidently not appropriate to treat information aimed at patients in the same way as one would, say, provide exhaustive scientific references in a professional journal. Nor was there any requirement to do so. Nevertheless, the fact that the statement was not 'formally' substantiated in the piece in question did not mean that it was not substantiable. It was incorrect to suggest that the statement was entirely a subjective view of Glaxo Wellcome.

Thus, in the 'Atlantic' study, referred to above, the authors concluded 'In all groups, treatment was safe and generally well tolerated'. Glaxo Wellcome could supply a large amount of additional data obtained with triple nucleoside regimens involving Glaxo Wellcome products. Finally, Glaxo Wellcome included with its response the section on triple nucleoside therapy of the draft revision of the BHIVA treatment guidelines (now published on the Internet), which included the phrase 'Major advantages of such regimens are good tolerability, a relative lack of drug/drug interactions and relative freedom from side effects.'

6 The final stab point was also unsubstantiated. There was no data to show whether patients initially treated with triple nucleoside therapy reserving 'other treatment options' for later had a better or even equivalent prognosis to patients starting with a protease inhibitor containing regimen. This was another reason why studies like INITIO were being carried out.

Glaxo Wellcome stated that the copy in question made no mention of the relative prognosis of triple nucleoside-treated patients versus those treated with protease inhibitors. It merely stated that 'by starting with triple nucleoside therapy, it was possible to reserve other treatment options … for future use'. This statement was incontrovertible. The draft revision of the BHIVA guidelines stated 'The other potential advantages of a triple nucleoside regimen is that virological failure will not be associated with the development of resistance to the other two classes of drugs (the NNRTIs and PIs) which are currently available'. Of course, further long-term work was needed before one could specify relative outcomes on different regimens.

7 On a more general note, there could be little doubt that the HIV-positive community represented a unique patient group in terms of their involvement in all aspects of their condition and its treatment (in this respect Glaxo Wellcome drew attention to an enclosure entitled 'Treatment update', also drawn from 'Axiom' magazine). Whilst this fact did not, of course, exempt companies from the need to comply with the Medicines Act and the Code, Glaxo Wellcome argued that it did justify a more direct approach to information provision for this patient group, especially as the rate of change of therapeutic advance in this field of medicine was particularly high. The complainant obviously agreed with this, as might be seen from Roche's advertorial from the same magazine, suggesting that patients discussed viral load measurements with their doctor.

In conclusion, Glaxo Wellcome strongly refuted the complainant's allegation that the piece in question was in any way covert promotion of a specific Glaxo Wellcome product. On the contrary, Glaxo Wellcome contended that it was designed to highlight, and provide information on the existence and possible advantages of a new approach to HIV treatment, involving a variety of possible polytherapeutic combinations. The message was directed at a highly aware and involved audience and presented in a responsible and ethical manner.

PANEL RULING

The Panel noted Glaxo Wellcome's comments about the HIV-positive community but did not accept that the involvement of the HIV community in all aspects of their therapy justified a more direct approach to information provision to this patient group compared with any other patient group. As acknowledged by Glaxo Wellcome, companies were obliged to comply with the Code and the legal requirements.

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

The Panel noted that the advertisement discussed triple nucleoside therapy and featured three bullet points:

- 'Triple nucleoside therapy can be easy to take with few tablets and no dietary restrictions – one regimen involves taking only two tablets twice a day'
- 'Triple nucleoside therapy is generally well tolerated'
- 'By starting with triple nucleoside therapy, it is possible to reserve other treatment options such as PIs and NNRTIs for future use'.

The bullet points were followed by 'Please discuss your treatment options carefully with your doctor or treatment adviser to ensure you choose the best option for you and your lifestyle'.

The advertisement advocated the use of triple nucleoside therapy in the treatment of HIV and referred to the regimen which involved taking only two tablets twice a day. The Panel noted that Combivir contained two nucleoside analogues and was administered twice a day. The Panel noted that in combination with another nucleoside analogue the only regimen which could involve taking two tablets twice a day would necessarily include Combivir. The Panel considered the reference to a dosage regimen which was solely associated with Combivir meant that the advertisement in question constituted an advertisement to the general public for a prescription only medicine and ruled a breach of Clause 20.1 of the Code.

The Panel considered that the advertisement encouraged patients to discuss treatment options with their physician. The nature of the advertisement was such that it would encourage patients to ask their doctors to prescribe the regimen referred to which would in effect lead to a prescription for Combivir. A breach of Clause 20.2 was ruled.

The Panel noted that there were also allegations about two of the three bullet points in the advertisement.

With regard to the claims 'generally well tolerated' and 'By starting with triple nucleoside therapy, it is possible to reserve other treatment options such as PIs and NNRTIs for future use', the Panel examined the draft of the British HIV Association guidelines for the treatment of HIV disease. These stated that a major advantage of triple nucleoside therapy was 'good tolerability… and relative freedom from side effects'. The guidelines also stated that a potential advantage was that virological failure would not be associated with the development of resistance to the other two classes of medicines (NNRTIs and PIs) which were currently available. The Panel noted that the advertisement as a whole had been ruled in breach of Clauses 20.1 and 20.2 of the Code. The Panel did not accept however that the two final bullet points were unsubstantiated as alleged and ruled no breach of Clause 20.2 of the Code in that regard.

Complaint received **27 July 1999**

Case completed **15 September 1999**

CASE AUTH/908/7/99

ROCHE v ABBOTT

Promotion of Norvir in combination with Fortovase

Roche complained about Abbott's promotion of Norvir (ritonavir) in combination with Roche's Fortovase (saquinavir soft gel capsules). Roche alleged that Abbott representatives were suggesting to prescribers that Fortovase alone provided insufficient levels of saquinavir and that ritonavir, which blocked saquinavir metabolism, should be given concurrently. This was promotion outside the licence and disparaging of Fortovase.

The Panel noted that HIV medicines were often used outside their licences. Representatives might frequently be asked about the unlicensed use of their own or a competitor product. It was of course unacceptable for companies to promote medicines that were not licensed or to promote unlicensed indications, doses, combinations etc. The Panel noted Abbott's submission that the material at issue, the medical information letter, the three slide presentations by company representatives and statements made by representatives to health professionals, were used only in response to specific requests for information from health professionals.

In the Panel's view the medical information letter was presented in a non-promotional style and format. The licensed indication for Norvir was given at the outset together with a statement that its use in dual protease inhibitor combinations was unlicensed. On balance the Panel decided that the document was not promotional in style or content and, if used appropriately in response to specific enquiries, was not subject to the Code.

The Panel noted that the slides would be presented to clinicians by representatives. In the Panel's view requests for information about the unlicensed use of medicines were best dealt with by the medical information department. Representatives might appropriately respond to such requests by providing scientific information but the Panel was concerned at the amount of material provided to representatives. The Panel had no way of knowing the degree to which representatives tailored the material to answer the request. There was, in the Panel's view, a difference between providing a scientific paper such as a report or a response from the medical information department and a representative giving a presentation about the data. The Panel noted that the slide presentations would only be made following a specific request from clinicians. The Panel queried whether every member of every audience would have made an unsolicited individual request for information on the use of the combination. The Panel was concerned that the representatives had been provided with detailed slide sets discussing the use of Abbott's product Norvir in an unlicensed combination. In the Panel's view the nature, content and use of the slide presentations were promotional and therefore subject to the Code. The Panel considered that as the slide presentations promoted Norvir in combination with Fortovase it was being promoted outside its licence. A breach of the Code was ruled.

A further breach of the Code was ruled because the Panel considered that the data had not been presented within the context of the Fortovase summary of product characteristics (SPC) and this was misleading and disparaging. The material gave the general impression that ritonavir ensured sufficient levels of saquinavir when administered in combination with Fortovase but the Fortovase SPC did not require this. The SPCs for both Norvir and Fortovase stated that a combination of the two should be used with caution.

Roche Products Limited complained about Abbott Laboratories Limited's promotion of Norvir (ritonavir) in combination with Roche's own product Fortovase (saquinavir soft gel capsules). Both medicines were protease inhibitors. Norvir was indicated in combination with antiretroviral nucleoside analogue(s) for the treatment of HIV-1 infected adult patients with advanced or progressive immunodeficiency. Fortovase was indicated, in combination with antiretroviral agents, to treat the same patient population.

COMPLAINT

Roche stated that it had been in correspondence with Abbott last year because it believed that Abbott's product Norvir was being promoted outside its licence as it was being promoted in combination with Roche's product Fortovase which was unavailable at that time except as named patient use.

Roche believed that Abbott representatives were suggesting to prescribers that Fortovase alone provided insufficient blood levels of saquinavir and therefore ritonavir (which blocked saquinavir metabolism) should routinely be given concurrently. Following correspondence on the matter Roche eventually received a letter assuring it that Abbott representatives did not promote this combination. It accepted that reassurance in good faith and took no further action.

Fortovase was launched on 12 April and since then Roche representatives reported that Abbott continued to promote Norvir in combination with Fortovase as detailed above. It presumed that lower doses of both medicines than those recommended in either summary of product characteristics (SPC) were promoted. Unfortunately it was difficult to find hard and fast evidence for this activity because no such promotional material was available.

However, recently it received a letter from a consultant physician asking for clarification. The letter stated:

'I wonder if you could be kind enough to clarify something for me regarding the use of saquinavir. My understanding from presentations at meetings and by saquinavir representatives was that soft gel saquinavir greatly increased the absorption and therefore active drug available as compared to saquinavir hard gel. My understanding was that this took the level well above the therapeutic dose required. However discussions with representatives from Abbott have given me the impression that simultaneous use of ritonavir greatly enhances the effectiveness of saquinavir, whereas saquinavir, whether soft gel or hard gel, used alone would be insufficient. I wonder if you would also clarify whether using ritonavir and saquinavir together, therefore allowing a reduction in dosage of each could be beneficial by reducing side effects and therefore enhancing compliance.

I would be very grateful if you could give me a clear statement on the correct use of saquinavir soft gel for maximum efficacy and best use of hard gel saquinavir, particularly in relation to ritonavir.'

Roche stated that it was clear from this that Abbott was promoting outside the licence (Clause 3.2), and disparaging Fortovase (Clause 8.1). The letter stated that Abbott maintained that ritonavir greatly enhanced that effectiveness of saquinavir, whereas saquinavir whether soft gel (Fortovase) or hard gel (Invirase) 'used alone would be insufficient'. In view of the past reports from its representatives, Roche considered that this was not an isolated event and possibly reflected a common promotional campaign.

Roche pointed out that the Fortovase formulation had been specifically developed so as to provide optimal levels of saquinavir so that it did not have to be taken with ritonavir. None of the pivotal efficacy trials that resulted in the licensing of Fortovase were in combination with ritonavir.

Fortovase was indicated in combination with antiretrovirals for the treatment of HIV-1 infected patients. It was established practice for all patients to receive combinations of at least three medicines as part of the so-called HAART regimen (highly active antiretroviral therapy). This usually comprised two nucleoside analogue reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor.

No mention was made in the Fortovase SPC for the necessity of combining with ritonavir. Indeed there was a special warning about this interaction (section 4.4). In 1998 prior to the licence of Fortovase, Roche provided this formulation on a named patient basis. It subsequently came to Roche's notice that Abbott representatives were informing physicians that Fortovase did not provide sufficient blood levels of saquinavir and that ritonavir should be given concurrently.

This was clearly outside the terms of the licence for Norvir as it was indicated 'in combination with antiretroviral nucleoside analogues'. Protease inhibitors such as Fortovase were not nucleoside analogues. The current SPC for Norvir did not include mention of combination with protease inhibitors within the therapeutic indication. The only reference to such a combination was the special warnings and special precautions for use (section 4.4) which stated that a pharmacokinetic study found that ritonavir greatly increased saquinavir plasma concentrations. However, it also warned that doses greater than 400mg of either medicines were associated with an increased incidence of adverse events.

Moreover in section 4.5 of the Norvir SPC another warning was provided in relation to ritonavir's interaction with the metabolism of several classes of

medicines in addition to those listed in the contra-indications section. This included 'other HIV-protease inhibitors'. As no protease inhibitors were listed in the contra-indications, 'other' must refer to protease inhibitors other than ritonavir. Thus 'due to the potential for significant elevation of serum levels of these drugs' (ie protease inhibitors) 'they should not be used concomitantly with ritonavir without a careful assessment of the potential risks and benefits. Careful monitoring of therapeutic and adverse effects was recommended when these drugs were concomitantly administered with ritonavir'. The specific warning relating to saquinavir was repeated here.

In earlier correspondence with Abbott, Roche was informed that a specific contraindication in previous SPCs about co-administration of the two medicines had been deleted. Nonetheless it was noteworthy that the warning about interactions with protease inhibitors described still remained.

Letters from Abbott included statements about how representatives were trained to answer questions about combinations, but despite requests from Roche for details none were provided. However the final letter from Abbott, 17 June 1998, stated quite categorically that representatives did not promote the combination. Roche was therefore concerned that Abbott continued to advocate routine combination of saquinavir plus ritonavir at doses of 400mg each twice daily. The letter from the consultant made no mention of any warning received from the representative on possible adverse effects of this combination.

Roche recognised that the treatment of HIV/AIDS was an evolving therapeutic area . It acknowledged that prescribers had to make difficult decisions based on many factors including previous treatment regimens the patient might have taken, and resistance patterns of the virus to one or several agents. Roche accepted that in certain situations, dual protease inhibitor therapy, given for enhanced antiviral, rather than for pharmacokinetic effect, might be considered a worthwhile option. It was not its intention to interfere with this prescribing freedom. What it objected to was misleading information about Fortovase, and promoting its routine use in combination with ritonavir. Roche would like Abbott to cease this at once and provide an undertaking that it would not be repeated in future.

RESPONSE

Abbott categorically refuted the allegation made by Roche that it had engaged in the promotion of Norvir outside the product licence.

Abbott stated that during the period May 1998 to June 1998, it had responded to an allegation made by Roche that Abbott representatives were engaged in promoting the concomitant use of ritonavir and saquinavir, which was contrary to the product licence for ritonavir. In its letter dated 1 June 1998, Abbott denied these allegations, and clearly outlined the training that its representatives received in relation to handling enquiries relating to the off-licence use of ritonavir.

Abbott acknowledged that representatives were frequently placed in difficult situations with regard to this issue in particular, and had deliberately adopted a proactive approach to ensuring that representative promotional activity fell within the bounds of the product licence for ritonavir, and that discussions between representatives and clinicians were conducted in a scientific and appropriate manner. In particular, the written response to Roche emphasised that Abbott representatives were instructed not to initiate discussion relating to the off-licence use of ritonavir, and to re-iterate that no recommendations could be made on usage or dose if questioned directly on this issue.

In its letter dated 12 June 1998, Roche was critical of the representative training that Abbott had provided.

Abbott drew the attention of the Authority to its willingness to thoroughly investigate the complaint submitted by Roche in May/June 1998, and freely provide comprehensive details regarding the training of the representatives in the absence of any objective evidence of a transgression of the Code.

On June 17 1998 Abbott responded to Roche's letter of June 12 by reiterating that its representatives did not engage in the promotion of ritonavir and saquinavir in combination, and that all promotional activity was in accordance with the terms of the ritonavir product licence.

No subsequent correspondence was received from Roche beyond this date. Abbott viewed this as an acceptance of the reassurance that it had made with regard to the appropriate and professional behaviour of its representatives, and the lack thereof of grounds for formal complaint. Abbott provided copies of the relevant correspondence.

Abbott acknowledged that medical representatives were frequently identified by clinicians as a source of information. Representatives were often approached for new data that might have been presented at major conferences and symposia. Abbott was firmly committed to ensuring that its representatives fully understood, and abided by, the ritonavir SPC. In addition, the role of the representative as information provider could not be overlooked, particularly in this rapidly evolving therapeutic area. As an acknowledgement of this, Abbott had clearly defined this aspect of the behaviour of representatives, primarily to ensure that any promotional activity remained consistent with the product licence for ritonavir.

Abbott stated that all of its representatives responsible for the promotion of ritonavir were fully conversant with the contents of the ritonavir SPC, and of the implications this had on the ability to promote ritonavir.

Abbott noted that the letter of complaint from Roche acknowledged that 'unfortunately it was difficult to find hard and fast evidence for this activity because no such promotional material was available'. Abbott would like to emphasise this point. There were no items of promotional material relating to the use of ritonavir and saquinavir combination therapy being used by Abbott representatives. This reaffirmed the

commitment that Abbott had in engaging only in promotional activities consistent with the terms of the ritonavir product licence.

Abbott noted that the current ritonavir SPC had been updated in March 1999 to include the following references to the concomitant use of ritonavir and saquinavir.

'4.4 Special warnings and special precautions for use A pharmacokinetic study demonstrated that ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations (see section 4.5 Interaction with other medicinal products and other forms of interaction). Doses greater than 400mg bid of either drug were associated with an increased incidence of adverse events.

4.5 Interaction with other medicinal products and other forms of interaction Saquinavir: data from pharmacokinetic studies in patients indicate that co-administration of ritonavir 400mg twice daily produce multifold increases in saquinavir steady state blood levels (AUC, 17 fold: Cmax, 14 fold increase). Doses greater than 400mg bid of either drug were associated with an increased incidence of adverse events.'

Ritonavir was indicated in combination with antiretroviral nucleoside analogue(s) for the treatment of HIV-1 infected patients with advanced or progressive immunodeficiency. Use in combination with saquinavir, a protease inhibitor, remained off-licence.

To remain within the terms of the current ritonavir product licence, Abbott forbade its representatives to initiate conversation with clinicians relating to the use of ritonavir in combination with saquinavir. However, following a specific physician enquiry, discussions relating to the pharmacokinetic interaction between these two products, and any relevant data pertaining to this, was permitted. Abbott insisted, however, that during the course of such discussions, its representatives informed the enquirer that the use of ritonavir and saquinavir in combination remained beyond the provision of the current ritonavir product licence.

Abbott stated that under no circumstances were its representatives permitted to engage in discussions of a derogatory nature regarding competitor products.

Abbott stated that, if during conversation with a clinician, a request was made for pharmacokinetic or clinical data relating to the combination of ritonavir or saquinavir, its representatives were instructed to record the personal details of that clinician and the nature of the enquiry. All requests for information of this nature were dealt with as indicated above. Requests for information that required a written response were returned to head office for further action, and a master file of such requests was centrally held. Depending on the nature of the enquiry, the clinician would be sent information pertaining to that specific enquiry. This information was presented as a standard or adapted letter despatched from the medical information department. Representatives were specifically prohibited from initiating any conversation relating to these issues.

Abbott stated that in light of the heightened interest regarding the use of dual protease inhibitor combination therapies in 1998, its representatives had been frequently asked to present pharmacokinetic and other relevant data relating to the combination of ritonavir and saquinavir. The current product licence for ritonavir did not prohibit the discussion of such data; however, it did prohibit promotional activity relating to the combination of ritonavir and saquinavir. Abbott noted that such presentations always followed a direct request from an interested clinician and were never representative initiated. To ensure this, all clinicians were asked to certify that they had formally requested such a presentation, and the details of the clinician (and attendees) were recorded and retained in the manner outlined above. Presentations given by the representative had been formally approved by the in-house promotional sign-off procedure, and were restricted to a purely scientific content, with no promotional claims. During a presentation, the representative reiterated to the audience that the use of ritonavir and saquinavir remained off-licence, and this point was reiterated on the cover slide of the majority of such presentations. Attendees were reminded to refer to the SPC for prescribing details, and copies of the ritonavir SPC were always made available. Copies of the presentation were provided.

Abbott stated that memoranda were periodically sent to its representatives to update them on therapeutically related issues. Such information was clearly marked for their personal educational use only, and carried a cautionary statement relating to the information being imparted. This reiterated Abbott's firm commitment to ensure that promotional activity by its representatives was in accordance with the terms of the current ritonavir product licence.

Abbott provided copies of all relevant items currently used by its representatives. They were as follows:

a) *Slide set:* Antiretroviral safety and durability of ritonavir (RTV) – saquinavir (SQV) in protease inhibitor-naïve patients in year two of follow-up. Date of preparation: May 1998

b) *Slide set:* Progress in Dual Protease Inhibitor (PI) Therapy, Update Since Geneva: Ritonavir (RTV) Plus Saquinavir (SQV). Date of preparation: December 1998

c) *Slide set:* Antiretroviral Activity of Ritonavir (RTV) – Saquinavir (SQV) in Protease Inhibitor-Naïve Patients (Study M96-462). Date of preparation: April 1998

d) *Study Report (PXNOR98129):* Antiretroviral safety and durability of ritonavir (RTV) – saquinavir (SQV) in protease inhibitor-naïve patients in year two of follow-up. Date of preparation: June 1998

Abbott Laboratories reiterated that these items were used by its representatives as detailed above.

Abbott reiterated that under no circumstances were its representatives permitted to engage in discussions of a derogatory nature regarding competitor products, and categorically denied that its representatives had in the past advised that ritonavir 'should routinely be

given concurrently with saquinavir'. As detailed above Abbott representatives were specially instructed only to engage in discussions with clinicians that remained within the bounds of the product licence for ritonavir. In the absence of objective evidence relating to this accusation, and following previous correspondence with Roche, this complaint was not pursued by Roche. Abbott viewed this outcome as an acceptance of the reassurance of the professional standing of its representatives provided to Roche.

The accusations made in paragraph three of the complaint were based on pure conjecture and hearsay, as exemplified by Roche in its statement that 'no hard and fast evidence' of inappropriate promotional activity existed.

Abbott noted that no evidence supporting inappropriate promotional activity had been provided. It was unclear from the complainant's letter exactly who had initiated the alleged discussion, what aspect of ritonavir/saquinavir combination therapy was discussed, and whether the 'impression' of the complainant had in fact been influenced by the Abbott representative at all.

Abbott stated that it had clearly identified the professional steps it had taken in ensuring that its representatives abided by the provisions of the current product licence for ritonavir. As such, Abbott considered that the statement that the behaviour of its representatives possibly reflected a common promotional campaign to be unsubstantiated, based on hearsay, and defamatory.

Abbott denied that the commitment made to Roche in its letter dated 17 June 1998 had been broken. On the contrary, following the communications between both companies in 1998, Abbott issued a memorandum to the sales force reiterating the professional conduct with which Abbott expected the representatives to continue to adhere to.

Abbott stated in summary that it had acted professionally and responsibly in all aspects relating to the manner in which it trained and monitored the performance of its representatives. In particular, Abbott placed utmost importance on the requirement of its representatives to fully adhere to the promotion of ritonavir within the bounds of the current product licence. Abbott fully investigated the allegations made by Roche in 1998 and dealt with this matter in an open, honest and helpful manner. Lack of subsequent communication from Roche was appropriately interpreted as a satisfactory resolution of the issues raised by the company. Abbott was concerned that this matter was referred to the Authority without any 'hard and fast' evidence of inappropriate behaviour on behalf of its representatives, and would like to reiterate that all promotional activity conducted by the representatives was in accordance with the terms of the current ritonavir product licence.

PANEL RULING

The Panel noted that HIV treatment was a difficult area. Medicines were often used outside their licences. The Panel noted that representatives might frequently be asked about the unlicensed use of their own or a competitor product. It was of course unacceptable under Clause 3 of the Code for companies to promote medicines that were not licensed or to promote unlicensed indications, doses, combinations etc. The Panel noted Abbott's submission that the material at issue, the medical information letter, the three slide presentations by company representatives and statements made by representatives to health professions were used in response to specific requests for information from health professionals. The Panel therefore had to decide whether the matter was subject to the Code given that Clause 1.2 of the Code stated that promotion did not include replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, …but only if the response related solely to the subject matter of the letter or enquiry, was accurate and did not mislead and was not promotional in nature.

The Panel noted that the medical information document was dated 18 March 1999. In the Panel's view the document was presented in a non-promotional style and format and discussed recent studies which had examined the efficacy of Norvir in dual protease inhibitor containing regimens. The licensed indication of Norvir was given at the outset together with the statement that the use of Norvir in dual protease inhibitor combinations was unlicensed. The document concluded that the studies summarised suggested that the use of ritonavir in dual protease inhibitor combinations might confer high antiviral potency and favourable pharmacokinetic interactions, with inhibition of cyctochrome P450 mediated drug metabolism. This had been found to increase protease inhibitor plasma levels, leading to greater potency and the ability to use twice daily dosing. On balance, the Panel decided that the document was not promotional in style or content and thus, if used in accordance with the criteria set out in Clause 1.2, it was not subject to the Code.

The Panel examined the three slide sets provided. The two entitled 'Progress in Dual Protease Inhibitor (PI) Therapy Update Since Geneva: Ritonavir (RTV) plus Saquinavir' and 'Antiretroviral Activity of Ritonavir (RTV) – Saquinavir (SQV) in Protease Inhibitor-Naïve Patients (Study M96-462)' discussed the results of separate studies. Each included prescribing information for Norvir. The title slide of each presentation stated, by way of footnote, that RTV/SQV combination was not licensed in the UK and referred to the prescribing information. The third presentation entitled 'Antiretroviral safety and durability of ritonavir (RTV)-saquinavir (SQV) in protease inhibitor-naïve patients in the year two of follow up' used emboldened headings to highlight statements favourable to Norvir. Prescribing information was provided although there was no statement at the outset as to the product's licensed indication. This study was also presented as a study report which, in the Panel's view, had the appearance of a promotional item, such as a leavepiece, and not of a scientific report.

The Panel noted that this material would be presented to clinicians by representatives. The role of the representative was to promote products. It was difficult to argue that a representative should deal with requests for information about unlicensed use of medicines using specially prepared material. In the Panel's view such requests were best dealt with by the medical information department. Representatives might appropriately respond to such requests by providing scientific information but the Panel was concerned at the amount of material provided to representatives. The Panel had no way of knowing the degree to which representatives tailored the material to answer the request. There was, in the Panel's view, a difference in providing a scientific paper such as a report or a response from the medical information department to a representative giving a presentation about the data.

The Panel noted that the presentations would only be made following a specific request from the clinicians. The Panel queried whether every member of every audience would have made an unsolicited individual request for information on the use of the combination. The Panel was concerned that the representatives had been provided with detailed slide sets discussing the use of Abbott's product Norvir in an unlicensed combination. In the Panel's view the nature, content and use of the slide presentations were promotional and therefore subject to the Code.

The Panel noted that Clause 3 of the Code required the promotion of a medicine to be in accordance with its marketing authorization and not inconsistent with the particulars listed in its SPC. The Panel noted that Norvir was indicated in combination with antiretroviral nucleoside analogues for the treatment of HIV-1 infected adults. Fortovase was not a nucleoside analogue. The Panel considered that as the slide presentations promoted Norvir in combination with Fortovase it was being promoted outside its licence. A breach of Clause 3.2 of the Code was ruled.

The Panel noted Roche's comment that the Fortovase formulation had been specifically developed so as to provide optimal levels of Fortovase such that it did not have to be taken with Norvir.

The Panel noted that the Fortovase SPC did not require it to be administered in combination with ritonavir to ensure sufficient blood levels of saquinavir. The Panel noted that section 4.4 of the Fortovase SPC stated that plasma concentrations of saquinavir increased if co-administered with ritonavir and stated that combination therapy of saquinavir and ritonavir should be used with caution. The Panel noted that the ritonavir SPC, updated in March 1999 included similar references to the concomitant use of ritonavir and saquinavir. The Panel considered that the Norvir material gave the general impression that ritonavir ensured sufficient levels of saquinavir were maintained when administered in combination with Fortovase. In this regard the Panel noted the letter written by the consultant physician to Roche regarding the impression he/she had gained from presentations and from company representatives. The Panel considered that the data had not been presented within the context of the Fortovase SPC. This was misleading and disparaging. The Panel ruled a breach of Clause 8.1 of the Code.

Complaint received **27 July 1999**

Case completed **20 September 1999**

CASE AUTH/909/7/99

PHARMACEUTICAL ADVISER v 3M HEALTH CARE

Qvar letter

A pharmaceutical adviser complained about a letter on Qvar (CFC-free beclomethasone dipropionate (BDP) inhaler) sent by 3M Health Care to directors of primary care, directors of public health, medical and pharmaceutical advisers and to medical directors of trusts. The letter referred to the transition to CFC-free inhalers.

The complainant alleged that one of the references in the letter was incorrectly cited. This was accepted by 3M Health Care which apologised for the error. The Panel ruled a breach of the Code.

It was also alleged that a claim 'Patients in the Qvar treated group showed a significant improvement in the overall Quality of Life scores compared with the CFC-BDP treatment group' was misleading. The Panel noted that the data demonstrated a statistically significant difference in favour of Qvar but did not demonstrate a clinically meaningful difference in quality of life. The letter was misleading as not all the relevant details had been provided. A breach of the Code was ruled.

A pharmaceutical adviser complained about a letter on Qvar sent by 3M Health Care Limited. Qvar was a CFC-free beclomethasone dipropionate (BDP) inhaler.

The letter had been sent to directors of primary care, directors of public health, medical and pharmaceutical advisers to health authorities and medical directors of NHS Trusts. The letter was headed 'The Transition to CFC free inhalers – What do you need to know?'

1 Clarity of references

The letter stated 'Data just published[2] shows that asthma control was maintained throughout 12 months of treatment…'. Reference 2 was given as Cohen RM *et al* (1999). The letter also referred to quality of life data referenced to reference 3 which was given as Prenner B *et al* 1999 Am J Resp & Crit Medicine 159; 1999.

COMPLAINT

The complainant referred to Clause 7.5 of the Code which stated that when promotional material referred to published studies, clear references must be given.

The quoted references 2 and 3 were incomplete. The complainant stated that he had eventually managed to obtain copies of the relevant posters (and the letter did not make it clear that these were posters) from the helpful medical information department at 3M Health Care. Reference 3 in the letter was actually from J Allergy Clin Immunol rather than as stated in the letter from Am J Resp Crit (Care) Medicine.

RESPONSE

3M Health Care stated that reference 2 (Cohen RM *et al* Am J Resp & Crit Care Med **159**; 1999) was clear, unambiguous, and easily found from the list of authors on page A940 of the relevant journal. As a pharmaceutical adviser the complainant would be aware that the easiest route to obtain the abstract and the full poster would be via the company's medical information group. The relevant contact number appeared on the prescribing information which was printed on the back of the letter.

3M Health Care accepted that reference 3 was wrongly cited. This was a simple mistake for which the company apologised. No attempt was being made to mislead the reader. The correct reference was Prenner B *et al*, J Allergy Clin Immunol 1999; **103** (1pt2): S129. All other items in which these data had been used had been checked to ensure the mistake was not repeated.

PANEL RULING

Clause 7.5 required that when promotional material referred to published studies clear references must be given. The Panel noted that 3M Health Care was obliged to give reference 2 as the letter referred to published data in relation to the maintenance of asthma control throughout 12 months of treatment. Reference 2 had been given clearly.

The Panel noted that the quality of life data, which appeared on the first and second page of the letter, was referenced, on the second page, to reference 3. There was no mention in the letter that the quality of life data was from a published study. There was, therefore, no need to provide a reference under Clause 7.5 and the Panel ruled no breach of that clause. The Panel noted that reference 3 was incorrectly cited. The matter was more appropriately dealt with under Clause 7.2 which required *inter alia* information to be accurate and the Panel therefore ruled a breach of that clause.

2 Significance of quality of life data

COMPLAINT

The complainant noted that reference 3 was used to support a claim in the letter that 'Patients in the Qvar treated group showed a significant improvement in the overall Quality of Life scores compared with the CFC BDP treatment group'.

This was correct in that the mean change from baseline was significantly in favour of Qvar with values of approximately 0.35 versus 0.1 on the relevant quality of life questionnaire. However, the actual poster presentation stated that a change of 0.5 indicated a clinically meaningful difference in quality of life. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

3M Health Care stated that the claim of significant improvements in quality of life were claims of

statistical significance and supported by the poster. The complainant had missed the difference between statistical and clinical significance. Furthermore, the data presented was a statistical comparison between the two products at the end of treatment, not a comparison of a change from baseline for each product. In the latter case, as the complainant correctly pointed out, there was a caveat in the poster that a change of 0.5 (or more) indicated a clinically significant change. However, 3M Health Care submitted that the poster was quite clear on both of these points. Furthermore the letter only stated that '…there may be beneficial effects in the asthma control and quality of life..' It was important to note that on recruitment to this particular study, subjects were patients with well controlled asthma, whose only treatment change was a switch to a non-CFC inhaler. To have demonstrated any improvement at all in quality of life in this group was a considerable feat. 3M Health Care considered that the reference clearly referred to statistically significant differences and that it ably supported the statements made and was accurate, balanced, fair, objective and unambiguous in accordance with Clause 7.2 of the Code.

PANEL RULING

The Panel examined the poster by Prenner *et al* which included a bar chart headed 'Mean Change[a] from Baseline in Asthma Quality of Life scores[b]'. The explanation for [b] was given below the bar chart as 'A change of 0.5 indicated a clinically meaningful difference in QOL [quality of life]'. This was referenced to Juniper *et al* (1994). The bar chart showed that the difference between CFC-free BDP and CFC-BDP with regard to mean change from baseline was statistically significant in favour of CFC-free BDP at 12 months.

The Panel noted that the data demonstrated a statistically significant difference. Neither product showed a change from baseline of 0.5, both were below this figure. The Panel therefore concluded that the data did not demonstrate a clinically meaningful difference in quality of life. The letter referred only to a significant difference and did not make it clear that this was only a statistically significant difference. The Panel considered that the letter was misleading with regard to the comparison in quality of life scores as not all the relevant details had been provided. A breach of Clause 7.2 of the Code was ruled.

Complaint received	**28 July 1999**
Case completed	**2 September 1999**

CASE AUTH/910/8/99

PROCTER & GAMBLE v MERCK SHARP & DOHME

Promotion of Fosamax

Procter & Gamble complained about promotion for Fosamax (alendronate sodium) by Merck Sharp & Dohme featuring the results of the Fosamax International Trial (FOSIT). Fosamax, 10mg daily, was indicated for the treatment of osteoporosis in post-menopausal women to prevent fractures. Procter & Gamble produced cyclical etidronate (Didronel PMO) which was indicated for the treatment of osteoporosis and prevention of bone loss in post-menopausal women considered at risk of developing osteoporosis. Didronel PMO was also licensed for the prevention and treatment of cortiscosteroid-induced osteoporosis.

A journal advertisement featured an advertising board at a bus stop which announced 'IT'S ARRIVED New data shows that your choice of treatment for osteoporosis is the only one that can build bone within just three months, nearly halving the risk of non-vertebral fracture within one year'. The claim was referenced to the FOSIT study. It was alleged that the claim was incorrect since the data available for cyclical etidronate as primary preventive therapy for corticosteroid-induced osteoporosis clearly showed the rapid bone building effects of that therapy. The Panel noted that the claim at issue clearly referred to the treatment rather than prevention of osteoporosis. Text at the bottom of the advertisement stated 'No other treatment for osteoporosis shows these results.' Given the clear reference to the treatment of osteoporosis, and that the data referred to by Procter & Gamble was a study designed to detect prevention of steroid-induced osteoporosis, the Panel did not consider that the claim was inaccurate, misleading and exaggerated without substantiation, as alleged, and ruled no breach of the Code.

The front cover of a mailing depicted a tube train in an underground station. The travel theme was continued inside the mailing with some claims appearing on what appeared to be season tickets. The claim at issue 'FOSAMAX helps stop fracture – FAST', appeared on page two of the mailing, underneath the headline banner 'GREAT NEWS FROM THE FOSAMAX INTERNATIONAL TRIAL (FOSIT)'. Text beneath the claim stated that Fosamax reduced non-vertebral fractures by 47% within one year. The Panel noted that the FOSIT study was a randomised, double blind placebo controlled trial to evaluate the safety, tolerability and effect on bone mineral density of alendronate in a large population of post-menopausal women with low bone mass. The study concluded that alendronate was well tolerated and produced significant, progressive increases in BMD at the lumber spine and hip in addition to a significant reduction in the risk of non-vertebral fracture. A limitation of the study was that fractures were captured through adverse event reporting only. Vertebral fractures could not be evaluated as spine radiographs were not obtained prior to study entry and thus it was not possible to be certain whether a compressed vertebra observed during the study represented a new as opposed to a pre-existing fracture. In the opinion of the Panel, the claim 'FOSAMAX helps stop fracture - FAST' was a broad claim which did not fairly reflect the findings of the FOSIT study. The Panel did not accept Merck Sharp & Dohme's submission that clarification appeared beneath the claim. The Panel did not consider that the reference to the reduction rate in non-vertebral fractures negated the impression given by the claim at issue, that Fosamax helped stop fractures at all sites, fast. The Panel considered the claim misleading and exaggerated as alleged and ruled breaches of the Code.

Pages two and three of the mailer opened as a double page spread. Page two gave details of the results of the FOSIT study and page three was headed with a further claim from the same study. The claim 'FOSAMAX helps stop fracture – EVERYWHERE' appeared in the middle of page three and was referenced to a study by Black *et al* 1996, the fracture intervention trial (FIT). Beneath the claim was another that Fosamax reduced the incidence of osteoporotic fracture at all major sites including hip 51%, wrist 48% and new vertebral 47%. The Panel noted that the data did not show a statistically significant reduction in the incidence of fracture at certain fracture sites. The Panel considered that the word 'everywhere' overstated the totality of the data and added an emphasis not reflected in the product's summary of product characteristics. The Panel considered the claim misleading, without substantiation and exaggerated as alleged and ruled breaches of the Code. The Panel noted that the claim was referenced to the FIT study and appeared in the middle of page three immediately beneath data relating to the FOSIT study and in a similar type face and style. The Panel thought that a reader might reasonably consider all of the data on pages two and three of the mailing to be covered by the highlighted banner headline on page two 'GREAT NEWS FROM THE FOSAMAX INTERNATIONAL TRIAL (FOSIT).' The Panel considered the juxtaposition of the data misleading as alleged and ruled a breach of the Code.

Procter & Gamble Pharmaceuticals UK, Limited submitted a complaint about the promotion of Fosamax (alendronate sodium) by Merck Sharp & Dohme Limited. Two promotional items were at issue; a journal advertisement (ref 04-00 FSM.99.GB.60079.J) which appeared in Hospital Doctor, 27 May 1999, and a four page mailing with a tear-off reply paid card (ref 04-00 FSM.99.GB.60059. M.40m. CW.499). Both items introduced the reader to the results of the Fosamax International Trial (FOSIT) which had been published by Pols *et al* (1999).

Fosamax, 10mg daily, was indicated for the treatment of osteoporosis in post-menopausal women to prevent fractures.

Procter & Gamble produced cyclical etidronate (Didronel PMO) which was indicated for the treatment of osteoporosis and prevention of bone loss in post-menopausal women considered at risk of developing osteoporosis. Didronel PMO was also licensed for the prevention and treatment of cortiscosteroid-induced osteoporosis.

A Journal Advertisement

The advertisement featured an advertising board at a bus stop which announced 'IT'S ARRIVED New data shows that your choice of treatment for osteoporosis is the only one that can build bone within just three months, nearly halving the risk of non-vertebral fracture within one year'. The claim was referenced to the FOSIT study. Text beneath the advertising board also referred to the study and stated that no other treatment for osteoporosis showed these results.

Claim 'New data shows that your choice of treatment for osteoporosis is the only one that can build bone within just three months…'

COMPLAINT

Procter & Gamble alleged that the claim was incorrect, since the data available for cyclical etidronate as primary preventive therapy for corticosteroid-induced osteoporosis clearly showed the rapid bone-building effects of this therapy. Mulder *et al* (1994) demonstrated an increase in lumbar spine bone mineral density (BMD) as early as 3 months after the start of therapy, that was statistically significant from baseline and placebo. Procter & Gamble alleged that to claim or imply that Fosamax was 'the only one that can build bone within just three months' without clarification was inaccurate, misleading and exaggerated without substantiation, and therefore in breach of Clauses 7.2, 7.3 and 7.8 of the Code.

Procter & Gamble referred to inter-company correspondence on this point. Merck Sharp & Dohme's response to its concerns suggested that it was necessary to read this claim in conjunction with the second claim appearing on the advertising board '… nearly halving the risk of non-vertebral fracture within one year'. However Procter & Gamble did not support this interpretation. Two separate claims had been made: the first relating to bone building, and the second, to reduction in the risk of fracture. If the two claims were to be intended to be linked in the way that Merck Sharp & Dohme suggested, Procter & Gamble believed that the word 'and' should have been inserted between them. In light of this, it remained strongly of the view that the claim and the copy that followed was inaccurate, misleading and exaggerated without substantiation. Further, it noted in Merck Sharp & Dohme's letters that this issue had already been the subject of a complaint to the Medicines Control Agency (MCA).

RESPONSE

Merck Sharp & Dohme pointed out that Procter & Gamble had chosen not to quote the full claim as it appeared in the advertisement, 'New data shows that your choice of treatment for osteoporosis is the only one that can build bone within just three months, nearly halving the risk of non-vertebral fracture within one year.' Procter & Gamble argued that etidronate had been shown to increase lumbar spine BMD at 3 months in a steroid-induced osteoporosis prevention study. The advertisement clearly referred to treatment of osteoporosis, rather than primary prevention. The Mulder *et al* study was very small and the authors themselves commented on the fact that studies with larger patient populations would be required to confirm the results. Merck Sharp & Dohme was not aware that a larger study had confirmed the 3 month results, and Procter & Gamble had not quoted one. The study was not randomised or blinded. That this might have caused bias in treatment allocation was suggested by the fact that the etidronate treated patients had a lower BMD at baseline. Further there was no significant reduction in fractures. Given that the study was in a different indication, that there were obvious reservations about the quality of this study and it did not contain any fracture data, Merck Sharp & Dohme did not believe it refuted the claim. A literature search for published osteoporosis treatment studies and meeting abstracts was conducted before placing the advertisements to ensure the accuracy of the claim. The claim must be viewed in its entirety – increase in BMD and decrease in fractures. Merck Sharp & Dohme was not aware of any data with cyclical etidronate, or any other product, which demonstrated both an increase in BMD by 3 months and a reduction in non-vertebral fractures within a year. It believed the entire claim was accurate, did not mislead and was substantiated by the reference quoted. It did not believe there to be a breach of Clauses 7.2, 7.3 or 7.8.

Merck Sharp & Dohme had informed Procter & Gamble that this claim was under discussion with the MCA. It had proposed changes to the claim in light of the MCA's comments and was awaiting its response. Part of the proposed change was to include the word 'and' as Procter & Gamble had suggested. Merck Sharp & Dohme was disappointed that Procter & Gamble had chosen not to wait for the outcome of the discussions with the MCA.

PANEL RULING

The Panel noted that Mulder *et al* (1994) was a prospective, parallel group study of etidronate's effect on corticosteroid-induced bone loss in post-menopausal women (n=20) with temporal arteritis for whom high dose prednisone therapy was indicated; in particular to see whether it could prevent the early accelerated bone loss associated with pharmacologic doses of prednisone. The authors concluded that the results suggested that corticosteroid-induced bone loss could be effectively prevented by instituting intermittent cyclical etidronate (bisphosphonate) therapy as soon as high dose prednisone therapy was begun. It was stated that further studies to confirm the efficacy of bisphosphonates in corticosteroid-induced bone loss (with larger patient populations, longer follow up and assessment of fractures) was warranted.

The Panel noted that the claim at issue clearly referred to the treatment rather than prevention of osteoporosis. Text at the bottom of the advertisement stated 'No other treatment for osteoporosis shows these results.' Given the clear reference to the treatment of osteoporosis and that the Mulder *et al* study was designed to detect prevention of steroid-induced osteoporosis the Panel did not consider that the claim was inaccurate, misleading and exaggerated without substantiation as alleged and ruled no breach of Clauses 7.2, 7.3 and 7.8 of the Code.

B Mailing

1 Claim 'FOSAMAX helps stop fracture – FAST'

The front cover of the mailing depicted a tube train in an underground station. The travel theme was continued inside the mailing with some claims appearing on what appeared to be season tickets. The claim at issue appeared on page two of the mailing, underneath the headline banner 'GREAT NEWS FROM THE FOSAMAX INTERNATIONAL TRIAL (FOSIT)'. Text beneath the claim stated that Fosamax reduced non-vertebral fractures by 47% within one year adjacent to which a similar claim appeared on a season ticket headed 'one year season'.

COMPLAINT

Procter & Gamble alleged that the claim gave the impression that alendronate 10mg stopped fracture at ALL sites. However, the FOSIT study, cited in support of the claim, clearly indicated that radiographically defined vertebral fractures were not evaluated. In addition the publication showed that alendronate 10mg also did not reduce the risk of clinical fractures, for example at the hip/femur or hand to a statistically significant degree after 12 months of therapy. In summary, this publication highlighted that alendronate 10mg only reduced the risk of pooled non-vertebral fractures. Therefore the claim was misleading and implied an all-embracing nature, and was a clear breach of Clauses 7.2 and 7.8 of the Code. Procter & Gamble did not consider that it was sufficient to seek to qualify the claim by referring under the claim to non-vertebral fractures as Merck Sharp & Dohme had suggested in inter-company correspondence.

RESPONSE

Merck Sharp & Dohme noted that further detail appeared underneath the claim ie 'FOSAMAX reduced non-vertebral fractures by 47% – *within one year*' and 'valid for a 47% reduction in non-vertebral fractures over one year.' Clarification of the claim at issue therefore appeared twice. The page as a whole made obvious the data on which the claim was based, and the nature of the fractures to which it related. Since no claims were made with regard to the individual non-vertebral fractures eg hip/femur, and it had been made clear that non-vertebral fractures were the basis of the claim, Merck Sharp & Dohme submitted it was obvious that the claim related to a pooled group of non-vertebral fractures rather than individual sites and it was not misleading or all embracing.

PANEL RULING

The Panel noted that the FOSIT study was a randomised, double blind placebo controlled trial to evaluate the safety, tolerability and effect on bone mineral density of alendronate in a large population of post-menopausal women with low bone mass. The study concluded that alendronate was well tolerated and produced significant, progressive increases in BMD at the lumber spine and hip in addition to a significant reduction in the risk of non-vertebral fracture. The report stated that a limitation of the study was that fractures were captured through adverse event reporting only. Vertebral fractures could not be evaluated as spine radiographs were not obtained prior to study entry and thus it was not possible to be certain whether a compressed vertebra observed during the study represented a new as opposed to a pre-existing fracture.

In the opinion of the Panel, the claim 'FOSAMAX helps stop fracture – FAST' was a broad claim which did not fairly reflect the findings of the FOSIT study. The Panel did not accept Merck Sharp & Dohme's submission that clarification appeared beneath the claim on the page at issue. The Panel did not consider that the reference to the reduction rate in non-vertebral fractures negated the impression given by the claim at issue, that Fosamax helped stop fractures at all sites, fast.

The Panel considered the claim misleading and exaggerated as alleged and ruled breaches of Clauses 7.2 and 7.8 of the Code.

2 Claim 'FOSAMAX helps stop fracture – EVERYWHERE'

Pages 2 and 3 of the mailer opened as a double page spread. Page 2 gave details of the results from the FOSIT study (see point B1 above) and page 3 was headed with a further claim from the same study. The claim in question appeared in the middle of page 3 and was referenced to a study by Black *et al* 1996 (the fracture intervention trial (FIT)). Beneath the claim was another that Fosamax reduced the incidence of osteoporotic fracture at all major sites including hip 51%, wrist 48% and new vertebral 47%.

COMPLAINT

Procter & Gamble noted the juxtaposition of the claim in question to the first claim on page 2 that 'FOSAMAX helps stop fracture – FAST' and the second claim at the top of page 3 that 'After only three months, FOSAMAX increases bone mineral density at total hip, trochanter, lumbar spine and femoral neck', both referenced to the FOSIT study. The layout appeared to give the misleading impression that the third claim that 'FOSAMAX helps stop fracture – EVERYWHERE' was also from the FOSIT study, and that Fosamax helped stop fracture fast and everywhere at the same time, specifically at the hip, wrist and vertebrae. This was compounded by the claim being in the same colour and font size as the first claim on page 2. Procter & Gamble alleged that this was misleading since the average length of follow-up in the FIT study was 2.9 years, which was omitted from the claim, and not within one year or only three months as highlighted in bold and italics in the earlier parts of the mailer. Therefore, Procter & Gamble alleged that the claim was in breach of Clause 7.2 of the Code. It noted that Merck Sharp & Dohme appeared to have conceded this point in company correspondence.

Procter & Gamble also alleged that the claim was an exaggerated claim and was not supported by the FIT study. The FIT study showed no statistically significant reduction in fracture risk for alendronate at

'Any non-vertebral' site or 'Other' clinical fracture site. Also, in view of the misleading impression due to the juxtaposition of claims 1, 2 and 3, it noted that the term 'everywhere' was not supported by the FOSIT study either, as evidenced by no statistically significant changes shown at the hand or hip/femur, and lack of evaluation of radiographically defined vertebral fractures. Procter & Gamble therefore alleged that this claim was inaccurate, misleading and exaggerated without substantiation and was in breach of Clauses 7.2, 7.3 and 7.8 of the Code.

Procter & Gamble referred to inter-company correspondence and stated that Merck Sharp & Dohme's response to its concerns did not address those issues satisfactorily. Even though the main secondary endpoint of the FIT study was 'any clinical fracture' and the result was statistically significant compared to placebo, an analysis of the data for the shoulder, arm, hand, fingers, other small wrist bones, ribs, chest/sternum, coccyx/sacrum, ankle and toes revealed results which were clearly not statistically significant. Further, the reference to the summary of product characteristics (SPC) failed to provide any additional evidence to justify an all-embracing claim relating to fractures at all sites. In light of this, it remained Procter & Gamble's belief that the mailing was misleading without substantiation and all-embracing, and thus breached Clauses 7.2, 7.3 and 7.8 of the Code.

RESPONSE

Merck Sharp & Dohme noted Procter & Gamble's comments regarding the juxtaposition of the third claim, type face etc. and undertook to make it very clear in any future materials (since this was a one-off mailing) when different studies were being referred to.

The claim 'FOSAMAX helped stop fracture – EVERYWHERE' was clearly referenced to the FIT study and was also qualified with data. In this case, results from the FIT study were quoted with reference to hip, wrist and new vertebral fracture data ie those fractures that were recognised as the most commonly associated with osteoporosis. Whilst Procter & Gamble quoted two sub-classes of fracture that had results that were not statistically significant in the FIT study, the results for the main secondary end-point, the proportion of women with any clinical fracture were significantly lower in the alendronate group in comparison with placebo (13.6% vs 18.2%, p=0.004). This substantiated the claim, since it included symptomatic vertebral as well as non-vertebral fractures. The licensed indication for alendronate was symptomatic vertebral as well as non-vertebral fractures. The licensed indication for alendronate was now 'for the treatment of osteoporosis in post-menopausal women to prevent fractures,' and the SPC also contained data from the FIT study regarding all the women who had osteoporosis, on reductions in vertebral fractures, any painful fractures and hip fractures. The statement 'Overall these results demonstrate the consistent effect of Fosamax to reduce the incidence of fractures, including those of the spine and hip' also appeared in the SPC.

Therefore, Merck Sharp & Dohme believed the claim was supported by, and consistent with, data and statements included within the SPC and there was no breach of the Code.

PANEL RULING

The Panel noted that the Fosamax SPC stated that it was indicated for the treatment of osteoporosis in post-menopausal women to prevent fractures. The pharmacodynamic properties section referred to the consistent effect of Fosamax to reduce the incidence of fractures including those of the spine and hip which were the sites of osteoporotic fracture associated with the greatest morbidity.

The Panel noted that the FIT study was a randomised placebo controlled trial designed to measure the effect of Fosamax on the risk of fracture in post-menopausal women with low BMD and existing vertebral fractures. The authors concluded that the women who received alendronate had a lower incidence of several types of fractures than those in the placebo group. There was no significant reduction in the risk of fractures other than those of the spine, hip and wrist. These were not a primary endpoint of the study so the power to detect an effect was limited. The authors noted that the study had limitations; the patient population included only post-menopausal women with low bone density and vertebral fractures; 97% of the patient population was Caucasian and the study did not address the effect of longer term treatment on the risk of fractures.

The Panel noted that the data did not show a statistically significant reduction in the incidence of fracture at certain fracture sites. The Panel considered that the word 'everywhere' overstated the totality of the data and added an emphasis not reflected in the product's SPC. The Panel considered the claim misleading, without substantiation and exaggerated as alleged and ruled breaches of Clauses 7.2, 7.3 and 7.8 of the Code.

The Panel noted that the claim at issue was referenced to the FIT study and appeared in the middle of page three immediately beneath data relating to the FOSIT study and in a similar type face and style. The Panel thought that a reader might reasonably consider all of the data on pages two and three of the mailing to be covered by the highlighted banner headline on page two 'GREAT NEWS FROM THE FOSAMAX INTERNATIONAL TRIAL (FOSIT).' The Panel noted that the average follow-up time in the FIT study was 2.9 years. This was not made clear. The data from the FOSIT study was used to support the claims in points A and B1 above. These referred to data after one year and data after three months. The claim at issue in point B2 related to a separate study with an average duration of 2.9 years although the time scale was not given. The Panel considered the juxtaposition of the data misleading as alleged and ruled a breach of Clause 7.2 of the Code.

Complaint received **4 August 1999**

Case completed **12 October 1999**

DIRECTOR/MEDIA v PHARMACIA & UPJOHN

Public health campaign on bladder problems

An article in The Express on Sunday entitled 'Drug campaign tries to beat advertising ban' referred to posters going up on the doors of public toilets headed 'Greater freedom from bladder problems', as part of a campaign by Pharmacia & Upjohn which in September would make the transition from toilet doors to national television. It was alleged that while this was ostensibly no more than an innocent public information campaign, to its critics it was the first shot in a battle, the ultimate goal of which was to create a hypochondriacs' charter, undermine the independence of general practitioners and pour billions into the coffers of multinational drug companies. The article included a comment from the Chairman of the British Medical Association's Prescribing Committee who stated that advertising was about encouraging people to go to their doctors and ask for certain medicines and that the campaign was an indirect way of achieving the same end. The article also stated that while the campaign was within the rule prohibiting advertising prescription only medicines to the public the campaign was a disguised plug for Detrusitol, a Pharmacia & Upjohn medicine. In accordance with established practice whereby criticisms of the activities of pharmaceutical companies are treated as complaints under the Code of Practice, the matter was taken up by the Director.

A number of materials had been developed for the campaign and the Panel noted that the claim 'Greater Freedom from Bladder Problems' was included together with a recommendation that members of the public talk to their doctors and ask about treatment and care options.The materials stated that they were health education sponsored by Pharmacia & Upjohn. Medicines were not mentioned at all.

The Panel considered that the materials would increase public awareness of bladder problems and encourage people to discuss possible treatment and care options with their general practitioner. There were a number of different treatments available for bladder problems. Not all of them were medicines. Pharmacia & Upjohn products could be used to treat overactive bladders but they were not the only products available. The materials referred to bladder problems generally and not only to overactive bladders. Patients visiting their doctors as a result of seeing the campaign would not necessarily be prescribed a Pharmacia & Upjohn product and would not necessarily be suffering from a bladder problem that could be treated with a Pharmacia & Upjohn product.

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.

COMPLAINT

An article in The Express on Sunday, 8 August 1999, entitled 'Drug campaign tries to beat advertising ban' referred to posters going up on the doors of public toilets headed 'Greater freedom from bladder problems', as part of a campaign by Pharmacia & Upjohn which in September would make the transition from toilet doors to national television. It was alleged that while this was ostensibly no more than an innocent public information campaign, to its critics it was the first shot in a battle, the ultimate goal of which was to create a hypochondriacs' charter, undermine the independence of general practitioners and pour billions into the coffers of multinational drug companies. The article included a comment from Dr George Rae, Chairman of the British Medical Association's Prescribing Committee, who stated that advertising was about encouraging people to go to their doctors and ask for certain medicines and that the Pharmacia & Upjohn campaign was an indirect way of achieving the same end. The article also stated that while the campaign was within the rule prohibiting advertising prescription only medicines to the public the campaign was a disguised plug for Detrusitol, Pharmacia & Upjohn's medicine for urinary incontinence.

In accordance with established practice whereby criticisms of the activities of pharmaceutical companies were treated as complaints under the Code of Practice, the matter was taken up by the Director with Pharmacia & Upjohn Limited, attention being drawn to Clauses 20.1 and 20.2 of the Code.

RESPONSE

Pharmacia & Upjohn stated that the public health education campaign was not specific for any product or treatment option, and was therefore in no aspect promotional for any prescription medicine. In particular:

- no prescription medicines were being advertised to the general public;
- as there was no mention of any specific treatment, the materials did not encourage members of the public to ask their doctors to prescribe a specific medication;
- the public health education campaign materials were factual and presented in a balanced way;
- the materials did not raise unfounded hopes of a successful treatment.

The public health education campaign for bladder problems did not advertise any prescription medicine in any of the materials, indeed no specific treatments or care options were mentioned. In addition,

although Pharmacia & Upjohn produced both Detrusitol (tolterodine) and oxybutynin for the treatment of unstable bladder, this campaign covered overactive bladder (including both unstable bladder and detrusor hyperreflexia), stress incontinence, mixed symptoms, urinary tract infections, and prostatic problems. It would be noted from the public health education campaign materials that neither Detrusitol nor oxybutynin were either mentioned or promoted.

The aim of this campaign was public health education, to help break the taboo of bladder problems, such that patients suffering from bladder problems were better informed, both regarding their various conditions, and that treatment and care options were available. Research had demonstrated that there were approximately six million sufferers of bladder problems in the UK, however the same research illustrated that:

- 48% of sufferers of overactive bladder symptoms, aged between 40 and 74 years, currently failed to seek medical help for their condition;
- 43% of sufferers of overactive bladder symptoms, aged between 40 and 74 years, were unaware that any form of treatment existed.

This was despite overwhelming evidence that bladder problems had a severely detrimental effect upon the quality of the lives of sufferers. Studies had shown that overactive bladder had a considerable negative effect on quality of life of sufferers, especially in the mental health and social domains.

The Pharmacia & Upjohn campaign arose as a result of working with the following groups:

- patient support groups, such as Incontact, The Continence Foundation, ARP 050, Wellbeing and the Patients' Association;
- carer groups, such as the Association for Continence Advice and the Royal College of Nursing;
- clinicians, including urologists, gynaecologists, urogynaecologists, care of the elderly physicians and members of the GpiUG (GPs with an interest in urology and gynaecology).

All of these groups expressed a pressing need for a public health education campaign to help break the taboo of bladder problems, and had given overwhelming support to the campaign, with many groups expressing a desire to be actively involved. Thus the logos of the RCN, ACA, Incontact, The Continence Foundation, Wellbeing, the Patients Association and ARP 050 were currently being added to the back cover of the patient information booklet, along with a brief description of the organisations.

Prior to the initiation of the public health education campaign, Pharmacia & Upjohn sponsored a survey of GPs, which illustrated that 91% of GPs being questioned agreed that patients should be educated and encouraged to present to them with bladder problems. In addition, 65% of the GPs said that they would be positive towards a pharmaceutical company backed public health education campaign.

The materials for the campaign were designed in consultation with all the above-mentioned groups, such that the most appropriate and up-to-date information was given. As previously outlined, no specific treatments had been mentioned in the materials, thus there could be no influence on the practitioners to decide the most appropriate form of treatment for the sufferers. The sole aim of the campaign was to ensure that the sufferers themselves were aware that there were care options available that might help with their condition.

Pharmacia & Upjohn was careful that no promises of a cure were made. The campaign informed patients that the practitioners had care options that could help, and that treatments and care options might reduce the number of times they had to go to the toilet and might reduce the risk of a wetting accident. The materials therefore did not raise unfounded hopes of successful treatments. The tear off slip at the bottom of the press notice and the tear off page of the patient booklet were designed to act as 'ice breakers', to decrease embarrassment for the patient when presenting to a practitioner. This would hopefully enable them to mention their problems earlier in a consultation, giving enough time during a consultation to deal with their problems properly.

The Authority had requested details of the treatments available for the various bladder problems. These were:

Overactive Bladder

Conservative Therapies
bladder retraining, pelvic floor exercises, electrostimulation, biofeedback

Pharmacotherapy
oxybutynin, Detrusitol (for unstable bladder), propiverine, flavoxate

Surgery
minimally invasive – sacral nerve implantation, invasive – cystoplasty

Containment
pads/pants, catheters/urinary condoms/leg bags

Stress Incontinence

Conservative Therapies
pelvic floor exercises, vaginal cones

Surgery
urethral injections/implants, colposuspension, sling procedures

Mixed Symptoms

Treatment was aimed initially at the predominant symptoms – ie treatment of either the stress incontinence or overactive bladder symptoms

Urinary Tract Infection

Treatment was aimed at curing the infection with appropriate antibiotic therapy, along with behavioural techniques to prevent future infections

Prostatic Disease

Conservative 'Watch and Wait' advice for benign prostatic hyperplasia (BPH) symptoms

Pharmacotherapy for BPH:
α – andrenoceptor blockers
alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, terazosin

5-α reductase inhibitors
finasteride

Surgery
TURP (transurethral resection of the prostate), open prostatectomy

All of the above were therapy options for the various bladder problems; the public health education campaign did not recommend any particular therapy option.

As the Authority was aware, Pharmacia & Upjohn took the Code of Practice seriously and as such it requested informal guidance from the Authority prior to the production of the campaign materials. In addition, it took advice from the Medicines Control Agency (MCA); its reply stated 'The material submitted is non-promotional and health educational and is therefore acceptable.' A copy of the MCA response was provided.

The materials used in the campaign were as follows:

- media notices which were being placed in national newspapers and magazines;
- posters to be displayed in public toilets in shopping centres;
- a freephone telephone number, with a recorded message which offered sufferers a free patient information booklet; this service was being managed by an independent organisation;
- a patient information booklet which offered advice to patients on the different types of bladder problems, and advised sufferers to talk to their doctor, nurse or continence adviser;
- a television notice which again advised sufferers to seek help from their doctor, nurse or continence adviser, and informed them of the freephone number.

In summary, therefore, it could be seen that the public health education campaign constituted pure public health education, developed in an attempt to break through the taboo surrounding bladder problems. The campaign aimed to inform sufferers that bladder problems were not a normal part of ageing, and that treatments and care options were available from doctors, nurses and continence advisers which might help their conditions. The campaign materials were not promotional, were factual and balanced, did not raise unfounded hopes of a successful treatment, and did not encourage patients to request specific treatments from their doctors. The public health education campaign did not, therefore, contravene either Clause 20.1 or Clause 20.2 of the Code.

PANEL RULING

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

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

The Panel examined the materials. The claim 'Greater Freedom from Bladder Problems' was included on the materials together with a recommendation for members of the public to talk to their doctors and ask about treatment and care options. Some of the material included a symptom questionnaire for the patient to complete and discuss with their doctor to help the doctor understand which type of bladder control problem the patient was experiencing. The booklet gave general details about bladder problems and the different types of problems. The booklet was available via a freephone number. The materials stated that they were health education sponsored by Pharmacia & Upjohn. Medicines were not mentioned at all. The Panel noted that the MCA had seen the materials and had stated that they were non promotional and acceptable.

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 medicines. The Panel considered that the materials would increase public awareness of bladder problems and encourage people to discuss possible treatment and care options with their general practitioner. This was not necessarily unacceptable. From the information provided patients were not being encouraged to ask their doctors specifically for a Pharmacia & Upjohn product. The Panel noted that there were a number of different treatments available for bladder problems. Not all of the treatments were medicines. Pharmacia & Upjohn's products could be used to treat overactive bladders but they were not the only products available. The materials referred to bladder problems generally and not only to overactive bladders. Patients visiting their doctors as a result of seeing the campaign would not necessarily be prescribed a Pharmacia & Upjohn product and would not necessarily be suffering from a bladder problem that could be treated with a Pharmacia & Upjohn product.

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.

Proceedings commenced 9 August 1999

Case completed 25 August 1999

CASE AUTH/916/8/99

DUPONT v GLAXO WELLCOME

Promotion of Ziagen

DuPont complained about Glaxo Wellcome's leavepiece for Ziagen, a nucleoside analogue, which detailed the product's use with another Glaxo Wellcome product, Combivir, a combination of two nucleoside analogues, in the treatment of HIV infected adults. It was alleged that two phrases 'Choose life' and 'life-enhancing power' might mislead doctors to believe that Glaxo Wellcome's triple nucleoside regimen (Ziagen/Combivir) had some special effects to prolong life expectancy or reduce mortality compared to other management options. DuPont also alleged that the phrase 'life-enhancing power' was not capable of substantiation.

On the front page of the leavepiece the phrase 'Choose life' was followed by the product name in logo type; 'life-enhancing power appeared as a strapline. The Panel did not accept Glaxo Wellcome's submission that the phrases were intended to imply that Ziagen, as part of a triple nucleoside regimen, did not impose lifestyle restrictions on patients. The front page made no reference to features of treatment with Ziagen and the overall message could be read as choose a longer life with Ziagen as opposed to a shorter life with something else.

The phrase 'life-enhancing power' also appeared on pages detailing efficacy, tolerability and convenience of therapy and in the Panel's view implied therapy incorporating Ziagen, particularly the Ziagen/Combivir combination, had an actual positive effect on life.

The Panel considered that both phrases were misleading and ambiguous and that in addition 'life-enhancing power' was not substantiated by data relating only to the dosage and administration benefits of Ziagen compared to products with more onerous treatment schedules. Breaches of the Code were ruled.

DuPont Pharmaceuticals Limited complained about a leavepiece for Ziagen (abacavir) (ref 20183709 – ALP/July 1999) which had been issued by Glaxo Wellcome UK Limited. Ziagen was a nucleoside analogue indicated in antiretroviral combination therapy for the treatment of HIV infected adults. The leavepiece detailed the use of Ziagen with Combivir. Combivir was also marketed by Glaxo Wellcome and was a combination of two other nucleoside analogues, lamivudine and zidovudine.

COMPLAINT

DuPont referred to use in the leavepiece of two phrases, 'Choose life' and 'life-enhancing power' which it alleged were misleading and might lead physicians to believe that the Glaxo Wellcome triple nucleoside therapy regimen [Ziagen/Combivir] had some special effects to prolong life expectancy and or reduce mortality compared to other available management options. DuPont alleged that these two phrases were in breach of Clause 7.2 of the Code.

DuPont stated that Glaxo Wellcome had refuted the charge that the two phrases were misleading or inappropriate and stated that the phrases 'Choose life' and 'life-enhancing' were indicative of the substantial lifestyle and quality of life benefits that might accrue to patients who used this regimen. In addition, when asked to substantiate the phrase 'life-enhancing power', Glaxo Wellcome referred to potency and not quality of life data. DuPont alleged that this particular phrase was not capable of substantiation, in breach of Clause 7.3.

RESPONSE

Glaxo Wellcome stated that the phrase 'Choose life', taken on its own, was not intended to imply, nor would any reasonable healthcare professional infer from it, that the alternative to taking abacavir was reduced life-span or increased mortality. The phrase, read in context with the statement 'life-enhancing power' and the other information contained in the piece, was intended to imply that, as part of a triple nucleoside regimen, abacavir might allow patients to conduct their lives without the impact of lifestyle restrictions imposed by their therapy. The word 'life' was thus being used in its broadest sense.

Unlike many other regimens (notably those including some protease inhibitors), triple nucleoside therapy did not require onerous treatment schedules, food restrictions or minimum fluid intake. Furthermore, it was discreet (two tablets twice daily) and well tolerated.

As these features of abacavir were simply a reflection of the dosage and administration instructions of the summary of product characteristics (SPC), and as they were self-evident benefits in comparison with products with more onerous treatment schedules, no additional substantiation was provided. However, to make clear the severity of the lifestyle burden placed on patients by many treatment regimens, Glaxo Wellcome provided the following:

1 An informational poster produced by Boehringer Ingelheim ('Daily dosing of antiretroviral agents') giving graphical representations of pill burdens, and detail of other restrictions, with individual agents.

2 A table prepared by Glaxo Wellcome showing the dosing schedules, pill burdens and additional complications of the most widely used combination regimens.

3 Graphical results from market research, carried out by Isis Research on behalf of a consortium of pharmaceutical companies, showing that the pill burden was one of the major reasons given by patients for refusing antiretroviral therapy; and that frequency of dosing and the number of tablets to be taken daily were the main parameters in influencing physicians' choice of one antiretroviral agent over another.

Although it was difficult to assess objectively the relationship between complexity of regimen and patient compliance, it was almost universally accepted in the medical community that more onerous treatment schedules resulted in poorer compliance, which, in turn, might well impact on long-term treatment outcomes.

As quality of life issues associated with the complexity of the treatment regimen were thus of crucial importance to both physician and patient in the HIV setting, Glaxo Wellcome contended that the phrases 'Choose life' and 'life-enhancing power' were, in context, legitimate and non-misleading expressions of the substantial lifestyle benefits accruing to patients on triple nucleoside therapy.

PANEL RULING

The Panel examined the leavepiece. The front page had a photograph of two men beneath which appeared the phrase 'Choose life' followed by the product name in logo form. The phrase 'life-enhancing power' appeared as the strapline on the front page and as a subheading on four further pages. Each time, the word 'power' was emboldened. The leavepiece discussed the efficacy and convenience of Ziagen in combination with Combivir and also the tolerability of Ziagen itself with reference to the number of patients treated to date.

The Panel noted Glaxo Wellcome's submission that the phrases 'Choose life' and 'life-enhancing power' were intended to imply that Ziagen as part of a triple nucleoside regimen might allow patients to conduct their lives without the impact of lifestyle restrictions imposed by their therapy. The Panel did not accept this submission. The front page of the leavepiece made no direct or implied reference to features of treatment with Ziagen apart from the fact that it was new in HIV. The overall message on the front page was very positive and could be read as choosing a longer life with Ziagen as opposed to a shorter life with something else.

The Panel noted that the phrase 'life-enhancing power' also appeared on the pages of the leavepiece detailing the efficacy, tolerability and convenience of Ziagen therapy. It did not merely relate to the lifestyle benefits as suggested by Glaxo Wellcome. In the Panel's view, however, 'life-enhancing power' implied that HIV therapy which incorporated Ziagen, and in particular the Ziagen/Combivir combination, had an actual positive effect on life and not that it had a less disruptive effect than other regimens which involved patients taking multiple tablets and the imposition of dietary restrictions. The Panel considered that it was a strong claim which required qualification.

The Panel considered that the phrases were misleading and ambiguous. They implied that not taking Ziagen or using other treatment would reduce life span and/or increase mortality as alleged and a breach of Clause 7.2 of the Code was ruled. The phrase 'life-enhancing power' was inadequately qualified. The only substantiation provided related to the dosage and administration benefits of Ziagen compared to products with more onerous treatment schedules. In the Panel's view the claim had not been substantiated and a breach of Clause 7.3 was ruled.

Complaint received **25 August 1999**

Case completed **4 October 1999**

CASE AUTH/917/8/99

PHARMACIA & UPJOHN v SCHWARZ PHARMA

Viridal Duo leavepiece

Pharmacia & Upjohn complained about a leavepiece for Viridal Duo (alprostadil for intracavernosal injection) entitled 'Why add to the pain of erectile dysfunction?' produced by Schwarz Pharma. The leavepiece favourably compared intracavernous alprostadil with intraurethral alprostadil. Pharmacia & Upjohn produced Caverject which was an alternative presentation of intracavernosal alprostadil.

The claim 'Viridal Duo is the preferred treatment of 93% of patients' was referenced to Meuleman *et al* and headed a page which discussed patient preference with regard to intracavernous and intraurethral alprostadil. It was alleged that it was a hanging comparison, the abstract referenced was of a study involving only 15 patients, there was no evidence of statistical significance and the claim was exaggerated. The Panel noted that the leavepiece sought to compare Viridal Duo with intraurethral alprostadil and considered that most readers would assume that 93% of patients preferred Viridal Duo to intraurethral alprostadil which was not so. The study was comprised of patients experienced in self-administration of intracavernosal injections who had compared Viridal Duo with previously used devices. The Panel considered that the claim was misleading as the comparator had not been made clear. The Panel noted that 14 out of the 15 patients in the study had rated Viridal Duo as much better, better or at least as good. In the opinion of the Panel the phrase 'at least as good' included those patients who had rated Viridal Duo as equivalent to their previous device; it did not necessarily indicate a preference. The abstract did not state how many patients had assessed the device as much better or better than their previously used devices but had provided a composite figure which necessarily included those patients who had ranked the device as equivalent. The Panel considered that it was inappropriate to base such a strong claim on a study of 15 patients. There was no statistical analysis to support the difference. The Panel considered that the claim was exaggerated and had not been substantiated. Breaches of the Code were ruled.

The seventh page of the leavepiece featured the heading 'Viridal Duo in erectile dysfunction is' … beneath which appeared five bullet points; 'safe' was the first bullet point listed. The Panel noted that the word safe had been used without qualification contrary to the requirements of the Code and a breach was ruled.

No breach of the Code was ruled in relation to an allegation that the date of preparation had not been given as this was clearly stated.

Pharmacia & Upjohn Limited complained about a leavepiece for Viridal Duo (alprostadil for intracavernosal injection) entitled 'Why add to the pain of erectile dysfunction?' produced by Schwarz Pharma Limited. Viridal Duo was presented in a double-chambered cartridge containing alprostadil powder and diluent for reconstitution. The leavepiece favourably compared intracavernous alprostadil with intraurethral alprostadil. Pharmacia & Upjohn produced Caverject which was an alternative presentation of intracavernosal alprostadil – alprostadil powder in a vial with a single-chambered pre-filled syringe of diluent.

Claim 'Viridal Duo is the preferred treatment of 93% of patients'

The claim was referenced to Meuleman *et al* (1997) and headed a page which discussed patient preference with regard to intracavernous and intraurethral alprostadil.

COMPLAINT

Pharmacia & Upjohn noted that this claim had also been observed in previous promotional material and that the medical adviser of Schwarz had been contacted in February 1999 to inform her that this statement breached Clauses 7.2 and 7.8 of the Code.

Pharmacia & Upjohn alleged that the claim breached Clause 7.2 of the Code in two ways. Firstly, the statement was a hanging comparison, whereby Viridal Duo was described as being preferred, without stating that with which Viridal Duo was compared. Secondly, the statement was referenced to Meuleman *et al* (1997). This reference was an abstract of a study involving only 15 patients. The abstract quoted that 'The impression of the new device compared to previously used devices was assessed as much better, better or at least as good in 14 patients (93%).' The previously used devices were not referred to in the abstract, and could have involved either mechanical devices such as vacuum pumps, traditional single chamber intracavernosal injection devices or transurethral devices. There was no mention of statistical significance, and for this claim to comply with Clause 7.2 statistical significance ought to have been reached. A breach of Clause 7.2 was alleged.

Pharmacia & Upjohn noted that the abstract supplied stated that the impression of the new device compared to previously used devices was assessed as much better, better or at least as good in 14 patients (93%). The patients who reported a device as being 'at least at good' were not stating a preference, and therefore this claim was exaggerated in breach of Clause 7.8 of the Code.

RESPONSE

Schwarz noted that Pharmacia & Upjohn had stated that for claims of preference to be used in promotional material and hence comply with Clause 7.2 of the Code statistical significance ought to be reached. Under the supplementary information for Clause 7.2 (statistical information) the Code stated that 'Care must be taken to ensure that there is a sound statistical basis for all information, claims and comparisons in promotional material. Differences which do not reach statistical significance must not be presented in such a way as to mislead.' The results of

the study presented by Meuleman *et al* at the European Society For Impotence Research in 1997 used descriptive statistics to analyse the results presented and this was of a sound statistical basis. The abstract and indeed the promotional piece made no claims regarding statistical significance (presence or absence). As Schwarz did not consider that the Code necessitated statistical significance to be achieved for such information to be used in promotional material (as long as this was not misrepresented) it submitted that the allegation was incorrect.

PANEL RULING

The Panel noted that Meuleman *et al* was supplied as an abstract which evaluated the efficacy, safety and acceptance of intracavernous self-injections using a new device (Viridal Duo) during home treatment for 6 months in 15 patients experienced with such injections. Acceptance was assessed by a self completion patient questionnaire. A total of 601 injections were administered. Fourteen patients (93%) assessed Viridal Duo as much better, better, or at least as good as previously used devices. There was no mention of whether the results were statistically significant.

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that hanging comparisons whereby a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared must not be made. The Panel noted that the leavepiece sought to compare Viridal Duo with intraurethral alprostadil and considered that most readers would assume that 93% of patients preferred Viridal Duo to intraurethral alprostadil which was not so. However the Panel noted that the patient population comprised patients experienced in self-administration of intracavernosal injections who had compared Viridal Duo with previously used devices. The Panel considered that the claim was misleading as the comparator had not been made clear.

The Panel noted the small study population, n=15, of whom 14 had rated Viridal Duo as much better, better or at least as good. In the opinion of the Panel the phrase 'at least as good' included those patients who had rated Viridal Duo as equivalent to their previous device; it did not necessarily indicate a preference. The abstract did not state how many patients had assessed the device as much better or better than their previously used devices but had provided a composite figure which necessarily included those patients who had ranked the device as equivalent. The Panel considered that it was inappropriate to base such a strong claim on a study of 15 patients. There was no statistical analysis to support the difference. The Panel considered that the claim was exaggerated and had not been substantiated by Meuleman *et al*.

The Panel ruled breaches of Clauses 7.2, 7.3 and 7.8 of the Code.

Claim 'Viridal Duo in erectile dysfunction is safe'

The seventh page of the leavepiece featured the heading 'Viridal Duo in erectile dysfunction is' … beneath which appeared five bullet points; 'safe' was the first bullet point listed.

COMPLAINT

Pharmacia & Upjohn alleged a breach of Clause 7.7 of the Code which stated that the word safe must not be used without qualification.

Pharmacia & Upjohn pointed out that Schwarz was contacted regarding this – and surprisingly did not consider it to be in breach. The correspondence was provided.

RESPONSE

Schwarz made no particular comment upon this allegation. Schwarz stated that it had taken the other comments relating to, *inter alia*, the claim 'Viridal Duo in erectile dysfunction is safe' into consideration and so would withdraw the leavepiece from use.

PANEL RULING

The Panel noted that Clause 7.7 of the Code stated, *inter alia*, that 'It must not be stated that a product has no side-effects, toxic hazards or risks of addiction. The word 'safe' must not be used without qualification.' The Panel noted that the word 'safe' had been used without qualification and therefore ruled a breach of Clause 7.7 of the Code.

Date of preparation

COMPLAINT

Pharmacia & Upjohn alleged that Clause 4.7 of the Code had also been broken, as there was no date of preparation on the leavepiece.

RESPONSE

Schwarz pointed out that the date of preparation of this document was quite clearly displayed next to the abbreviated prescribing information.

PANEL RULING

Clause 4.7 of the Code required promotional material to include the date on which the promotional material was drawn up or last revised. The Panel noted that the date of preparation was clearly stated adjacent to the prescribing information on the final page of the leavepiece as July 1998. The Panel ruled no breach of the Code in this regard.

Complaint received **26 August 1999**

Case completed **15 October 1999**

CASE AUTH/924/9/99

GENERAL PRACTITIONER v HOECHST MARION ROUSSEL

Telfast promotional material sent by facsimile

A general practitioner complained about a three page facsimile sent to him by Hoechst Marion Roussel. The facsimile referred to the discontinuation of Triludan 60mg and went on to promote Telfast (fexofenadine) as an alternative therapy. The complainant objected to the advertisement's presentation, pointing out that the first page was marked urgent and to be circulated to all doctors in the practice.

The Panel noted that the Code prohibited the use of telephone, telemessages, e-mail, telex and facsimile for promotional purposes except with the prior permission of the recipient. The document in question was clearly promotional for Telfast. Prior permission had not been obtained from the recipient. It should not have been sent to him by facsimile. A breach of the Code was ruled as acknowledged by Hoechst Marion Roussel.

The Panel noted that the Code did not prohibit companies from sending letters by facsimile if a product had been withdrawn or recalled as long as the letters were factual and accurate and were not promotional.

A general practitioner complained about material sent by Hoechst Marion Roussel Ltd by facsimile to his practice. The facsimile consisted of three pages. The first page was headed with the company name followed by 'Urgent fax. Important product information attached. Please circulate to all the doctors in the practice'. Page two was a 'Dear Doctor' letter which announced that Hoechst Marion Roussel had discontinued the manufacture of the 60mg tablet formulation of Triludan. The page then stated that Telfast (fexofenadine) was available as an alternative therapy for hay fever and chronic idiopathic urticaria in adults currently prescribed Triludan. The letter included details about Telfast and was signed by a senior product manager. The final page bore the prescribing information for Telfast.

COMPLAINT

The complainant pointed out that the first page was marked urgent and to be circulated to all doctors in the practice. However, the following pages were mainly an advertisement for a medicine to replace Triludan.

In the complainant's view, when a medical practice received a fax headed as this the secretaries would understandably take it as being an important and urgent fax and photocopy it and circulate it to all the doctors. The complainant initially thought this was going to be an urgent recall of a medicine; in the past faxing had proved to be quite an effective way of informing doctors of important news quickly.

The complainant strongly objected to how this advertisement had been presented and would like to ensure that this type of approach by a pharmaceutical company was not repeated.

RESPONSE

Hoechst Marion Roussel stated that the inadvertent inclusion of facsimile distribution as part of the mailing was an error, which it acknowledged as being clearly in breach of Clause 9.8 of the Code. As soon as this was brought to the company's attention during the course of the mailing operation, all facsimile communication was stopped immediately.

Whilst Hoechst Marion Roussel was well aware of the Code's requirements relating to facsimile transmission, it regrettably assumed that the third party agency involved in the distribution of this material would have obtained appropriate prior approval. Hoechst Marion Roussel assured the Authority that as the responsible party it took this matter very seriously and had taken steps to ensure that a similar situation would not arise in the future.

The company apologised to the complainant for the inconvenience caused and fully understood his objections.

PANEL RULING

The Panel noted that Clause 9.8 of the Code prohibited the use of telephone, telemessages, e-mail, telex and facsimile for promotional purposes except with the prior permission of the recipient.

The document in question was clearly promotional for Telfast. Prior permission had not been obtained from the recipient. It should not have been sent to the recipient's facsimile machine. A breach of Clause 9.8 of the Code was ruled.

The Panel noted that the Code did not prohibit companies from sending letters by facsimile if a product had been withdrawn or recalled as long as the letters were factual and accurate and were not promotional.

Complaint received	**10 September 1999**
Case completed	**15 October 1999**

CODE OF PRACTICE REVIEW – NOVEMBER 1999

Cases in which a breach of the Code was ruled are indexed in **bold type**.

796/11/98	**Lilly v Lundbeck**	**Promotion of Cipramil**	**Six breaches Clause 7.2 Breach Clause 7.7**	**Appeals by complainant and respondent**	**Page 4**
801/11/98	**Consultant Cardiologist v Eastern**	**Sampling of Isocard Transdermal Spray**	**Breaches Clauses 17.3 and 17.10**	**No appeal Reported to ABPI Board**	**Page 21**
824/1/99 & 825/1/99	**Pierre Fabre v Rhône-Poulenc Rorer and Chugai**	**Promotion of Taxotere**	**Twenty breaches Clause 7.2 Seven breaches Clause 7.3 Two breaches Clause 7.6**	**Appeal by complainant**	**Page 22**
832/1/99	**Allergan v Pharmacia & Upjohn**	**Sponsored meeting report**	**Breaches Clauses 4.1 and 7.6**	**Appeal by respondent**	**Page 49**
837/1/99	**Biogen/Director v Schering Health Care**	**Promotion of Betaferon and failure to comply with undertaking**	**Three breaches Clause 7.2 Breaches Clauses 20.1 and 20.2 Three breaches Clause 21**	**Appeal by respondent**	**Page 54**
850/3/99 to 855/3/99	**University Professor v Bristol-Myers Squibb, Napp, Novartis, Pharmacia & Upjohn, Sanofi Winthrop and SmithKline Beecham**	**Articles in NHS Doctor and Commissioning GP**	**Breaches Clauses 4.1, 9.9 and 10.1 by Bristol-Myers Squibb, Napp, Novartis, Pharmacia & Upjohn and Sanofi Winthrop Breach Clause 6.1 by SmithKline Beecham**	**No appeals**	**Page 60**
858/3/99	**Lilly v Janssen-Cilag**	**Promotion of Risperdal**	**Four breaches Clause 7.2 Breach Clause 7.6**	**No appeal**	**Page 66**
863/4/99	**Medicines Control Agency v Bristol-Myers Squibb**	**Internet site**	**Breaches Clauses 20.1 and 20.2**	**Appeal by respondent**	**Page 73**
869/4/99	**Merck Sharp & Dohme v Glaxo Wellcome**	**Naramig leavepiece**	**Three breaches Clause 7.2. Breach Clause 7.3**	**No appeal**	**Page 78**
870/4/99	**Lorex Synthélabo v Trinity**	**Promotion of Angitil**	**Breaches Clauses 3.2, 4.1, 4.6, 4.7 and 7.3 Two breaches Clause 7.4**	**No appeal**	**Page 84**
874/5/99	**Lundbeck v Lilly**	**Prozac leavepiece**	**Breach Clause 7.3**	**No appeal**	**Page 88**
877/5/99	Glaxo Wellcome v Merck Sharp & Dohme	Maxalt leavepiece	No breach	No appeal	Page 90
878/5/99	**Zeneca v Schering Health Care**	**Cyprostat detail aid**	**Breaches Clauses 3.2, 7.2 and 7.8**	**No appeal**	**Page 94**
880/5/99	**Glaxo Wellcome v AstraZeneca**	**Zomig advertisements**	**Breach Clause 7.8**	**No appeal**	**Page 96**
881/6/99 & 882/6/99	**Health Authority Primary Care Medical Adviser v Sanofi Winthrop and Bristol-Myers Squibb**	**Payment for meeting**	**Breach Clause 9.1**	**No appeal**	**Page 98**
883/6/99	**General Practitioner v Schering-Plough**	**Nasonex detail aid**	**Breaches Clauses 7.2 and 7.7**	**No appeal**	**Page 100**

884/6/99	Pharmacia & Upjohn v Merck Sharp & Dohme	Cosopt detail aid	No breach	No appeal	Page 102
886/6/99	**General Practitioner v Goldshield**	**Marevan 'Dear Doctor' letter**	**Breach Clause 4.1**	**No appeal**	**Page 105**
887/6/99	**Schering Health Care v Roche**	**Promotion of MabThera**	**Breaches Clauses 4.1 and 20.2**	**No appeal**	**Page 106**
888/6/99 & 897/7/99	**Director v Amgen and Roche**	**Breach of undertaking**	**Breach Clause 21**	**Appeal by respondents**	**Page 108**
889/6/99 & 890/6/99	**Boehringer Ingelheim v Sanofi Winthrop and Bristol-Myers Squibb**	**Promotion of Plavix**	**Breaches Clauses 7.2 and 7.8**	**No appeal**	**Page 112**
891/6/99	**Director v Lilly**	**Breach of undertaking**	**Breaches Clauses 2 and 21**	**No appeal**	**Page 114**
892/6/99	**Dermal v Searle**	**Powergel tissue box**	**Breaches Clauses 7.2 and 7.6**	**No appeal**	**Page 116**
893/7/99 & 894/7/99	**General Practitioner v Rhône-Poulenc Rorer and Merck Pharmaceuticals**	**'Dear Colleagues' letter**	**Breach Clause 10.1**	**No appeal**	**Page 119**
896/7/99	Director v Glaxo Wellcome	Possible breach of undertaking	No breach	No appeal	Page 121
898/7/99	**General Practitioner v Goldshield**	**Fenbid Forte 10% Gel mailing**	**Two breaches Clause 7.2 Breach Clause 18.1**	**Appeal by respondent**	**Page 123**
899/7/99	**Napp v Janssen-Cilag**	**Promotion of Durogesic**	**Breach Clause 7.7**	**No appeal**	**Page 127**
900/7/99	**Novo Nordisk v Hoechst Marion Roussel**	**Promotion of Amaryl**	**Breaches Clauses 7.2 and 7.8**	**No appeal**	**Page 133**
901/7/99	Pharmacist v Allen & Hanburys	Promotion of Flixotide	No breach	No appeal	Page 135
903/7/99	**Novo Nordisk v Lilly**	**Promotion of Humalog Mix25**	**Two breaches Clause 7.2**	**No appeal**	**Page 136**
906/7/99	**Schering Health Care v Roche**	**Promotion of MabThera**	**Breach Clause 7.2**	**No appeal**	**Page 139**
907/7/99	**Roche v Glaxo Wellcome**	**'Choose life' advertisement in Axiom magazine**	**Breaches Clauses 20.1 and 20.2**	**No appeal**	**Page 141**
908/7/99	**Roche v Abbott**	**Promotion of Norvir in combination with Fortovase**	**Breaches Clauses 3.2 and 8.1**	**No appeal**	**Page 144**
909/7/99	**Pharmaceutical Adviser v 3M Health Care**	**Qvar letter**	**Two breaches Clause 7.2**	**No appeal**	**Page 150**
910/8/99	**Proctor & Gamble v Merck Sharp & Dohme**	**Promotion of Fosamax**	**Three breaches Clause 7.2 Breach Clause 7.3 Two breaches Clause 7.8**	**No appeal**	**Page 152**
911/8/99	Director/Media v Pharmacia & Upjohn	Public health campaign on bladder problems	No breach	No appeal	Page 156
916/8/99	**DuPont v Glaxo Wellcome**	**Promotion of Ziagen**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 159**
917/8/99	**Pharmacia & Upjohn v Schwarz Pharma**	**Viridal Duo leavepiece**	**Breaches Clauses 7.2, 7.3, 7.7 and 7.8.**	**No appeal**	**Page 161**
924/9/99	**General Practitioner v Hoechst Marion Roussel**	**Telfast promotional material sent by facsimile**	**Breach Clause 9.8**	**No appeal**	**Page 163**

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, more than sixty 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 Philip Cox 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 0171-930 9677 facsimile 0171-930 4554).