PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 33 AUGUST 2001

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

2000 ANNUAL REPORT

The Annual Report of the Prescription Medicines Code of Practice Authority for 2000 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

There were 121 complaints in 2000 as compared with 127 in 1999. The number of cases dealt with usually differs from the number of complaints because some complaints involve more than one company and some complaints are not proceeded with, for example when no *prima facie* case is established.

There were 134 cases in 2000 as compared with 126 in 1999. The number of matters which had to be ruled upon in 2000 was, however, at 350, the same as in 1999.

In 2000 the number of complaints from health professionals exceeded the number of complaints from pharmaceutical companies, there being 57 from health professionals and 51 from pharmaceutical companies. It is usually the case that the greatest number of complaints come from health professionals, though this was not the case in 1996 and 1999.

Of the 350 rulings made by the Code of Practice Panel in 2000, 287 (82%) were accepted by the complainants and respondents involved, 40 (11.4%) were unsuccessfully appealed to the Code of Practice Appeal Board and 23 (6.6%) were successfully appealed.

The Code of Practice Panel met 86 times in 2000, the same as in 1999, and the Code of Practice Appeal Board met 9 times, 8 in 1999.

New Code of Practice and Constitution and Procedure now in operation

The 2001 edition of the Code of Practice for the Pharmaceutical Industry came into operation on 1 July but, during the period 1 July to 30 September inclusive, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements newly introduced.

The new Constitution and Procedure for the Prescription Medicines Code of Practice Authority applies to complaints received on and after 1 July.

Copies of the 2001 Code of Practice booklet, which incorporates the Constitution and Procedure, are available on request.

Resits for ABPI representatives examinations

The Association of the British Pharmaceutical Industry (ABPI) now holds additional examinations to allow those who have failed to pass the relevant examination to resit it at an early opportunity. The resit examinations take place in January and July following the main examinations in November and May.

Details can be obtained from Ian Irving at the ABPI (020 7747 1420).

Use of data from *in-vitro*, animal and human volunteer studies

Companies are reminded that the supplementary information to Clause 7.2 of the Code of Practice states, in relation to the use in promotional material of data derived from *in-vitro*, animal or human volunteer studies, that:

'Care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance.'

Readers of promotional material are entitled to assume that data shown is based on clinical studies on patients unless told otherwise. It must therefore be made clear when data is derived from *in-vitro*, animal or human volunteer studies and it must be demonstrable that such data is of clinical significance.

Information for patients

Proposals for amendment and consolidation of EC pharmaceutical legislation were adopted by the Commission on 18 July. They include proposed changes to the current Directive on the advertising of medicinal products for human use which are said to be intended to make information more readily available to the public in relation to medicines for use in AIDS, asthma and diabetes.

The proposals are available at:

http://pharmacos.eudra.org/F2/review/index.htm

Articles 86 to 100 relate to advertising

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 December

Monday, 21 January

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1101/11/00

CLEMENT CLARKE v ASTRAZENECA

Promotion of the Turbohaler and information about the In-Check device

Clement Clarke complained about information provided to health professionals by AstraZeneca concerning Clement Clarke's In-Check device and AstraZeneca's Turbohaler. The In-Check device measured inspiratory flow rates through different types of inhaler and bore optimum flow rates for each particular inhaler.

Clement Clarke alleged that AstraZeneca representatives had made misleading statements disparaging the In-Check device, to the effect that it was inaccurate, was unable to accurately reproduce the resistance of the Turbohaler, was using incorrect data, was wrongly calibrated, was shortly to be withdrawn from the market and was the subject of legal action by AstraZeneca. None of these were true. It was also alleged that AstraZeneca representatives were making misleading statements about the performance of the Turbohaler.

A 'Dear Pharmacist' letter sent by AstraZeneca advising of a price reduction and stating that the Turbohaler was recommended for treating childhood asthma and newly diagnosed asthmatics was alleged to be ambiguous and misleading. It was stated that the 'low Peak Inspiratory Flow Rate (PIFR) required for its use' was achievable by virtually all children over the age of six. The referenced work by Pedersen (1990) documented a response to treatment that was only reduced when inspiratory flow rates fell below 28L/min through the device. 30L/min inspiratory flow rate was achieved by 17 out of 19 children with acute asthma, but none achieved more than 54L/min (range 30 to 54, mean = 39L/min). Clement Clarke recognised that the minimum inspiratory flow rate for the Turbohaler to effectively deliver drug to the lungs was 30L/min. Clement Clarke also recognised that the majority of children in this study could achieve inspiratory flow rates between 30 and 54L/min.

Clement Clarke stated that the British Journal of Community Nursing featured product news regarding the same price reduction and stated 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI' [pressurised metered dose inhaler]. This piece of 'advertorial', which was not accompanied by any prescribing information, might mislead readers to believe that all users of the Turbohaler would receive twice as much drug when compared to the use of a conventional pMDI. According to AstraZeneca's 'Objection Handling Document', the claim for twice the lung deposition of a pMDI could only be made when the inspiratory flow rate was 60L/min. AstraZeneca's reference to the British Guidelines on Asthma Management (1997) was only possible because of the Guidelines' reference to the original research (Thorsson *et al*, 1994). Importantly, the subjects of this study were instructed to inhale at a flow of 60L/min through the Turbohaler and 30L/min through the pMDI. The journal did not write such articles without press release or pre-written copy and requested a separation fee for reproducing photographs. Its definition of this section of the magazine was 'advertorial'.

It was misleading for AstraZeneca to state that the deposition from the Turbohaler was double that from a pMDI without also stating that the inspiratory flow needed to be 60L/min.

To advise in the briefing document that the dose of corticosteroids could be halved when given by Turbohaler, without assessing the ability of the patient to achieve 60L/min, was alleged by Clement Clarke to be irresponsible. Clement Clarke stated that AstraZeneca, within its own briefing material, acknowledged that drug delivery at 30L/min was only 50% of that delivered at 60L/min. However, it did not present this information in a way that was balanced and unambiguous. Clement Clarke believed that in disparaging the In-Check products, AstraZeneca was preventing healthcare professionals from improving care for patients with respiratory disease as the In-Check product had already shown value in identifying patients who could not inhale at the right speed for the inhaler they had been prescribed.

The Panel noted that the Code applied to the promotion of medicines. It did not apply to the promotion of devices *per se*. The In-Check Dial was a device for measuring inspiratory flow and the Code thus did not apply to the promotion of the In-Check Dial *per se*. The Panel noted AstraZeneca's submission that the Code did not apply to the discussion of devices such as the In-Check Dial. Clearly this would be the position if a representative was only promoting the In-Check Dial. The situation was more complicated as the AstraZeneca representatives would presumably be promoting Turbohalers and discussion of the In-Check Dial might be part of the representative's detail to the health professional or might be something raised by the health professional. In that regard the Panel noted that the representatives briefing material about inspiratory flow rates and the Turbohaler referred to the In-Check Dial and stated that it was apparently being used to show that some patients might have difficulty generating sufficient inspiratory flow rates to gain maximum benefit from the Turbohaler. The objection handler continued by detailing the design and efficacy of the Turbohaler across a range of inspiratory flow rates. It did not criticise the In-Check Dial in any way. Given that AstraZeneca had briefed its representatives about inspiratory flow rates and had produced an objection handler which referred to the In-Check Dial, the Panel considered that the discussion of the In-Check Dial in association with the promotion of the Turbohaler meant that the matter was covered by the Code.

The Panel noted that there was a complaint about a specific representative who had allegedly told a respiratory nurse involved in a study that the In-Check Dial was inaccurate. The Panel noted AstraZeneca's submission that the representative had advised the nurse that the information accompanying the In-Check device appeared to present a higher peak inspiratory flow requirement for effective use of the Turbohaler than AstraZeneca

believed to be necessary. The Panel noted that the report of the exchange between the nurse and the representative had not come from the nurse herself. It was difficult to know exactly what had transpired between the two parties and impossible to know where the truth lay. The Panel ruled no breach of the Code. It was also alleged that AstraZeneca representatives had made misleading statements to health professionals, disparaging the In-Check Dial. Clement Clarke had not provided detailed information relating to such exchanges so that the allegations could be properly investigated by AstraZeneca. In such circumstances it was impossible to know what representatives had said and the Panel ruled no breach of the Code.

The Panel noted that the 'Dear Pharmacist' letter announcing the price reduction of Bricanyl Turbohaler stated that it was '… a highly effective choice for treating childhood asthma and newly diagnosed asthmatics …'. The letter further referred to the low peak inspiratory flow rate required to use a Bricanyl Turbohaler citing Pedersen *et al* in support. The Panel noted that the Bricanyl Turbohaler was indicated for use in children; it was not restricted to second-line use in any patient group. The data sheet stated that treatment with the Bricanyl Turbohaler was effective even at low inspiratory flow rates, such as those present during an acute asthma attack. There was data to show that the minimum inspiratory flow rate needed for the operation of the Turbohaler was 30L/min, which was accepted by Clement Clarke. The Panel did not consider that the information given in the 'Dear Pharmacist' letter in this regard was either ambiguous or misleading as alleged and no breach of the Code was ruled.

The news item which had appeared in the British Journal of Community Nursing was headed 'Bricanyl Turbohaler price reduction' and had been published subsequent to AstraZeneca's issue of a press release announcing the price change. The item made claims for the Bricanyl Turbohaler and included a pack shot of the product for which AstraZeneca had paid. In the Panel's view, such payment constituted an activity to promote the prescription, sale, supply or administration of the Bricanyl Turbohaler and in effect the news item was an advertisement. The information given exceeded that allowed in an abbreviated advertisement. In the Panel's view the item was an advertisement which failed to meet the requirements of the Code as no prescribing information had been provided. A breach of the Code was ruled. The advertisement stated that 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI'. In the Panel's view readers would assume that the Turbohaler always delivered approximately twice the amount of drug to the lungs which was not so. The Objection Handling Document gave details of a range of inspiratory flow rates. It stated that the 'Turbohaler is effective at inspiratory flow rates of 30L/min and will deliver approximately 15% of nominal dose to the lungs. This is higher than a pMDI which delivers typically between 10-15% with good inhalation technique. Doubling the inspiratory rate to 60L/min approximately doubles lung deposition via Turbohaler. This is acknowledged in the BTS guidelines to the extent that it is recommended that the dose of inhaled corticosteroid should be halved when given by Turbohaler compared to the pMDI – recognition of the improved deposition'. It appeared that the Turbohaler delivered twice the amount of medicine to the lungs than a conventional pMDI when a patient's inspiratory flow rate was 60L/min. The Panel considered that the statement was misleading and ruled a breach of the Code.

Upon appeal by AstraZeneca, the Appeal Board noted that the item had appeared as a result of a press release. The last paragraph of the press release stated that the Turbohaler delivered '… approximately twice the amount of drug to the lungs as a conventional pMDI'. Having received the press release, the publishers of the journal sent AstraZeneca a colour separation request form. The Appeal Board considered that the press release which gave rise to the article had gone beyond being a factual, informative announcement about a price change. It had included claims for the product which had been repeated word for word in the article in question. AstraZeneca had had control over the placement of the article, the company press release was about a price change and had included product claims and a fee had been paid for the printing of the pack shot. The Appeal Board considered that the circumstances were such that the article was in fact promotional material for the Bricanyl Turbohaler and so should have included the prescribing information. The Appeal Board upheld the Panel's ruling of a breach of the Code.

With regard to lung deposition, the Appeal Board noted that at an inspiratory flow rate of 30L/min the Turbohaler delivered 15% of the nominal dose to the lungs. Increasing the inspiratory flow rate to 60L/min doubled lung deposition to 30%. Good inhalation technique with a pMDI typically delivered between 10-15% to the lungs. There was, however, no evidence to show that all patients, notably children, would be able to achieve an inspiratory flow rate of 60L/min and therefore a lung deposition of 30% of the nominal dose. In patients with inspiratory flow rates of less than 60L/min the Turbohaler would not deliver twice the amount of drug to the lungs as a conventional pMDI. The Appeal Board thus considered that the claim in the press release, which also appeared in the article in the British Journal Community Nursing, 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI', was misleading and upheld the Panel's ruling of a breach of the Code.

The Objection Handling Document referred to the improved drug deposition seen with the Turbohaler and stated that 'This is acknowledged in the BTS Guidelines [British Thoracic Society Guidelines on Asthma Management] to the extent that it is recommended that the dose of inhaled corticosteroids should be halved when given by Turbohaler, compared to pMDI'. The BTS Guidelines actually stated that 'The Turbohaler delivers approximately twice as much inhaled

steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be titrated against control of asthma and treatment reduced when control is achieved'. The Panel considered that the objection handler had thus not wholly reflected the advice regarding the dose of inhaled steroids via a Turbohaler as given in the BTS Guidelines. The information given was too brief and in the Panel's view would lead to representatives giving misleading information. A breach of the Code was ruled.

Clement Clarke International Ltd complained about information provided to health professionals by AstraZeneca UK Limited concerning Clement Clarke's In-Check device and AstraZeneca's Turbohaler. The In-Check device measured inspiratory flow rate through different types of inhaler and bore optimum flow rates for each particular inhaler.

COMPLAINT

Clement Clarke stated that as incorrect information was being provided to health professionals AstraZeneca was breaching the Code in both the spirit and the letter. Breaches of Clauses 7.2, 7.3, 8.1 and 15.2 were alleged.

Clement Clarke stated that in September 1997 it introduced a new medical device to healthcare practitioners in the UK. The device, 'In-Check', was a small, hand-held mechanical flow meter that recorded how quickly a patient inhaled. It was able to accurately measure the speed at which someone breathed in and was the result of a development programme that utilised Clement Clarke's knowledge of the relevance of air flow monitoring to respiratory disease (the company developed the first truly portable peak flow meter – the Mini-Wright – in the 1970s).

During 1996 and 1997 reviews of literature within respiratory publications, and current scientific comment, revealed that the performance of the majority of pulmonary inhaler delivery devices was affected by the inspiratory flow rate through them. Specifically, dry powder inhalers such as the Turbohaler (AstraZeneca's delivery system for the branded products, Pulmicort, Bricanyl and Oxis) had demonstrated reduced performance at lower flow rates as assessed by the following parameters:

- total lung deposition (the amount of medicine that would reach the lungs);
- fine particle fraction (the size distribution of the particles inhaled);
- consistency of dose at different flows (the variation in dose in repeated use).

Patients using inhalers to deliver medication to the lungs breathed in through them and the air passed through the inhaler before carrying the medication into the mouth and respiratory system. Because the air must follow the internal structure of the inhaler, any diversion or partial physical barrier would impede the free passage of air – hence the 'resistance' a patient felt when inhaling through each device. Several designs of inhaler were available within the UK. The range of designs was reflected in a different resistance for each device – eg AstraZeneca's Turbohaler device had a high resistance compared to the low resistance of Glaxo Wellcome's Accuhaler device.

Clement Clarke stated that in an original paper by Richards and Saunders (1993), a method of determining the resistance of several different inhalers was documented. This method formed the basis for assessments of resistance for various pharmaceutical inhalers marketed in the UK; the available data was then used to design a 'resistance adaptor' for each delivery device. By placing the resistance adaptor between the patient and the In-Check flow-measuring device, it was possible to simulate the resistance of inhaling through the actual device, whilst measuring the inspiratory flows achieved. To ensure that this new medical device was capable of simulating the resistance of each different inhaler, and measuring the flow accurately, the devices were subject to testing internally, and by external testing authorities. The result of this testing was the ability to demonstrate that the In-Check Inhaler Assessment Kit could measure the speed at which a patient with respiratory disease could inhale through their inhaler.

The importance of good inhaler technique had been well documented; the performance of various dry powder inhalers had been shown to be flow dependent, and the effect of inspiratory flow on drug deposition had also received much attention.

Enquiries regarding inspiratory flow were made to medical information departments at the relevant pharmaceutical company offices, both directly by Clement Clarke and independently by a third party. Information provided was added to documentation obtained from published clinical research, with a resulting body of evidence that identified the minimum and optimum flow rates for these inhalers. This body of evidence was discussed with knowledgeable health professionals to ensure that Clement Clarke had taken a responsible position and had not drawn incorrect conclusions from the data available.

September 1998 saw the introduction of the In-Check Inhaler Assessment Kit – a small pack that combined an inspiratory flow meter with up to six 'resistance adaptors' that allowed the inspiratory flow to be assessed for patients using several inhaler devices. Accompanying the pack was an instruction booklet that detailed the flow rates for each device – specifically stating the minimum and optimum thresholds and whether there was a variation in the amount of drug between the two stated figures. For example, Turbohaler: minimum 30 litres per minute; optimum 60 litres per minute; high variation in dose over range.

The product was being sold successfully both in the UK and internationally and had stimulated interest amongst academics involved in respiratory medicine. Several abstracts had been published where the In-Check device had been used in research and there were clinical papers awaiting publication in relevant journals.

A development of this product, the In-Check Dial, was first made available at the European Respiratory

Society's Annual Scientific Meeting in October 1999. This new product simplified further the equipment needed to measure inspiratory flow through inhalers, by incorporating a rotating dial that allowed the health professional to select one of several inhalers (without the need to fit 'resistance adaptors' that were used in the first product).

Feedback from users of the In-Check Inhaler Assessment Kit recommended simplifying the data for each inhaler. As the product was frequently used to train patients how to modify their inhaler technique (to suit the flows recommended for each device), the optimum inspiratory flow threshold for each device was identified from the research data, and used to represent the target flow range for patient training.

It was recognised that the change of information supplied with the products (from minimum and optimum, to just optimum) had coincided with the activity by AstraZeneca to disparage the In-Check range of products.

As might be expected of a responsible company, Clement Clarke had taken pharmaceutical and legal advice on the ability to represent the information as stated in literature accompanying the In-Check Dial.

AstraZeneca threatened Clement Clarke with a court injunction and legal proceedings in a letter dated 27 April 2000. Its legal representatives required withdrawal of the In-Check Dial product internationally and a public retraction of the statements Clement Clarke had made that documented the optimum flow range for AstraZeneca's device being '60 to 90 litres per minute'. Clement Clarke had replied fully to AstraZeneca's questions and referenced much *in vitro* and *in vivo* work that supported Clement Clarke's position – it took advice from academics with acknowledged expertise in this area and had maintained the product information without a change. Clement Clarke's solicitors continued to advise that it had a strong defence against any action brought by AstraZeneca due to the detailed information available on the Turbohaler product. Interestingly although AstraZeneca's first letter threatened legal proceedings – none had been brought. Clement Clarke had not withdrawn the In-Check Dial as requested, nor modified the way it had presented the information. Clement Clarke's most recent reply to AstraZeneca, dated 18 July 2000, remained unanswered and unacknowledged.

Clement Clarke invited the Authority to review the exchange of correspondence, which would be made available on request, if it would be beneficial to the complaint.

Importantly, many of the scientific references Clement Clarke had cited were the same as those used by AstraZeneca itself to support its product.

Activity undertaken by AstraZeneca that Clement Clarke believed to be in breach of the Code

1 Representatives had made misleading statements, disparaging the In-Check product

Until 20 October 2000, Clement Clarke was aware of, but unable to document, oral comments made by AstraZeneca representatives that disparaged the In-Check. On several occasions health professionals had told Clement Clarke that the following assertions had been made: the In-Check device was inaccurate; it was unable to accurately reproduce the resistance of the Turbohaler; it used incorrect data; it was wrongly calibrated; the In-Check was shortly to be withdrawn from the market and it was the subject of legal action taken by AstraZeneca.

Clement Clarke commented on each of the allegations:

The In-Check Dial was inaccurate.

Clement Clarke submitted that this was not an allegation made by AstraZeneca in its correspondence with Clement Clarke and its solicitors. Extensive research and testing had been carried out to ensure the accuracy of the device and there had been no formal allegation, whether from AstraZeneca or elsewhere, of inaccuracy of the device.

The In-Check was unable to accurately reproduce the resistance of the Turbohaler.

Again Clement Clarke submitted that this was not an allegation made by AstraZeneca in its correspondence with Clement Clarke and its solicitors. Extensive research and testing had been carried out to ensure that the In-Check system could demonstrate equivalent resistance to the Turbohaler device and there had been no formal allegation, whether from AstraZeneca or elsewhere, of inability to reproduce the resistance of the Turbohaler product.

The In-Check was using incorrect data.

Clement Clarke stated that in a solicitor's letter, AstraZeneca had formally alleged that Clement Clarke had used incorrect data. A comprehensive response to this allegation was sent to AstraZeneca's solicitors. There had been no answer from AstraZeneca to that letter in the three months since it was sent to them, and it was reasonable to assume that AstraZeneca no longer maintained that argument. Clement Clarke stated that its own extensive review of research data, AstraZeneca's previous correspondence on the performance of the Turbohaler, and the advice from academics with acknowledged expertise on the subject, supported the data as correct and appropriate.

The In-Check was wrongly calibrated.

Clement Clarke stated that this remained an issue with AstraZeneca and was reflected in the correspondence between the two companies' solicitors. It came down to the research into the performance of the Turbohaler and the description of optimum range. Clement Clarke remained of the view that the description it had given of the Turbohaler's optimum range was appropriate.

Over the past two years Clement Clarke had been aware of the issues as to the optimum range of the Turbohaler and had offered discussions and attempted resolution of this question with AstraZeneca, but unfortunately without resolving it. Clement Clarke had suggested that the relevant issues

be submitted to a review by a suitably qualified medical and pharmaceutical panel, but to no response.

Clement Clarke's product was not a competing product to the AstraZeneca range – it was used for interpretation and training on a number of commonly used inhaler devices. As a company Clement Clarke would be more than happy to reach an agreement with AstraZeneca on the appropriate way to show the range of the Turbohaler device if AstraZeneca was able to provide credible and substantive evidence that the optimum range was not that shown on the chart with the In-Check Dial. However, until such evidence was produced, Clement Clarke had a duty, as reflected in comment in its solicitors' letters to AstraZeneca's solicitors, to provide the public and the professionals within the health service with an accurate representation of the performance of the Turbohaler.

The In-Check was shortly to be withdrawn from the market.

Clement Clarke stated that this was completely wrong – the company had no intention of withdrawing the product from any country worldwide.

AstraZeneca's competitor in Sweden, Glaxo Wellcome, had been required to withdraw its use of the product following a recent ruling by the 'NBL', an authority with a similar role to that of the Authority.

There was a complaint by Draco AB (AstraZeneca Sweden) to the NBL against the use of the words 'optimum inspiratory flow' on the chart which accompanied the In-Check Dial. Clement Clarke had no notice of that complaint which was directed at Glaxo Wellcome's reference to the In-Check Dial. Whilst the complaint was upheld by the NBL, because of a lack of understanding a Swedish speaker might have of that English phrase, it appeared that at no time was it drawn to the NBL's attention that two pages of the booklet describing the use of the In-Check Dial were in Swedish and that that booklet accompanied every In-Check Dial. Clement Clarke was appealing the ruling of the NBL.

The In-Check was the subject of legal action taken by AstraZeneca.

Clement Clarke stated that neither it nor its solicitors were aware of any legal action. Indeed, it appeared that AstraZeneca, having threatened immediate action in a letter in April, had now withdrawn from that decision.

To attempt to resolve this sensibly, Clement Clarke sought a meeting with the relevant AstraZeneca product manager. E-mails requesting a meeting to discuss the misleading comments made by AstraZeneca's representatives were sent in October.

On 20 October Clement Clarke received a reply from AstraZeneca which did not accept that such comments had been made.

This correspondence was sent to Clement Clarke 17 days after AstraZeneca's product manager and medical adviser were invited to a meeting at a university. This meeting, on 3 October, was called after a research nurse at a hospital had been told by an AstraZeneca representative that the In-Check device was inaccurate.

2 Representatives had made misleading statements about the performance of the Turbohaler

At the General Practitioners in Asthma Group / Primary Care International summer meeting Clement Clarke asked to speak with the AstraZeneca representative at the exhibition stand. Clement Clarke asked for clarification of the flow rates and pulmonary drug deposition of the Turbohaler device. To help with the explanation, the representative used an electronic device – the Turbohaler Usage Trainer – to explain that all that was needed to operate the Turbohaler effectively was one light, which equated to 30 litres per minute inspiratory flow. This, he said, would result in 30% drug deposition. Clement Clarke asked what drug deposition would occur if two lights were lit – the representative stated that 30% would still occur. As the instructions for use of the device showed, the Turbohaler Usage Trainer would show one light at 30L / min and two lights at 40L / min. Only when the inspiratory flow rate through the device reached 60L / min and above would all three lights be illuminated.

Clement Clarke had obtained a copy of AstraZeneca's representative briefing document 'Objection Handling Document – Inspiratory Flow Rates and Turbohaler' (BTH006258) which explained, on page 2 (The Turbohaler works across a range of inspiratory flow rates): 30L / min inspiratory flow rate will deliver 15% of nominal dose to the lungs; only when the inspiratory flow rate is doubled, to 60L / min, is 30% deposition likely to occur.

This representative had provided misleading information about the Turbohaler when specifically asked about flow rate and deposition. Clement Clarke maintained that this was indicative of the lack of knowledge within the AstraZeneca field force about how changes in inspiratory flow affected the amount of drug that was released from the Turbohaler product.

3 Information provided by AstraZeneca on the performance of the Turbohaler was ambiguous and misleading

In a 'Dear Pharmacist' letter, dated 1 February 2000, a price reduction was notified to pharmacists with additional comments that the Turbohaler product was recommended for treating childhood asthma and newly diagnosed asthmatics. A justification for this was stated as that the 'low Peak Inspiratory Flow Rate (PIFR) required for its use' was achievable by virtually all children over the age of six. This referenced work by Pedersen 1990 who documented a response to treatment that was only reduced when inspiratory flow rates fell below 28L / min through the device. 30L / min inspiratory flow rate was achieved by 17 out of 19 children with acute asthma, but none achieved more than 54L / min (range 30 to 54, mean = 39L / min). Clement Clarke recognised that the minimum inspiratory flow rate for the Turbohaler to effectively deliver drug to the lungs was 30L / min. Clement Clarke also recognised that the majority of

children in this study could achieve inspiratory flow rates between 30 and 54L / min.

At the same time, the British Journal of Community Nursing (February 2000 edition) featured product news (page 101) regarding the same price reduction, stating: 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI' [pressurised metered dose inhaler]. This piece of 'advertorial', which was not accompanied by any prescribing information, might mislead readers to believe that all users of the Turbohaler would receive twice as much drug when compared to the use of a conventional pMDI. As could be seen from AstraZeneca's 'Objection Handling Document', the claim for twice the lung deposition of a pMDI could only be made when the Turbohaler was used with an inspiratory flow rate of 60L / min. AstraZeneca's reference to the British Guidelines on Asthma Management (1997) was only possible because of the Guidelines' reference to the original research (Thorsson *et al*, 1994). Importantly, the subjects of this study were instructed to inhale at a flow of 60L / min through the Turbohaler and 30L / min through the pMDI.

The publication British Journal of Community Nursing did not write such articles without a press release or pre-written copy, and requested a separation fee for reproducing photographs. Its definition of this section of the magazine was 'advertorial'.

It was misleading for AstraZeneca to state that the deposition from the Turbohaler was double that from a pMDI without reference to the inspiratory flow through the device needing to be 60L / min. If the inspiratory flow was only 30L / min, then the Turbohaler was only as effective as a pMDI used with good inhalation technique.

To advise in the briefing document that the dose of corticosteroids could be halved when given by Turbohaler, without assessing the ability of the patient to achieve 60L / min, was irresponsible.

Summary

Clement Clarke developed the In-Check products to enable clinicians to measure the speed of inhalation for different delivery devices. A substantial body of data existed that documented the performance of inhalers such as the Turbohaler.

AstraZeneca, within its own briefing material, acknowledged that drug delivery at 30L / min was only 50% of that delivered at 60L / min. However, it did not present this information to health professionals in a way that was balanced and unambiguous.

Clement Clarke believed that in disparaging the In-Check products, AstraZeneca was preventing health professionals from improving care for patients with respiratory disease as the In-Check product had already shown value in identifying patients who could not inhale at the right speed for the inhaler they had been prescribed.

With recognition that the ideal inhaler device should deliver a predetermined dose of medicine to the lungs, in an easy-to-use, reproducible and cost-effective manner, clinicians were now becoming aware that the Turbohaler might deliver varying amounts of medicine even to the same patient because the inspiratory flow fluctuated (and drug delivery from that inhaler was flow dependent).

The In-Check system had enabled professionals such as general practitioners and specialist asthma nurses (who were responsible for the majority of asthma care in the UK) to both teach the correct technique for maximum benefit from each inhaler and also ensure that patients who were to be prescribed a new inhaler actually had sufficient inspiratory flow to operate it – ideally optimally, but, at the very least, effectively.

It was unfortunate for AstraZeneca that its Turbohaler device had a high internal resistance that prevented some patients from achieving the 60L / min required for optimum drug deposition.

Clement Clarke believed that AstraZeneca's actions breached the Code. AstraZeneca had not only disparaged Clement Clarke's medical device, but acted irresponsibly by continuing to provide ambiguous information on its product in the light of an opportunity to improve the rationale behind prescribing an inhaler device for patients with asthma and other respiratory diseases.

The matters of which Clement Clarke complained were:

That AstraZeneca was publishing false information about the performance on the In-Check Dial. In particular, there was no evidence to support the claims being made by AstraZeneca that the In-Check Dial was: inaccurate; unable accurately to reproduce the resistance of the Turbohaler; using incorrect data; wrongly calibrated.

AstraZeneca was, through its sales force, making disparaging comments on the In-Check Dial. In addition to the four inaccurate representations referred to above, the suggestions that the In-Check Dial was about to be withdrawn from the market and was the subject of legal action must be designed to lower its reputation and to give the impression that it was not a reliable product.

The statements made by the representatives of AstraZeneca were inaccurate as must be known to AstraZeneca.

The information provided to health professionals was ambiguous and misleading and did not accurately represent the variable performance of the Turbohaler product.

RESPONSE

AstraZeneca stated that it had been difficult to respond to some of the issues raised, particularly in view of the extensive and wide-ranging nature of the information provided and the issues complained about. AstraZeneca was concerned that a Code of Practice complaint had been used inappropriately as a forum to raise a number of issues that were outside the scope of the Code. However, in view of the fact that some of the issues raised might fall within the scope of the Code, it would like to make the following comments:

1 Application of the Code

AstraZeneca drew the Panel's attention to the first paragraph of Clause 1.1 'Scope of the Code and Definition of Certain Terms'. This made it clear that the Code applied to the promotion of medicines to members of the health professions and appropriate administrative staff. Similarly, Clause 8.1 referred to the 'medicines, products and activities of other pharmaceutical companies', not to other types of companies. AstraZeneca did not believe, therefore, that the Code applied to the discussion of devices such as the In-Check that could not be defined as medicines. AstraZeneca therefore did not accept that the complaints made by Clement Clarke in respect of information alleged to have been disseminated by AstraZeneca and its representatives about the In-Check device came within the scope of the Code and asked that the Panel ruled accordingly.

2 Allegations concerning conduct of AstraZeneca representatives

AstraZeneca acknowledged that, notwithstanding the above comments, Clement Clarke had also taken issue with statements alleged to have been made by AstraZeneca representatives about the Turbohaler. AstraZeneca accepted that such statements might be considered to be within the scope of the Code. However, as the Panel would appreciate, it was very difficult to respond to any allegations concerning what had or had not been said or done by representatives, without substantive evidence. The complainant had not identified the representatives concerned, or the precise occasions on which it alleged that specific comments were made, or to whom, in relation to the Turbohaler device. AstraZeneca therefore was unable to comment on these allegations. If Clement-Clarke was able to provide specific details concerning the matters complained of AstraZeneca would of course investigate further.

In response to a request for more information with regard to the conduct of its representatives, AstraZeneca noted that the original report about the conversation between a research nurse and a representative had come from a third party; this report had in turn been sent to Clement Clarke by another party. Neither of these parties was seemingly present at the meeting referred to. AstraZeneca was therefore concerned that this allegation was based on a conversation effectively at three steps removed from the complainant.

AstraZeneca noted that the element of the conversation about which concern was expressed appeared to be in reference to the 'In-Check' device. The company was therefore somewhat unclear as to how this matter *per se* related to the Code.

AstraZeneca confirmed that its representative recalled a conversation with the research nurse during which the minimum peak inspiratory flow requirement for the Turbohaler was the main subject of discussion. The In-Check device was only briefly mentioned. The representative advised the nurse that the information accompanying the In-Check device appeared to present a higher peak inspiratory flow requirement for effective use of the Turbohaler than AstraZeneca believed to be necessary. The representative confirmed that she did not state that the In-Check device itself was inaccurate.

The representative further confirmed that on her own initiative she telephoned in order to arrange a meeting at the university to discuss the inspiratory flow requirements of the Turbohaler. This meeting was arranged for 3 October. The representative did not attend; she agreed with her colleagues that they would attend since her telephone conversation led her to the view that detailed technical discussion was proposed, that these colleagues would be in a position to provide. These colleagues duly attended the meeting, as referred to in the e-mails provided by the complainant.

With regard to the conversation that allegedly took place at the General Practitioners in Asthma Group / Primary Care International summer meeting, AstraZeneca stated that it had contacted all of its representatives who attended its exhibition stand at the meeting and none of them recalled having had a conversation as described with a representative from Clement Clarke. AstraZeneca stated that without knowing the identity of the particular representative allegedly involved or of the representative from Clement Clarke, it was difficult for it to provide definitive information on this matter.

Before proceeding to address some of the other matters complained of, it might be helpful to provide some background information from AstraZeneca's own perspective.

The In-check device

AstraZeneca stated that Clement Clarke had informed the Authority that the first In-Check device was introduced in the UK in September 1997. The device was essentially an inspiratory flow meter that could be used to measure the speed at which a subject was able to breathe in. In September 1998 the Inhaler Assessment Kit was marketed as a means to assist health professionals in selecting suitable inhalers for different patients. The kit included the flow meter and various 'resistance adapters' that could be attached to the meter to simulate the resistance properties of different types of inhaler device, including AstraZeneca's Turbohaler. The accompanying literature incorporated a table providing information on which adapter was appropriate for each type of inhaler and giving minimum and optimum inspiratory flow rates, as recommended by the respective manufacturers, for each named inhaler.

The In-Check Dial was introduced in 1999. This product was a further development of the device, which obviated the need for resistance adapters to be fitted. Instead the user selected the device in question via a dial mechanism. The literature accompanying this new device differed significantly from that which accompanied previous versions. Of relevance to the matters under discussion was the fact that reference to 'minimal' inspiratory flow rates had been omitted from the display of comparative data on different devices. Information was presented in the form of a

graph, in which a range of optimum inspiratory flow rates were depicted as bars against a scale. The optimum inspiratory flow rate for the Turbohaler was depicted as 60-90L / min.

AstraZeneca's concerns related to the depiction of Turbohaler in the accompanying literature, which it considered to be misleading. As the Panel would be aware following previous correspondence from AstraZeneca, similar concerns had been raised in a number of other fora:

- AstraZeneca referred the Panel to its letter dated 31 October;
- Clement Clarke had itself referred to a complaint for which a ruling was recently made in favour of AstraZeneca's Swedish affiliate at the Swedish NBL with regard to the promotional use being made of the In-Check device by another pharmaceutical company.

From AstraZeneca's perspective, there were a number of issues: firstly, its concern derived from the fact that it believed that this graphical presentation misrepresented the efficacy in use of the Turbohaler, suggesting that a Turbohaler was unsuitable for patients who could not achieve an inspiratory flow rate of 60L / min and above. Secondly, the change in the data provided with the different versions of the In-Check device had the potential to create confusion for health professionals. As evidence for this AstraZeneca cited the letter that the Authority recently sent to AstraZeneca following correspondence from two practice nurses. Thirdly, it was in AstraZeneca's view far too simplistic to base selection of a suitable inhaler on inspiratory flow rates alone.

The chart accompanying the In-Check Dial, in AstraZeneca's opinion, created a misleading impression because the information did not clearly distinguish between effective inspiratory flow rates and optimal inspiratory flow rates, which had different implications for inhalers that operated via different mechanisms.

AstraZeneca was well aware that the In-Check Dial was used as a marketing tool by some of its competitors. In this context, AstraZeneca asked the Panel to bear in mind its recent letter of complaint (Case AUTH / 1096 / 11 / 00).

3 Information about the Turbohaler

To address the issues pertaining specifically to Turbohaler, about which Clement Clarke had complained, AstraZeneca made the following comments.

The Turbohaler was an inspiratory flow-driven dry powder inhaler prefilled with a set number of doses of active drug as follows: Bricanyl Turbohaler (terbutaline sulphate), Pulmicort Turbohaler (budesonide) or Oxis Turbohaler (eformoterol). The Turbohaler had been shown to be effective at low inspiratory flow rates (reference the Pulmicort Turbohaler and Bricanyl Turbohaler data sheets). The Turbohaler was designed to offer a moderate resistance to inhalation. It was believed that this created a particular muscular configuration in the oropharynx that favoured optimal deposition of drug in the lungs.

Bricanyl Turbohaler had been shown to be effective in an acute clinical setting in both adults and children at an inspiratory flow rate of 30L / min. Pedersen specifically examined the influence of inspiratory flow rate on the effect of the Turbohaler. This study showed that a flow rate above 30L / min could be generated by virtually all children of 6 years of age or older, indicating, in the opinion of the authors, that 'they would all be able to benefit optimally from Turbohaler treatment'. Brown *et al* showed that 98% of asthma patients could achieve an inspiratory flow rate of 30L / min through a Turbohaler in an acute setting.

Turbohaler would deliver approximately 15% of nominal dose to the lungs at an inspiratory flow rate of 30L / min. This needed to be viewed in the context of a pMDI, which delivered typically between 10-15% of nominal dose, with good inhalation technique. Doubling the inspiratory flow rate to 60L / min approximately doubled the lung deposition via the Turbohaler. This fact was acknowledged within the British Thoracic Society (BTS) Guidelines on Asthma Management which suggested that the dose of a corticosteroid should probably be halved if changing to a Turbohaler from a pMDI. This would seem to be a reasonable generalisation based on likely inspiratory flow rates which could be achieved by patients with asthma. In a group of stable asthmatics using the Turbohaler, average inspiratory flow rates of 68L / min were recorded. A mean rate of 60L / min was achieved by adult patients during an acute asthma exacerbation. Whilst the Turbohaler showed variability in lung deposition over the range of inspiratory flow rates, 30-60L / min, this must be seen in the context of the high lung deposition observed even at lower flow rates and the fact that there were also many factors affecting lung deposition with other types of inhaler. For example, Everard *et al* showed the variability in respirable dose as a function of shaking or not shaking a metered dose inhaler. A study by Borgström *et al* demonstrated that in an asthmatic patient population, inhalation of terbutaline from a Turbohaler actually produced a more reproducible dose to the lungs than did inhalation of an equivalent dose from the corresponding pMDI. Variability was thus not a property that was unique to the Turbohaler, nor was inspiratory flow rate the only significant variable pertinent to effective use of a particular device.

To turn now to the specific issues raised by Clement Clarke.

4 Allegations concerning a 'Dear Pharmacist' letter dated 1 February 2000

AstraZeneca was unable to understand the precise nature of Clement Clarke's complaint. The main purpose of the letter was to advise pharmacists of a price reduction to the cost of Bricanyl (terbutaline) Turbohaler. Clement Clarke appeared to take issue with the information that Bricanyl Turbohaler was highly effective for treating childhood asthma and

newly diagnosed asthmatics and that it was effective even at low inspiratory flow rates. AstraZeneca submitted that those statements were reflective of the balance of evidence and consistent with the data sheet for Bricanyl Turbohaler. There was nothing misleading or ambiguous in these statements.

The letter also reminded pharmacists of the data from the Pedersen study which AstraZeneca referred to above, under point 3. AstraZeneca found it timely to take the opportunity to remind pharmacists of the conclusions of this data, namely that Turbohaler was effective at inspiratory flow rates of 30L / min, precisely because there appeared to be a misconception amongst some health professionals that the Turbohaler could not be used effectively by patients incapable of generating a flow rate of 60L / min or more. This misconception could at best have only been fostered by the information accompanying the In-Check Dial device, as discussed above.

5 News item appearing in British Journal of Community Nursing, February 2000

The above item appeared following the issue of a medical press release by AstraZeneca concerning the price reduction for Bricanyl Turbohaler. The press release was accompanied by a pack shot. The claim concerning drug delivery was referenced to the BTS Guidelines and to a study by Borgström. The rationale was explained in point 3 above. AstraZeneca did not accept that readers could be misled by this information which, again, reflected the balance of the evidence. Nor did AstraZeneca believe that they would construe this to mean that all users would receive twice as much drug in all circumstances with a Turbohaler, as alleged.

The allegation that the information published in the journal should have been accompanied by prescribing information was spurious. There was no requirement under the Code for press information to be accompanied by prescribing information. The published information appeared on a page in the journal on which product and device announcements were routinely published, unaccompanied by prescribing information. The editors of the journal were at liberty to amend the information and indeed were in a position to choose whether or not to include it at all.

In response to a request for further information regarding payment for publication of the photograph of the Bricanyl Turbohaler, AstraZeneca confirmed that a public relations agency, working on its behalf, received a request from the publishers of the journal for a separation fee for reproducing a photograph of the company's product. This request was subsequent to the receipt by the publishers of a press release, sent by the agency on AstraZeneca's behalf, which concerned a price reduction for Bricanyl Turbohaler. The publisher had taken the view that the information was relevant to the 'Product and Services' sections of particular journals in its portfolio, including the one in question, and that it would be appropriate, from an editorial perspective, to publish a pack shot. The publishers subsequently sent the public relations agency a fax back 'colour separation request' form listing costing for publication of a pack shot in named journals. The agency indicated agreement for publication in specific journals and payment was subsequently made. In the case of the British Journal of Community Nursing, the charge was £150.

6 Allegation concerning information in briefing document

Clement Clarke referred in its letter to AstraZeneca's briefing document on the Turbohaler (BTH 006784). The text referred to merely reiterated the guidance that appeared in the BTS Guidelines concerning dosage of corticosteroids and, AstraZeneca believed, reflected the balance of evidence as AstraZeneca had explained under section 3.

The BTS Guidelines also stated that dosage of corticosteroids should be titrated against control of asthma and reduced when control was achieved and AstraZeneca agreed that it was clinical outcome that should ultimately dictate the dosage used.

Clement Clarke's position would appear to be that the BTS Guidelines, as written, were in error in failing to draw the reader's attention to the inspirational flow rates for the Turbohaler. Whilst AstraZeneca disagreed, it submitted that this was not a matter that was within the scope of the Code.

To summarise AstraZeneca's position with respect to Clement Clarke's allegations.

AstraZeneca contended that allegations that it had disparaged the In-Check device were outside the scope of the Code and it could not reasonably be expected to address them within its response. It did not believe that Clement Clarke had provided any concrete information to support its allegation that AstraZeneca representatives were providing inaccurate or misleading information about the Turbohaler. Alleged instances involving representatives, quoted in Clement Clarke's letter, were matters of hearsay and AstraZeneca was unable to comment without further conclusive evidence on what had or had not been said.

AstraZeneca did not accept that the written information that it had provided to health professionals in respect of the Turbohaler was misleading or that the material cited by Clement Clarke provided any support for this view. AstraZeneca thus denied any breach of the Code.

PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff and to information made available to the general public about medicines so promoted. The Code did not apply to the promotion of devices *per se*. Clause 1.3 of the Code defined the term 'medicine' as meaning any branded or unbranded medicine intended for use in humans which required a marketing authorization. The In-Check Dial was a device for measuring inspiratory flow. The Code thus did not apply to the promotion

of the In-Check Dial *per se*; such promotion would be covered by general advertising legislation. The Panel noted that it could be argued that AstraZeneca was not using the In-Check Dial for a promotional purpose as such. The company might be seen as responding to the activities of Clement Clarke and other pharmaceutical companies. The Panel noted that a previous case, Case AUTH/1096/11/00, concerned a complaint made under the Code by AstraZeneca about Allen & Hanburys' use of the In-Check Dial in a promotional mailing. The Panel noted that in one of its rulings in that case it considered that the table of inspiratory flow rates on the In-Check Dial created the impression, in conjunction with a 'Dear Doctor' letter, that the Turbohaler could not be used at all with inspiratory flow rates of less than 60 L/min. In this regard the Panel considered that the use of the In-Check Dial device as a prize in a promotional competition was misleading and a breach of Clause 7.2 had been ruled. The Panel had considered that the alleged breach of Clause 18.1 was covered by this ruling. The Panel noted that that case had not yet been completed.

The Panel noted AstraZeneca's submission that the Code did not apply to the discussion of devices such as the In-Check Dial. Clearly this would be the position if a representative was only promoting the In-Check Dial. The situation was more complicated as the AstraZeneca representatives would presumably be promoting Turbohalers and discussion of the In-Check Dial might be part of the representative's detail to the health professional or might be something raised by the health professional. In that regard the Panel noted that it had been provided with a copy of representatives briefing material headed 'Objection Handling Document – Inspiratory Flow Rates and Turbohaler'. The 'Background' paragraph of this document referred to the In-Check Dial and stated that it was apparently being used to show that some patients might have difficulty generating sufficient inspiratory flow rates to gain maximum benefit from the Turbohaler. The objection handler continued by detailing the design and efficacy of the Turbohaler across a range of inspiratory flow rates. The document did not criticise the In-Check Dial in any way. Given that AstraZeneca had, however, briefed its representatives about inspiratory flow rates and had produced an objection handler which referred to the In-Check Dial, the Panel considered that the discussion of the In-Check Dial in association with the promotion of the Turbohaler meant that the matter was covered by the Code.

Clause 8.1 of the Code stated that the medicines, products and activities of other pharmaceutical companies must not be disparaged. The Panel noted that Clement Clarke was not a pharmaceutical company. The supplementary information to Clause 8.1 stated that critical references to another company's products were acceptable if such critical references were accurate, balanced, fair etc and could be substantiated.

Turning to the case now before it, the Panel noted that there was a complaint about a specific representative who had allegedly told a respiratory nurse involved in a study that the In-Check Dial was inaccurate. The Panel noted AstraZeneca's submission that the representative had advised the nurse that the information accompanying the In-Check device appeared to present a higher peak inspiratory flow requirement for effective use of the Turbohaler than AstraZeneca believed to be necessary. The Panel noted that the report of the exchange between the nurse and the representative had not come from the nurse herself. It was difficult to know exactly what had transpired between the two parties. It was impossible to know where the truth lay. The Panel ruled no breach of Clauses 7.2, 8.1 and 15.2 of the Code.

The Panel noted that it was alleged that AstraZeneca representatives had made misleading statements to healthcare professionals, disparaging the In-Check Dial. Clement Clarke had not provided detailed information relating to such exchanges so that the allegations could be properly investigated by AstraZeneca. In such circumstances it was impossible to know what representatives had said. The Panel ruled no breach of Clauses 8.1 and 15.2 of the Code.

It was also noted that it had been alleged that AstraZeneca representatives had made misleading statements about the performance of the Turbohaler to a representative of Clement Clarke. AstraZeneca had stated that none of its representatives at the meeting in question could recall having had a conversation with a representative from Clement Clarke. The Director had some concerns about the matter but considered that on the available facts the information given by the AstraZeneca representative to the Clement Clarke representative was not covered by the Code and decided that there was no *prima facie* case to answer in this regard.

The Panel noted that the 'Dear Pharmacist' letter announcing the price reduction of Bricanyl Turbohaler stated that it was '… a highly effective choice for treating childhood asthma and newly diagnosed asthmatics …'. The letter further referred to the low peak inspiratory flow rate required to use a Bricanyl Turbohaler citing Pedersen *et al* in support. The Panel noted that Bricanyl Turbohaler was indicated for use in children; it was not restricted to second-line use in any patient group (ref Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). The data sheet stated that treatment with Bricanyl Turbohaler was effective even at low inspiratory flow rates, such as those present during an acute asthma attack. The Panel noted there was data to show that the minimum inspiratory flow rate needed for the operation of the Turbohaler was 30L/min, which was accepted by Clement Clarke. The Panel did not consider that the information given in the 'Dear Pharmacist' letter in this regard was either ambiguous or misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the news item which appeared in the British Journal of Community Nursing, February 2000, was headed 'Bricanyl Turbohaler price reduction' and had been published subsequent to AstraZeneca's issue of a press release announcing the price change. The item made claims for Bricanyl Turbohaler and included a pack shot of the product for which AstraZeneca had paid. In the Panel's view such payment constituted an activity to promote the

prescription, sale, supply or administration of Bricanyl Turbohaler and in effect the news item was an advertisement. The information given exceeded that allowed in an abbreviated advertisement. In the Panel's view the item was an advertisement which failed to meet the requirements of Clause 4.1 of the Code as no prescribing information had been provided. A breach of Clause 4.1 was ruled. This ruling was appealed by AstraZeneca.

The Panel noted that the advertisement stated that 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI'. In the Panel's view readers would assume that the Turbohaler always delivered approximately twice the amount of drug to the lungs which was not so. The Panel noted that the Objection Handling Document gave details of a range of inspiratory flow rates. It stated that the 'Turbohaler is effective at inspiratory flow rates of 30L/min and will deliver approximately 15% of nominal dose to the lungs. This is higher than a pMDI which delivers typically between 10-15% with good inhalation technique. Doubling the inspiratory rate to 60L/min approximately doubles lung deposition via Turbohaler. This is acknowledged in the BTS guidelines to the extent that it is recommended that the dose of inhaled corticosteroid should be halved when given by Turbohaler compared to the pMDI – recognition of the improved deposition'. It appeared that the Turbohaler delivered twice the amount of medicine to the lungs than a conventional pMDI when a patient's inspiratory flow rate was 60L/min. The Panel considered that the statement in the advertisement was misleading and ruled a breach of Clause 7.2 of the Code. This ruling was appealed by AstraZeneca.

The Objection Handling Document referred to the improved drug deposition seen with the Turbohaler and stated that 'This is acknowledged in the BTS Guidelines [British Thoracic Society Guidelines on Asthma Management] to the extent that it is recommended that the dose of inhaled corticosteroids should be halved when given by Turbohaler, compared to pMDI'. The Panel noted that the BTS Guidelines actually stated that 'The Turbohaler delivers approximately twice as much inhaled steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be titrated against control of asthma and treatment reduced when control is achieved'. The Panel considered that the objection handler had thus not wholly reflected the advice regarding the dose of inhaled steroids via a Turbohaler as given in the BTS Guidelines; the information given was too brief and in the Panel's view would lead to representatives giving misleading information. A breach of Clause 15.9 was ruled.

APPEAL BY ASTRAZENECA

News item in 'British Journal of Community Nursing'

AstraZeneca stated that it was concerned that the Panel's ruling of a breach of Clause 4.1, if upheld, would set a far-reaching precedent for the industry and indeed publishers of medical journals. The company therefore considered it was important that it was subject to the scrutiny of the Appeal Board. The company considered that the ruling was open to question for the following reasons.

- It appeared to be based on the assumption that the item in question constituted an advertisement, by virtue of the fact that a colour separation fee was paid by AstraZeneca, for publication of a pack shot.
- The news item appeared as a result of an AstraZeneca press release concerning a price reduction for Bricanyl (terbutaline) Turbohaler. The press release was directed at the editors of journals and not at those responsible for selling advertising space. AstraZeneca stated that whilst the content of the press release was naturally subject to its internal copy approval process, it did not approve (and was not given the opportunity to approve) the final news item which appeared at the discretion of, and with full editorial control of, the journal publishers.
- The colour separation request form, which was sent to AstraZeneca's agency by the journal publishers, showed that inclusion of a news item was not guaranteed merely by the fact of its having been sent. Payment was made after the publishers had decided to include an item and after the company had agreed that a pack shot might appear.
- An advertisement was generally regarded to be a promotional tool whereby the advertiser purchased publishing space for which he supplied and controlled the copy and in a situation moreover where, barring unforeseen problems, his copy was guaranteed to appear. This was not the case with press information. The Panel's ruling would appear to challenge the industry's understanding of what generally constituted an advertisement.
- The practice of requesting colour separation fees was widespread amongst publishers of journals aimed at health professional. The company noted that many journals included product news sections in which items of news similar to the Bricanyl Turbohaler information routinely appeared without the inclusion of prescribing information.
- These product news sections were not marked as advertorials and the type style, styles of the headings, photographic style used and so on, did not differ significantly from the general editorial style of the publications concerned. Examples of product news sections and general editorial copy from the following were provided: British Journal of Community Nursing, Chemist & Druggist and Hospital Doctor. AstraZeneca stated that to the best of its knowledge, all these titles requested colour separation fees. The company suggested that the effect of submitting this type of press material to these journals was therefore no different in its outcome to submitting it to other publications, for example the Pharmaceutical Journal or Prescriber, which did not charge colour separation fees but did publish product news

items. Examples of the layout of product news section and other editorial copy for the above two journals were provided. AstraZeneca also submitted that similar considerations applied to other types of press information issued by companies, which might also contain product claims. The question of when press information became an advertisement was far from clear.

- AstraZeneca had a rigorous process in place to ensure that all of its advertising materials were fully compliant with the Code. Had it taken the view that the item in question was indeed an advertisement, prescribing information would have been supplied. However the company did not view it as such and in no way knowingly breached the Code on this point. AstraZeneca requested that the Appeal Board reviewed this matter accordingly.

Statement concerning lung deposition rates with the Turbohaler when compared to a conventional pressurised metered dose inhaler

AstraZeneca noted that the Panel ruled a breach of Clause 7.2 in relation to the claim that Turbohaler delivered approximately twice as much drug to the lungs as a conventional pressurised metered dose inhaler (pMDI). The Panel stated that such a claim would lead readers to assume that the Turbohaler always delivered twice as much drug to the lungs as a conventional pMDI, which was not so.

AstraZeneca noted that the statement appeared in the news item referred to above. In its press release the company had referenced this statement to two sources, one being the BTS Guidelines and the other being a study by Borgström *et al*. Copies of these references were provided. There were a number of points that AstraZeneca considered were pertinent to its defence of this claim.

- The claim appeared in a news item and the company did not have the opportunity to review the copy. The company considered that the claim was appropriately referenced in its press release; therefore it submitted it was not responsible for its appearing without being appropriately referenced in the final news item.

- Both the news item and the press release upon which it was based, stated clearly that the Turbohaler delivered approximately twice as much drug to the lungs as a pMDI. AstraZeneca did not consider that readers would understand this to mean that the Turbohaler always delivered twice as much drug as a pMDI, because it had not claimed this.

- It was also germane to this issue that the Turbohaler was not a device that was available for use independently of the drugs it contained. As stated in the response to the complaint, the Turbohaler was pre-filled with a number of different drugs used in the treatment of asthma. In each case the dosage instructions were specific to each drug and to the device. AstraZeneca stated that there was no question, therefore, that a health professional would be misled as to the actual dosage of drugs used via the Turbohaler as a result of its press material; the statement was included as evidence of the performance characteristics of the Turbohaler.

- AstraZeneca submitted that, given what was known about the performance of the Turbohaler, the statement about drug deposition was an acceptable generalisation and was not misleading in the context of a short news item. The company noted that the statement in the BTS guidelines, to which the claim was referenced, made a similar generalisation (albeit indirectly), without reference to inspiratory flow rates. Furthermore the BTS was considered the foremost authority in this country on asthma treatment and therefore AstraZeneca considered that it was a reliable source of information.

- The issue of delivery of inhaled drugs to the lungs was complex and influenced by several factors, some of which were device-related and some patient-related. These included such issues as: peak inspiratory flow rates and resulting drug deposition in the lungs; user technique and training; age group.

Peak inspiratory flow/drug deposition

Dry powder inhalers, such as the Turbohaler, relied on the patient's inspiratory effort to disperse the drug into small particles and deliver it the lungs. As noted in the objection handling document, at a relatively low inspiratory flow rate of 30L / min the Turbohaler had been shown to produce a lung deposition rate with inhaled budesonide of approximately 15%. This figure increased to 30% at an inspiratory flow rate of approximately 60L / min.

In a pMDI the drug was dissolved or suspended in a propellant under pressure and when activated a valve released a metered volume of drug and propellant. The inhalation needed to be slow at around 30L / min. Even when used with optimal efficiency a pMDI only achieved lung deposition rates of around 10-15%.

Usage technique/Training

Since the Turbohaler required no co-ordination between actuation and inhalation, it might be considered easier to use than a pMDI. Borgström *et al* (2000) showed less day-to-day variability in lung deposition with a Turbohaler than for a pMDI and concluded that performance of a Turbohaler was more subject independent than that of a pMDI.

An audit by general practitioners reported by Hilton (1990) showed that metered dose inhalers had a low proportion of users who exhibited good technique (45%). By contrast, 75% of Turbohaler users exhibited good technique. Lenney *et al* (2000) showed that even after expert instruction, only 79% of patients could use a pMDI effectively.

Everard *et al* (1995) assessed the total and 'respirable' doses delivered by a salbutamol metered dose inhaler under various conditions and reported that the delivered dose might be reduced by failing to shake the device, by very rapid repeated actuation, or by inappropriate storage of the device during use. Failing to shake the MDI before use, for example,

resulted in a reduction in the total and respirable dose by 25.5% and 35.7% respectively. Storing the device stem side down reduced the total and respirable dose delivered in the first actuation by 25% and 23% despite shaking it before use.

Age range

Ability to use an inhaler device might be to some degree age-dependent. For example young children might lack the ability to co-ordinate inspiration and actuation that was required for effective use of a pMDI or the ability to inhale sufficiently forcefully to use a dry powder inhaler.

An inspiratory flow rate of 60L / min was average for an adult. Meijer *et al* (1996), reported that amongst a group of 30 adult asthmatic patients using the Turbohaler, whose peak inspiratory flows (PIFs) were recorded at home, these flows were found to be remarkably constant with mean individual PIFs ranging from 55 to 95L / min. Only 13 of 5248 PIFs recorded were <40L / min.

AstraZeneca stated that from sales data 82% of Turbohaler patients were aged 12 or over and 62% were aged 19 or more. Therefore a majority of users were capable of achieving the inspiratory flow rate required to achieve a lung deposition rate of 30%.

AstraZeneca stated that in summary, collectively this information would suggest that the optimal lung deposition of 10-15% with pMDI was unlikely to be consistently achieved in practice. High lung deposition rates were demonstrable with the Turbohaler. It followed therefore that it was not 'only' at an inspiratory flow rate of 60L / min that the lung deposition rate of a Turbohaler was twice that of a pMDI but that this phenomenon might well hold true at lower flow rates. Bearing in mind all the issues elaborated upon above, AstraZeneca argued that its claim was not unreasonable in this overall context and would request the Appeal Board's consideration of this in respect of the ruling of a breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the item in the British Journal of Community Nursing had appeared as a result of a press release entitled 'AstraZeneca Reduces the Cost of Bricanyl Turbohaler'. The press release consisted of four short paragraphs of text; the first three referred to issues of cost while the last paragraph made claims with regard to the clinical efficacy and the performance of the Turbohaler in terms of drug delivery. This paragraph stated that the Turbohaler delivered '… approximately twice the amount of drug to the lungs as a conventional pMDI'. Having received the press release the publishers of the journal sent AstraZeneca a colour separation request form. From this form it was clear that AstraZeneca could request in which journals it wanted the information to appear; in each case the information would appear in the 'Products and Services' sections and a fee would be charged for each image produced. An invoice would follow on publication. The form referred to AstraZeneca as the advertiser. AstraZeneca had indicated that it wished the information from its press release to appear in, *inter alia*, the British Journal of Community Nursing for which the colour separation fee was £150. The Appeal Board noted that the content of the journal article was almost identical to that of the press release and so, although the article was headed 'Bricanyl Turbohaler price reduction', the information given was not restricted to cost but included the same claims for the product as had been included in the press release.

The Appeal Board noted the submission that journals frequently asked for a colour separation fee. The representatives stated that the Pharmaceutical Journal did not charge colour separation fees.

The Appeal Board considered that with regard to certain journals AstraZeneca had had control over where information about the Turbohaler had appeared. The implication of the payment of the colour separation fee was that without payment no article would have been published. The Appeal Board noted that all of the articles on the page in the British Journal of Community Nursing on which the Turbohaler information had been published included a photograph of some kind. The Appeal Board considered that the press release which gave rise to the article had gone beyond being a factual, informative announcement about a price change. It had included claims for the product which had been repeated word for word in the article in question. The Appeal Board noted the arrangements. AstraZeneca had had control over the placement of the article, the company press release was about a price change and had included product claims and a fee had been paid for the printing of the pack shot. The Appeal Board considered that the circumstances were such that the article was in fact promotional material for the Bricanyl Turbohaler and so should have included the prescribing information as required by Clause 4.1 of the Code. The Appeal Board thus upheld the Panel's ruling of a breach of that clause. The appeal on this point was unsuccessful.

With regard to lung deposition, the Appeal Board noted that at an inspiratory flow rate of 30L / min the Turbohaler delivered 15% of the nominal dose to the lungs. Increasing the inspiratory flow rate to 60L / min doubled lung deposition to 30%. Good inhalation technique with a pMDI typically delivered between 10-15% to the lungs. The Appeal Board noted, however, that there was no evidence to show that all patients, notably children, would be able to achieve an inspiratory flow rate of 60L / min and therefore a lung deposition of 30% of the nominal dose. In patients with inspiratory flow rates of less than 60L / min, the Turbohaler would not deliver twice the amount of drug to the lungs as a conventional pMDI. The Appeal Board thus considered that the claim in the press release, which also appeared in the article in the British Journal Community Nursing, 'The Turbohaler delivers approximately twice the amount of drug to the lungs as a conventional pMDI' was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

Complaint received **7 November 2000**

Case completed **1 June 2001**

CASE AUTH/1107/11/00

GENERAL PRACTITIONER v NOVARTIS

Arrangements for audit

A general practitioner complained about difficulties which her practice had had with Novartis over an audit and a therapeutic switch for fluvastatin (Lescol).

One of the doctors in the practice had been asked whether an audit could be done of the practice's use of statins in patients with ischaemic heart disease. He was happy for an audit to be performed. Two Novartis representatives subsequently saw the practice manager to explain that they were about to perform this audit. The practice manager signed a form to give permission. Then, without any express permission from any of the partners, indeed even without any discussion between the partners, all of the patients were switched from any other statin to fluvastatin. Also, and without discussion with the practice manager or the doctor, all of the patients on any of the sartan medicines were switched to valsartan.

The complainant alleged that the letter sent out to patients was inadequate in explanation and caused alarm and despondency. The practice had lost credibility. Clearly, the practice's access to computers had been too trusting, but separate from this, Novartis needed to apologise and to investigate the actions of some of its staff.

Novartis provided full details of the audit and the activities of the staff. The company submitted from its investigations and a meeting with the practice that there were differing accounts of the exact details of the audit process. Novartis deeply regretted the experiences in the practice where company instructions had not been followed explicitly.

The Panel noted that Novartis accepted that its representatives were involved in an inappropriate conversion of patients taking any of the sartan medicines to Novartis' product Diovan (valsartan). This was not authorized by the company. In this regard the Panel considered that the representatives had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled.

With regard to the statin audit, the Panel noted that Novartis had laid down procedures such that a GP must give positive responses to four questions before a review could be considered. The Panel had not been supplied with copies of the letters sent to patients. Novartis had stated that these were not part of the programme and had agreed that the letters were inadequate for the purpose. The letters had been modelled on similar versions used by other practices involved in the audit programme. It was not clear to the Panel whether the letters were drafted by the representatives or by the practice manager. Revised audit materials included a template to help avoid problems in the future.

The Panel noted that the arrangements for the audit had led to all patients being switched from any other statin to fluvastatin. Novartis had since changed the arrangements to ensure that written consent was obtained from two general practitioners before Novartis agreed to train practice staff in conducting an audit and that the written consent of all general practitioners in a practice was obtained if any therapy changes were proposed.

The Panel considered that Novartis had not maintained a high standard in relation to the statin audit at the practice and a breach of the Code was ruled.

On balance, the Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. This was appealed by the complainant.

Upon appeal by the complainant, and with additional information before it, the Appeal Board noted that it had to decide the matter on the conduct and activities of Novartis and its employees. The arrangements within the practice were not for the Appeal Board and were not subject to the Code, but were not irrelevant to the case.

The Appeal Board noted that Novartis' medical representative and practice support specialist had not followed Novartis' instructions with regard to the statin audit. The prescribing review process required a search authorization form, which specifically stated that no therapy changes would be carried out at this stage, to be completed, and signed by two partners. A further document authorized agreed changes to patients' therapy to be performed, again signed by two partners unless the practice was dual or single-handed. The Appeal Board noted that the medical representative and the prescribing support specialist believed that they had verbal authorization for the statin switch.

The Appeal Board noted that on the day of the switch the practice manager had provided computer access to patient records for a practice administrative assistant to carry out the conversion but the assistant had subsequently been called away. The Novartis practice support specialist was left alone using the computer with the agreement of the practice manager. The practice support specialist stated that the practice manager had given him a list of patients. The complainant stated that she had not seen this list. Novartis stated that the practice support specialist felt that he was in a very difficult situation but continued with the conversion when he was left on his own. The practice support specialist carried out the statin conversion and the sartan conversion. He believed that verbal authorization had been given to perform the switches but acknowledged that he ought not to have executed the switches himself.

With regard to the letters to patients, the Appeal Board noted that the practice manager stated that she had provided the letterhead and had approved the content of the statin letter on the basis that she thought it had been pre-discussed at previous meetings. The practice manager assumed that the valsartan letter was sent with the fluvastatin letter. Novartis stated that a specimen letter produced by another surgery was shown and discussed and left

with the practice manager. It had emerged that the practice computer was unable to do a mail merge and thus the letter was produced on the personal computer of the prescribing support specialist. Novartis stated that the practice manager had photocopied the letters and this was accepted by the practice manager. The correspondence from the practice stated that at no time did the practice manager read the letters. She understood they had been approved by the partners. Novartis stated that the practice manager had said that the practice computer could not print labels. A second practice support specialist from Novartis had typed the names and addresses for labels. The practice manager had helped put the letters in envelopes. It was not disputed that the practice manager agreed to the letters being posted with the practice mail.

The Appeal Board noted that there had been a number of changes of staff in the practice during the period leading up to the audit and subsequent switch.

The Appeal Board considered that the medical representative and the practice support specialist had not followed company procedures for audits and conversions as acknowledged by Novartis. It was not acceptable for the practice support specialist to have access to patient details even if this was with the agreement of the practice manager. The Guidelines on the provision of medical and educational goods and services published in the November 1999 Code of Practice Review clearly stated that only an appropriately qualified person, for example a sponsored registered nurse not employed as a medical/generic representative, might undertake activities relating to patient contact and that neither the company nor its medical/generic representatives might be given access to data/records that could identify or could be linked to, particular patients.

The Appeal Board was concerned that the instructions to the practice support specialist were promotional in nature. The Appeal Board was also concerned that a percentage of practice support specialists' salaries, albeit a small percentage, was paid in relation to the successful transfer of appropriate patients to practice satisfaction. This was not in accordance with the Guidelines.

The Appeal Board was concerned that as a result of the activities and due to the issuing of repeat prescriptions, patients had had their medication changed from one cholesterol lowering medicine to Lescol and from a sartan medicine to Diovan without the involvement of a general practitioner. There had been no clinical evaluation. A cholesterol checking clinic had been arranged but had been cancelled. The Appeal Board noted that the results of the activities could have compromised patient safety. The Appeal Board noted that the practice acknowledged that it had made mistakes. Novartis had altered the arrangements following notification of the practice's concerns. Novartis had accepted breaches of the Code ruled by the Panel. Overall, the Appeal Board considered that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

COMPLAINT

A general practitioner complained that her practice had had difficulties with Novartis Pharmaceuticals UK Ltd over an audit and a therapeutic switch for fluvastatin (Lescol). A copy of a letter sent to Novartis was provided. Unbidden, at the same time as the audit a switch was made of patients taking any of the sartan medicines to valsartan (Novartis' product Diovan). A meeting had been held with the medical director of Novartis and the prescribing adviser to the practice's primary care group (PCG). Although an apology had been received, the practice was still unhappy about the way the 'audit' was performed.

The letter to Novartis which was provided stated that the complainant wished to register a formal complaint about the treatment that they had received from some of Novartis' staff. One of the doctors in the practice had been approached in July to ask whether he would be happy for an audit to be done of the practice's ischaemic heart disease patients with regard to their statin usage. He was very happy for an audit to be performed. The two medical representatives subsequently saw the practice manager to explain that they were about to perform this audit. The practice manager signed a form to give permission for this. Then, without any express permission from any of the partners, indeed even without any discussion between the partners, all of the patients were switched from any other statin to fluvastatin. Also, and this had not been discussed in any way either with the practice manager or the doctor, all of the patients on any of the sartan medicines were switched to valsartan.

As if this were not bad enough, the letter sent out was inadequate in explanation and caused a great deal of alarm and despondency. The practice had lost credibility and the partners were extremely cross about the way it had been handled and about the fact that it had been done without permission. Clearly, it had brought to the practice's attention that its access to computers had been entirely too trusting, but separate from this, Novartis really needed to apologise and to investigate the actions of some of its staff.

RESPONSE

Novartis stated that it was very surprised indeed to learn that a formal complaint had been made regarding the Lescol audit programme. As the complainant mentioned in her letter, the company had already been in extensive discussion with practice members regarding this matter and believed that every effort had already been taken to address the concerns which the practice had expressed in its letter to the Authority. Immediately following the original letter from the complainant to Novartis dated 19 September, its medical director responded with a letter offering both an unreserved apology and the promise of an urgent internal investigation of the events described. As a result of the initial findings of this investigation the complainant was contacted on 29 September in order to arrange a meeting with her to review in detail the complaints that had occurred.

This meeting took place on 18 October at the practice with the complainant, her two partners and two of her colleagues from the PCG. In addition to looking at the difficulties that had occurred, there was a detailed discussion of how these issues might have been avoided. Immediately after this visit Novartis suspended the entire Lescol audit programme in order to assess appropriate action and the circumstances under which it might restart.

As some 59 practices had successfully utilised the facilitation offered by the audit programme, the changes discussed at the meeting with the complainant and partners were incorporated into a draft revised programme. This amended programme was forwarded to the complainant and the PCG pharmacy advisor for their comments. Novartis' medical director then met with them both at a second meeting held at the PCG offices on 21 November. At this meeting, both the complainant and her colleague agreed that, with a few further minor clarifications, the audit programme should prove acceptable to them. Novartis was surprised therefore that the following day a complaint should be sent to the Authority.

Looking at the specific issues raised by the complainant, it was clear that the representative concerned was involved in an inappropriate conversion of sartan patients which was unauthorized by Novartis. The audit programme was directed only at the identification of patients who might be considered by a practice for a change to their statin therapy.

It was clear, however, from Novartis' initial investigations and the subsequent meeting with the practice that there were differing accounts of the exact details of the audit programme process and procedures as carried out at the practice. Whilst Novartis was indeed satisfied that the sartan switch was actually at the behest of, and authorized by, the practice manager, this was not documented and therefore could not be proven and, regardless, would not have been authorized by the company. The statin audit was also organised and supported by the practice manager on behalf of her practice colleagues. Novartis had chosen not to explore these differing accounts in a way that might prove detrimental to relationships with, and within, the practice, but instead to build in to any revised and restarted programme safeguards that would ensure that all parties were fully protected in a way that did not occur in the practice in question. These changes included, for example, the written consent of two general practitioners before Novartis agreed to train practice staff in conducting an audit and the written consent of all general practitioners in a practice should any therapy changes be proposed. Novartis was confident that this programme fully complied with Clause 18.1 of the Code and that the changes implemented as a result of the problems and misunderstandings experienced ensured that it was fully robust and that any risks of misinterpretation had been removed. Novartis deeply regretted the experiences in the practice where company instructions were not followed explicitly and could confirm that the sartan matter had been taken up formally with the representatives concerned.

Novartis provided copies of the audit programme in its original form, together with copies of the briefing materials associated with it. A copy of the letter from Novartis' medical director to the complainant dated 25 September and a second letter of 19 October following the first visit to the practice were also provided. Novartis did not have copies of the letters sent by the practice to patients referred to in the complainant's letter of 19 October, as these were not part of the programme. These letters were, however, seen and discussed at the meeting on 18 October where it was understood that they had been modelled on versions of similar letters used by other practices involved in the audit programme. Novartis agreed that these letters were inadequate for the purpose and a template had now been included in the revised audit programme materials to avoid issues of this type from occurring in the future, along with a template for advising local pharmacies.

From the above summary and enclosed materials, Novartis hoped that the Authority would appreciate that Novartis had taken the difficulties experienced extremely seriously and had worked constructively with the complainant's practice to learn from their experiences. Novartis trusted that by having done so it could ensure that any future reinstatement of the programme would avoid any similar difficulties and would accommodate and safeguard patient interests where there might be differing views within a practice. Novartis had taken urgent action, in addition, to address the erroneous sartan involvement in the programme and was confident that this would not recur whatever the circumstances within a practice.

Novartis hoped the above information and enclosures would put the events into context and reiterated that it would prefer not to enter into debate over the exact circumstances and authorizations within the practice if this could be avoided. Novartis felt, however, that it was important that the Panel be made aware that the situation was not straightforward.

PANEL RULING

The Panel noted that one of the doctors in the practice had agreed to an audit being undertaken of the practice's ischaemic heart disease patients with regard to their statin usage. The practice manager had given permission for this. The complainant stated that permission had not been obtained from the partners to switch patients from any other statin to fluvastatin. The complainant stated that without discussion either with the practice manager or the doctor all of the patients on any of the sartan medicines were switched to valsartan. The Panel noted that Novartis stated that the sartan switch had been carried out at the behest of and authorized by the practice manager.

The Panel noted that the guidelines on the provision of medical and educational goods and services, published in the Code of Practice Review in November 1999, stated that a recipient of a service must be provided with a written protocol to avoid misunderstandings as to what the recipient had agreed. Such a document might have been helpful in this case. The Panel observed that it was difficult to

know exactly what had transpired between the parties.

The Panel noted the documents supplied by Novartis. These comprised a document headed 'Novartis Prescribing Review' for internal use and what appeared to be copies of overheads entitled 'Prescribing Revision Programme' used at a training course in May. The Panel noted that Novartis accepted that its representatives were involved in an inappropriate conversion of patients taking any of the sartan medicines to Novartis' product Diovan (valsartan). This was not authorized by the company. In this regard the Panel considered that the representatives had failed to maintain a high standard of ethical conduct and a breach of Clause 15.2 of the Code was ruled.

With regard to the statin audit, the Panel noted that the 'Prescribing Revision Programme' materials included a practice selection form. The form clearly stated that a GP must give positive responses to four questions before a review could be considered, these being; was Lescol already first line for all appropriate new patients?; for appropriate patients already on other statins was the GP prepared to recommend a practice switch to Lescol?; were the practice partners likely to be amenable to a therapy switch?; was the practice willing to provide a dedicated member of staff to be trained in, and to perform the switch process? The form was to be completed and returned to the prescribing revision programme specialist.

The Panel noted that it had not been supplied with copies of the letters sent by the practice to patients. The Panel noted that Novartis stated that these were not part of the programme. Novartis had agreed that the letters were inadequate for the purpose. The letters had been modelled on similar versions used by other practices involved in the audit programme. It was not clear to the Panel whether the letters were drafted by the representatives or by the practice manager. The revised audit materials included a template to help avoid problems in the future.

The Panel noted that the arrangements for the audit in the practice in question had led to all patients being switched from any other statin to fluvastatin. Novartis had changed the arrangements to ensure that written consent was obtained from two general practitioners before Novartis agreed to train practice staff in conducting an audit and the written consent of all general practitioners in a practice should be obtained if any therapy changes were to be proposed.

The Panel considered that with regard to the arrangements for the statin audit in the practice in question, Novartis had not maintained a high standard and a breach of Clause 9.1 of the Code was ruled.

On balance the Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

APPEAL BY THE COMPLAINANT

The complainant stated that she could have sent more details with her letter of complaint but she was under the impression that more information would have been requested if further action were to be taken.

The complainant stated that the practice view was that the implication that the practice manager was responsible for much of this problem was not correct. Also, the implication that the practice wrote to the patients regarding their change of medication was not correct. Photocopies of the letters regarding valsartan and fluvastatin were provided. There was no partner's or practice manager's signature on these letters. The complainant stated that the practice would not consider sending a letter out without signing it, particularly if it was something of this importance.

The practice's belief was that the practice manager was misled, probably deliberately. The only discussion had been with one of the partners suggesting that an audit could be performed and that as a result of that the partners would discuss whether a therapeutic switch should occur. The sartan group of medicines was not mentioned at any time.

It was this misleading information which initially led to the complaint because of the implications that this might have not only within Novartis but also between other pharmaceutical companies and medical practitioners.

The complainant was seeking clarification. She did not know whether this constituted an appeal. In other respects the practice was satisfied that the Authority had adequately investigated the problem. However the practice did not wish a continued assumption of fault on its part.

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The Authority advised the complainant that the Panel's decision had been made on the information put before it by the parties. The material supplied after notification of the Panel's ruling could not be considered if there was no appeal and the case was completed at Panel level.

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The complainant stated that the practice did wish to appeal the decision of no breach of Clause 2. The complainant was sorry that her initial letter did not give all the information available. Never having made a complaint of this type before, she had assumed that any further steps would involve contacting the complainant for more detail.

The complainant stated that the implication of blame on the practice manager was incorrect. The practice manager was not involved in sending out the letters to patients, and was not aware of the letters being sent out. They were not sent from the practice, or typed in-house, or signed by any member of the practice team. They referred to sartan medicines as well as to statins. The former was at no time discussed with any member of the practice team, either with regard to an audit, or with regard to a therapeutic switch.

Copies of letters given to the complainant by disgruntled patients, sent to them 'from the practice' were provided.

The practice had discussed why it considered that it should take the matter further. It did not plan any legal action, nor did it wish financial gain, but it wanted the practice and its staff to be seen to be clearly innocent of the actions taken, save only from the initial wish to perform an audit to try to improve patient care and to strive for best value in prescribing. The complainant stated that clearly the practice was more trusting than it should have been and innocently allowed more access to records than it should have. This was not a mistake it would repeat.

RESPONSE FROM NOVARTIS

Novartis was very disappointed to learn that the complainant had chosen to appeal the Panel's ruling of no breach of Clause 2. It was Novartis' firm belief that no such breach had occurred.

Novartis had accepted that its representative was involved in inappropriate actions that were unauthorised by Novartis and to this end, Novartis had not disputed being found in breach of Clause 15.2 of the Code. In respect of Clause 9.1, the finding of breach was again not contested by Novartis. In this complex case, Novartis submitted that it was better not to highlight matters pertaining to the conduct of practice staff and accept that the Novartis process had not been adopted in this practice to the high standards expected from representatives. It was Novartis' sincere wish that such contentious matters would not need to be raised and the relationship with the practice be maintained. However, the suggestion that the representative's actions were entirely independent of practice staff and, as such, could constitute a breach of Clause 2 was not correct.

In order to address the particular area under appeal, the company clarified the course of events thus far from the Novartis' perspective. Prior to the complaint to the Authority, the company had already been in extensive discussion with practice members and considered that every effort had already been made to address the concerns which the practice expressed in its original letter of complaint. On receipt of the letter from the practice to the company, its medical director offered both an unreserved apology and the promise of an urgent internal investigation of the events described. A meeting then took place on 18 October at the practice between the medical director and the complainant, her two partners and two colleagues from the primary care group. In addition to looking at the difficulties that had occurred there was a detailed discussion of how these issues might be avoided in the future. Immediately after this visit Novartis suspended the entire Lescol audit programme in order to assess appropriate action and the circumstances under which it might restart.

Novartis submitted that the programme was revised incorporating the changes discussed with the practice members and a draft forwarded to the complainant and the PCG pharmacy advisor, for comments. Novartis' medical director then met with them both at a second meeting held at the PCG offices on 21 November. At this meeting both the complainant and her colleague agreed that with a few minor clarifications the audit programme should prove acceptable to them. Novartis was surprised and disappointed, therefore, that the following day a complaint letter should be forwarded to the Authority.

As part of the initial investigation Novartis obtained a detailed diary of events from its representative, which was subsequently confirmed and a copy was provided. It highlighted many areas which contradicted the practice claim of lack of involvement by the practice manager. One such area regarded computer access. As one would expect, the practice operated a password-protected system. Moreover, this system operated at different levels so that the most sensitive information was privy to only the most senior members of staff. On the day in question, the representative was accompanied by a practice administrator to a room where the conversion was to take place. The administrator subsequently found that she did not have the necessary clearance to carry out the conversion and so the practice manager logged on instead since she had the appropriate authority to do so. Therefore, it would not be possible for the representative to have carried out this action without the knowledge of either the practice manager or another senior member of staff.

During the course of the day, the room allocated to the conversion process was needed by the physiotherapist. The practice manager relocated the representative to the nurses room where she again logged on to the system on his behalf. In relation to the letters sent to patients regarding the proposed change of medication, the representative confirmed that these had been seen and approved by the practice manager. Moreover, owing to difficulties with the photocopier, the practice manager copied the letters herself. Finally, Novartis underlined that the representative was not responsible for posting the letters. He informed the practice that he was not allowed to take such letters out of the building and, accordingly, the practice manager agreed to post the letters herself. Novartis was not sure whether the complainant was aware of these facts and it was for that precise reason that Novartis had hitherto sought to refrain from such comment.

Novartis did not believe that the representative's actions or the company's process could be held to constitute a breach of Clause 2. With many conversions having already taken place, including a significant number by the representative in question, Novartis was confident that the programme had always complied with all of the requirements of the Code. To support the value of the conversion process in its original form, a confidential anonymised, pre-publication draft of a paper written by a participating general practitioner which gave a clear indication of the successful outcome of a similar programme was provided. Novartis submitted that this demonstrated the high standards which it continually strove to achieve. Novartis' actions following the experiences in the practice were carried out to improve an already effective and Code-compliant process rather than as a result of any issues with the process itself. As

highlighted in the original response, the issues arose because the process was not followed to the letter leading to errors on both sides.

Novartis stated that any subsequent improvements which it had incorporated into the process had been made using the advice of the practice. Most importantly, Novartis stressed that such steps were taken prior to any recourse to the Code by the practice. The changes made represented updates and improvements to a system which, if adhered to properly, would never have given rise to these most unfortunate events. Novartis deeply regretted the experiences in this practice where company instructions were not followed explicitly but was confident that this represented an isolated incident both in terms of the programme, and of the company representative involved. Indeed, from the testimonials included in this submission that the representative in question was highly regarded for his professionalism, and even in this case he acted in good faith throughout.

Novartis contended that its prompt actions in visiting the practice, suspending and amending the programme, and reprimanding the representative were not those of a company showing disregard to the reputation of the industry. In fact, Novartis submitted that it had made every effort to act in a responsible and reputable manner.

In conclusion Novartis believed that it had demonstrated that the practice claim to have had no involvement in the conversion programme, which would appear to be its basis for appeal against the Panel's ruling of no breach of Clause 2, was incorrect. Whilst Novartis would not seek to dispute that errors were committed by the company's representatives in this practice, it did not accept the practice's claim of lack of involvement. It was clear from its investigations that the practice manager was party to the conversion programme taking place in the practice and was instrumental in the approval, photocopying and mailing of the letters sent to patients. Novartis regretted having to detail these events and realised that this might cause some distress within the practice. However, it had proved unavoidable in the face of such serious allegations.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the letter from Novartis responding to the appeal was particularly helpful. Although the practice had received an apology from Novartis and it had worked with the company to avoid such a problem arising in the future, it had not received a full explanation of how the problem arose. The practice was therefore unable to understand how such changes could have occurred without discussion with the partners. The practice's suggestion to the Authority was therefore that the representative's actions were independent of the partners, and that the practice staff had been misled to believe that the partners were in full agreement with the changes when in fact this was not so.

Certainly following the initial complaint the discussions with Novartis' medical director were clearly seen as an attempt by the company to avoid any such events in the future. However, what Novartis failed to address was how this had happened. The practice accepted Novartis' apology and statement that its representatives had not followed procedure, but the practice was still unable to understand how such a breach of procedure had occurred. The practice was not happy with the implication of blame on practice staff. The complainant and the PCG prescribing advisor had met again with the medical director and were content that action had been taken to avoid future problems, but the reason for the appeal was that the practice was still unable to understand what had gone wrong initially.

The complainant stated that one area of great concern was the implication of blame on the practice manager. The practice accepted that the practice manager was very much involved in helping the representative to access information on the practice computer. However, the practice's understanding was that she had been misled to believe that this was an audit and not a therapeutic switch. The complainant stated that the practice staff were all also unable to understand why letters would go out on the practice's behalf unsigned by any partners or staff from the practice.

Detailed comments on Novartis' sequence of events were provided. The practice agreed with many of the points made by Novartis.

The practice stated that the practice manager was contacted several times in June and was told that the audit needed to be soon as the representatives were only working in the area for a further two weeks. She pointed out that this was inconvenient to the practice but pressure was exerted to conduct the audit soon. She understood this to be an audit; no authorization for a therapeutic switch was made by her. On 28 June, the practice manager came in to the practice to conclude details of the audit. She was told that any changes would be made with the full agreement of the doctors. Discussion of savings from a switch to valsartan were made. The understanding was that this was to be discussed with the partners and might go ahead thereafter.

On 13 July the practice manager gave the numbers of patients on sartan medicines as she was told this had the agreement of the partners for an audit. It had in fact not been discussed with any of the partners. She did not give permission for patients to be converted to valsartan.

On 25 July there was a discussion about the format of letters for patients. The complainant stated that the practice manager understood this to be letters to be used in the future after full agreement with the doctors.

On 27 July the staff were told that the conversion had been fully agreed with the partners. At this time one of the partners was about to return from leave and the complainant had just started her leave so that there were an unusual number of locums in the practice.

The complainant stated that the error in the practice was that the staff were too trusting and also that they were not in the room and themselves performing all changes. In this respect the practice was at fault.

Two years previously the practice had performed an audit of proton pump inhibitors with the help of the health authority's prescribing advisor working with one of the partners. This was performed partly by a co-opted member of staff. It was as a result of this that the practice manager had not understood the exact role of the Novartis representatives. However, she was repeatedly led to believe that all actions were undertaken with the full agreement and permission of the partners.

With regard to photocopying and posting of letters, the practice manager said that she did not read the letters, she told the complainant that she received a bundle of letters in envelopes and offered to post them with the practice mail.

The complainant stated that during early August the practice worked hard to remedy the changes. The statin switch, however, involved so many patients that it was decided to accept it even though it was not performed on the practice's behalf. Attempts were made to contact the representatives and the company, but no adequate explanation or contact was received for some six weeks. At this stage a formal complaint was made.

On 22 November, although an apology had been received and steps had been taken to avoid such a problem in the future, the practice still did not feel reassured that it understood how these changes could have occurred. In particular the practice staff had been misled.

The complainant stated that the practice therefore resented the implication of blame on the practice manager. She was helpful and co-operative, as the staff were. She clearly did allow access to the computer system, but was repeatedly assured that the actions taken were with the full agreement and on behalf of the partners. This was not an error which would be repeated by any of the staff as it had been a singularly painful learning experience. The practice had lost credibility and goodwill with the patients, when the initial objective was to assess more cost-effective prescribing and to establish a coronary heart disease register.

The practice was satisfied that Novartis had acted appropriately to avoid future problems and that since the complaint the company had acted in a responsible and reputable manner. The practice had accepted that it was only the misguided, overzealous, or possibly malicious action of one or two members of Novartis staff which had caused the problems. However, the practice considered that its staff were misled and given false assurances. The staff were too trusting and allowed inappropriately supervised access to the computer system. The staff were party to the audit, photocopying and mailing, but not to the approval for the conversion.

The complainant stated that realising the serious implications of such a chain of events and the implications for other practices and the pharmaceutical industry, it felt obliged to take recourse by making a complaint because the practice considered that the details had not been adequately dealt with, even though procedures for the future had been changed appropriately.

APPEAL BOARD RULNG

The Appeal Board noted that it had to decide the matter on the conduct and activities of Novartis and its employees. The arrangements within the practice were not for the Appeal Board and were not subject to the Code but were not irrelevant to the case. Clause 15.10 of the Code stated that companies were responsible for the activities of their representatives.

The Appeal Board noted that the medical representative and the practice support specialist had not followed Novartis' instructions with regard to the statin audit. The Novartis prescribing review process required a search authorization form to be completed. This was to be signed by two partners and specifically stated that no therapy changes would be carried out by the Novartis prescribing review specialist at this stage. A further document, the therapy change authorization, authorized agreed changes to patients' therapy to be performed according to a table provided. The table would be completed with the medicine name, dose and details of the new medicine and dose. The form was to be signed by two partners unless the practice was dual or single-handed. The Appeal Board noted that the medical representative and the prescribing support specialist believed that they had verbal authorization for the statin switch.

The Appeal Board examined the information provided by the parties. Novartis stated that in February 2000 the Prescribing Revision Programme was being carried out by Baker Norton. One of its representatives had left a form to be signed for permission to do a search. This had been signed by a doctor and a copy later seen by the medical representative. (At the appeal hearing the representatives stated that the form had been signed by both that doctor and by a partner.) The medical representative stated that the Baker Norton search had identified a number of patients taking statins. After 18 February the process set in motion by Baker Norton was put on hold due to cancellation of a lunchtime meeting. Novartis stated that the Prescribing Revision Programme was brought in house in March 2000 and all Baker Norton involvement ceased. Novartis stated that the Novartis medical representative had met with one of the partners on 4 May. The partner had agreed a review of statin patients and confirmed that he would contact the other partners. On 12 June Novartis stated that its representative had called on the practice manager who had confirmed that she was keen to carry out the review and transfer of appropriate statin patients to Lescol. She would discuss and confirm with the practice GPs. Potential cost savings of transferring existing sartan patients to valsartan was also discussed. On 28 June the representative and the practice support specialist met with the practice manager to conclude arrangements for the transfer of appropriate patients from other statins to Lescol and to agree patients that might be transferred to Diovan. The complainant stated that on 12 June the practice manager had understood that she had agreed to an audit. No authorization for a therapeutic switch was given by her. On 28 June she had been told that any changes would be made with the full agreement of the doctors. Discussion of savings from a switch to

Diovan was made and the understanding was that this was to be discussed with the partners and might go ahead thereafter.

The Appeal Board noted that on the day of the switch, 27 July, the practice manager had provided computer access to patient records for a practice administrative assistant to carry out the conversion who had subsequently been called away. The practice support specialist was left alone using the computer with the agreement of the practice manager. The practice support specialist stated that the practice manager had given him a list of patients. The complainant stated that she had not seen this list. Novartis stated that the practice support specialist felt that he was in a very difficult situation but continued with the conversion when he was left on his own. The practice support specialist carried out the statin conversion and the sartan conversion. He believed that verbal authorization had been given to perform the switches but acknowledged that he ought not to have executed the switches himself.

With regard to the letters to patients, the Appeal Board noted that the practice manager stated that she had provided the letterhead and had approved the content of the statin letter on the basis that she thought it had been pre-discussed at previous meetings. The practice manager assumed that the valsartan letter was sent with the fluvastatin letter. Novartis stated that a specimen letter produced by another surgery was shown and discussed and left with the practice manager. On 27 July it emerged that the practice computer was unable to do a mail merge and thus the letter was produced on the personal computer of the prescribing support specialist. Novartis stated that the practice manager had photocopied the letters and this was accepted by the practice manager. The correspondence from the practice stated that at no time did the practice manager read the letters. She understood they had been approved by the partners. Novartis stated that the practice manager had said that the practice computer could not print labels. A second practice support specialist from Novartis had typed the names and addresses for labels. The practice manager had helped put the letters in envelopes. It was not disputed that the practice manager agreed to the letters being posted with the practice mail.

The Appeal Board noted that there had been a number of changes of staff in the practice during the period leading up to the audit and subsequent switch. One doctor had gone on maternity leave, two practice nurses had left and on the day of the switch two of the partners were on leave.

The Appeal Board considered that the medical representative and the practice support specialist had not followed company procedures for audits and conversions as acknowledged by Novartis. It was not acceptable for the practice support specialist to have access to patient details even if this was with the agreement of the practice manager. The position in this regard was clearly stated in the Guidelines on the provision of medical and educational goods and services published in the November 1999 Code of Practice Review. Paragraph 1(iv) stated that only an appropriately qualified person, for example a sponsored registered nurse not employed as a medical/generic representative, might undertake activities relating to patient contact. Paragraph 1(v) stated that neither the company nor its medical/generic representatives might be given access to data/records that could identify. or could be linked to, particular patients.

The Appeal Board was concerned that the instructions to the practice support specialist were promotional in nature. In this regard it was noted that phrases such as 'to sell Lescol 40mg with passion and belief' and 'ensuring leads turned into Lescol switches' were used in the training materials. The Appeal Board was also concerned that a percentage of practice support specialists' salaries, albeit a small percentage, was paid in relation to the successful transfer of appropriate patients to practice satisfaction. This was not in accordance with the Guidelines on the provision of medical and educational goods and services.

The Appeal Board was concerned that as a result of the activities and due to the issuing of repeat prescriptions, patients had had their medication changed from one cholesterol lowering medicine to Lescol and from a sartan medicine to Diovan without the involvement of a general practitioner. There had been no clinical evaluation. A cholesterol checking clinic had been arranged for 15 July but had been cancelled. The Appeal Board noted that the results of the activities could have compromised patient safety. The Appeal Board noted that the practice acknowledged that it had made mistakes. Novartis had altered the arrangements following notification of the practice's concerns. Novartis had accepted breaches of Clauses 9.1 and 15.2 of the Code. Overall, the Appeal Board considered that Novartis had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled. The appeal was successful.

Complaint received **27 November 2000**

Case completed **13 June 2001**

CASE AUTH/1121/1/01

SMITHKLINE BEECHAM v TAKEDA

Promotion of Actos

SmithKline Beecham complained about the promotion of Actos (plioglitazone) by Takeda. Actos was indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea: in combination with metformin only in obese patients and in combination with a sulphonylurea only in patients who showed intolerance to metformin or for whom metformin was contraindicated. SmithKline Beecham produced a competitor product Avandia (rosiglitazone) which had a similar licensed indication.

SmithKline Beecham stated that it had been brought to its attention that Takeda representatives were claiming that Actos was significantly cheaper than Avandia. A letter from a general practitioner which highlighted this practice was provided. It was clear that Takeda representatives were implying that Avandia's usual maintenance dose was 8mg on the grounds that most patients were not controlled on 4mg and they were subsequently comparing the cost of Avandia 8mg with their promoted dose of Actos 30mg. The licensed dose for Avandia was 4mg, which could be increased to 8mg/day after 8 weeks in combination with metformin. It was therefore misleading to imply that most patients would be maintained on Avandia 8mg. Current Avandia data revealed that 95% of tablets prescribed were for 4mg. In the product appraisal by the National Institute for Clinical Excellence (NICE) of Avandia it was estimated that 75% of patients would receive 4mg daily in the UK. SmithKline Beecham alleged that this activity was disparaging as it implied Avandia lacked efficacy at 4mg in contradiction to the summary of product characteristics (SPC). To assume all patients were on Avandia 8mg and then make cost comparisons with Actos 30mg was misleading and this comparison could not be substantiated. This representative activity was inaccurate, misleading and disparaging and Takeda representatives were failing to maintain a high standard of ethical conduct. SmithKline Beecham also alleged there was a breach of Clause 2 as this activity brought the industry into disrepute. The Panel noted that the letter of complaint from a general practitioner addressed to SmithKline Beecham stated that a Takeda representative had given the impression that Actos was substantially cheaper than Avandia. This was based on the premise that the dose of Avandia was 8mg rather than 4mg/day. The effect of this was that the cost of Actos was about £36 per month as opposed to about £56 for Avandia. The GP concerned wanted to remain anonymous to Takeda and thus it was not possible for Takeda to identify its representative and investigate. In such circumstances the Panel could not determine where the truth lay. The Panel ruled no breach of the Code in this regard. The Panel did not consider that there was evidence to support the general allegation that Takeda representatives were implying that the usual maintenance dose of Avandia was 8mg as most patients were not controlled on 4mg and that they were subsequently comparing the cost of Avandia 8mg with Actos 30mg. The Panel ruled no breach of the Code.

The statement 'And because it's Actos, this advanced drug offers additional glycaemic control in combination with metformin or a sulphonylurea, with favourable effects on the lipid profile' appeared in a journal advertisement. SmithKline Beecham alleged that the statement was misleading as it failed to reflect the Actos SPC which stated that Actos should only be used in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy in combination with metformin in obese patients and in combination with a sulphonylurea in patients who showed intolerance to metformin or for whom metformin was contraindicated. Takeda's response was that the statement was consistent with the SPC but SmithKline Beecham considered that the impression from the advertisement was that Actos could be used in any patient with type 2 diabetes on metformin or a sulphonylurea. SmithKline Beecham therefore believed that this advertisement was misleading. The Panel noted that the advertisement featured the main claim 'Announcing a major breakthrough in insulin resistance' and discussed features of Actos including the statement at issue. The advertisement concluded 'That means a major breakthrough has indeed occurred in Type 2 diabetes'. The strapline read 'Tough on Type 2 diabetes. Friendly to lipids'. The Panel considered that the journal advertisement failed to make it clear that Actos was indicated for use as add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the advertisement was that Actos could be used in any patient with type 2 diabetes and that was not so. The Panel did not accept Takeda's submission regarding the fact that the full indication was given in the prescribing information. It was an established principle under the Code that a misleading claim or impression could not be corrected by reference to the prescribing information. The Panel considered the advertisement misleading and a breach of the Code was ruled.

A leavepiece featured a flow chart entitled 'When to prescribe Actos'. There were two starting points, sulphonylurea treated patient and metformin treated patient. The first arm of the flow chart indicated that Actos 30mg od should be added to sulphonylurea treated patients in whom metformin was contraindicated or not tolerated and whose HbA1c > 7%; the second arm indicated that Actos 30mg od should be added to metformin treated patients who were obese and whose HbA1c > 7%. SmithKline Beecham stated that the flow chart was not in keeping with the Actos SPC, as it did not state that the product was indicated in oral combination in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea. Insufficient information had been

given and the material was misleading as it implied that Actos could be used beyond its licensed indications in type 2 diabetes. The Panel considered that its ruling at the second point above was relevant here. The flow chart created the impression that Actos was indicated for any patient taking a sulphonylurea in whom metformin was contraindicated or not tolerated or in any obese patients taking metformin. It did not state that patients should be inadequately controlled on maximal doses of metformin or a sulphonylurea. Insufficient detail had been given. The only mention of maximal tolerated doses was in the prescribing information. In the Panel's view this should have been stated on the chart. The flow chart was misleading and a breach of the Code was ruled.

A page of a leavepiece entitled 'New Actos. Questions and answers' included the question 'Does Actos continue to be effective in the long term?'. The answer described a 40 week open study where the glycaemic control seen with Actos combined with a sulphonylurea or metformin was sustained in the long-term. SmithKline Beecham pointed out that Takeda claimed in this section that Actos was effective in the long-term. This was based on 40 week data. In the context of type 2 diabetes which was a chronic disease process with up to an average duration of 9.1 years from diagnosis, SmithKline Beecham considered that an effect less than one year should not be deemed to be long-term. The Actos SPC stated that 'The long-term benefits with pioglitazone have not been demonstrated'. SmithKline Beecham therefore alleged that to claim that Actos had long-term effects was misleading and was not consistent with the SPC. In the Panel's view the question at issue related to the efficacy of the product with regard to day-to-day metabolic control. The answer clearly stated that over 40 weeks glycaemic control was sustained. The SPC stated that 'Experience from clinical trials with pioglitazone is currently limited to 18 months. The long-term benefits of therapy with pioglitazone have not been demonstrated (see section 5.1)'. Section 5.1 stated that 'An outcome study has not been conducted with pioglitazone, and therefore the long-term benefits associated with improved metabolic control have not been demonstrated'. In the Panel's view long-term benefit related to the prevention of diabetic complications, not to day-to-day glycaemic control. The Panel did not consider that the answer to the question was inconsistent with the SPC or misleading as alleged; the question related to day-to-day metabolic control and the SPC referred to long-term outcomes. The answer clearly stated the duration of the study. No breach of the Code was ruled. Upon appeal by GlaxoSmithKline, the Appeal Board noted that each case was considered on its own merits. It was not acceptable for the phrase 'long term' to be defined as there were many variables, not least the therapeutic area. The Appeal Board noted that the question 'Does Actos continue to be effective in the long term' was answered clearly by stating that over 40 weeks glycaemic control was sustained. The Appeal Board noted the relevant statements in the SPC. It did not consider that the answer to the question was misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of the Code.

SmithKline Beecham Pharmaceuticals complained about the promotion of Actos (pioglitazone) by Takeda UK Limited.

Actos was indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea: in combination with metformin only in obese patients and in combination with a sulphonylurea only in patients who showed intolerance to metformin or for whom metformin was contraindicated. SmithKline Beecham produced Avandia (rosiglitazone) which had a similar licensed indication.

1 Representative activity

COMPLAINT

SmithKline Beecham stated that it had been brought to its attention that Takeda representatives were claiming that Actos was significantly cheaper than Avandia. This had been reported to it by a number of its representatives who had been challenged by GPs following a detail from one of Takeda's representatives. A letter from a GP which highlighted this practice was provided.

SmithKline Beecham stated that it was clear that Takeda representatives were implying that Avandia's usual maintenance dose was 8mg on the grounds that most patients were not controlled on 4mg and they were subsequently comparing the cost of Avandia 8mg with their promoted dose of Actos 30mg.

Actos was licensed in the UK at 15mg and 30mg doses. However there were no data on the use of 15mg Actos with metformin and Takeda was only promoting the 30mg dose to doctors in the UK, eg in press advertisements and booklets. SmithKline Beecham referred to a Takeda booklet entitled 'New Actos. Questions and answers' (Ref AC00906) produced for UK doctors, which stated on the front cover '30mg once daily' and the answer to 'What is the dose of [Actos]?' in the booklet which was 'One [Actos] 30mg tablet once daily irrespective of mealtimes'.

The licensed dose for Avandia was 4mg, which could be increased to 8mg / day after 8 weeks in combination with metformin. It was therefore misleading to imply that most patients would be maintained on Avandia 8mg.

Current UK IMS Health data for Avandia revealed that 95% of tablets prescribed were for 4mg.

On the basis of the above licence, in the product appraisal by the National Institute for Clinical Excellence (NICE) of Avandia it was estimated that 75% of patients would receive 4mg daily in the UK.

SmithKline Beecham stated that it had been informed by Takeda that it had no evidence to suggest its representatives were making comparisons of Avandia 8mg with Actos 30mg or that Avandia was ineffective at 4mg. From the letter from a GP it was clear that

this was indeed what they had been doing.

SmithKline Beecham alleged that this activity was disparaging as it implied Avandia had lack of efficacy at 4mg in contradiction to the summary of product characteristics (SPC). SmithKline Beecham alleged a breach of Clause 8.1.

SmithKline Beecham alleged that to assume all patients were on Avandia 8mg and then make cost comparisons with Actos 30mg was misleading in breach of Clause 7.2. SmithKline Beecham alleged that this comparison could not be substantiated and was therefore in breach of Clause 7.3.

SmithKline Beecham alleged breaches of Clauses 15.1 and 15.2 as this representative activity was inaccurate, misleading and disparaging and Takeda representatives were failing to maintain a high standard of ethical conduct.

SmithKline Beecham also alleged there was a breach of Clause 2 as this activity brought the industry into disrepute as general practitioners were being intentionally misadvised by representatives of a pharmaceutical company.

RESPONSE

Takeda stated that it had not received any letters from any GPs expressing concern about the conduct of a Takeda representative with respect to the promotion of Actos.

It was puzzled by the letter sent to SmithKline Beecham from the GP on 27 November 2000, which was not sent to Takeda, and the interpretation of this letter by SmithKline Beecham. The GP had not asserted that its representative had suggested that Avandia 4mg was ineffective or that claims for the relative efficacy of Actos 30mg and Avandia 8mg were made. The GP had only stated that he/she was given the impression that Actos was 'substantially cheaper' than Avandia based on the comparison of the top doses of the two products – 30mg for Actos and 8mg for Avandia. The GP stressed that this was not based on written documentation but was verbal information. It was clear that the GP knew the SmithKline Beecham representative, yet had not named the representative from Takeda so Takeda had been unable to investigate the complaint by individual interview with the representative. If Takeda could be made aware of the name of the representative who saw the GP it might be able to provide additional information before the case was reviewed.

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

Actos was licensed and available at two doses. The range of cost for the two doses 15mg and 30mg was £26.60 – £36.96 for 28 days' treatment.

Takeda stated that Avandia was licensed and available at two doses in combination with metformin and licensed and available at one dose in combination with sulphonylureas. The range of cost for the two doses 4mg and 8mg was £26.60 – £53.20 (or up to £54.60 using the 8mg tablet) for 28 days.

Takeda provided copies of 'The Actos Resource Folder' which was available at the launch of Actos and the briefing material about Avandia which was sent to all representatives after the initial letter from SmithKline Beecham and requested that these documents remain confidential. They gave factual information about the range of prices of the two medicines. The briefing materials did not make the claims that Actos was cheaper than Avandia, as SmithKline Beecham had suggested.

In combination with sulphonylurea, Avandia could be prescribed only at a dose of 4mg once daily in the UK. As the 2mg tablet had not been made available it was appropriate to consider only the data from the trials of rosiglitazone 4mg od which was available, was the marketed dose and currently the most widely prescribed dose. The only clinical trial evaluating this dose showed a reduction in HbA1c of –0.8%. Although Takeda had made clear in briefing materials that there were no direct comparisons of Actos with Avandia, from trials in combination with sulphonylurea it had seen that Actos 15mg led to a reduction in HbA1c of –0.9% and Actos 30mg had led to reductions of –1.3%. From the data available on doses that could be prescribed in the UK it seemed that Actos 15mg and Avandia 4mg od gave comparable efficacy. Takeda had not suggested to representatives that Avandia 4mg was ineffective.

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

Takeda submitted that it had not made a comparison of Actos 30mg with Avandia 8mg as SmithKline Beecham had suggested.

The data sent by SmithKline Beecham to support the claim that 95% of patients were maintained on 4mg od showed that in November 2000 95% of prescriptions were for Avandia 4mg tablets. However it was not possible from this information to be sure whether the 4mg tablets were being taken once or twice daily. As the 8mg tablet was more expensive than two 4mg tablets doctors might prescribe 2 x 4mg of Avandia if the patients required 8mg Avandia daily. It might be anticipated that as Avandia had only been available since July 2000 that there would be increased prescribing of 8mg daily, as the SPC recommended that patients should be initiated on 4mg Avandia and the dose increased after 8 weeks of treatment if there was insufficient glycaemic control. It was pertinent to consider the US experience of the patients taking combination therapy. Recent data from IMS from September 2000 (which was after the medicine had been available for over one year) indicated that 61% of patients receiving combination therapy of Avandia with metformin were prescribed 8mg per day or 55% of patients taking Avandia with sulphonylurea received 8mg per day. This meant that in the US most patients receiving Avandia as combination with

metformin or sulphonylurea were prescribed the 8mg dose. NICE had predicted that 25% of patients would be maintained on Avandia 8mg daily and the average annual cost for Avandia would be £430. The NICE review for Actos was due to be completed and made public in February 2001.

Currently it was hard to predict accurately what proportion of patients would be maintained on each dose as neither product had been available for long enough in the UK for the prescribing patterns to be established. But Takeda anticipated that for both Actos and Avandia some patients would receive the highest recommended doses.

In the briefing materials for Actos there was no suggestion that Takeda was encouraging representatives to suggest that Actos was significantly cheaper than Avandia, Avandia 4mg was ineffective, or comparison of Actos 30mg with Avandia 8mg.

The GP had not suggested in the letter that a Takeda representative made an assumption that all patients would be maintained on Avandia 8mg or that Avandia 4mg was ineffective.

Takeda did not believe and had seen no evidence to suggest that its representatives had been making disparaging claims about lack of efficacy of Avandia 4mg and so it believed that it had not breached Clause 8.1 of the Code.

It had not made any assumption that all patients would take Avandia 8mg and all cost information given to its representatives had given a fair representation of the range of costs of the range of available doses so it believed that it had not breached Clause 7.2 of the Code.

It had seen no evidence that its representatives were giving inaccurate, misleading or disparaging information about Avandia and believed that they were maintaining a high standard of ethical conduct so had not breached Clauses 15.1 and 15.2 of the Code.

PANEL RULING

The Panel noted that according to its SPC the licensed dosage of Actos, in combination with metformin or a sulphonylurea, was 15mg or 30mg once daily. The Avandia SPC stated that therapy was usually initiated at 4mg/day; in combination with metformin that dose could be increased to 8mg/day after 8 weeks if greater glycaemic control was required. There was currently no experience of doses above 4mg/day in combination with sulphonylureas. The Panel noted that the daily cost of the lowest doses of both products was the same 95 pence (£26.60/28 days' treatment). The daily cost of Actos 30mg was £1.32 (£36.96/28 days' treatment) while the daily cost of Avandia 8mg was £1.90 (£53.20/28 days' treatment) if 4mg tablets were used or £1.95 (£54.60/28 days' treatment) if 8mg tablets were used.

The Panel noted it had been provided with two pages from a representatives briefing document dated October 2000. The briefing material referred to page 15 of a promotional item, the Actos Resource Folder. It was stated that the cost of Actos ranged between 95p – £1.32 per day and Avandia between 95p – £1.95 per day. In combination with a sulphonylurea it was stated that although there were no direct comparative studies, results from separate studies suggested that 15mg Actos and 4mg Avandia were comparable in efficacy and price. For a relatively small price premium a greater reduction in HbA1c plus improvements to patients' lipid profiles could be achieved with 30mg Actos. In combination with metformin it was stated that the maximum dose of Avandia was 8mg at a cost of £1.90/£1.95 per day. It was not stated in the two pages provided that patients should be started on 4mg daily and the dose increased to 8mg daily only if greater glycaemic control was required. The briefing material stated that the maximum dose of Actos was 30mg at a cost of £1.32 per day.

A memorandum dated 8 December to, *inter alia*, the field force headed 'Questions about competitor products' dated December 2000 stated the licensed indication and dosage of Avandia. A section headed 'Efficacy' stated that 'There is no head to head study of efficacy for Actos and [Avandia] so no comparison of equivalent doses can be made'.

The Panel noted the letter of complaint from a general practitioner addressed to SmithKline Beecham stated that a Takeda representative had given the impression that Actos was substantially cheaper than Avandia. This was based on the premise that the dose of Avandia was 8mg rather than 4mg/day. The effect of this was that the cost of Actos was about £36 per month as opposed to about £56 for Avandia. The GP stated that this was based on verbal information. The Panel noted that the GP concerned wanted to remain anonymous to Takeda and thus it was not possible for Takeda to identify its representative and investigate the specific circumstances which gave rise to this specific allegation. In such circumstances the Panel could not determine where the truth lay. The Panel ruled no breach of Clauses 15.1, 15.2 and 8.1 of the Code in this regard.

The Panel did not consider that there was evidence to support the general allegation that Takeda representatives were implying that the usual maintenance dose of Avandia was 8mg as most patients were not controlled on 4mg and they were subsequently comparing the cost of Avandia 8mg with Actos 30mg. The Panel noted its comments above on the memorandum and representatives' briefing material. The Panel ruled no breach of Clauses 15.1, 15.2, 8.1 and 2 of the Code.

2 Actos journal advertisement AC00801a

The following statement appeared in the advertisement: 'And because it's Actos, this advanced drug offers additional glycaemic control in combination with metformin or a sulphonylurea, with favourable effects on the lipid profile'

COMPLAINT

SmithKline Beecham alleged that the statement was misleading as it failed to reflect the Actos SPC which stated that Actos should only be used in patients with

insufficient glycaemic control despite maximal tolerated doses of oral monotherapy in combination with metformin in obese patients and in combination with a sulphonylurea in patients who showed intolerance to metformin or for whom metformin was contraindicated.

Takeda's response was that the statement was consistent with the SPC. However SmithKline Beecham stated that the impression from the advertisement was that Actos could be used in any patient with type 2 diabetes on metformin or a sulphonylurea.

SmithKline Beecham therefore believed that this advertisement was misleading and in breach of Clause 7.2.

RESPONSE

Takeda pointed out that the advertisement contained the prescribing information as was required by the Code, which gave the indication for Actos in full. The prescribing information was on the same page as all other text, and clear for all prescribers.

The statement was supported by clinical trials in which Actos had been shown to give significant reductions in HbA1c in combination with metformin or sulphonylurea. In addition to the effects on glycaemic control Actos had been shown to reduce total plasma triglycerides and increase HDL cholesterol (Actos SPC).

Takeda believed that the statement within the text was consistent with the licensed indications for Actos and the full licensed indication appeared prominently on the facing page and so this was not misleading and not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the advertisement featured the main claim 'Announcing a major breakthrough in insulin resistance' and discussed features of Actos including the statement at issue. The advertisement concluded 'That means a major breakthrough has indeed occurred in Type 2 diabetes'. The strapline read 'Tough on Type 2 diabetes. Friendly to lipids'. The Panel considered that the journal advertisement failed to make it clear that Actos was indicated for use as add on therapy for patients inadequately controlled on maximal doses of metformin or a sulphonylurea. The impression from the advertisement was that Actos could be used in any patient with type 2 diabetes and that was not so. The Panel did not accept Takeda's submission regarding the fact that the full indication was given in the prescribing information. The Panel noted that it was an established principle under the Code that a misleading claim or impression could not be corrected by reference to the prescribing information.

The Panel considered the advertisement misleading as alleged and a breach of Clause 7.2 was ruled.

3 Leavepiece AC00905

Page three of the four-page leavepiece featured a flow chart entitled 'When to prescribe Actos'. There were two starting points, sulphonylurea treated patient and metformin treated patient. The first arm of the flow chart indicated that Actos 30mg od should be added to sulphonylurea treated patients in whom metformin was contraindicated or not tolerated and whose HbA1c > 7%; the second arm indicated that Actos 30mg od should be added to metformin treated patients who were obese and whose HbA1c > 7%.

COMPLAINT

SmithKline Beecham stated that the flow chart was not in keeping with the Actos SPC, as it did not state that the product was indicated in oral combination in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea. SmithKline Beecham alleged that insufficient information had been given and the material was misleading as it implied that Actos could be used beyond its licensed indications in type 2 diabetes and was therefore in breach of Clause 7.2.

RESPONSE

Takeda stated that the flow chart summarised the areas where Actos could be used. The full indication was included overleaf in the prescribing information.

The flow chart showed that patients who were already on a sulphonylurea whose HbA1c remained greater than 7% and in whom metformin was contraindicated or not tolerated could be treated with Actos 30mg added in to the existing therapy. It also showed that patients who were already on metformin and were obese could have Actos 30mg added to existing therapy. Takeda believed that the flow chart reflected the meaning of the licensed indication, and the anticipated clinical practice where doctors would routinely increase the first agent used to the maximal tolerated dose before adding in another agent.

Takeda believed that the flow chart was consistent with the licensed indications for Actos, it was not misleading and thus not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that its ruling at point 2 above was relevant here.

The flow chart created the impression that Actos was indicated for any patient taking a sulphonylurea in whom metformin was contraindicated or not tolerated or in any obese patients taking metformin. It did not state that patients should be inadequately controlled on maximal doses of metformin or a sulphonylurea. Insufficient detail had been given. The only mention of maximal tolerated doses was in the prescribing information. In the Panel's view this should have been stated on the chart. The flow chart was misleading as alleged. A breach of Clause 7.2 was ruled.

4 Leavepiece entitled 'New Actos. Questions and answers' (ref AC00906)

SmithKline Beecham referred to page 7 of this 12 page leaflet. The page included the question 'Does Actos

continue to be effective in the long term?'. The answer described a 40 week open study where the glycaemic control seen with Actos combined with a sulphonylurea or metformin was sustained in the long-term. The section was referenced to data on file, Takeda UK Ltd.

COMPLAINT

SmithKline Beecham pointed out that Takeda claimed in this section that Actos was effective in the long term. This was based on 40 week data. In the context of type 2 diabetes which was a chronic disease process with up to an average duration of 9.1 years from diagnosis, SmithKline Beecham considered that an effect less than one year should not be deemed to be long-term.

SmithKline Beecham noted that the Actos SPC in section 4.2 stated that 'The long-term benefits with pioglitazone have not been demonstrated'.

SmithKline Beecham therefore alleged that to claim that Actos had long-term effects was misleading and in breach of Clause 7.2. SmithKline Beecham also believed that it was in breach of Clause 3.2 as this promotion was not consistent with the particulars listed in its SPC.

RESPONSE

Takeda stated that the data contained in the answer stated clearly that the information was from a 40 week open study. The data in these studies had been published where it was referred to as long-term data. In addition, continued long-term extension data had now been published for over one year and the SPC for Actos referred to data from 60 weeks and 18 months.

It appeared that SmithKline Beecham might have misread the SPC for Actos, which included the statement 'Experience from clinical trials with pioglitazone is currently limited to 18 months'. This appeared immediately before the sentence quoted by SmithKline Beecham which clearly referred the prescriber to another statement in section 5.1 'An outcome study has not been conducted with pioglitazone, and therefore long-term benefits associated with improved metabolic control have not been demonstrated'. There had been no claims in the Actos promotional materials to suggest that long-term outcomes had been studied.

Takeda believed that the information in response to the question 'Does Actos continue to be effective long term?' was consistent with the SPC, fair, balanced and unambiguous so was not in breach of Clauses 7.2 or 3.2 of the Code.

PANEL RULING

In the Panel's view the question 'Does Actos continue to be effective in the long term' related to the efficacy of the product with regard to day-to-day metabolic control. The answer clearly stated that over 40 weeks glycaemic control was sustained.

The Panel noted that Section 4.2 of the Actos SPC headed 'Posology and method of administration' stated that 'Experience from clinical trials with pioglitazone is currently limited to 18 months. The long-term benefits of therapy with pioglitazone have not been demonstrated (see section 5.1)'. Section 5.1 stated that 'An outcome study has not been conducted with pioglitazone, and therefore the long-term benefits associated with improved metabolic control have not been demonstrated'. In the Panel's view long-term benefit related to the prevention of diabetic complications, not to day-to-day glycaemic control.

The Panel did not consider that the answer to the question was inconsistent with the SPC or misleading as alleged; the question related to day-to-day metabolic control and the SPC referred to long-term outcomes. The answer clearly stated the duration of the study. No breach of Clauses 3.2 and 7.2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline noted that in the original complaint made by SmithKline Beecham it was alleged that a duration of 40 weeks did not constitute 'long-term' data. In its ruling, the Panel disagreed on this point, basing its finding on the fact that the duration of the study was clearly cited in the leavepiece.

GlaxoSmithKline stated that regardless of whether or not the duration of a trial was cited in a particular piece, there must be a lower limit at which data could be classified as 'long-term', especially in a chronic, lifelong and progressive condition such as diabetes mellitus. While, to its knowledge, no specific ruling on this issue has previously been made, it believed that the tacit assumption throughout the industry and the medical community had been that this lower limit was at least 52 weeks; and, therefore, that in claiming long-term status for 40 week data, Takeda was presenting misleading information in breach of Clause 7.2 of the Code.

Given the nature of the appeal, GlaxoSmithKline stated that it was not possible to produce any documentation in support of its position. It nevertheless asked that the issue be referred to the Appeal Board as a 'test case' on the appropriate use of the terminology at issue.

RESPONSE FROM TAKEDA

Takeda believed that the data presented was accurate, fair, balanced, objective, unambiguous and reflected the up-to-date evidence clearly.

The text adjacent to the question in the leavepiece clearly stated that the effect of pioglitazone on glycaemic control was seen in an open label study with a time frame of 40 weeks and was referenced to data on file. This data was now published.

The published evidence on the longer term effects of pioglitazone consisted of three studies (two of them were Actos in combination with sulphonylurea and one study in combination with metformin) where the authors referred to long-term maintenance of glycaemic control. In addition there was data published demonstrating the maintenance of effect up to 72 weeks in combination with metformin.

Data from the studies in combination with sulphonylurea or metformin for up to 40 weeks from the US had been published and the authors clearly referred to this as long-term both within the text and the tables. A Japanese open extension study was entitled 'Clinical usefulness of long-term treatment with AD 4833 of patients with non-insulin dependent diabetes mellitus – Phase III study on long-term treatment' with data up to 28 weeks.

Takeda believed that these were clear signs that the medical community believed that the effects of pioglitazone on glycaemic control had demonstrated in the long-term. The material was not misleading and represented the body of evidence and so was not in breach of Clause 7.2 of the Code.

Takeda noted that in addition to the challenge of a breach of the Code, GlaxoSmithKline wished to make a much broader challenge to establish what data could be considered as long-term and had suggested using this case as a test case. This was an inappropriate challenge and any decision on this case should not hinge on whether a study of 40 weeks was long-term data but whether the material complied with the Code.

Takeda however addressed the issue. GlaxoSmithKline stated that the tacit assumption throughout the industry and the medical community had been that this lower limit was at least 52 weeks and in addition that it was not possible to produce any evidence to support this position. It was unclear why GlaxoSmithKline came to this conclusion with no evidence.

There was published data to contradict the position of GlaxoSmithKline. A literature search revealed that most studies made no comment on whether the study was short- or long-term. However in the few papers where a comment was made in the published literature there appeared to be no agreement within the medical community for a time when treatment of type 2 diabetes became long-term.

Studies of well established treatments for type 2 diabetes (insulin, metformin or sulphonylurea) were described as long-term by the authors with large variation in duration ranging from 6 months to 9 years. This suggested that studies of a duration of 6 months or more were accepted by the medical community as long-term studies of metformin, sulphonylureas or insulin in type 2 diabetes. There was no evidence to show that studies of 40 weeks could not be deemed long-term.

Takeda believed that if leading physicians in the field of diabetes described studies as long-term then it was inappropriate for this to be challenged by pharmaceutical companies.

It was worth noting that regulatory authorities did not specify how long study should be before it was considered long-term.

GlaxoSmithKline suggested that this case should not be viewed as an individual case but as a 'test case' to decide on the appropriate use of the terminology 'long-term'. Takeda believed that it was not appropriate for any pharmaceutical company to try to dictate to the medical community what data could be considered as long-term. This was an area for discussion first within clinicians in the field of diabetes and then this could broaden out for discussion within the pharmaceutical industry.

The data presented was not misleading and so not in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

Firstly, the Appeal Board noted that each case was considered on its own individual merits. It was not acceptable for the phrase 'long term' to be defined as there were many variables, not least the therapeutic area.

Turning to the specific matter before it, the Appeal Board noted that the question 'Does Actos continue to be effective in the long term' was answered clearly by stating that over 40 weeks glycaemic control was sustained.

The Appeal Board noted the relevant statements in the SPC. It did not consider that the answer to the question was misleading as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal was unsuccessful.

Complaint received **10 January 2001**

Case completed **18 April 2001**

CASE AUTH/1123/1/01

TAKEDA v SMITHKLINE BEECHAM

Promotion of Avandia

Takeda complained about the promotion of Avandia (rosiglitazone) by SmithKline Beecham. The items at issue were two slide sets, a journal advertisement, a product monograph, a press release, three leavepieces and a letter. Takeda supplied Actos (pioglitazone).

Takeda alleged that the claim on a slide 'Only Avandia takes control of type 2 diabetes by directly reducing insulin resistance and preserving ß-cell function' was exaggerated and could not be substantiated. Avandia was not the only medicine that affected insulin resistance and beta-cell function. SmithKline Beecham had not provided any data to show that rosiglitazone had a direct effect on beta-cell function. There was evidence to show that Actos reduced insulin resistance and led to significant improvements in beta-cell function. Although the Actos summary of product characteristics (SPC) included the statement '… no direct effect on beta-cell function', the two statements '… no direct effect on beta-cell function' and 'improved beta-cell function' were not mutually exclusive.

The Panel noted that the Avandia SPC stated that it reduced glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver. It further stated that 'results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic ß-cell function with rosiglitazone in combination with sulphonylurea or metformin'. The Actos SPC stated that 'Pioglitazone effects may be mediated by a reduction of insulin resistance' and 'There is no direct effect of pioglitazone on beta-cell function'. There were published reports which demonstrated that the addition of pioglitazone to sulphonylurea or metformin therapy preserved beta-cell function over time (Rosenstock and Einhorn *et al*). On balance the Panel did not consider the claim misleading and exaggerated as alleged and no breach of the Code was ruled. Upon appeal by Takeda, the Appeal Board noted that Rosenstock demonstrated a 38.04% change in beta-cell function versus baseline of pioglitazone 30mg in combination with sulphonylurea versus a change of 8.23% for placebo plus sulphonylurea. The Appeal Board also noted the references to beta-cell function in the SPCs. The Appeal Board considered that the claim at issue was too sweeping; it implied that other products had not been shown to preserve beta-cell function and that was not so. There was relevant evidence with regard to the use of pioglitazone in combination with a sulphonylurea. The claim overstated the data and was misleading and exaggerated in this regard. Breaches of the Code were ruled.

The heading 'Avandia effect on lipids and blood pressure' appeared in a slide above a table which showed that, at six and eighteen months, triglyceride levels either remained unchanged or, in the case of patients with triglycerides at >4.5mmol/l at baseline, decreased. Takeda alleged that the claim that Avandia reduced triglycerides or that triglycerides were unchanged was a misleading and selective presentation of the data. There were actually significant increases in triglycerides compared to baseline in combination with sulphonylurea in study SB015 yet this was not included. In addition, in combination with metformin in patients treated with Avandia there was an increase in triglycerides for patients with baseline triglycerides below 2.2mmol/l. A reduction in triglycerides had only been seen in a subset of patients in one study but not as a consistent effect, whereas increases in triglycerides had been seen both in the total study population and in subset analysis. The Avandia SPC made no reference to change in triglycerides (except in the adverse event section where hypertriglyceridaemia was noted). The Panel noted that the table indicated that a typical patient with type 2 diabetes had elevated triglycerides. A footnote immediately beneath the table indicated that the decrease in triglyceride levels applied to patients whose level was >4.5mmol/l at baseline. The table did not indicate that a statistically significant decrease only occurred in those receiving the 8mg dose. In this regard the Panel noted that '4mg once daily' appeared beneath the product logo in the bottom right hand corner of the slide. No reference was made on the slide to the 8mg dose. The NICE assessment concluded that the 'overall effect of rosiglitazone combination therapy on cardiovascular risk is also unclear'. The Panel considered that the slide was misleading and a breach of the Code was ruled.

The table indicated that the TC: HDLC ratio was elevated in the typical patient with type 2 diabetes and remained unchanged at six months and decreased at 18 months in patients receiving Avandia. Takeda alleged that the bold claim for a reduction in the TC:HDLC ratio was misleading and did not reflect the evidence. In rosiglitazone studies in combination with metformin or sulphonylurea there was no change in the TC:HDLC ratio. In the long-term studies in patients who had a statin added the TC:HDLC ratio decreased. However in the patients who did not have a statin added there was essentially no change in the TC:HDLC ratio. The SPC for Avandia stated that the ratio of TC:HDLC was unchanged or improved in long-term studies. The 'unchanged' had been omitted here. No levels of statistical significance were given; it was not clear that the 18 month data was taken from open extension studies in which statins might have been added to the patients' therapy. The Panel noted the Avandia SPC stated that the elevated total cholesterol levels were associated with an increase in both LDLC and HDLC, but the HDLC ratio was unchanged or improved in long-term studies. The table showed that the TC: HDLC ratio was unchanged at six months and decreased at 18 months. It was unclear whether this was a fair reflection of the studies cited on this point as neither company had provided the references. The Panel considered the slide was misleading and a breach of the Code was ruled.

Beneath the table the claim 'Effect on blood pressure' appeared above two bullet points; 'In

comparison to glibenclamide, Avandia reduces ambulatory diastolic blood pressure (–3mmHg), systolic blood pressure (–4mmHg) and mean arterial pressure (–3mmHg) at six months' and 'These effects are sustained at 1 year'. Takeda stated that this data was from a monotherapy study, which was an unlicensed indication in the UK. In the studies of combination of rosiglitazone with metformin there were no significant changes in blood pressure. In the studies of combination of rosiglitazone with sulphonylurea, in most studies there were no significant changes in blood pressure and in a meta-analysis of six-month blood pressure levels there was no significant difference between the groups. Avandia had not been shown to lower blood pressure significantly in combination with metformin or sulphonylurea. It did not have a licence as an agent to lower blood pressure and there was no mention of this effect within the SPC. Takeda alleged that these claims could not be substantiated, did not represent the body of evidence and were outside the terms of the licence. The Panel noted that Avandia had been administered as monotherapy. It had not been administered in accordance with its licensed indication. This was not stated. The Panel considered that the claim was misleading and not in accordance with the SPC and breaches of the Code were ruled.

A graph on a slide beneath the heading 'Avandia combination with SU [sulphonylurea] mean change HbA1c at 6 months' depicted the percentage mean change in HbA1c from baseline of SU + Avandia 4mg daily and SU + placebo. Text beneath the graph stated that 'After 6 months of treatment, 60% of patients in the sulphonylurea plus Avandia 4mg daily group achieved a reduction in HbA1c ≥ 0.7% compared with only 19% in the sulphonylurea plus placebo group ($p<0.0001$)'. Takeda alleged that the data presented was misleading as it was selective and did not represent the body of evidence or reflect the effects seen using the currently available dose. The data presented for the efficacy of Avandia in combination with a sulphonylurea was study SB015, which used rosiglitazone 2mg bd. It was not possible to prescribe rosiglitazone as 2mg bd as no 2mg tablet was available in the UK and the 4mg or 8mg tablets could not reliably be halved. The difference between the available data and the data presented in the promotional items was most prominent when one looked at the responder rate for HbA1c. This was only 29% in the group treated with 4mg once daily (the only dose which could be prescribed with a sulphonylurea in the UK) compared to the group treated with rosiglitazone 2mg twice daily who were cited in the text for this slide as having a 60% response rate. Takeda alleged that this selective presentation of the data using rosiglitazone 2mg bd, instead of 4mg was misleading, and that these were exaggerated claims for the efficacy of rosiglitazone in combination with sulphonylurea.

The Panel noted that Avandia was available as a 4mg and 8mg tablet and that according to the SPC, Avandia 'may be given once or twice a day'. The Panel further noted that the EPAR stated that generally 8mg/d appeared more effective than 4mg/d and twice daily dosing more effective than once daily dosing but 'statistically significant differences between dose levels and regimens were not demonstrated'. The Panel considered that this was a difficult area. It was concerned that in the study demonstrating the therapeutic equivalence of the 4mg od and 2mg bd dosage regimens Avandia had not been administered in accordance with its SPC. The Panel queried whether the results quoted on the slide represented the balance of evidence. On balance the Panel considered that the claim was misleading and did not reflect the balance of evidence and a breach of the Code was ruled. Upon appeal by GlaxoSmithKline, the Appeal Board noted the percentage responder HbA1c rates and that in study SB 096 not all patients appeared to have received Avandia in accordance with its SPC . The Appeal Board considered that the magnitude of the difference in responder rates between the two studies was such that the data presented on the slide did not represent the balance of the evidence. It further considered that equivalence between the 2mg bd and 4mg od dose had not been demonstrated. The Appeal Board upheld the Panel's ruling of a breach of the Code.

On a slide headed 'Efficacy: summary' appeared five bullet points the second of which read 'Magnitude of improvement is clinically important –0.9% ↓ HbA1c = 25%↓ microvascular complications'. Takeda stated that this implied that the claim for a reduction in microvascular complications was related to Avandia usage. There was no evidence to suggest that use of Avandia could lead to a reduction of microvascular complications of 25%. Reference was made to the SPC. This presentation of outcome data was misleading, could not be substantiated and was an exaggerated claim which was outside the licensed indications. The Panel noted that the Avandia SPC stated that 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated …. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin'. The Panel considered that the statement at issue was an outcome claim. It appeared on a page which purported to summarize the efficacy of Avandia and was thus inconsistent with the Avandia SPC and misleading about the product's licensed indication. Breaches of the Code were ruled.

The journal advertisement featured the main claim 'I think control of type 2 diabetes will reach new heights' above three bullet points, 'fighting insulin resistance', 'defending beta-cells' and 'sustaining control'. The product logo appeared at the bottom right hand corner of the advertisement above the phrase '4mg once daily'. Takeda stated that an accepted target level for control of type 2 diabetes was an HbA1c of <7%. The published data suggested that using rosiglitazone 8mg daily would not achieve or sustain control in the majority of patients. In combination with metformin only 28% of patients achieved the target HbA1c of 7%. The

percentage of patients achieving target with 4m, had not been shown. Takeda believed that this was an exaggerated claim which could not be substantiated. The Panel considered that the word control would be read in light of the clinical claims in the advertisement; fighting insulin resistance and defending beta-cells. The Panel noted that the Avandia SPC stated that 'In studies with a maximal duration of two years, rosiglitazone given once or twice daily in combination with a sulphonylurea or metformin produced a sustained improvement in glycaemic control (FPG and HbA1c)'. The Panel did not consider the claim to be incapable of substantiation or exaggerated and no breach of the Code was ruled.

The claim '… other members of the drug class, troglitazone and pioglitazone, are metabolised through CYP3A4, a common metabolic pathway for a wide range of drugs (Figure 1, Table 1) and, thus, have associated potential for drug interactions. This is a particular concern, given the levels of polypharmacy in patients with type 2 diabetes' appeared in the product monograph in a section headed 'Drug Interactions' which discussed Avandia's 'low potential for interaction with co-administered drugs'. A table listed those medicines including pioglitazone which were metabolised by CYP3A4 and CYP2C8 pathways. A figure depicted the proportion of medicines metabolised by the cytochrome P450 enzymes. The claim '… unlike other glitazones, Avandia has a low potential for interactions with commonly co-prescribed therapies for people with Type 2 diabetes' appeared in a press release. Takeda stated that these promotional items and feedback through its representatives had indicated that GlaxoSmithKline was suggesting that Actos had a greater potential for drug interactions because one of the pathways of metabolism was through CYP3A4. This was not supported by the body of evidence. No drug interactions had been identified with Actos, and it had not been shown to inhibit or induce cytochrome P450, so it was thought that Actos had a low potential for drug interactions. The SPC for Actos had no drug interactions listed yet the Avandia SPC advised caution for use with paclitaxel. The statements were being used to mislead prescribers to believe that pioglitazone had drug interactions. This could not be substantiated, was misleading and disparaging. The Panel noted that GlaxoSmithKline accepted that there was no firm data to indicate significant drug interactions with pioglitazone but pharmacologically the potential for such interaction remained higher for pioglitazone than for Avandia. The Panel noted that neither party had provided evidence to show a problem in practice. It also noted the different metabolic pathways of Avandia and pioglitazone and their different potential for associated drug interactions. The Panel considered that given the absence of firm data to indicate significant drug interaction with pioglitazone and the lack of data in patients, the product monograph and press release both created the overall impression that pioglitazone had a high incidence of drug interactions and this was misleading and disparaging. Breaches of the Code were ruled.

Takeda alleged that the statement 'Only Avandia improves both fundamental causes of type 2 diabetes: insulin resistance and beta cell dysfunction' could not be substantiated. Avandia was not the only medicine that affected insulin resistance and beta-cell function. The Panel considered that the claim at issue was different to that at issue in the first point above. The Panel did not consider that 'preserving ß-cell function' was the same as 'improves … beta cell dysfunction' as in the claim now at issue. Nonetheless the Panel considered that the same principles applied and no breach of the Code was ruled. Upon appeal by Takeda, the Appeal Board considered that its ruling in the first point above applied here. Breaches of the Code were ruled.

Takeda alleged that the claim 'Therefore Avandia has the potential to delay disease progression and reduce complications' was not consistent with the SPC for Avandia which stated clearly that 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated'. In addition, it was not consistent with the EPAR which stated 'The potential long-term effects of the observed changes in the lipid profile on the cardiovascular system cannot be predicted and therefore raise concerns'. The Panel noted that NICE had stated that further research was needed to investigate long-term outcomes with rosiglitazone combination therapy. The Avandia SPC referred to a sustained improvement in glycaemic control in studies with a maximal duration of two years. It was further stated that 'The long-term benefits associated with glycaemic control have not been demonstrated'. The Panel considered that the claim would be seen as a specific claim for Avandia; it would not be seen as a general statement of the benefits of improved glycaemic control. The Panel considered that the statement at issue claimed an outcome improvement and there was no evidence before it that Avandia delayed the rate of progression of the disease or reduced complications. The claim was misleading and inconsistent with the SPC and breaches of the Code were ruled. Upon appeal by GlaxoSmithKline, the Appeal Board considered that the claim was for the outcome of treatment with Avandia. The company had no endpoint data to support such a claim which the Appeal Board considered was not in accordance with the SPC. The Appeal Board upheld the Panel's ruling of breaches of the Code.

Takeda stated that the statement 'More than one year's global post-marketing experience has shown that most patients take Avandia 4mg daily' was referenced to NICE Technology Appraisal Guidance – No 9, which referred to the US usage in the early months post launch. This included patients on monotherapy which was not a licensed indication in the UK. The data relevant to UK usage was only the patients taking combination therapy. Recent data from IMS (US) indicated that currently 61% of patients receiving combination therapy of rosiglitazone with metformin were prescribed 8mg per day and 55% of patients taking rosiglitazone

with sulphonylurea received 8mg per day. This meant that in the US most patients receiving rosiglitazone as combination with metformin or sulphonylureas were prescribed the 8mg dose. The data for monotherapy should be excluded as this was an unlicensed indication in the UK. This statement did not reflect the most up-to-date evidence of the dose patients were prescribed in combination therapy and was misleading. The Panel noted GlaxoSmithKline's submission that in the UK since the launch of Avandia, approximately 95% of patients had been treated with the 4mg dose. The claim at issue, however, referred to global post-marketing experience and was based on monotherapy use. The claim was misleading and a breach of the Code was ruled.

The claim 'Diabetes UK recommends an HbA1c level of ≤7%' appeared in a box headed 'Glycaemic control'. The claim 'Avandia .. sustaining control' appeared at the bottom of the page adjacent to the brand name beneath the claims 'fighting insulin resistance' and 'defending beta-cells'. Takeda stated that treatment with rosiglitazone only allowed a small minority of patients to achieve an HbA1c of <7%, the level recommended by Diabetes UK. In a published study using rosiglitazone 8mg daily in combination with metformin, only 28% of patients achieved the target HbA1c of 7%. The percentage of patients achieving target with 4mg rosiglitazone (the dose promoted in the leavepiece) had not been shown. This claim for sustaining control was an exaggerated claim that could not be substantiated. The Panel firstly considered the heading 'Glycaemic control' and the associated claim 'Diabetes UK recommends an HbA1c level of ≤7%' and considered that the context in which the word 'control' was used was different to that considered in a point above. The word 'control' was now specifically linked with the Diabetes UK recommendation of HbA1c level of ≤7%. The Panel noted that the leavepiece referred solely to the 4mg dose; '4mg once daily' was incorporated into the product logo. The Panel considered that the claims gave the impression that, in terms of glycaemic control, Avandia 4mg once daily achieved the Diabetes UK recommendation, ie HbA1c levels of ≤7%, and that was not so. The claims were misleading and exaggerated and breaches of the Code were ruled.

Takeda stated that there was an error in the spelling of the generic name in three different places adjacent to the brand name in this item. The Panel noted that the non-proprietary name of the medicine had to appear immediately adjacent to the most prominent display of the brand name. The non-proprietary name had been misspelt and thus the requirement had not been satisfied. A breach of the Code was ruled.

The claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for Primary Care Organisations (PCO)†' appeared beneath the heading 'Maximising scarce resources'. The obelus referred the reader to the footnote 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period' beneath a table which compared the annual cost of Avandia 4mg with pioglitazone 30mg. Takeda stated that the doses that had been compared for rosiglitazone and pioglitazone had not been shown to be comparable. There was no data to support the statement 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period'. The costs shown in the claim had compared the lowest dose of rosiglitazone and the highest dose of pioglitazone. This was not a fair and balanced comparison. The claim was misleading as the doses were not comparable and not all patients in a PCO could be expected to be treated with the maximum recommended dose of one yet the minimum available dose of the other.

The Panel noted that the Avandia SPC stated that therapy was usually initiated at 4mg/day; in combination with metformin that dose could be increased to 8mg/day after 8 weeks if greater glycaemic control was required. There was currently no experience of doses above 4mg/day in combination with sulphonylureas. The pioglitazone SPC stated that its licensed dose in combination with metformin or a sulphonylurea was 15mg or 30mg once daily. The Panel considered that the claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for primary care organisations (PCO)' and its footnote 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period' created the impression that the doses stated were clinically comparable. There were no direct head-to-head studies of Avandia and pioglitazone. The Panel considered that claim misleading as the basis of the comparison had not been made sufficiently clear. Breaches of the Code were ruled.

The claim 'Pioglitazone 30mg daily is the starting dose recommended by the licence holders' appeared as a bullet point at the bottom of the page. Takeda stated that the SPC recommended that Actos in combination with metformin or sulphonylurea may be used at the dose of 15mg or 30mg once daily. There was no recommendation in the reference given or the SPC that pioglitazone 30mg was the starting dose. The Panel considered that the claim at issue implied that 30mg daily was the licensed starting dose and that was not so. A breach of the Code was ruled.

Takeda alleged that the table in a leavepiece was misleading. The table indicated that Avandia 4mg once daily improved beta-cell function whilst pioglitazone 30mg once daily had no direct effect. The two statements were not mutually exclusive and both might apply to both of these medicines. Pioglitazone had been shown to improve beta-cell function even though it had no direct effect on beta-cell function. The Panel considered that its ruling at the first point above was relevant with reference to the claim 'Only Avandia takes control of type 2 diabetes by directly reducing insulin resistance and preserving beta-cell function'. The table implied that Avandia had a unique effect on beta-cell function. It implied that pioglitazine had no effect on beta-cell function and that was not so. A breach of the Code was ruled.

The table stated that Avandia, in combination with a sulphonylurea or metformin, produced a 1% reduction in HbA1c from baselines of 9.2 and 8.9 respectively. The equivalent data from pioglitazone was a 1.3% reduction (baseline 9.9) with a sulphonylurea and a 0.8% reduction (baseline 9.9) with metformin. Takeda stated that these were not head-to-head comparisons and the studies were of different durations so no valid comparison of the results could be made. This presentation of the rosiglitazone and pioglitazone data side by side was misleading. It was not made clear that the changes shown were the mean or median differences from placebo – not the change from baseline (the changes from baseline were rather smaller). The data shown for the effect of rosiglitazone with sulphonylurea appeared under the heading Avandia 4mg once daily, yet the data shown was for a twice daily dose. If the correct change from baseline was inserted into the table using the once daily dose this figure would read a change in HbA1c of just –0.3% from baseline or a change from placebo of –0.8%. The use of the study using the twice daily dose gave an exaggerated level of efficacy; it was misleading to make a claim for a once daily dose when the study was clearly using a twice daily dose and the citation of the reference was inaccurate. It was also misleading to use the data from a study using twice daily dosing when the dose 2mg bd could not be prescribed as there was no 2mg tablet available in the UK. Takeda alleged that these claims for efficacy of once daily dosing when twice daily was used in the study were misleading and exaggerated. The Panel considered that its general comments about the absence of head-to-head studies made above were relevant. The Panel considered that its ruling above regarding the use of the 2mg bd dosage regimen applied and breaches of the Code were ruled.

The table stated that Avandia demonstrated improvement in TC: HDL ratio over an 18 month period whilst for pioglitazone improvement was demonstrated over a 40 week period. Takeda stated that here the 18 month results for rosiglitazone had been compared with 40 week results for pioglitazone. This presentation of the data was misleading as the data was not from comparable studies and the presentation of the rosiglitazone data was highly selective. The Panel considered that a ruling above applied here and a breach of the Code was ruled.

Takeda stated that the cost comparison was again comparing the cost of the highest dose of pioglitazone with the lowest dose of rosiglitazone. This was misleading. The Panel considered that its ruling above was relevant and a breach of the Code was ruled.

Takeda also complained about a letter signed by the medical director and sent unsolicited to general practitioners on SmithKline Beecham headed paper. There was no clear indication on the front of the letter that it was a promotional piece and the signature of the medical director implied that it was an important communication with information about cost implications and cost effectiveness. However, it merely gave highly selected information about the costs of the lowest dose of rosiglitazone and the highest dose of pioglitazone. The up-to-date evidence for efficacy of pioglitazone had not been included. At the time that this piece was prepared data on the efficacy of pioglitazone for up to 72 weeks had been published; the omission of this data was misleading. With regard to the claim 'I hope that this comparison clarifies the cost implications of prescribing the two glitazones should you consider issuing local guidelines to prescribers', Takeda stated that NICE estimated that at least 25% of patients would receive the higher dose of rosiglitazone. Therefore the average annual cost of using rosiglitazone would be expected to be £430 instead of £364.74 as in this letter. This had been ignored. The average annual cost of pioglitazone would clearly not be as high as had been suggested as it was very unlikely that all patients would receive the maximum dose. The letter had not clarified the costs and the suggestion that this misleading cost comparison should be used as a basis for local guidelines raised concern. Takeda believed that this letter did not recognise the responsibility of professionals issuing guidelines and that high standards must be maintained for promotion of medicines. In addition, Takeda alleged that this was disguised promotion and brought the industry into disrepute.

The Panel noted that the first sentence referred to the launch of Avandia and the subsequent NICE Guidance. The letter sought to compare Avandia favourably with pioglitazone. Avandia was referred to throughout in prominent upper case. Prescribing information appeared on the reverse. The letter was clearly promotional. The fact that it was signed by the medical director did not change the fundamentally promotional nature of the letter. The Panel did not consider the letter was disguised promotion. The Panel noted that the data presented in the table was similar to that at issue above. The Panel firstly considered the allegation that up-to-date evidence for the efficacy of pioglitazone at 72 weeks had not been included and noted GlaxoSmithKline's response that such data included an unlicensed dose in the UK (45mg) and there was no indication as to how many patients received this dosage. No breach of the Code was ruled on this particular point. The Panel considered that its rulings above regarding the short term effect on HbA1c, impact on TC:HDL and the cost comparison applied to the 'Dear Doctor' letter and breaches of the Code were ruled. The Panel did not consider that there had been a failure to maintain high standards or that the letter brought the industry into disrepute.

Takeda stated that it had requested SmithKline Beecham to withdraw the materials. However, SmithKline Beecham had declined to respond to the issues raised. Takeda believed that the promotion of Avandia with the deliberately misleading presentation of information brought the industry into disrepute and so was in breach of Clause 2. The Panel noted that Clause 2 was reserved as a sign of particular censure. On balance the Panel did not consider that the circumstances warranted a breach of Clause 2.

Takeda UK Limited complained about the promotion of Avandia (rosiglitazone) by SmithKline Beecham Pharmaceuticals. The items at issue were a slide set (ref AVSL00094H), a slide set entitled 'A Turning Point in the Management of Type 2 Diabetes', a journal advertisement (ref AVAD000119), a product monograph (ref AVMN00043), a press release, three leavepieces (refs AVLT00154, ALVP00152a and AVLP00152b) and a letter dated 5 January. Takeda supplied Actos (pioglitazone).

Takeda stated that it had expressed concern to SmithKline Beecham about the materials and had requested changes to them but had not been reassured by the response.

GlaxoSmithKline, which SmithKline Beecham had by now become, stated firstly that several of the items (leavepieces AVLP00152a and AVLP00152b, and the letter from the then SmithKline Beecham medical director to general practitioners) were produced in response to reports that Takeda representatives were seeking to equate the 4mg and 8mg doses of rosiglitazone with the 15mg and 30mg doses of pioglitazone, respectively, and from this comparison deriving a spurious cost argument in favour of pioglitazone. A complaint had been made to the Authority (Case AUTH/1121/1/01).

Secondly, GlaxoSmithKline stated that in a recent review of all of its promotional materials for Avandia (prior to receiving Takeda's complaint), it became clear that, while there was no intention to mislead, a small number of statements were potentially ambiguous or open to misinterpretation, including some of those raised in Takeda's letter. Accordingly, these materials had been, or were being, withdrawn, and, where appropriate, modified.

A Slide set AVSL00094H

A1 Slide 3

Claim 'Only Avandia takes control of type 2 diabetes by directly reducing insulin resistance and preserving ß-cell function'

COMPLAINT

Takeda alleged that the claim could not be substantiated. Avandia was not the only medicine that affected insulin resistance and beta-cell function.

Takeda had requested data from SmithKline Beecham but none had been provided. Takeda therefore assumed that there was no data to support that rosiglitazone had a direct effect on beta-cell function.

There was evidence to show that Actos reduced insulin resistance and led to significant improvements in beta-cell function (Hanefeld and Göke 2000). Therefore the effect on improving beta-cell function was not unique to Avandia. Although the Actos summary of product characteristics (SPC) included the statement '… no direct effect on beta-cell function', the two statements '… no direct effect on beta-cell function' and 'improved beta-cell function' were not mutually exclusive.

This exaggerated claim with the use of the word 'only' could not be substantiated and breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that Takeda had chosen to interpret the word 'directly' in the above claim as applying to both the reduction in insulin resistance and the preservation of beta-cell function. However, the word was only intended to refer to the effect of Avandia on insulin resistance.

The SPC for Avandia unequivocally stated that 'consistent with the mechanism of action of rosiglitazone, results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved beta-cell function with rosiglitazone in combination with sulphonylurea or metformin'. No other non-glitazone medicine could make this claim. Thus the SPCs for metformin, glibenclamide, gliclazide, glipizide, repaglinide and acarbose did not document any improvements in beta-cell function and insulin resistance taken together.

The question then remained as to whether pioglitazone itself could substantiate the claim. The Actos SPC stated that 'There is no direct effect of pioglitazone on beta-cell function'. While GlaxoSmithKline accepted Takeda's assertion that 'no direct effect on beta-cell function' and 'improved beta-cell function' were not mutually exclusive, the less positive wording of the Actos SPC compared to the Avandia SPC reflected the paucity of data with pioglitazone with respect to this parameter. The review by Hanefeld and Göke was published after preparation of the slide-set in question. Furthermore, this secondary reference contained the phrase 'Beta-cell preservation markers … in patients treated with pioglitazone have also been reported to be significantly superior to placebo and from baseline after 16 weeks of monotherapy or combination therapy with metformin or sulphonylurea'. This statement was inaccurate. In the primary reference cited by Hanefeld and Göke (Rosenstock 2000), there were no significant improvements in beta-cell function observed with pioglitazone and metformin, relative to the metformin-placebo combination (comparison with placebo being the most accurate method of assessing treatment effects in a progressive disease). Thus, it was true at the time of publication of the slide-set, and to the best of GlaxoSmithKline's knowledge remained true, that Avandia was the only agent that had been shown to reduce insulin resistance and improve beta-cell function in combination with both sulphonylurea and metformin.

PANEL RULING

Section 5.1 of the Avandia SPC headed 'Pharmacodynamic Properties' stated that it reduced glycaemia by reducing insulin resistance at adipose tissue, skeletal muscle and liver. It further stated that 'results from a homeostatic model assessment (HOMA) indicate reduced insulin resistance and improved pancreatic ß-cell function with rosiglitazone in combination with sulphonylurea or metformin'.

Section 5.1 of the Actos SPC stated, *inter alia*, that 'Pioglitazone effects may be mediated by a reduction

of insulin resistance' and 'There is no direct effect of pioglitazone on beta-cell function'.

The Panel noted that Hanefeld and Göke referred to recent reports which demonstrated that the addition of pioglitazone to sulphonylurea or metformin therapy preserved beta-cell function over time (Rosenstock 2000 and Einhorn *et al* 2000).

Rosenstock 2000 was presented as an abstract. The purpose of the study was to assess insulin resistance and beta-cell function. The results were presented as percentage at endpoint versus baseline. With regard to beta-cell function for pioglitazone in combination with sulphonylurea, the percentage change versus baseline was 38.04% compared to 8.23% for sulphonylurea and placebo. The result for metformin and pioglitazone was 37.56% compared to 36.79% for metformin and placebo. The study concluded that the data suggested that pioglitazone therapy was associated with an improvement in beta-cell responsivity when used as monotherapy or in combination with metformin or sulphonylurea. The Panel noted that this was disputed by GlaxoSmithKline which stated that there was no significant improvement in beta-cell function.

Einhorn *et al* concluded, *inter alia*, that treatment with pioglitazone and metformin resulted in a statistically significant (p= 0.05) decrease in insulin resistance compared with baseline and placebo plus metformin. With regard to beta-cell function the between group difference was not statistically significant. The study authors concluded that the positive effect of pioglitazone in combination with metformin 'on dyslipidemia and possibly beta-cell function may provide addition benefit in reducing the known risks for complications of the disease'.

The Panel noted the pioglitazone data with regard to beta-cell function and the reference in the product's SPC and further noted that Hanefeld and Göke, Rosenstock and Einhorn had not been published at the time of publication of the slide set. The Panel noted that promotional material had to comply with the Code not only at the time of publication but also when it was later used or distributed.

The Panel noted GlaxoSmithKline's submission that it was not aware of any other agent that had been shown to reduce insulin resistance and improve beta-cell function in combination with metformin and sulphonylurea. The claim in question referred to preserving ß-cell function.

The Panel did not accept Takeda's submission that the term 'directly' referred to 'preserving ß-cell function'. In the Panel's opinion the construction of the sentence was such that 'directly' referred to the reduction in insulin resistance alone.

The Panel noted that the SPCs for the products were different. The effect of metformin and Actos on beta-cell function appeared to be different to that of sulphonylurea and Actos. The Rosenstock study concluded that the data suggested that there was an improvement in beta-cell function. Einhorn stated that the positive effect of pioglitazone in combination with metformin possibly on beta-cell function may provide additional benefit. On balance the Panel did not consider the claim misleading and exaggerated as alleged. No breach of Clauses 7.2 and 7.8 of the Code was ruled.

APPEAL BY TAKEDA

Takeda stated that the statements at issue in the slide and leavepiece, at point E1, were very similar and made the claim that rosiglitazone was the only medicine that both reduced insulin resistance and had a positive effect on beta-cell function. Takeda therefore outlined its concerns for both point A1 and E1 together.

The Oxford English dictionary defined 'only' as one of which there existed no more or no others of its kind; unique in quality or character; peerless; pre-eminent. These were superlatives, which implied that there was some special merit and Takeda did not believe that this was the case for the effect of rosiglitazone on beta-cell function.

All three thiazolidinediones which had reached the UK market (pioglitazone, rosiglitazone and troglitazone), had been shown to improve beta-cell function in patients with type 2 diabetes. Rosiglitazone did not have a unique effect on beta-cell function so claims that only Avandia improved beta-cell function were unfounded.

There was evidence to show that pioglitazone reduced insulin resistance and led to significant improvements in beta-cell function (Rosenstock). In clinical trials of pioglitazone in monotherapy, or in combination with metformin or sulphonylurea, reduction in insulin resistance and significant improvements in beta-cell function were seen after 16 weeks of treatment compared to baseline. Therefore it could not be claimed that rosiglitazone was the only medicine to have been shown to reduce insulin resistance and improve beta-cell function (Rosenstock, Hanefeld and Göke and Einhorn *et al*).

The Actos SPC included the statement '… no direct effect on beta-cell function', but the two statements '… no direct effect on beta-cell function' and 'improved beta-cell function' were not mutually exclusive.

The mechanism of the improvement in beta-cell function seen with thiazolidinediones had not been fully elucidated. This was confirmed in one of the promotional items at issue (slide set AVSL00094H) which claimed that Avandia preserved beta-cell function by an as yet undefined mechanism; but suggested that it might be by lowering glucose and free fatty acid levels and by reducing hyperinsulinaemia. These were effects seen with all the thiazolidinediones. There was evidence to demonstrate that pioglitazone lowered glucose, and free fatty acids and reduced hyperinsulinaemia. No data had been provided by SmithKline Beecham to suggest that any effect on beta-cell function was due to a direct effect of rosiglitazone on the beta-cell.

Pioglitazone had been shown to improve beta-cell function even though it was believed that pioglitazone had no direct effect on beta-cell function.

In addition there was data to show that troglitazone reduced insulin resistance and improved beta-cell

function both in animal and human studies. This was additional evidence illustrating that the effect in improving beta-cell function with a thiazolidinedione was not unique to rosiglitazone but was a feature of the mechanism of action of this class of medicines.

Takeda maintained that the claim that rosiglitazone was the only agent to reduce insulin resistance and improve beta-cell function was not accurate and did not reflect all the evidence. The word 'only' was used as a superlative to make this an exaggerated and all embracing claim, implying that rosiglitazone had some special merit, that could not be substantiated. Takeda alleged that the claim in both the slide and leavepiece (A1 and E1) was in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that whilst it might be true that the word 'only' could be used to confer some special merit, the word itself was not a superlative. A superlative was defined, of an adjective or adverb, as 'expressing the highest or a very high degree of a quality (eg 'bravest', 'most fiercely')' (Concise Oxford English Dictionary). As, by definition, the concept of 'oneness' did not allow for degrees of quality, the word 'only' could not be considered as a superlative. GlaxoSmithKline stated that it made this rather trivial point only because the word 'superlative' could have potentially adverse implications under the Code.

Turning to the substance of the question at issue, that Avandia had significantly beneficial effects on beta-cell function was beyond dispute. Importantly, these effects were seen in combination with both sulphonylureas and metformin (the only licensed indications for both Avandia and pioglitazone). GlaxoSmithKline provided nonparametric analyses for beta-cell function and insulin resistance for the combination of Avandia at various doses with metformin (study 094) and with sulphonylurea (study 015). For both studies, for both parameters, and for all doses, the comparison with control was statistically significant. This could be seen by the fact that the 95% confidence interval for comparison to control excluded zero, equivalent to a p-value of less than 0.05.

The Actos SPC stated that 'There is no direct effect of pioglitazone on beta-cell function'. Whilst GlaxoSmithKline accepted Takeda's assertion that 'no direct effect on beta-cell function' and 'improved beta-cell function' were not mutually exclusive, the less positive wording of the Actos SPC compared to the Avandia SPC reflected the paucity of data with Actos with respect to this parameter.

The secondary reference cited, Hanefeld and Göke, contained the phrase 'Beta-cell preservation markers … in patients treated with pioglitazone have also been reported to be significantly superior to placebo and from baseline after 16 weeks of monotherapy or combination therapy with metformin or sulphonylurea'.

As noted in its original response to Takeda's complaint, this statement was inaccurate. If one turned to the *primary* reference cited by Hanefeld and Göke (Rosenstock), it could be seen that there were no significant improvements in beta-cell function observed with pioglitazone and metformin, relative to the metformin-placebo combination (comparison with placebo being the most accepted and accurate method of assessing treatment effects). Thus, the percentage change in beta-cell function observed with metformin plus pioglitazone 30mg was 37.56%; whereas that seen with metformin plus placebo was 36.79%. These values were practically identical.

Furthermore, this lack of any discernible effect on beta-cell function in combination with metformin was seen with the highest available dose of pioglitazone (30mg); whereas the clearly significant effects obtained in this combination with Avandia were seen at both 4mg od and 8mg od (the full range of dosages available in the UK).

Takeda cited one other paper (Einhorn *et al*) to support its contention that pioglitazone significantly improved beta-cell function in combination with metformin. Here again, however, Takeda seemed to have some difficulty in interpreting the significance of its own data. In the tabulated HOMA data for this study, whilst it was true that there was a significant improvement (45.0%) in beta-cell function, compared to baseline, for the metformin-pioglitazone combination, *the same was also true for metformin plus placebo* (39.3%). The table made it quite clear that only for insulin resistance was there a significant difference between metformin plus pioglitazone and metformin plus placebo. As noted above, the true effects of the combination could only be assessed accurately in relation to placebo, *not* to baseline. Again, this lack of significant effect was seen with the highest available (30mg) dose of pioglitazone.

As such, GlaxoSmithKline rejected Takeda's assertion that there were essentially no differences between Avandia and pioglitazone with respect to the parameter of beta-cell function (the case of troglitazone was irrelevant, as it was no longer available in the UK). There was clear-cut evidence that Avandia significantly improved beta-cell function in combination with sulphonylurea and metformin; whereas all available evidence for pioglitazone suggested that it did not have a significant effect on this parameter in combination with metformin. It was therefore true at the time of publication of the slide-set and leavepiece, and to the best of GlaxoSmithKline's knowledge remained true, that Avandia was the *only* agent that had been shown to reduce insulin resistance and improve beta-cell function in both licensed combinations.

FURTHER COMMENTS FROM TAKEDA

Takeda noted the matters raised by GlaxoSmithKline about the points of grammar but maintained that the claims were constructed so that the use of the word 'only' was designed to imply that Avandia had some special merit or was unique in quality. This could not be supported.

Takeda was most surprised that GlaxoSmithKline had ignored some of the data for pioglitazone and dismissed the effects of troglitazone as irrelevant, when there was clear evidence that an increase in

beta-cell function had been seen with all medicines in the class. Takeda had not questioned the effects of rosiglitazone or the class of agents on beta-cell function.

In the response from GlaxoSmithKline there had been no acknowledgement that pioglitazone had been shown to significantly increase beta-cell function in combination with sulphonylurea which was a licensed indication for Actos. In a study of Actos in combination with sulphonylurea, there was a significant increase in beta-cell function compared to baseline of 38.04% ($p<0.001$) whilst the placebo treated group did not have a significant change in beta-cell function (Rosenstock). This data meant that it was not possible to claim that an improvement in beta-cell function was unique to Avandia.

Takeda believed that these claims therefore were exaggerated and all embracing claims that could not be substantiated and so were in breach of Clauses 7.2 and 7.8 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that Rosenstock demonstrated a 38.04% change in beta-cell function versus baseline of pioglitazone 30mg in combination with sulphonylurea ($p<0.001$) versus a change of 8.23% for placebo plus sulphonylurea ($p=0.07$). The Appeal Board also noted the references to beta-cell function in the products' respective SPCs.

The Appeal Board considered that the claim at issue was too sweeping; it implied that other products had not been shown to, *inter alia*, preserve beta-cell function and that was not so. There was relevant evidence with regard to the use of pioglitazone in combination with a sulphonylurea. The claim overstated the data and was misleading and exaggerated in this regard. Breaches of Clauses 7.2 and 7.8 were ruled. The appeal was successful.

A2 Slide 10 Headed 'Avandia effect on lipids and blood pressure'

This heading appeared above a table which compared the effect of Avandia at six and eighteen months on HDLC, triglycerides, LDLC, LDLC particle size and TC: HDLC ratio with the typical profile in patients with type 2 diabetes.

A2 (i) Effect on triglycerides

The table showed that, at six and eighteen months, triglyceride levels either remained unchanged or, in the case of patients with triglycerides at >4.5mmol/l at baseline, decreased.

COMPLAINT

Takeda stated that the claim that Avandia reduced triglycerides or that triglycerides were unchanged was a misleading and selective presentation of the data.

There were actually significant increases in triglycerides compared to baseline in combination with sulphonylurea in study SB015 (Avandia product monograph) yet this was not included.

In addition, in combination with metformin in patients treated with Avandia there was an increase in triglycerides for patients with baseline triglycerides below 2.2mmol/l. A reduction in triglycerides had only been seen in a subset of patients in one study but not as a consistent effect, whereas increases in triglycerides had been seen both in the total study population and in subset analysis.

This claim for reduction in triglycerides was not consistent with the Avandia SPC, which made no reference to change in triglycerides (except in the adverse event section where hypertriglyceridaemia was noted).

These claims for effects on triglycerides were misleading and not consistent with the SPC. Breaches of Clauses 7.2 and 3.2 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that Takeda focussed on the changes in triglycerides with Avandia compared to baseline values. However, as type 2 diabetes was a progressive disease, the correct comparison should be made with placebo. That said, there was evidence to show that Avandia (at a dosage of 8mg/day) did indeed reduce baseline triglyceride levels in hypertriglyceridaemic patients. GlaxoSmithKline referred to a correction to a study by Fonseca *et al* (2000) published in the Journal of the American Medical Association. This stated 'In the rosiglitazone groups, the median baseline triglyceride value increased… by 0.07mmol/L (6mg/dL) from 1.34 mmol/L (119mg/dL) in 55 patients taking 8mg/d' should have read 'decreased by 0.72mmol/L (64mg/dL) from 9.16mmol/L (280mg/dL) in 37 patients taking 8mg/d'.

GlaxoSmithKline acknowledged that it was true that this reference dealt with patients who had elevated triglycerides at baseline. Patients in most of the Avandia clinical trials were normotriglyceridaemic (baseline levels were 1.8mmol/l in combination with sulphonylurea and 2.77mmol/l in combination with metformin), and triglycerides did rise in some cases, no doubt as a consequence of the progression of disease. However, it was acknowledged in the literature that the typical dyslipidaemic profile of a type 2 diabetes patient included hypertriglyceridaemia, and it was appropriate for physicians to be aware of the effects of Avandia in this large sub-group.

The facts that triglyceride reduction was not specifically mentioned in the SPC and that hypertriglyceridaemia was mentioned as an uncommon side-effect of Avandia administration, did not make the statement itself any the less valid.

PANEL RULING

The Panel noted that the table included on the slide indicated that a typical patient with type 2 diabetes had elevated triglycerides.

The Panel noted that Fonseca *et al* evaluated the efficacy of metformin-rosiglitazone therapy in patients whose type 2 diabetes was inadequately controlled with metformin alone. Changes in triglyceride levels were evaluated based on baseline values using two

subgroups; levels <2.26mmol/l and those ≥2.26mmol/l. In the higher subgroup the median baseline triglyceride value in the Avandia group increased by 0.15mmol/l in 43 patients taking 4mg/day and decreased by 0.072mmol/l in 37 patients taking 8mg/day. The study authors noted overall 'that no significant changes in triglyceride levels were noted in any treatment group and segregation of patients into subgroups revealed non-significant increases in patients with baseline triglyceride levels lower than 2.26mmol/l. Among patients in the 8mg/day rosiglitazone group whose baseline was higher than 2.26mmol/l there was a significant statistical decrease observed. The clinical significance of lipid level changes may be minimal because lipid-lowering therapy may often be administered to patients with diabetes irrespective of prior heart disease history'. The study authors further commented that 'since this study was not designed to assess long-term lipid effects, the long-term significance of these changes is unknown'.

The Panel noted that a footnote immediately beneath the table indicated that the decrease in triglyceride levels applied to patients whose level was >4.5mmol/l at baseline. The table did not indicate that a statistically significant decrease only occurred in those receiving the 8mg dose. In this regard the Panel noted that '4mg once daily' appeared beneath the product logo in the bottom right hand corner of the slide. No reference was made on the slide to the 8mg dose. The Panel also noted the reservations expressed by the study authors.

The Panel noted that the NICE assessment of Avandia (August 2000) concluded that the 'overall effect of rosiglitazone combination therapy on cardiovascular risk is also unclear'.

The Panel considered that the slide was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the claim was inconsistent with the SPC as alleged; it was not an outcome claim, nor were triglyceride levels referred to in the SPC (although hypertriglyceridaemia was mentioned as an adverse event). No breach of Clause 3.2 was ruled.

A2 (ii)Reduction in TC-HDLC ratio

The table indicated that the TC: HDLC ratio was elevated in the typical patient with type 2 diabetes and remained unchanged at six months and decreased at 18 months in patients receiving Avandia.

COMPLAINT

Takeda stated that the bold claim for a reduction in the TC:HDLC ratio was misleading.

In the placebo-controlled arms of the rosiglitazone studies in combination with metformin or sulphonylurea there was no change in the TC:HDLC ratio. In the long-term studies in patients who had a statin added the TC:HDLC ratio decreased. However in the patients who did not have a statin added there was essentially no change in the TC:HDLC ratio (SmithKline Beecham data on file AVDF 0150).

The Avandia SPC stated that the ratio of TC:HDLC was unchanged or improved in long-term studies. The 'unchanged' had conveniently been omitted here.

Takeda believed that these claims for reduction in the TC:HDLC ratio were misleading and did not reflect the body of evidence. A breach of Clause 7.2 of the Code was alleged.

There were no levels of statistical significance attached to the changes in the various parameters; it was not clear that the 18 month data was taken from open extension studies in which statins might have been added to the patients' therapy. Takeda believed that this was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

GlaxoSmithKline stated that the Avandia SPC clearly stated that 'The elevated total cholesterol levels were associated with increase in both LDLc and HDLc, but the ratio of total cholesterol:HDLc was unchanged or improved in long-term studies'. Therefore, the statement that Avandia might lead to improvements in this ratio was consistent with the SPC, and not in itself misleading. GlaxoSmithKline accepted that the word 'unchanged' should have been included in the slide for completeness. This omission was noted on reviewing the promotional materials and the slide in question had been withdrawn, pending modification.

PANEL RULING

The Panel noted that Section 4.8 of the Avandia SPC headed 'Undesirable effects' stated that the elevated total cholesterol levels were associated with increase in both LDLC and HDLC, but the ratio of total cholesterol: HDLC was unchanged or improved in long-term studies. The table showed that the TC: HDLC ratio was unchanged at six months and decreased at 18 months. It was unclear whether this was a fair reflection of the studies cited on this point as neither company had provided the references. However the Panel noted Takeda's submission regarding the possible use of statin therapy within the 18 month data and the SmithKline Beecham data on file. The Panel considered the slide was misleading in this regard. A breach of Clause 7.2 was ruled.

A2 (iii) Claim 'Effect on blood pressure'

Beneath the table at issue in points 2(i) and 2(ii) the claim 'Effect on blood pressure' appeared above two bullet points. The first bullet point stated that 'In comparison to glibenclamide, Avandia reduces ambulatory diastolic blood pressure (–3mmHg), systolic blood pressure (–4mmHg) and mean arterial pressure (–3mmHg) at six months'. The second bullet point stated 'These effects are sustained at 1 year'.

COMPLAINT

Takeda stated that this data was taken from a monotherapy study, which was an unlicensed indication in the UK.

In the studies of combination of rosiglitazone with metformin there were no significant changes in blood pressure, Lord *et al* NICE (2000).

In the studies of combination of rosiglitazone with sulphonylurea, in most studies there were no significant changes in blood pressure and in a meta-analysis of six-month blood pressure levels there was no significant difference between the groups.

Avandia had not been shown to lower blood pressure significantly in combination with metformin or sulphonylurea. It did not have a licence as an agent to lower blood pressure and there was no mention of this effect within the SPC. These claims for reduction in blood pressure could not be substantiated, did not represent the body of evidence and were outside the terms of the licence for Avandia. Breaches of Clauses 3.2, 7.2 and 7.3 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that the study on which this slide was based, Bakris *et al* (2000), was a cardiac safety study, in which ambulatory blood pressure recordings were taken – the 'gold standard' for this type of investigation. Clinic blood pressure records were difficult to interpret, and the blood pressure data recorded incidentally in the Avandia combination studies were not ambulatory. Nor were these studies specifically designed to observe blood pressure as an end-point. In the Bakris study, which was so designed, statistically and clinically significant reductions in diastolic blood pressure (of around 2mmHg) were noted, together with reductions in systolic and mean blood pressure. The fact that, in the study, Avandia was administered as monotherapy did not negate the findings, or render them inappropriate for use in promotional materials, inasmuch as they represented a real pharmacodynamic effect of the product. Indeed, the monotherapy nature of the study served to strengthen the reliability of the findings, as concomitant administration of other agents would have introduced confounding factors into the study. There was no reason to suppose that combination of Avandia with sulphonylureas or metformin would change the effects of Avandia on blood pressure.

Furthermore, in the NICE Technology Appraisal Guide (No 9) for Avandia, it was clearly stated that the results of *post-hoc* meta-analysis from the clinical trials programme showed that 'diastolic blood pressure was lower with rosiglitazone / metformin compared with metformin alone at six months: weighted mean difference 1.8mmHg'.

GlaxoSmithKline did not claim in the slide, nor had it ever claimed, that Avandia had a licence for use as an antihypertensive agent, or might be used as a substitute for an antihypertensive agent in those patients who might require one, but it believed that it was perfectly appropriate to present these data as evidence supporting the general improvement in a variety of cardiac risk factors with Avandia.

PANEL RULING

The Panel noted that Bakris *et al* was a 52 week, open label, randomized active comparison study which determined the effect of Avandia 8mg and glibenclamide on ambulatory blood pressure in patients with type 2 diabetes. The authors concluded that Avandia produced a modest sustained and significant reduction in blood pressure at 52 weeks of treatment. The magnitude of the reduction was similar in both hypertensive and non-hypertensive subjects.

The Panel noted that Avandia had been administered as monotherapy, it had not been administered in accordance with its licensed indication. This was not stated. The Panel considered that the claim was misleading and not in accordance with the SPC. Breaches of Clauses 3.2, 7.2 and 7.3 were ruled.

B Slide set entitled 'A Turning Point in the Management of Type 2 Diabetes'

B1 Slide 70 Avandia in combination with SU

A graph on slide 70 beneath the heading 'Avandia combination with SU [sulphonylurea] mean change HbA1c at 6 months' depicted the percentage mean change in HbA1c from baseline of SU + Avandia 4mg daily ($p<0.0001$) and SU + placebo (p = ns). The graph was referenced to Wolffenbuttel *et al* (2000). Text beneath the graph discussed the study and stated that 'After 6 months of treatment, 60% of patients in the sulphonylurea plus Avandia 4mg daily group achieved a reduction in HbA1c $\geq$ 0.7% compared with only 19% in the sulphonylurea plus placebo group ($p<0.0001$)'.

COMPLAINT

Takeda stated that the data presented in this slide was misleading as it was selective and did not represent the body of evidence or reflect the effects seen using the currently available dose.

The data presented here (and elsewhere) for the efficacy of Avandia in combination with sulphonylurea was study SB015, which used rosiglitazone 2mg bd and had been published by Wolffenbuttel. It was not possible to prescribe rosiglitazone as 2mg bd as no 2mg tablet was available in the UK and the 4mg or 8mg tablets could not reliably be halved. It was only possible to administer rosiglitazone 4mg daily as a once daily dose.

The study using the available dose of rosiglitazone in combination with sulphonylurea had rather more modest efficacy than that cited in the promotional materials. This was misleading.

The difference between the available data and the data presented in the promotional items was most prominent when one looked at the responder rate for HbA1c. This was only 29% in the group treated with 4mg once daily (the only dose which could be prescribed with a sulphonylurea in the UK) compared to the group treated with rosiglitazone 2mg twice daily who were cited in the text for this slide as having a 60% response rate. The 4mg od data was abstracted from Lord *et al* 2000.

Takeda believed that this selective presentation of the data using rosiglitazone 2mg bd, instead of 4mg od (which was the available dose that was being promoted), was misleading, and that these were exaggerated claims for the efficacy of rosiglitazone in

combination with sulphonylurea. Breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that Takeda suggested that presentation of data using Avandia 2mg bd (as opposed to 4mg od) was misleading. This would be correct if there was evidence to show that the two dosing regimens were not equivalent; or, alternatively, if there was no evidence to show that they were. The former was certainly not the case. As for the latter, there was considerable independent evidence in favour of the equivalence of od and bd dosing.

Thus, the Avandia SPC stated that 'Rosiglitazone given once or twice daily with sulphonylurea or metformin produced a sustained improvement in glycaemic control'. More specifically, the European Public Assessment Report (EPAR) on Avandia stated that 'Statistically significant differences between dose levels and regimens were not demonstrated'. The relevant pages from the Avandia EPAR included a summary of the glycaemia findings from phase III trials obtained with different dosing regimens. There was no clear evidence from this summary to suggest any significant difference between bd and od dosing. GlaxoSmithKline referred to an abstract by Grunberger *et al* (1999) which, in a study of 959 patients, demonstrated that the 4mg od and 2mg bd regimens were therapeutically equivalent with respect to reduction in HbA1c levels.

Finally, it should be noted that, with respect to the daily dose of 8mg, od dosing was found to produce better glycaemia results in combination with metformin than did bd dosing. This would tend to indicate that there was no consistent therapeutic advantage for the bd dosing regimen, and that the relatively minor differences seen between the data sets were a result of experimental variability.

GlaxoSmithKline contended that all available evidence indicated that od and bd dosing with Avandia were therapeutically equivalent, only the total daily dose being significant. As such, GlaxoSmithKline did not believe that the use of data from the paper by Wolffenbuttel *et al*, which had been fully published in a peer-reviewed journal, was in any way misleading or inappropriate.

PANEL RULING

The Panel noted that Avandia was available as a 4mg and 8mg tablet and that according to Section 4.2 of the Avandia SPC headed 'Posology and method of administration', Avandia 'may be given once or twice a day'. The Panel further noted that the EPAR report stated that generally, 8mg/d appeared more effective than 4mg/d and twice daily dosing more effective than once daily dosing but 'statistically significant differences between dose levels and regimens were not demonstrated'.

Wolffenbüttel *et al* concluded that Avandia at doses of 1 and 2mg bd plus sulphonylurea produced significant decreases, compared with sulphonylurea plus placebo, in HbA1c (–0.59% and –1.03%, respectively; both $p<0.0001$).

The Panel further noted that Grunberger *et al* evaluated the efficacy of Avandia as monotherapy at total daily doses of 4mg and 8mg once daily or in two divided doses in improving glycaemic control compared with placebo. The study concluded, *inter alia,* that 4mg once daily and 2mg bd regimens met the definition of therapeutic equivalence but Avandia at 4mg bd was more effective than 8mg once daily. The Panel noted that Avandia had been administered as monotherapy and thus not in accordance with its SPC. It was not stated whether the differences between 4mg bd and 8mg od achieved statistical significance.

The Panel noted that in relation to study SB096 referred to by Takeda, not all patients had received Avandia in accordance with its UK SPC in that it was administered to patients who were inadequately controlled on at least half maximal dose (10mg/day) of glibenclamide. Avandia was indicated to treat patients with insufficient glycaemic control despite maximal tolerated doses of monotherapy with either metformin or a sulphonylurea.

The Panel considered that this was a difficult area. It was concerned that the study demonstrating the therapeutic equivalence of the 4mg od and 2mg bd dosage regimen Avandia had not been administered in accordance with its SPC. The Panel however noted the comments in the SPC and EPAR. The Panel queried whether the results quoted on the slide represented the balance of evidence. The Panel noted the table provided by Takeda. On balance the Panel considered that the claim was misleading and did not reflect the balance of evidence. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that the central issue here was whether it was permissible to use Avandia 2mg bd data in promotional materials, given that no 2mg tablet was available in the UK, and that it was therefore only possible to administer Avandia 4mg/day as a single dose.

The Panel admitted that this was a difficult area. GlaxoSmithKline remained confident that the balance of evidence upheld its contention that the 2mg bd dosing regimen was therapeutically equivalent to the 4mg od regimen.

The Avandia EPAR stated categorically that 'Statistically significant differences between dose levels and regimens were not demonstrated'. In its ruling, the Panel noted that the EPAR also stated that, *generally*, 8mg/day appeared to be more effective than 4mg/day, and twice-daily dosing more effective than once-daily dosing. However, the latter was not consistently the case; and examination of the actual reductions in HbA1c obtained with the different dosing regimens in pivotal trials supported the view that such small differences as might exist were attributable only to experimental variability.

For the 4mg/day dose, in combination with sulphonylurea, the 2mg bd regimen led to a reduction in HbA1c of 1.0% (Wolffenbüttel *et al*), relative to placebo; whereas that with the 4mg od

regimen was 0.8% (data on file). In combination with metformin, for which only 4mg od data was available, the reduction was 0.97% (Fonseca *et al*).

For the 8mg / day dose, for which only metformin combination data were available, the reductions were 0.8% with 4mg bd (data on file) and 1.18% with 8mg od (Fonseca *et al*).

Thus, while for the sulphonylurea combination the HbA1c reductions were slightly lower with 2mg bd than with 4mg od, the reduction with the 4mg od metformin combination was almost identical to that with the 2mg bd sulphonylurea combination. Furthermore, for the 8mg / day dose, the od dosing regimen with metformin produced markedly greater HbA1c reductions than the bd regimen. No consistent therapeutic advantage could therefore be adduced for the bd dosing regimen versus the od regimen, supporting the independent EPAR assessment that there were no demonstrable statistically significant differences between dosing regimens.

In a study conducted by Grunberger *et al*, Avandia 4mg od and 2mg bd regimens were administered as monotherapy to a total of 959 diabetic patients. The findings confirmed the above conclusion that the two regimens were therapeutically equivalent with respect to reduction in HbA1c levels. As the Panel pointed out in its ruling, this study was conducted with Avandia as monotherapy, for which the product did not have a licence in the UK. As such, GlaxoSmithKline did not cite it in its promotional materials. However, GlaxoSmithKline believed it was valid and relevant to cite it in the context of establishing whether the two regimens under discussion were therapeutically equivalent. There could be no more convincing evidence of the equivalence of two dosing regimens than a large-scale, double-blind, placebo-controlled, randomised trial, in which confounding factors (eg concomitant therapy) were kept to a minimum. It was not immediately obvious why two regimens that were equivalent as monotherapy should suddenly become inequivalent when administered in combination with another non-interacting drug.

Two other points need to be addressed. Firstly, in its original complaint on this matter, Takeda drew attention to responder rates. Whilst these were interesting as supplementary efficacy information, GlaxoSmithKline believed that the most reliable and generally recognised criterion of antidiabetic efficacy was the absolute reduction in HbA1c relative to placebo. In particular, responder rates were extremely difficult to compare across studies, and their validity in this respect was highly questionable.

Finally, in its judgement, the Panel cast doubt on the validity of one study (Wolfenbüttel *et al*), inasmuch as the patients included in it were controlled on at least half the maximal dose (10mg / day) of glibenclamide, whereas the Avandia SPC indicated the treatment of patients inadequately controlled on maximal tolerated doses of monotherapy with either metformin or a sulphonylurea. GlaxoSmithKline believed there might be some confusion here between 'maximal tolerated dose' and 'maximum recommended dose'. On the one hand, the dose-response curve for sulphonylureas was known to plateau sharply in many patients, so that 'maximal' might not necessarily equate to 'maximum' doses. On the other, there might be other factors, such as high body mass index or an increased incidence of intermittent hypoglycaemic attacks, rendering a further increase in sulphonylurea dosage inadvisable. While it was impossible to tell from the paper in question whether these factors were operative in the patients concerned, the bare fact that not all patients were on the maximum recommended dose of sulphonylurea did not necessarily mean that Avandia was being prescribed outside of its licence indications.

In conclusion, GlaxoSmithKline believed that the balance of evidence from double-blind, randomised trials published in peer-reviewed journals to opinion from independent bodies such as the Committee for Proprietary Medicinal Products fully supported its contention that the 2mg bd Avandia regimen was therapeutically equivalent to the 4mg od regimen. As such, it believed that using 2mg bd data in promotional materials for Avandia did not constitute a breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted the percentage responder HbA1c rate (where HbA1c was reduced by at least 0.7%) in study SB 015 (2mg bd) was 60%, in study SB 079 (2mg bd) was 38% and in study SB 096 (4mg od) was 29%. The Appeal Board noted that in study SB 096 not all patients appeared to have received Avandia in accordance with its UK SPC in that it was administered to patients who were inadequately controlled on at least half maximal dose (10mg / day) of glibenclamide. Avandia was indicated to treat patients with insufficient glycaemic control despite maximal tolerated doses of monotherapy with either metformin or a sulphonylurea. The Appeal Board considered that the magnitude of the difference in responder rates between the two studies was such that the data presented on the slide did not represent the balance of the evidence. The Appeal Board further considered that equivalence between the 2mg bd and 4mg od dose had not been demonstrated. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 . The appeal on this point was unsuccessful.

B2 Slide 76

Slide 76 was headed 'Efficacy: summary' beneath which appeared five bullet points the second of which read 'Magnitude of improvement is clinically important –0.9% ↓ HbA1c = 25% ↓ microvascular complications'.

COMPLAINT

Takeda stated that this slide summarised the effects of Avandia. It implied that the claim for reduction in microvascular complications was related to Avandia usage.

There was no evidence to suggest that use of Avandia could lead to a reduction of microvascular complications of 25%. In fact, the SPC clearly stated

that 'The long term benefits of rosiglitazone have not been demonstrated' and 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated'.

This presentation of outcome data was misleading, could not be substantiated for rosiglitazone and was an exaggerated claim which was outside the licensed indications for rosiglitazone. Breaches of Clauses 3.2, 7.2, 7.3 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that the information on this single slide had to be considered in the context of the other information presented in the slide set. Thus, the United Kingdom Prospective Diabetes Study (UKPDS) data with respect to the effects of glycaemia reductions on the incidence of microvascular complications was cited in several slides, and was clearly referenced to the UKPDS – a landmark study, and one that was very widely cited.

GlaxoSmithKline did not make the claim that administration of Avandia would necessarily result in a 25% reduction in complications; nor did it make any outcome claims for Avandia. Nevertheless, it was true that, in clinical trials, Avandia administration led to an average 0.9% reduction in HbA1c levels; and, given that hard outcome data for type 2 diabetes did exist, GlaxoSmithKline felt that it was appropriate to highlight the potential outcome benefits of seemingly small reductions in HbA1c.

PANEL RULING

The Panel noted that Section 5.1 of the Avandia SPC headed 'Pharmacodynamic Properties' stated that 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated …. There are no studies assessing long-term cardiovascular outcome in patients receiving rosiglitazone in combination with a sulphonylurea or metformin'. The Panel noted the UKPDS data cited by Glaxo Wellcome and referred to throughout the slide presentation. The Panel considered that the statement at issue was an outcome claim, it appeared on a page which purported to summarize the efficacy of Avandia and was thus inconsistent with the Avandia SPC and misleading about the product's licensed indication. Breaches of Clauses 3.2, 7.2 and 7.3 of the Code were ruled. The Panel considered that the alleged breach of Clause 7.8 was covered by these rulings.

C Journal advertisement AVAD000119

Claim 'sustaining control'

The advertisement featured the main claim 'I think control of type 2 diabetes will reach new heights' above three bullet points, 'fighting insulin resistance', 'defending beta-cells' and 'sustaining control'. The product logo appeared at the bottom right hand corner of the advertisement above the phrase '4mg once daily'.

COMPLAINT

Takeda stated that an accepted target level for control of type 2 diabetes was an HbA1c of <7%.

The published data suggested that using rosiglitazone 8mg daily would not achieve or sustain control in the majority of patients. In combination with metformin only 28% of patients achieved the target HbA1c of 7% ie a minority of the patients achieved control (72% of patients did not achieve the target level).

The percentage of patients achieving target with the lower dose of rosiglitazone, 4mg, the dose promoted in the advertisement, had not been shown.

Takeda believed that this was an exaggerated claim which could not be substantiated. Breaches of Clauses 7.3 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that Takeda had chosen to interpret the word 'control' in a highly specific sense, namely the Diabetes UK target level for HbA1c of less than 7%. GlaxoSmithKline maintained that 'control' was more commonly used in a far less restricted way. Thus, one might speak of 'improved control' with an antidiabetic agent, or of a level of 'control' such that the need for insulin was delayed, without by any means having achieved this ideal target. The advertisement in question made no reference to an ideal HbA1c target, and GlaxoSmithKline did not claim that administration of Avandia would automatically result in such a target being attained.

GlaxoSmithKline did claim, however, that Avandia offered the potential of sustained improvements in diabetic control, and the data available fully supported this assertion. Thus, Avandia significantly reduced blood glucose levels when used in combination with metformin or a sulphonylurea and, in open-label extension studies, this level of control was sustained for at least two years. The SPC for Avandia stated that 'In studies with a maximal duration of two years, rosiglitazone given once or twice daily with a sulphonylurea or metformin produced a sustained improvement in glycaemic control'.

Therefore, using the word 'control' in its more inclusive and generally accepted sense, GlaxoSmithKline did not believe that the claim made was in any way exaggerated, or in breach of Clauses 7.3 and 7.8 of the Code.

PANEL RULING

The Panel noted that the advertisement did not refer to the Diabetes UK target level for HbA1c. The Panel considered that the word control would be read in light of the clinical claims in the advertisement; fighting insulin resistance and defending beta-cells. The Panel noted that Section 5.1 of the Avandia SPC stated that 'In studies with a maximal duration of two years, rosiglitazone given once or twice daily in combination with a sulphonylurea or metformin produced a sustained improvement in glycaemic control (FPG and HbA1c)'. The Panel did not consider the claim to be incapable of substantiation or

exaggerated as alleged. No breach of Clauses 7.3 and 7.8 of the Code was ruled.

D Product monograph and press release

D1 Product monograph:

Claim: '… other members of the drug class, troglitazone and pioglitazone, are metabolised through CYP3A4, a common metabolic pathway for a wide range of drugs (Figure 1, Table 1) and, thus, have associated potential for drug interactions. This is a particular concern, given the levels of polypharmacy in patients with type 2 diabetes'

This claim appeared on page 41 of the product monograph in a section headed 'Drug Interactions' which discussed Avandia's 'low potential for interaction with co-administered drugs' and concluded with the claim at issue. A table listed those medicines including pioglitazone which were metabolised by CYP3A4 and CYP2C8 pathways. A figure on page 42 depicted the proportion of medicines metabolised by the cytochrome P450 enzymes.

D2 Press release:

Claim: '… unlike other glitazones, Avandia has a low potential for interactions with commonly co-prescribed therapies for people with Type 2 diabetes'

COMPLAINT

Takeda stated that these promotional items for rosiglitazone and feedback through its representatives had indicated that GlaxoSmithKline was suggesting that pioglitazone had a greater potential for drug interactions than rosiglitazone because one of the pathways of metabolism was through CYP3A4. In response to Takeda's concerns, GlaxoSmithKline had asserted that it felt ' … it is correct to say that the potential for drug interactions with rosiglitazone is lower than with pioglitazone as a result of the difference in routes of metabolism' (letter dated 19 December 2000). This was not supported by the body of evidence.

No drug interactions had been identified with pioglitazone, and pioglitazone had not been shown to inhibit or induce cytochrome P450, so it was thought that pioglitazone had a low potential for drug interactions.

A comparison of the UK SPCs for rosiglitazone and pioglitazone did not support these claims. The Actos SPC had no drug interactions listed under Section 4.5 'Interaction with other medicinal products and other forms of interaction' yet the Avandia SPC advised caution for use with paclitaxel.

Takeda noted that it was stated in a letter to Takeda from GlaxoSmithKline that 'representatives have never been briefed to tell doctors or pharmacists that pioglitazone is likely to have drug interactons' (dated 19 December 2000). This statement was not consistent with data presented in the promotional materials. Takeda was concerned that GlaxoSmithKline denied that its representatives had had materials suggesting that pioglitazone had drug interactions.

The statements were being used to mislead prescribers to believe that pioglitazone had drug interactions. Takeda believed that this could not be substantiated, was misleading and disparaging. Breaches of Clauses 7.2, 7.3 and 8.1 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that whilst it accepted that there was no firm data as of this moment to indicate significant drug interactions with pioglitazone, it maintained that, pharmacologically, the potential for such interactions remained higher for pioglitazone than for Avandia. This was based on the fact that pioglitazone was, in part, metabolised by the cytochrome P450 enzyme CYP3A4, which was also responsible for metabolism of the widest range of other pharmacological agents. The metabolism of Avandia, in contrast, was primarily via the enzyme CYP2C8, responsible for the metabolism of only a few clinically utilised agents.

At the time that the Avandia monograph went to press, GlaxoSmithKline had no access to the UK Actos SPC, as it had not at that time received marketing authorisation. The only available information in this area was the US prescribing information and other sources in the public domain at that time.

GlaxoSmithKline noted from the US prescribing information for pioglitazone that *in vitro* studies of pioglitazone and ketoconazole resulted in a significant inhibition of pioglitazone metabolism, and that 'Pending the availability of additional data, patients receiving ketoconazole concomitantly with Actos (pioglitazone) should be evaluated more frequently with respect to glycaemic control'. Until interaction studies had been carried out with pioglitazone and significant CYP3A4 inducers and inhibitors (eg ketoconazole, fluvoxamine, the protease inhibitors and carbamazepine), GlaxoSmithKline submitted that it remained correct to say that the potential for drug interactions with Avandia was lower than that with pioglitazone, as a result of the difference in their routes of metabolism.

Finally, a BMJ editorial (Krentz *et al* 2000) stated 'Pioglitazone induces cytochrome P450 isoform CYP3A4, raising the possibility of drug interactions, such as with oral contraceptives'.

GlaxoSmithKline thus did not believe that the statements made in the monograph and press release with respect to the potential for drug interactions were incorrect or disparaging, but rather took into account currently available evidence.

That said, the Avandia monograph was currently out of print and GlaxoSmithKline was currently reviewing the content for an updated version to be published in the near future, taking account of all currently available information.

PANEL RULING

The Panel noted the submission that when the product monograph was published, pioglitazone had not received its marketing authorisation. It noted that the embargo date on the press release was 24 July 2000. The Panel noted that promotional material not only had to be correct at date of publication but also when it was later used or distributed by the company. The Panel noted that the product monograph was currently out of print and it did not know whether the product monograph was used or distributed after publication of the Actos SPC. The Panel noted that at the time of publication GlaxoSmithKline had access to the US prescribing information for pioglitazone which indicated a potential for interaction pending further studies. The BMJ editorial (Krentz *et al*) was also available which raised the possibility of drug interactions (with pioglitazone) such as oral contraceptives. The Panel noted that GlaxoSmithKline accepted that there was no firm data to indicate significant drug interactions with pioglitazone but pharmacologically the potential for such interaction remained higher for pioglitazone than for Avandia.

The Panel noted that neither party had provided evidence to show a problem in practice. It also noted the different metabolic pathways of Avandia and pioglitazone and their different potential for associated drug interactions. The Panel considered that given GlaxoSmithKline's submission regarding the absence of firm data to indicate significant drug interaction with pioglitazone and the lack of data in patients, the product monograph and press release each created the overall impression that pioglitazone had a high incidence of drug interactions and this was misleading and disparaging. Breaches of Clauses 7.2, 7.3 and 8.1 of the Code were ruled.

E Leavepiece AVLT 00154

E1 Page 2 Claim 'Only Avandia improves both fundamental causes of type 2 diabetes: insulin resistance and beta cell dysfunction'

COMPLAINT

Takeda stated that this statement could not be substantiated. Avandia was not the only medicine that affected insulin resistance and beta-cell function.

There was evidence to show that pioglitazone reduced insulin resistance and led to significant improvements in beta-cell function (Hanefeld and Göke 2000). Therefore the effect on improving beta-cell function was not unique to rosiglitazone. This exaggerated claim with the use of the word 'only' could not be substantiated. Breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that this issue had been dealt with above in point A1.

PANEL RULING

The Panel considered that the claim at issue was different to that at issue at point A1; the Panel did not consider that 'preserving ß-cell function' (as in point A1 above) was the same as 'improves … beta cell dysfunction' as in the claim now at issue. Nonetheless the Panel considered that the principles set out at point A1 applied here. No breach of Clauses 7.2 and 7.8 was ruled.

APPEAL BY TAKEDA

Takeda referred to its appeal and comments at point A1 above.

RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline referred to its response at point A1 above.

FURTHER COMMENTS FROM TAKEDA

Takeda referred to its further comments at point A1 above.

APPEAL BOARD RULING

The Appeal Board considered that its ruling at point A1 above applied here. Breaches of Clauses 7.2 and 7.8 were ruled. The appeal was successful.

E2 Claim 'Therefore Avandia has the potential to delay disease progression and reduce complications'

COMPLAINT

Takeda stated that this claim was not consistent with the SPC for rosiglitazone which stated clearly that 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated'. In addition, it was not consistent with the views of the EMEA from the European Public Assessment Report which stated 'The potential long-term effects of the observed changes in the lipid profile on the cardiovascular system cannot be predicted and therefore raise concerns'. Takeda believed that this claim was speculative and not consistent with the body of evidence or the SPC. Breaches of Clauses 3.2 and 7.2 were alleged.

RESPONSE

GlaxoSmithKline stated that it was true that the SPC for Avandia stated that 'An outcome study has not been conducted with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated'. Nevertheless, the UKPDS had incontrovertibly established that improvements in glycaemic control were associated with a reduced incidence of complications. Inasmuch as Avandia – among other things – significantly improved glycaemic control, it surely could not be denied that it had the potential to delay disease progression and reduce complications. GlaxoSmithKline did not claim that Avandia did this in all cases, and thus it believed the claim to be fair and not exaggerated. One might ask the question that, if an antidiabetic agent did not have the potential

to improve glycaemic control and reduce complications, what point there would be in prescribing it at all?

Finally, to quote the NICE Technology Appraisal Guidance for Avandia once again: 'There is no direct evidence from comparative trials that the addition of rosiglitazone to oral monotherapies will reduce the incidence of diabetic complications …. However, the results of the UKPDS trial demonstrated that improved glycaemic control reduces the incidence of diabetic complications. Thus, it is likely that, by lowering blood glucose levels and further maintaining glycaemic control, rosiglitazone combination therapy for patients who fail to meet glycaemic targets on oral monotherapy will reduce the risk of diabetic complications'.

PANEL RULING

The Panel noted that the NICE Technology Appraisal Guidance 2000 stated that further research was needed to investigate long-term outcomes with rosiglitazone combination therapy. This research should determine the effect of rosiglitazone combination therapy on 'the long-term (greater than two years) maintenance of glucose lowering effects and the longer-term impact on cardiovascular risk factors'. The Avandia SPC referred to a sustained improvement in glycaemic control in studies with a maximal duration of two years. It was further stated that 'The long-term benefits associated with glycaemic control have not been demonstrated'. The Panel noted GlaxoSmithKline's submission regarding NICE and the UKPDS trial.

The Panel considered that the claim would be seen as a specific claim for Avandia; it would not be seen as a general statement of the benefits of improved glycaemic control.

The Panel considered that the statement at issue claimed an outcome improvement and there was no evidence before it that Avandia delayed the rate of progression of the disease or reduced complications. The Panel considered that the claim was misleading and inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline noted that the Panel considered that the statement amounted to a claim of an outcome improvement with Avandia; the company did not believe this to be the case. It accepted that no hard outcome data currently existed for Avandia, and agreed with the NICE Technology Appraisal Guidance 2000 that further research was needed to investigate long-term outcomes with rosiglitazone therapy. Such research was in progress.

However, it contended that the claim was fully in line with current medical opinion in diabetes, following the publication of the United Kingdom Prospective Diabetes Study (UKPDS). This landmark study finally established for type 2 diabetes that improvements in glycaemic control were associated with a reduced incidence of complications.

By improving glycaemic control in patients who would otherwise have little choice but to go on to insulin, Avandia undoubtedly had the potential to delay disease progression. Likewise, it at least had the potential to reduce complications, in line with UKPDS findings.

This view was endorsed by NICE in the Technology Appraisal Guidance cited above. To quote the relevant passage (italics added): 'There is no direct evidence from comparative trials that the addition of rosiglitazone to oral monotherapies will reduce the incidence of diabetic complications …. However, the results of the UKPDS trial demonstrated that improved glycaemic control reduces the incidence of diabetic complications. *Thus, it is likely that, by lowering blood glucose levels and further maintaining glycaemic control, rosiglitazone combination therapy for patients who fail to meet glycaemic targets on oral monotherapy will reduce the risk of diabetic complications*'.

GlaxoSmithKline therefore believed that, if a prestigious and independent body such as NICE stated that Avandia was 'likely' to reduce the risk of complications in suitable patients, it was justifiable to make the weaker claim that Avandia 'has the potential' to do so. The statement as it stood was accurate, balanced, not all-embracing, and fully reflected current expert medical opinion. As such, GlaxoSmithKline would ask the Appeal Board to reassess this particular claim, as it did not believe that it represented a breach of either Clause 3.2 or 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Therefore Avandia has the potential to delay disease progression and reduce complications' was a claim for the outcome of treatment with Avandia. The company had no endpoint data to support such a claim which the Appeal Board considered was not in accordance with the SPC. The Appeal Board upheld the Panel's ruling of breaches of Clauses 3.2 and 7.2 of the Code. The appeal on this point was unsuccessful.

E3 Claim 'More than one year's global post-marketing experience has shown that most patients take Avandia 4mg daily'

COMPLAINT

Takeda stated that this statement was referenced to NICE Technology Appraisal Guidance – No 9 which referred to the US usage in the early months post launch. This included patients on monotherapy which was not a UK licensed indication.

The data which was relevant to the UK usage was only the patients taking combination therapy. Recent data from IMS (US) from October 2000 indicated that currently 61% of patients receiving combination therapy of rosiglitazone with metformin were prescribed 8mg per day and 55% of patients taking rosiglitazone with sulphonylurea received 8mg per day. This meant that in the US most patients receiving rosiglitazone as combination with metformin or sulphonylureas were prescribed the 8mg dose. (The data for monotherapy should be excluded as this was an unlicensed indication in the UK.)

This statement did not reflect the most up-to-date evidence of the dose patients were prescribed in combination therapy and was misleading. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline stated that it accepted that, given the various doses of rosiglitazone in use globally (including doses unlicensed in the UK), and the differing dosing regimens (including monotherapy in the US, an unlicensed regimen in the UK), it was possible to 'cut' the data in various ways to arrive at different conclusions. To avoid unnecessary complexities, GlaxoSmithKline pointed out that this leavepiece was being withdrawn and amended, and that this statement would no longer be included in it. It also pointed out that post-marketing data in the UK had demonstrated that, since the launch of Avandia, approximately 95% of patients had been treated with the 4mg dose; and therefore that, in the context of UK experience alone (the particular issue raised by Takeda), the essence of the claim made was correct, however inclusive or exclusive one might be with respect to non-UK data.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that in the UK since the launch of Avandia, approximately 95% of patients had been treated with the 4mg dose. The claim at issue, however, referred to global post-marketing experience and was based on monotherapy use. The Panel noted the data supplied by Takeda with regard to use in the US of 8mg of Avandia in combination therapy. The claim was misleading and the Panel ruled a breach of Clause 7.2 of the Code.

E4 Claims 'Diabetes UK recommends an HbA1c level of ≤7%' and 'Avandia .. sustaining control'

The first claim appeared in a box headed 'Glycaemic control'. The second claim appeared at the bottom of the page adjacent to the brand name beneath the claims 'fighting insulin resistance' and 'defending beta-cells'.

COMPLAINT

Takeda stated that treatment with rosiglitazone only allowed a small minority of patients to achieve an HbA1c of <7%, the level recommended by Diabetes UK.

In a published study (Fonseca *et al* 2000) using rosiglitazone 8mg daily in combination with metformin only 28% of patients achieved the target HbA1c of 7% ie a minority of the patients achieved control. (72% of patients did not achieve the target level.) The percentage of patients achieving target with 4mg rosiglitazone (the dose promoted in the leavepiece) had not been shown.

Takeda believed that this claim for sustaining control was an exaggerated claim that could not be substantiated. Breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline stated that this issue had been substantially addressed above in point C. To reiterate, GlaxoSmithKline believed that Takeda had chosen to interpret the word 'control' in an inappropriately restrictive sense and that, in the more common usage of the word, the claim made was justifiable and not in breach of the Code.

PANEL RULING

The Panel firstly considered the heading 'Glycaemic control' and the associated claim 'Diabetes UK recommends an HbA1c level of ≤ 7%' and considered that the context in which the word 'control' was used was different to that considered at point C above. The word 'control' was now specifically linked with the Diabetes UK recommendation of HbA1c level of ≤ 7%.

The Panel noted that the pages of the leavepiece provided referred solely to the 4mg dose; '4mg once daily' was incorporated into the product logo. GlaxoSmithKline had referred to its response at point C. The Panel considered that the claims gave the impression that, in terms of glycaemic control, Avandia 4mg once daily achieved the Diabetes UK recommendation, ie HbA1c levels of ≤ 7%, and on the evidence before it that was not so. The Panel considered the claims misleading and exaggerated as alleged. Breaches of Clauses 7.2 and 7.8 were ruled.

E5 Spelling of generic name

COMPLAINT

Takeda stated that it had also alerted GlaxoSmithKline to the error in the spelling of the generic name in three different places adjacent to the brand name in this item (pages 1 and 3). It had been called 'rosiglitzone' so therefore the non-proprietary name had not appeared immediately adjacent to the most prominent display of the brand name. A breach of Clause 4.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline stated that this unfortunate error obviously represented an embarrassing and regrettable lapse in the proof-reading process, and a *de facto* – if inadvertent and 'harmless' – breach of the Code. As noted, the material in question was being withdrawn and amended. A review of the approvals process would be undertaken to ensure that such an error did not recur.

PANEL RULING

The Panel noted that Clause 4.2 listed the content of prescribing information and required that in addition the non-proprietary name of the medicine must appear immediately adjacent to the most prominent display of the brand name. The Panel noted that the non-proprietary name had been misspelt and thus the requirements of Clause 4.2 had not been satisfied. A breach of that clause was ruled.

F Leavepiece AVLP00152b

F1 Claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for Primary Care Organisations (PCO) †'

The obelus referred to the footnote 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period'

The claim appeared beneath the heading 'Maximising scarce resources' and the obelus referred the reader to the footnote beneath a table which compared the annual cost of Avandia 4mg with pioglitazone 30mg.

COMPLAINT

Takeda stated that the doses that had been compared for rosiglitazone and pioglitazone had not been shown to be comparable. There was no data to support the statement 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period'. Therefore it could not be substantiated and breaches of Clauses 7.2 and 7.3 of the Code were alleged.

In relation to the claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for primary care organisations (PCO)', Takeda stated that the costs shown had compared the lowest dose of rosiglitazone and the highest dose of pioglitazone. This was not a fair and balanced comparison and breaches of Clauses 7.2 and 8.1 were alleged.

If the costs were examined for the lowest doses of pioglitazone and rosiglitazone, there was no difference in the cost as both were priced at 95p per day for the lowest doses.

However, if one looked at the highest doses of rosiglitazone and pioglitazone, then the cost of treating 110 patients with rosiglitazone would be £70,224 (if 4mg bd) or £72,072 (if 8mg od) yet the cost of treating 110 patients with pioglitazone would be £48,787.

It was interesting to note that NICE also suggested that the expected average annual cost for each patient treated with rosiglitazone would be £430. This information had been omitted from the calculation of the cost to the PCO. This was very misleading and a selective presentation of the data.

If one substituted the expected costs based on the NICE Technology Appraisal Guidance it would be seen that to treat 110 patients with rosiglitazone would cost £430 x 110 = £47,300 instead of £35,112 as suggested in this piece.

The claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for primary care organisations (PCO)' was misleading as these were not comparable doses and not all patients in a PCO could be expected to be treated with the maximum recommended dose of one yet the minimum available dose of the other. Breaches of Clauses 7.2, 7.6 and 8.1 of the Code were alleged.

RESPONSE

GlaxoSmithKline noted that the objections raised by Takeda to this leavepiece were essentially twofold. Firstly that it was inappropriate to compare the efficacy of Avandia and pioglitazone, irrespective of dose, as no direct head-to-head data comparing the two agents currently existed. Secondly that it was unfair and unbalanced to compare, in cost terms, the 'lower' dose of Avandia (4mg od) with the 'higher' dose of pioglitazone (30mg od).

GlaxoSmithKline contended that, if primary- or secondary-care physicians were to make an informed decision between two agents, it was right and proper that they should have all the information on which to base such a decision. It was true that direct head-to-head data comparing Avandia and pioglitazone did not exist at present. In the absence of such data, the only indications the clinician had with respect to comparative efficacy and tolerability must come from the results of broadly similar trials conducted with each agent separately and it was this that was presented in the leavepiece in question. Naturally, in presenting such data, it was important that it be made quite clear that the results from different studies were being compared, and that any differences between the study populations that might affect interpretation of these results were made explicit. GlaxoSmithKline had been scrupulously careful to include this information in the leavepiece (eg the baseline HbA1c levels and durations of the various study populations were clearly presented).

GlaxoSmithKline therefore contended that, always providing sufficient information was supplied as to the provenance of the data (which it believed was the case in this instance), presentation of the only available information on the relative efficacy and tolerability of the two agents was not only justifiable, but crucial, if physicians were to make informed prescribing decisions.

With respect to the actual doses compared, Takeda glossed over a crucial point in its complaint, namely that the 30mg dose of pioglitazone was the only dose promoted by Takeda, in all communications media.

Indeed, it was a moot point whether, in so doing, Takeda was not itself in breach of the Code. Thus, in its Questions and Answers booklet, the question was posed: 'What is the dose of [pioglitazone]'; to which the answer given was 'One [pioglitazone] 30mg tablet once daily irrespective of mealtimes'. The view could be taken that, by implying that only one possible dose of pioglitazone existed, whereas, in reality, a lower dose (15mg) was also licensed and available in the UK, Takeda was supplying misleading and inaccurate information to the medical community.

However one viewed this matter, or the possible motivations underlying the omission of the 15mg dose from Takeda's promotional materials, the fact remained that this restricted dose promotion had a crucial bearing on the issues raised by Takeda. Thus, whereas (as noted above), UK post-marketing data indicated that approximately 95% of diabetics treated with Avandia were started at the 4mg dose, one might expect that the great majority of diabetics treated with pioglitazone would be started at 30mg, as this was the only promoted dose.

GlaxoSmithKline maintained that, since it was highly likely that a patient being started on Avandia would receive the 4mg dose, whereas one started on pioglitazone would receive the 30mg dose, it was perfectly appropriate to draw attention to the cost implications of choosing between the two agents, when a glitazone was being considered It was quite disingenuous of Takeda to suggest that 'If the costs are examined for the lowest doses of pioglitazone and rosiglitazone, there is no difference in the cost …', as it was not promoting the lower pioglitazone dose at all. The correct cost comparison, therefore, should be made between Avandia 4mg and pioglitazone 30mg. Other factors being equal, it was incontrovertible that Avandia 4mg was less expensive than pioglitazone 30mg and, as such, GlaxoSmithKline believed that pointing out the cost differential between the two doses mentioned was justifiable and in no way misleading. Similarly GlaxoSmithKline believed that Takeda's attempt to compare the costs of Avandia 8mg and pioglitazone 30mg was based on spurious assumptions.

GlaxoSmithKline contended that the overall comparison between the 4mg dose of Avandia and the 30mg dose of pioglitazone showed that they were broadly comparable in efficacy and tolerability terms. As such, GlaxoSmithKline believed it was not in any way improper to point out to clinicians the cost implications of their prescribing decisions.

To sum up GlaxoSmithKline believed that it was not misleading to compare the costs of Avandia 4mg and pioglitazone 30mg , inasmuch as these were the most likely choice of doses for initiation of therapy in the UK. Further, in the absence of any direct comparison between the two agents, it was appropriate and justifiable to compare the results of studies conducted with each agent separately, provided that the basis of the comparison was made quite clear.

GlaxoSmithKline therefore contended that, in making these comparisons, it was not in breach of Clauses 7.2, 7.6 and 8.1 of the Code.

A subsidiary point raised by Takeda needed to be addressed. It cited the NICE Technology Appraisal Guidance (No 9) with respect to Avandia, in which the expected average annual cost for each patient treated with Avandia was stated as £430. This amount was based on projected figures supplied to NICE by SmithKline Beecham, in which a ratio between prescription of the 4mg and 8mg doses of Avandia of 75% to 25% was assumed. However, it should be noted that this was a medium- to long-term projection of usage ratios, as available data suggested that patients were likely to be stabilised on the 4mg dose for up to two years. Furthermore, the vast majority of patients newly treated with Avandia in any one period of time would receive this dose, whereas the majority of those receiving pioglitazone would receive 30mg. It was therefore not misleading to compare the annual cost of these two doses. If one were to take into account those patients who might have their dose of Avandia increased to 8mg, one would also have to take account of those on pioglitazone who went on to insulin (as there was no higher licensed dose of pioglitazone than 30mg). Assuming a roughly similar failure rate between the two products, this would probably result in a still greater cost advantage in favour of Avandia. As such failure rates remained speculative, GlaxoSmithKline believed that the annual cost comparison made was equally fair to both products.

PANEL RULING

The Panel noted that the Avandia SPC stated that therapy was usually initiated at 4mg / day; in combination with metformin that dose could be increased to 8mg / day after 8 weeks if greater glycaemic control was required. There was currently no experience of doses above 4mg / day in combination with sulphonylureas. The pioglitazone SPC stated that its licensed dose in combination with metformin or a sulphonylurea was 15mg or 30mg once daily.

The Panel considered that the claim 'Using Avandia 4mg daily instead of pioglitazone 30mg daily represents a significant saving for primary care organisations (PCO)' and its footnote 'Assuming similar glycaemic control is maintained on Avandia 4mg daily or pioglitazone 30mg daily over a 12 month period' created the impression that the doses stated were clinically comparable. The Panel noted that there were no direct head-to-head studies of Avandia and pioglitazone. The Panel 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 etc. The Panel noted GlaxoSmithKline's submission that it was not misleading to compare these doses because these were the most likely choice of doses for initiation of therapy in the UK. GlaxoSmithKline referred to the presentation of results from non-comparative studies in the leavepiece at issue. The relevant pages of the leavepiece had not however been provided to the Panel. On the information before it the Panel considered that claim misleading as the basis of the comparison had not been made sufficiently clear. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel did not consider the claim disparaging. No breach of Clause 8.1 was ruled.

F2 Pioglitazone 30mg daily is the starting dose recommended by the licence holders

This claim appeared as a bullet point at the bottom of the page at issue.

COMPLAINT

Takeda stated that the SPC recommended that 'Pioglitazone in combination with metformin may be used at the dose of 15mg or 30mg once daily' and 'Pioglitazone in combination with sulphonylurea may be used at the dose of 15mg or 30mg once daily'.

There was no recommendation in the reference given or the SPC that pioglitazone 30mg was the starting dose and the statement in the piece did not accurately reflect the range of doses and was therefore not accurate or balanced. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

With respect to the statement 'Pioglitazone 30mg daily is the starting dose recommended by the license holders', GlaxoSmithKline accepted that this was unfortunately worded, inasmuch as there was no recommended 'starting dose' for pioglitazone. A more accurate phraseology would have been 'Pioglitazone 30mg daily is the only dose promoted by the licence holders'. Accordingly, this leavepiece had been withdrawn and would be amended.

PANEL RULING

The Panel considered that the claim at issue implied that 30mg daily was the licensed starting dose and that was not so. A breach of Clause 7.2 was ruled.

G Leavepiece AVLP00152a

Takeda alleged that the table in this item was misleading. There was no head-to-head comparison of the two medicines.

GlaxoSmithKline stated that several of the issues raised by Takeda concerning this leavepiece were identical to those raised elsewhere. As noted above, it had accepted that some statements required amendment, and the leavepiece had been withdrawn prior to receiving Takeda's formal complaint, and would be modified as above. Only those issues raised that did not duplicate points responded to above would be dealt with.

G1 Effect on beta-cell function

The table indicated that Avandia 4mg once daily improved beta-cell function whilst pioglitazone 30mg once daily had no direct effect.

COMPLAINT

Takeda alleged that the two statements were misleading.

The table implied that the two claims for effects on beta-cell function were due to different effects. However the two statements here were not mutually exclusive and both might apply to both of these medicines.

Pioglitazone had been shown to improve beta-cell function even though pioglitazone had no direct effect on beta-cell function.

To date it appeared that the mechanism of the improvement in beta-cell function seen with rosiglitazone had not been elucidated, and as no data had been provided after requests to SmithKline Beecham, Takeda must assume that this was not a direct effect of rosiglitazone on the beta-cell.

Takeda believed juxtaposing these two statements about beta-cell function was meant to mislead the reader to believe that rosiglitazone had a unique effect on the beta-cell.

It was therefore misleading and an exaggerated claim and breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

GlaxoSmithKline accepted that the two statements were not mutually exclusive, and potentially confusing, and the table would be amended.

GlaxoSmithKline maintained that, at the time of writing, only Avandia had been shown to result in improvements in beta-cell function, compared to placebo, in combination with both sulphonylurea and metformin (see point A1 above).

GlaxoSmithKline did not claim that the improvements seen with Avandia on beta-cell function were a result of a 'direct' effect.

PANEL RULING

The Panel considered that its ruling at point A1 above was relevant with reference to the claim 'Only Avandia takes control of type 2 diabetes by directly reducing insulin resistance and preserving beta-cell function'.

The Panel noted GlaxoSmithKline accepted that the two statements were not mutually exclusive and were potentially confusing. The Panel considered that the table implied that Avandia had a unique effect on beta-cell function. The mechanism of effect had not been elucidated. It implied that pioglitazine had no effect on beta-cell function and that was not so. A breach of Clause 7.2 was ruled. The Panel considered that this ruling covered the alleged breach of Clause 7.8.

G2 Short term impact on HbA1c

The table stated that Avandia, in combination with a sulphonylurea or metformin, produced a 1% reduction in the HbA1c from baselines of 9.2 and 8.9 respectively. The equivalent data for pioglitazone was a 1.3% reduction (baseline 9.9) with sulphonylurea and a 0.8% reduction (baseline 9.9) with metformin. It was stated that the data were taken from different studies.

COMPLAINT

Takeda stated that these were not head-to-head comparisons and the studies were of different durations so no valid comparison of the results could be made. Takeda believed that this presentation of the rosiglitazone and pioglitazone data side by side was misleading and so in breach of Clauses 7.2 and 7.6 of the Code.

It was not made clear that the changes shown were the mean or median differences from placebo – not the change from baseline (the changes from baseline were rather smaller).

The data shown for the effect of rosiglitazone with sulphonylurea appeared under the heading Avandia 4mg once daily yet the data shown was for a twice daily dose. (The reference cited was incorrect as the reference referred to a study combining rosiglitazone with metformin.) If the correct change from baseline was inserted into the table using the once daily dose (Study SB0960), this figure would read a change in HbA1c of just –0.3% from baseline or a change from placebo of –0.8%.

The use of the study using the twice daily dose gave an exaggerated level of efficacy; it was misleading to make a claim for a once daily dose when the study was clearly using a twice daily dose and the citation of the reference was inaccurate.

It was also misleading to use the data from a study using twice daily dosing when the dose 2mg bd could not be prescribed as there was no 2mg tablet available in the UK.

Takeda believed these claims for efficacy of once daily dosing when twice daily was used in the study were misleading and exaggerated and so in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

GlaxoSmithKline stated that this complaint duplicated that made for slide 70 of the Avandia slide set, and had been responded to above in point B1.

PANEL RULING

The Panel considered that its general comments about the absence of head-to-head studies made at point F1 above were relevant. The Panel considered that its ruling at point B1 above applied regarding the use of the 2mg bd dosage regimen. Breaches of Clauses 7.2 and 7.8 were ruled.

G3 Impact on TC:HDL ratio

The table stated that Avandia demonstrated improvement over an 18 month period whilst for pioglitazone improvement was demonstrated over a 40 week period.

COMPLAINT

Takeda stated that here the 18 month results for rosiglitazone had been compared with 40 week results for pioglitazone. This was very misleading. (It noted in this table that in each case for rosiglitazone the time point represented was different even though the data was from the same study. It appeared that the best results and not necessarily the body of evidence had been represented.) Takeda believed that the selective presentation of the data was misleading and so in breach of Clause 7.2 of the Code.

If one looked at the short-term placebo controlled phases of the studies one saw a different effect to the one claimed in this piece. From SmithKline Beecham data on file it was clear in controlled trials that the initial effects of rosiglitazone in combination with metformin or sulphonylurea showed either an increase or no change of the TC:HDL ratio in the first 6 months. It was only in the open extension studies (where statins could be added) that the decrease of the TC:HDL cholesterol ratio was seen.

The SPC for rosiglitazone stated that the ratio of total TC:HDL cholesterol was unchanged or improved in long term studies. The 'unchanged' had conveniently been omitted here. This was a selective presentation of the data which was misleading and in breach of Clause 7.2 of the Code.

In contrast to this, in the placebo controlled trials with pioglitazone improvements in the TC:HDL ratio had been seen and in the long-term open extension studies these changes were maintained.

During the long-term extension studies rosiglitazone was used at either a once or twice daily dose so again the appearance of this data under the heading 'Avandia 4mg once daily' was misleading.

This presentation of the data was misleading as the data was not from comparable studies and the presentation of the rosiglitazone data was highly selective. Breaches of Clauses 7.2, 7.6 and 7.8 of the Code were alleged.

RESPONSE

Again, this complaint largely duplicated that made for slide 10 of the Avandia slide set in point A2. GlaxoSmithKline reiterated that the CPMP agreed that the long-term data with Avandia presented in this table warranted the SPC statement that 'the ratio of total cholesterol:HDLc was unchanged or improved in long-term studies'. As noted, GlaxoSmithKline accepted that the word 'unchanged' should have been included in the table for completeness, and this would be amended.

PANEL RULING

The Panel considered that its ruling at point A2(ii) applied here. A breach of Clause 7.2 was ruled.

G4 Cost comparison

COMPLAINT

Takeda stated that this cost comparison was again comparing the cost of the highest dose of pioglitazone with the lowest dose of rosiglitazone. This was highly misleading. Breaches of Clauses 7.2 and 8.1 of the Code were alleged.

RESPONSE

This had been dealt with in detail above in point F1.

PANEL RULING

The Panel considered that its ruling at point F1 above was relevant. A breach of Clause 7.2 was ruled. The Panel did not consider the claim disparaging; no breach of Clause 8.1 was ruled.

H Letter to diabetes lead from medical director of SmithKline Beecham

COMPLAINT

Takeda stated that this letter was sent unsolicited to general practitioners. It was on SmithKline Beecham headed paper and was signed by the medical director. There was no clear indication on the front of the letter that this was a promotional piece, and the signature of the medical director implied that it was an important communication with information about cost implications and cost effectiveness. However, it merely gave highly selected information about the

costs of the lowest dose of rosiglitazone and the highest dose of pioglitazone. There was no data presented on cost effectiveness of either of these medicines.

The up-to-date evidence for efficacy of pioglitazone had not been included. At the time that this piece was prepared (5 January 2001) data on the efficacy of pioglitazone for up to 72 weeks had been published. The omission of the most up-to-date published data was misleading. A breach of Clause 7.2 of the Code was alleged.

With regard to the claim 'I hope that this comparison clarifies the cost implications of prescribing the two glitazones should you consider issuing local guidelines to prescribers', Takeda stated that in the NICE Technology Appraisal, NICE estimated that at least 25% of patients would receive the higher dose of rosiglitazone. Therefore the average annual cost of using rosiglitazone would be expected to be £430 instead of £364.74 as was listed in this letter. This had been ignored. (The average annual cost of pioglitazone would clearly not be as high as had been suggested as it was very unlikely that all patients would receive the maximum dose.) This piece had not clarified the costs, and the suggestion in this letter that this misleading cost comparison should be used as a basis for local guidelines raised concern. Takeda believed that this letter did not recognise the responsibility of professionals issuing guidelines and that high standards must be maintained for promotion of medicines. A breach of Clause 9.1 of the Code was alleged.

Similar misleading claims were made to those in the promotional item AVLP00152a. Breaches of Clauses 7.2, 7.6 and 7.8 of the Code were alleged. Takeda alleged that this was disguised promotion in breach of Clause 10.1 of the Code.

Takeda believed that the content of this letter brought the industry into disrepute and was in breach of Clause 2 of the Code.

RESPONSE

GlaxoSmithKline stated that there was no requirement in the Code that envelopes containing promotional material should have any indication on their exterior as to the nature of their contents, only that any such indications should not mislead. There was, therefore, no case to answer on this point.

Likewise, there was no prohibition or other indication in the Code as to who might or might not sign promotional materials addressed to clinicians. The fact that, on this occasion, the letter in question was signed by the then medical director of SmithKline Beecham could not, therefore, in itself, be a breach of the Code.

Takeda alleged that this letter represented 'disguised promotion'. One must ask, then, what it was disguised as. The Code mentioned several ways in which promotion might be disguised (for instance, as market research, post-marketing surveillance, etc), but the letter quite evidently did not fall into any of these categories. On the contrary, it was written on SmithKline Beecham letterhead, carried prescribing information on the reverse, and compared the efficacy and costs of a SmithKline Beecham product with that of a direct competitor. As such, it would not be mistaken for anything other than a promotional piece.

With the exception of the initial and final paragraphs, the content of the letter was essentially identical to that of leavepiece AVLP00152a (point G). As Takeda did not claim that this leavepiece constituted disguised promotion when it was shown to clinicians by representatives, it was difficult to see why the same information should suddenly become disguised promotion by its inclusion in a letter signed by the medical director.

GlaxoSmithKline therefore emphatically denied that this letter represented a breach of Clause 10.1 of the Code, and still less of Clause 2.

As to the contents of the letter itself, most of the points had already been addressed, particularly concerning the appropriateness of the cost comparisons made, and the basis of the NICE estimates with respect to cost.

In its letter, Takeda stated that 'data on the efficacy of pioglitazone for up to 72 weeks' had been published. Unfortunately these data were inadmissible as, during the open-label section of the cited trial (ie from 16 to 72 weeks), clinicians had the option to titrate patients up to 45mg of pioglitazone, an unlicensed dose in the UK. There was no indication in the reference as to how many patients received this dose, but the data must be regarded as contaminated.

Finally, GlaxoSmithKline found it somewhat ironic that Takeda should take it to task for discussing cost issues and local guidelines with general practitioners, given that this letter, and the associated leavepiece, were produced in response to similar activities by Takeda representatives. These activities, as already noted, were the subject of an earlier complaint by GlaxoSmithKline.

PANEL RULING

The Panel noted that the first sentence referred to the launch of Avandia and the subsequent NICE Guidance. The letter sought to favourably compare Avandia with pioglitazone. Avandia was referred to throughout in prominent upper case. Prescribing information appeared on the reverse. The Panel considered that the letter was clearly promotional. The fact that the letter was signed by the medical director did not in itself change the fundamentally promotional nature of the letter. The Panel did not consider the letter was disguised promotion as alleged. No breach of Clause 10.1 of the Code was ruled. The Panel noted that the piece was similar to that at issue at point G above.

The Panel firstly considered the allegation that up-to-date evidence for the efficacy of pioglitazone at 72 weeks had not been included. The Panel noted GlaxoSmithKline's response that such data included an unlicensed dose in the UK (45mg) and there was no indication as to how many patients received this dosage. No breach of Clause 7.2 was ruled on this particular point.

The Panel also considered that its rulings at point G2 and G3 regarding short-term effect on HbA1c, impact on TC:HDL and its rulings at F1 and G4 regarding the cost comparison applied to the 'Dear Doctor' letter. With regard to short-term impact on HbA1c breaches of Clauses 7.2 and 7.8 were ruled; impact on TC:HDL ratio a breach of Clause 7.2 was ruled and with regard to the cost comparison a breach of Clause 7.2 and no breach of Clause 8.1 were ruled. The Panel also ruled no breach of Clause 9.1 in relation to the cost comparison.

The Panel noted that Clause 2 was reserved as a sign of particular censure. The Panel did not consider that the content of the letter reduced confidence in or brought discredit upon the pharmaceutical industry. The circumstances did not warrant a ruling of a breach of Clause 2 .

J Bringing the industry into disrepute

COMPLAINT

Takeda stated that it requested by fax on 21 December that SmithKline Beecham withdrew these materials and other items containing these misleading claims. However, SmithKline Beecham had declined to respond to the issues raised. Takeda believed that the promotion of Avandia with the deliberately misleading presentation of information brought the industry into disrepute and so was in breach of Clause 2.

RESPONSE

GlaxoSmithKline said that to address the final point raised by Takeda, and based on the above response, it asserted that Avandia promotional materials had not been intentionally misleading. On the contrary, where a small number of statements had, on review, been thought to be unclear or open to misinterpretation, it had taken steps to withdraw the material concerned and amend it. It strongly refuted the suggestion that any part of the promotional campaign for Avandia had been such as to bring the industry into disrepute, and firmly believed that it was therefore not guilty of any breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that Clause 2 was reserved as a sign of particular censure. On balance the Panel did not consider that circumstances warranted a ruling of a breach of Clause 2.

Complaint received **15 January 2001**

Case completed **5 July 2001**

CASE AUTH/1130/1/01

CONSULTANT PSYCHIATRIST v LILLY

Zyprexa 'Dear Healthcare Professional' letter

A consultant psychiatrist complained about a 'Dear Healthcare Professional' letter headed 'Discontinuation of droperidol tablets, suspension and injection' sent by Lilly. The letter stated that the manufacturers of droperidol had voluntarily withdrawn this product as a result of concerns about QTc interval prolongation. The advice given to prescribers by the manufacturers of droperidol was then stated. The letter continued by noting that Zyprexa (olanzapine) was an alternative for use in acute schizophrenia and concluded with promotional claims for Zyprexa.

The complainant stated that the letter was addressed to him personally. There was no indication on the envelope that it contained promotional material. The heading 'Discontinuation of droperidol tablets, suspension and injection' suggested that it referred to a warning about drug safety of a product produced by the company. The letter did not indicate that droperidol was in fact a product of a rival company. The letter promoted Lilly's own product, Zyprexa, disguised as a warning about droperidol. The complainant felt that this sort of behaviour brought the pharmaceutical industry into disrepute and eroded trust in it. He would be grateful for action to ensure that the company maintained higher standards of behaviour.

The Panel noted that the letter was sent in a plain white envelope with a typewritten address label. The Panel did not consider that the design of the envelope created the impression that it contained a non-promotional personal communication or was otherwise misleading about its contents. The envelope did not constitute disguised promotion. No breach of the Code was ruled in that regard.

The Panel noted that the letter did not have the appearance of a glossy promotional item; the Lilly logo appeared in red in the top right-hand corner but the letter was otherwise printed in black on a plain white background. The four promotional claims for Zyprexa were, however, in an emboldened typeface. The reader was invited to contact Lilly's medical information department. Prescribing information for Zyprexa tablets and Velotabs appeared overleaf. The Panel noted that the letter referred to the manufacturer of droperidol but did not identify it. Nevertheless the Panel did not accept the complainant's view that the letter did not indicate that droperidol was a product of a rival company. The Panel did not consider that this was a relevant factor. The Panel considered that the letter could have been better worded to make it clearer from the heading that it was promoting Zyprexa for use in patients withdrawn from droperidol therapy. The second half of the letter was clearly promotional and in the Panel's view the letter would be seen as such by the recipients. Prescribing information was supplied. On balance the Panel did not consider that the letter was disguised and no breach of the Code was ruled. The Panel did not consider that the envelope and letter failed to recognize the special nature of medicines or the professional standing of the audience and nor did they bring discredit upon or reduce confidence in the pharmaceutical industry.

Upon appeal by the complainant, the Appeal Board considered that the heading and overall design of the letter gave the impression that it was a business communication. The letter required to be read in order to realise that it was not a safety warning about droperidol. Whilst the Appeal Board noted the company's submission that the letter was sent to a specialist audience, psychiatrists and psychiatric pharmacists, it further noted that the complainant, a consultant psychiatrist, had not initially realised that droperidol was produced by another company. The heading to the letter referred only to the discontinuation of droperidol. The Appeal Board considered that the impression was that the letter was a warning letter about a discontinued product. Insufficient effort had been made to make it obvious that the letter promoted Zyprexa. On balance the Appeal Board considered that the letter was promotional for Zyprexa and that its purpose had been disguised. A breach of the Code was ruled. The Appeal Board considered that the letter failed to recognize the special nature of medicines and the professional standing of the audience. High standards had not been maintained. A further breach of the Code was ruled. The Appeal Board did not consider that the material reduced confidence in the pharmaceutical industry.

A consultant psychiatrist complained about a 'Dear Healthcare Professional' letter headed 'Discontinuation of droperidol tablets, suspension and injection' (ref ZY727 January 2001) sent by Eli Lilly and Company Limited.

The letter began by stating that the manufacturers of droperidol had voluntarily withdrawn this product as a result of concerns about QTc interval prolongation. The advice given to prescribers by the manufacturers of droperidol was then stated. The letter continued by noting that Zyprexa (olanzapine) was an alternative for use in acute schizophrenia and concluded with promotional claims for Zyprexa.

COMPLAINT

The complainant alleged that the letter breached Clause 10.1 of the Code.

The complainant stated that the letter was addressed to him personally. There was no indication on the envelope that the letter contained promotional material. The heading of the letter: 'Discontinuation of droperidol tablets, suspension and injection' suggested that the letter referred to a warning about drug safety of a product produced by the company. The letter did not indicate that droperidol was in fact a product of a rival company.

It turned out that the letter promoted Lilly's own product, Zyprexa, disguised as a warning about droperidol. The complainant felt that this sort of

behaviour brought the pharmaceutical industry into disrepute and eroded trust in the industry. The complainant stated that he would be grateful for action to ensure that the company maintained higher standards of behaviour.

When writing to Lilly the Authority drew attention to Clauses 2 and 9.1 of the Code in addition to Clause 10.1 mentioned by the complainant.

RESPONSE

Lilly stated that it was sorry that this psychiatrist was unhappy about the letter but failed to see how it could constitute disguised promotion or indeed be accused of bringing the pharmaceutical industry into disrepute.

The item in question was obviously a promotional letter from Lilly. The Lilly logo was prominent at the letterhead and Lilly product information was highlighted on the reverse.

Rather than the letter being 'disguised as a warning', it was intended as useful information to doctors subsequent to the warning from the Committee on Safety of Medicines (CSM) on the discontinuation of droperidol – a number of prescribers were likely to be left in an awkward situation with the withdrawal from sale of this well-known antipsychotic drug. As well as highlighting the original CSM warning, the letter offered potentially useful information with regard to transferring patients currently treated with droperidol onto another pharmacotherapy for acute schizophrenia.

The complainant expressed concern that the letter did not indicate that droperidol was a product of a rival company. By its reference to 'the manufacturer' it made it clear that droperidol was not a Lilly product; direct reference to the manufacturer of droperidol without permission could have been in contravention of Clause 7.10 of the Code and Lilly obviously therefore refrained from mentioning the manufacturer by name.

The complainant was concerned that the letter was addressed to him personally with no indication on the envelope that the letter contained promotional material. Distribution of promotional material in this way was in fact in compliance with the Code providing there was no use of envelopes or postcards 'addressed in real or facsimile handwriting' or bearing words 'implying that the contents are non-promotional'. Lilly confirmed that it had abided fully by the Code, the letters being sent out in envelopes which were plain apart from the use of a typewritten sticky address label.

Lilly was sorry that a member of the healthcare community had been upset by what was a genuine attempt to address the expected confusion in the minds of health professionals following the discontinuation of droperidol by the manufacturer. The discontinuation of droperidol might present clinicians with a therapeutic dilemma. The letter was intended to in part address this whilst promoting Zyprexa as an evidence based alternative, and Lilly refuted any suggestion that it had contravened the Code.

PANEL RULING

The Panel noted that Clause 10.1 stated that promotional material and activities must not be disguised. Its supplementary information stated, *inter alia*, that envelopes addressed in real or facsimile handwriting were inappropriate. Envelopes should not be used for the despatch of promotional material if they bore words implying that that the contents were non-promotional. The Panel noted that the letter was sent in a plain white envelope with a typewritten address label. The Panel did not consider that the design of the envelope created the impression that it contained a non-promotional personal communication or was otherwise misleading about its contents. The envelope did not constitute disguised promotion. No breach of Clause 10.1 was ruled.

The Panel noted that the letter did not have the appearance of a glossy promotional item; the Lilly logo appeared in red in the top right-hand corner but the letter was otherwise printed in black on a plain white background. The four promotional claims for Zyprexa were, however, in an emboldened typeface. The reader was invited to contact Lilly's medical information department. Prescribing information for Zyprexa tablets and Velotabs appeared overleaf.

The Panel noted that the letter referred to the manufacturer of droperidol but did not identify it. Nevertheless the Panel did not accept the complainant's view that the letter did not indicate that droperidol was a product of a rival company. The Panel did not consider that this was a relevant factor. The Panel noted Lilly's submission that reference to the manufacturer of droperidol without consent could have been in breach of Clause 7.10. That was not so; Clause 7.10 only prohibited reference without prior consent to the brand names of other companies' products.

The Panel considered that the letter could have been better worded to make it clearer from the heading that it was promoting Zyprexa for use in patients withdrawn from droperidol therapy. The second half of the letter was clearly promotional and in the Panel's view the letter would be seen as such by the recipients. Prescribing information was supplied. On balance the Panel did not consider that the letter was disguised as alleged. No breach of Clause 10.1 of the Code was ruled.

The Panel did not consider that the envelope and letter failed to recognize the special nature of medicines or the professional standing of the audience and nor did they bring discredit upon or reduce confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 of the Code was ruled.

APPEAL BY THE COMPLAINANT

The complainant stated that he disagreed with the Panel's ruling for the following reasons:

1 There was no information on the envelope to indicate that it contained promotional material. The complainant did not intend to imply that the envelope itself was in breach of the Code. The point was that such a plain envelope addressed to him personally might contain a genuine warning letter. Most

advertising material came in envelopes that clearly suggested that the contents were likely to be promotional. The envelope containing this item gave no hint of the nature of its contents.

2 The Panel noted that the letter did not have the appearance of a glossy promotional item. The printed letterhead and paper was identical to that used by the company in the correspondence with the Authority regarding this case. There was no statement on the top of the letter or elsewhere to indicate that it was an advertisement. There was therefore nothing in the overall appearance of the letter to distinguish it from a genuine item of correspondence. It certainly did not have the appearance of a promotional item.

3 The fact that four sentences in the latter half of the letter that contained promotional claims for Zyprexa were in a bold typeface was of no significance. Indeed the heading of the letter was in a bold typeface and was underlined. The fact that a bold typeface was used did not indicate that a letter contained promotional material. The heading of the letter in bold typeface suggested that it was a drug warning. The letter required to be read in order to realise that it was not a drug warning but a promotional item for Zyprexa. An invitation to contact the company's medical information department was compatible with a letter containing a drug warning.

4 The Panel did not consider it relevant that droperidol was a product of a rival company. The complainant disagreed with this opinion and suggested that most healthcare professionals who received this letter would not know who the manufacturers of droperidol were. Since the letter created the appearance of a genuine drug warning and was on Lilly letterhead paper, the reader was likely to assume that droperidol was a product manufactured by Lilly. The statements referring to '… the *manufacturers* of droperidol …' gave no indication that Lilly might not be one of several manufacturers of the product. The warnings about droperidol therefore did not dispel the impression that this was a letter of warning from a company about one of its own products. It was only by reading the remainder of the letter that its promotional purpose became apparent. It required the complainant to look up the manufacturers of droperidol in the ABPI Data Sheet Compendium to discover that Lilly was not amongst them.

5 The Panel seemed to agree that the letter did not make clear from its heading that it was a promotional item. However, it felt that the recipients would be aware that the second half was promotional. The complainant stated that it was precisely because of the manner in which Lilly presented the information that the complainant regarded this letter as disguised promotion. It had an appearance which created the impression that it contained an important warning about a company's product (the disguise). This obliged the recipient to read the letter in order to discover that it was not a warning after all, but a promotion of the company's product (its true purpose).

The complainant found Lilly's response to the complaint disingenuous. He disagreed with Lilly's claim that the logo on the front of the letter and product information on the reverse indicated that the letter was *'obviously a promotional letter'*. The stationery used in the correspondence with the Authority was the same as used in this letter. What distinguished one letter as obviously promotional and the other as not?

The comment that the letter was *'intended as useful information to doctors…'* was patronising and contradicted Lilly's statement that the letter was *'obviously a promotional letter'*.

In its response, Lilly incorrectly quoted its letter as referring to *'the manufacturer'* when it referred to *'the manufacturers'* in the plural. The letter did not make it clear that Lilly was not a manufacturer of droperidol.

Lilly made the point that the envelope did not contravene the Code. The complainant stated that he had not suggested that it did. However the fact that the envelope gave no indication that it contained a promotional item was consistent with the initial impression created by the letter that it was a genuine drug warning.

The distribution of a letter such as this which was designed to create the impression that it was a drug warning but which was in fact a promotional item, was an important breach of professional behaviour on the part of the company. It raised serious safety concerns. Advertising should be easily distinguishable from drug warnings. If pharmaceutical companies were allowed to use disguised promotion in this way, true drug warning letters might be disregarded by health professionals in the future and patient safety might be compromised.

FURTHER COMMENTS FROM LILLY

Lilly stated that the company aspired to the highest standard of good practice and compliance with the letter and the spirit of the Code. It regretted that the complainant found its response disingenuous or patronising. It disagreed most strongly with the complainant's concern that it had behaved unprofessionally.

Lilly agreed there was no issue with regard to the envelope.

The safety warnings and decisions to discontinue droperidol were taken and communicated to health professionals in advance of the letter. Its letter was a response to the therapeutic dilemma raised and was intended to communicate an effective alternative therapeutic strategy to clinicians faced with choosing an alternative to droperidol. The letter was branded and entitled to enable clinicians to readily see that Lilly was contributing to this process.

The discontinuation of droperidol presented a therapeutic dilemma for many physicians, particularly psychiatrists and anaesthetists. Lilly had an established involvement in the pharmacotherapy of schizophrenia and the provision of information around its management to those categories of persons whose need for or interest in the particular information could reasonably be assumed.

The letter was intended to stand in its entirety and Lilly would agree with the complainant that it was

necessary to read the complete letter in order to understand its content and nature. For this reason the letter was confined to one side of A4 with prescribing information on the reverse side.

Lilly stated that the Code currently precluded its use of proprietary names hence its use of the generic name droperidol (Clause 7.10 of the Code).

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that his complaint had to do with a specific item. His reason for making the complaint was because of concern for the potential safety implications of such a form of marketing. It was not a complaint about any other standards of Lilly's practice. The item in question and Lilly's responses to the complaint did Lilly no credit.

The complainant stated that he used the terms disingenuous and patronising to describe Lilly's claim *'Our letter is a response to the therapeutic dilemma raised'* by the discontinuation of droperidol *'and it is intended to communicate an effective alternative therapeutic strategy to clinicians faced with choosing an alternative to droperidol. The letter is branded and entitled to enable clinicians to readily see that Eli Lilly and Company are contributing to this process'*. He would suggest that the withdrawal of droperidol offered Lilly a marketing opportunity which it exploited by distributing the letter in question. It was disingenuous to argue that its purpose was other than to promote Lilly's own product. The item was either intended to be promotional or it was not. Lilly maintained that the item was intended to be promotional. However, its presentation suggested that it was a letter warning about the withdrawal of another medicine.

It was patronising to suggest that a promotional item such as this was intended as an aid to clinicians faced with a therapeutic dilemma.

The complainant pointed out that despite Lilly's claim in its response that: *'The item in question is obviously a promotional letter from Eli Lilly and Company'* in its comments on the appeal, it stated: *'… we would agree with the complainant that it is necessary to read the complete letter in order to understand its content and nature'*.

Despite its protests, Lilly seemed to agree with the central argument that the item was intended to be promotional but its presentation did not make this purpose obvious. The item's presentation gained the reader's attention because it appeared to be a drug warning letter. It was only after fully reading the item that its promotional nature became apparent. An item such as this which disguised advertising as a drug warning raised concerns for patient safety. Such behaviour by pharmaceutical companies might result in true drug warning letters being disregarded by health professionals in the future and patient safety might be compromised.

APPEAL BOARD RULING

The Appeal Board considered that the heading and overall design of the letter gave the impression that it was a business communication. The letter required to be read in order to realise that it was not a safety warning about droperidol. Whilst the Appeal Board noted the company's submission that the letter was sent to a specialist audience, psychiatrists and psychiatric pharmacists, it further noted that the complainant, a consultant psychiatrist, had not initially realised that droperidol was produced by another company.

The Appeal Board noted that the heading to the letter referred only to the discontinuation of droperidol. The Appeal Board considered that the impression was that the letter was a warning letter about a discontinued product. Insufficient effort had been made to make it obvious that the letter promoted Zyprexa. On balance the Appeal Board considered that the letter was promotional for Zyprexa and that its purpose had been disguised. A breach of Clause 10.1 was ruled. The appeal on this point was successful.

The Appeal Board considered that the letter failed to recognize the special nature of medicines and the professional standing of the audience. High standards had not been maintained. A breach of Clause 9.1 was ruled. The appeal on this point was successful.

The Appeal Board did not consider that the material reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled. The appeal on this point was unsuccessful.

During its consideration of this case the Appeal Board noted that the generic name (olanzapine) did not appear adjacent to the most prominent display of the Zyrexa brand name on the front of the letter as required by Clause 4.2 of the Code. The Appeal Board requested that Lilly be advised of its views in this regard.

Complaint received **25 January 2001**

Case completed **12 June 2001**

CASE AUTH/1131/1/01

BOEHRINGER INGLEHEIM v NOVARTIS

Promotion of Aredia

Boehringer Ingelheim complained about the promotion of Aredia (pamidronate disodium) by Novartis, the items at issue being a hospital detail aid and a leavepiece. Boehringer Ingelheim supplied Bonefos (sodium clodronate). Both products were bisphosphonates and both were licensed for hypercalcaemia of malignancy and osteolytic lesions and bone pain in patients with skeletal metastases associated with breast cancer or multiple myelomia.

Boehringer Ingelheim stated that throughout the detail aid there was the strap-line 'High potency delivered straight to the bone'. Aredia was administered by intravenous infusion at a dosage of 90mg once a month; Bonefos was administered orally at a dosage of 1600 – 3200mg per day. Both products had the same licensed indications and the difference between them was the route of administration. The claim 'High potency delivered straight to the bone' implied that Aredia had some special merit because a smaller dose of the active substance needed to be administered. Such special merit had not been substantiated.

The Panel noted the submission from Novartis that pamidronate was the most potent bisphosphonate licensed to date for bone metastases associated with breast cancer or multiple myeloma and that it was rapidly cleared from the blood stream into the bone. The Aredia summary of product characteristics (SPC) stated that pamidronate 'is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals *in vitro*. Inhibition of osteoclastic bone resorption *in vivo* may be at least partly due to binding of the drug to the bone mineral. Pamidronate suppresses the accession of osteoclast precursors onto the bone. However, the local and direct anti-resorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*'. The SPC also stated that it had 'a strong affinity for calcified tissue'. The Panel considered that the claim 'High potency delivered straight to the bone' could be substantiated. The Panel did not consider that the claim implied any comparison with Bonefos. No breach of the Code was ruled.

The claims 'Additionally offers subgroup survival benefits', 'Aredia significantly increases survival in subgroups' and 'Increased survival in women aged <50' in the detail aid were related to the use of Aredia in women with breast cancer and osteolytic bone metastases. The page headed with the second claim featured a bar chart, with supporting text, which showed that in the subgroup of women aged less than 50, treatment with Aredia resulted in a survival benefit compared to placebo. The bar chart consisted of three pairs of columns labelled 'Lipton (pooled)', 'Theriault' and 'Data on file'. Boehringer Ingelheim noted that Lipton *et al* was a long-term follow-up of two placebo-controlled trials. The primary end-point of the study was the incidence of skeletal morbidity in the two groups. All patients were included in a survival analysis with 78.7% dying in the pamidronate group and 76.7% dying in the placebo group. However, a retrospective analysis showed that within the subgroup of women aged up to 50 years (about 25% of the study population) survival was longer in the pamidronate group than in the placebo group. The authors concluded that 'The significance of this finding may be inflated because this was a subgroup analysis and the overall survival rates were not significantly different'. Theriault *et al* was an earlier report that included the same study population and came to the same conclusions. Likewise the data on file appeared to include the same study population. Boehringer Ingelheim considered that the scientific basis for claiming that Aredia significantly increased survival in women under 50 (the studies included 50 year-old women) was at best questionable, as indicated by the authors, and was certainly unacceptable in supporting the claim 'Aredia significantly increases survival in subgroups'. Boehringer Ingelheim believed that this survival claim was inadequately substantiated. Boehringer Ingelheim further believed that citing Lipton *et al*, Theriault *et al* and Data on File in support of the bar chart, without indicating that many of the patients were common to these reports, and that they were written by the same authors, was misleading.

The Panel noted that Lipton *et al* combined the results of two previous trials to provide a larger dataset for evaluating the long-term efficacy and safety of Aredia when given as a supplement to antineoplastic therapy. The authors stated that an exploratory analysis showed that within the subgroup of women aged ≤50 years, survival was longer with Aredia than with placebo (p=0.009). The authors added that the significance of this finding might be inflated because this was a subgroup analysis and the overall survival rates of the two groups were not significantly different. Identical findings were reported by Theriault *et al*. The Data on File supplied by Novartis showed the same results although no comment was made with regard to the significance of the beneficial survival data in women ≤50 years old. The Panel noted that the claims were based on an exploratory subgroup analysis and that Lipton *et al* and Theriault *et al* had advised caution in the interpretation of the results. The Panel considered that the claims in the detail aid for increased survival of women aged ≤50 years could not be substantiated and a breach of the Code was ruled. With regard to the bar chart, the Panel noted that it showed three pairs of bars representing the data from Lipton *et al*, Theriault *et al* and Data on File respectively. Although it was clear that the Lipton data was pooled the Panel did not consider that it was clear from where the pooled data had come. The Panel considered that the overall impression was that there were three separate studies each supporting the claims for an increased survival in women aged ≤50 years which was not so. The Panel considered that the presentation of the data was misleading and ruled a breach of the Code.

Boehringer Ingelheim alleged that the headline 'Once started, stay with the most effective treatment' implied that Aredia was 'the most effective treatment' and was in breach of the Code because of the use of a superlative. The Panel considered that '… the most effective treatment' was a superlative and a breach of the Code was ruled.

The claim '… oral clodronate 1,600 mg daily reduces the frequency of morbid skeletal events by more than one fourth, whereas monthly [Aredia] infusions of 90 mg … reduce by more than one third the frequency of all skeletal-related events' appeared in the detail aid referenced to Body *et al* (1998). Boehringer Ingelheim stated that although this was a quotation from a review paper, it was based on two separate studies rather than a direct comparison of clodronate with pamidronate. It might be the authors' opinion, but Novartis should be able to substantiate the claim. This it had been unable to do from a direct comparison and a breach of the Code was alleged. The Panel noted that the data for oral clodronate and for Aredia had come from different trials. Although the trials had separately reported a bigger percentage reduction in skeletal morbidity rate for Aredia compared with that reported for clodronate, there was no way of knowing if the observed differences between the two medicines were statistically significant. The study authors noted that it 'was difficult to compare the trials of pamidronate and clodronate. Most of the pamidronate studies have been performed over a relatively short course (1 year) whereas the studies with clodronate have generally been performed over the lifetime of the patients'. The Panel considered that most readers would assume that the claim came from a head-to-head trial of Aredia and clodronate which was not so. The quoted figures were not directly comparable. The Panel considered that the claim was misleading and a breach of the Code was ruled.

The statements 'Oral clodronate has demonstrated no impact on time to first skeletal event, requirement for radiotherapy or overall survival' and 'Attempts to use oral bisphosphonates have produced fewer clinical benefits in these patients' appeared across two pages in the detail aid, the latter appearing as a quotation from Berenson (1999). Boehringer Ingelheim stated that these 'negative' claims for a competitor should be unacceptable as they implied that Aredia had been shown to be effective in these variables. The statement on overall survival was particularly inappropriate Furthermore, the statements were factually incorrect as Kristensen *et al* (1999) had demonstrated an overall survival benefit with oral clodronate. The Panel noted that the two statements appeared under the headline 'Once started, stay with the most effective treatment'. The pages featured claims for Aredia and statements about clodronate to substantiate the claim that Aredia was the most effective treatment. In this context the Panel considered that negative statements about a competitor would imply that the opposite was true for Aredia. With regard to survival the Panel referred to the studies cited in support of the claims considered above (Lipton *et al*, Theriault *et al* and Data on File). The data from those studies showed that overall survival with Aredia therapy was not statistically different to that with placebo. The Panel considered that in the context of the two pages the statement 'Oral clodronate has demonstrated no impact on … overall survival' implied that Aredia had demonstrated an impact on overall survival which was not so. The Panel ruled a breach of the Code. The Panel noted that although Boehringer Ingelheim had referred to the statement 'Attempts to use oral bisphosphonates have produced fewer clinical benefits in these patients' it had not given any details as to why it considered that it was in breach of the Code. Novartis' response had concentrated on the statement regarding survival. The Panel decided that in the circumstances it could make no ruling on this matter.

The quotation 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions. Low oral bioavailability is the most likely reason for this difference. Oral dosing should not be substituted for intravenous administration in the treatment of malignant osteolysis' appeared in the detail aid referenced to Major *et al* 2000. Boehringer Ingelheim stated that this quotation was taken from the American Society of Clinical Oncology (ASCO) guidelines and was in contradiction to the British Association of Surgical Oncology (BASO) guidelines which endorsed both oral and intravenous administration of bisphosphonates for continuing therapy once severe pain or hypercalcaemia was controlled. As this promotion was intended for clinicians in the UK, it was inappropriate to quote American guidelines. The Panel noted that the quotation had been taken from a review by Major *et al*, not the American guidelines as submitted by Boehringer Ingelheim, and had been correctly cited. The Panel noted that the British guidelines recommended the use of intravenous bisphosphonates for the acute treatment of both hypercalcaemia and severe bone pain. Oral clodronate could then be given to prevent/treat recurrent hypercalcaemia or as continuing therapy once severe bone pain was controlled. With regard to the use of bisphosphonates to decrease skeletal morbidity in the presence of skeletal metastases, the guidelines made no distinction between the efficacy and use of either intravenous or oral agents. The Panel considered that although the quotation was not an exact reflection of the British guidelines, it was not contradictory to them as alleged. No breach of the Code was ruled.

The quotation 'Gastrointestinal toxicity and poor oral bioavailability have limited the use of oral bisphosphonates to treat bone metastases' appeared in the detail aid and was referenced to Lipton (1998). Boehringer Ingelheim stated that this American quotation did not accurately reflect the situation in the UK where oral bisphosphonates were licensed for, and widely used in, the treatment of bone metastases. The Panel noted that the statement appeared on a double page spread which contained several specific references to clodronate. The Panel noted Novartis' submission that the pages illustrated the differences between Aredia and oral clodronate. The Panel considered that within the

context of the two pages readers would assume that the statement also applied to clodronate. The Bonefos (clodronate) SPC stated 'Side-effects include gastrointestinal disturbances, for example nausea, vomiting and diarrhoea may occur during oral treatment, but these are usually mild'. The Panel considered that, in the context in which it appeared, the statement was misleading with regard to the gastrointestinal tolerability of clodronate and a breach of the Code was ruled.

Boehringer Ingelheim drew attention to the statement in the leavepiece 'Intravenous administration of bisphosphonates appears to be more effective than oral bisphosphonates'. This statement was referenced to the review by Major *et al* (2000) which stated 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions'. Boehringer Ingelheim believed that this not only misquoted but misled. The Panel noted that the statement in question was not presented as a quotation; it could therefore not be a misquote. The review by Major *et al* stated 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions.' The Panel therefore considered that if oral bisphosphonates appeared not to be as effective as intravenous administration, then intravenous administration must appear to be more effective than oral dosing as stated in the leavepiece. The Panel did not consider that the statement was misleading or a misquote as alleged and no breach of the Code was ruled.

Boehringer Ingelheim Limited complained about the promotion of Aredia (pamidronate disodium) by Novartis Pharmaceuticals UK Ltd. The materials at issue were a hospital detail aid (ref ARE/00/13 June 2000) and a leavepiece (ref ARE/00/21). Boehringer Ingelheim supplied Bonefos (sodium clodronate). Both pamidronate and sodium clodronate were bisphosphonates.

A Hospital detail aid

1 Claim 'High potency delivered straight to the bone'

COMPLAINT

Boehringer Ingelheim stated that throughout the piece there was the strap-line 'High potency delivered straight to the bone'. Aredia was administered by intravenous infusion at a dosage of 90mg once a month and from the prescribing information in this piece was for: 'Tumour-induced hypercalcaemia. Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma'. In comparison, Bonefos was administered orally at a dosage of 1600 – 3200mg per day for: 'Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in breast cancer or multiple myeloma. Hypercalcaemia of malignancy'. Thus, both products were licensed for the treatment of the same conditions and the difference between them was the routes of administration. The claim 'High potency delivered straight to the bone' implied that Aredia had some special merit because a smaller dose of the active substance needed to be administered. Such special merit had not been substantiated; a breach of Clause 7.8 of the Code was alleged.

RESPONSE

Novartis stated that Aredia was a high potency bisphosphonate (the most potent bisphosphonate licensed for bone metastases associated with breast cancer or multiple myeloma to date demonstrated both *in vitro* and *in vivo*) and was rapidly cleared from the blood stream into the bone (45%–80%).

Novartis did not agree with Boehringer Ingelheim's assertion that it inferred any special merits out of this fact (nowhere in the detail aid were potency and efficacy linked) but it was indeed a differentiation from oral clodronate which was absorbed with high inter-subject (thirtyfold differences in AUC) and intra-subject (eightfold differences in AUC) variability even when taken according to the summary of product characteristics (SPC). Between 1–4% of oral clodronate (taken as Bonefos) was absorbed and only a percentage of the absorbed clodronate in the bloodstream would finally end up in the bone. Novartis added that the claim in question had formed an integral part of its promotional position for Aredia for a number of years, and had not been the subject of previous complaint.

In summary, Aredia was more bioavailable than any other bisphosphonate licensed for the treatment of bone lesions associated to breast cancer and myeloma and a greater proportion of the bioavailable product reached the bone than was the case for oral bisphosphonates. No claim for superior efficacy derived from the claim at issue was made in the detail aid. Novartis therefore did not agree that this claim represented a breach of Clause 7.8.

PANEL RULING

The Panel noted the submission from Novartis that pamidronate was the most potent bisphosphonate licensed to date for bone metastases associated with breast cancer or multiple myeloma and that it was rapidly cleared from the blood stream into the bone (45%–80%). The Panel also noted that with regard to the pharmacodynamic properties of Aredia the SPC stated that pamidronate 'is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals *in vitro.* Inhibition of osteoclastic bone resorption *in vivo* may be at least partly due to binding of the drug to the bone mineral. Pamidronate suppresses the accession of osteoclast precursors onto the bone. However, the local and direct anti-resorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action *in vitro* and *in vivo*'. In a section of the SPC detailing the pharmacokinetic properties of Aredia it was stated that it had 'a strong affinity for calcified tissue'.

The Panel considered that the claim 'High potency delivered straight to the bone' could be substantiated. The Panel did not consider that the claim implied any comparison with Bonefos. No breach of Clause 7.8 was ruled.

2 Claims 'Additionally offers subgroup survival benefits'
'Aredia significantly increases survival in subgroups'
'Increased survival in women aged <50'

The claims above related to the use of Aredia in women with breast cancer and osteolytic bone metastases. The first claim appeared on the front cover of the detail aid and the third was on the back cover. Page 4 of the detail aid was headed with the second claim and featured a bar chart, with supporting text, which showed that in the subgroup of women aged less than 50, treatment with Aredia resulted in a survival benefit compared to placebo. The bar chart consisted of three pairs of columns labelled 'Lipton (pooled)', 'Theriault' and 'Data on file'.

COMPLAINT

Boehringer Ingelheim noted that the claims were supported by Lipton *et al* (2000), Theriault *et al* (1999) and Data on File. Lipton *et al* was a long-term follow-up of two placebo-controlled trials. The primary end-point of the study was the incidence of skeletal morbidity in the two groups. All patients were included in a survival analysis with 289 out of 367 (78.7%) dying in the pamidronate group and 297 out of 387 (76.7%) dying in the placebo group. However, a retrospective analysis showed that within the subgroup of women aged up to 50 years (about 25% of the study population) survival was longer in the pamidronate group than in the placebo group. The authors concluded that 'The significance of this finding may be inflated because this was a subgroup analysis and the overall survival rates were not significantly different'. Theriault *et al* was an earlier report that included the same study population and came to the same conclusions. Likewise the data on file appeared to include the same study population.

Boehringer Ingelheim considered that the scientific basis for claiming that Aredia significantly increased survival in women under 50 (the studies included 50 year-old women) was at best questionable, as indicated by the authors, and was certainly unacceptable in supporting the claim 'Aredia significantly increases survival in subgroups'. Boehringer Ingelheim believed that this survival claim was inadequately substantiated and was therefore in breach of Clause 7.3.

Boehringer Ingelheim further believed that citing Lipton *et al*, Theriault *et al* and Data on File in support of the bar chart, without indicating that many of the patients were common to these reports, and that they were written by the same authors, was misleading and therefore in breach of Clause 7.2.

RESPONSE

Novartis stated that the studies cited were performed in a group of patients covered by the Aredia licence. The claim was limited to a survival advantage in a subgroup of the patient population where it was found to be statistically significant. Novartis stated that throughout the text it had taken care to state that any survival advantage was in the context of a defined patient subgroup only. Novartis did not agree that the author's further comments made the results of this statistical analysis invalid in this context.

In the bar chart, Novartis had clearly stated that one pair of columns represented the pooled data from the other two pairs of columns depicted. All data was referenced appropriately. With reference to Boehringer Ingelheim's assertion that this represented a breach of Clause 7.2, Novartis argued that all information, claims and comparison presented with regard to these trials were accurate and unambiguous. This data presented the most up-to-date evaluation of all evidence for Aredia.

Novartis submitted that retrospective subgroup analysis in patients treated according to the SPC were used commonly in the field of oncology and reflected the need in this therapeutic area to make treatments available to the subgroups of patients most likely to benefit from them. Furthermore the British Association of Surgical Oncology metastatic guidelines highlighted the beneficial use of bisphosphonates in long-term use to decrease skeletal morbidity in the presence of skeletal metastases where significant reductions (25–50%) in skeletal morbidity had been shown. They did however highlight that treatment was relatively expensive and targeting of treatment to subgroups which might benefit most seemed the rational approach based on current knowledge. For these reasons Novartis submitted that it was valid to highlight this potential and statistically significant finding in this subgroup.

Novartis did not accept that the presentation of this data represented a breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that Lipton *et al* combined the results of two previous trials to provide a larger dataset for evaluating the long-term efficacy and safety of Aredia when given as a supplement to antineoplastic therapy. The authors stated that an exploratory analysis showed that within the subgroup of women aged ≤50 years, survival was longer with Aredia than with placebo ($p=0.009$). The authors added that the significance of this finding might be inflated because this was a subgroup analysis and the overall survival rates of the two groups was not significantly different. Identical findings were reported by Theriault *et al*. The Data on File supplied by Novartis showed the same results although no comment was made with regard to the significance of the beneficial survival data in women ≤50 years old.

The Panel noted that the claims were based on an exploratory subgroup analysis and that Lipton *et al* and Theriault *et al* had advised caution in the interpretation of the results. The Panel considered that the claims in the detail aid for increased survival of women aged ≤50 years could not be substantiated. A breach of Clause 7.3 was ruled.

With regard to the bar chart the Panel noted that it showed three pairs of bars representing the data from Lipton *et al*, Theriault *et al* and Data on File respectively. Although it was clear that the Lipton data was pooled the Panel did not consider that it was clear from where the pooled data had come. The Panel considered that the overall impression was that

there were three separate studies each supporting the claims for an increased survival in women aged ≤50 years which was not so. The Panel considered that the presentation of the data was misleading as alleged. A breach of Clause 7.2 was ruled.

3 Headline 'Once started, stay with the most effective treatment'

This appeared across the double page spread of pages 8 and 9.

COMPLAINT

Boehringer Ingelheim stated that the headline clearly implied that Aredia was 'the most effective treatment' and it believed it was thereby in breach of Clause 7.8 because of the use of a superlative.

RESPONSE

Novartis stated that the headline related to the information contained in pages 8 and 9 of the detail aid, which illustrated the differences between Aredia and oral clodronate. The term effective in this context related to the levels of compliance, side-effects, pain control, rate of skeletal events, and patient acceptability, which were all indicators used by clinicians in this therapy area to judge the efficacy of a medicine. References used to support the detail aid stated that the intravenous route was necessary for optimal analgesia and that oral bisphosphonates had produced fewer clinical benefits and were less effective than intravenous bisphosphonates. Novartis submitted that these points together justified the use of the heading within this context. On this basis Novartis did not accept that this heading represented a breach of Clause 7.8 when it was clearly substantiated by the body of text contained within pages 8 and 9.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.8 of the Code, Superlatives, stated 'Superlatives are those grammatical expressions which denote the highest quality or degree, such as best, strongest, widest etc. A claim that a product was 'the best' treatment for a particular condition, for example, could not be substantiated as there are too many variables to allow such a sweeping claim to be proven. The use of a superlative which could be substantiated is a simple statement of fact … such as that a particular medicine is the most widely prescribed …'.

The Panel thus considered that '… the most effective treatment' was a superlative which could not be substantiated; it was not a simple statement of fact. A breach of Clause 7.8 was ruled.

4 Claim '… oral clodronate 1,600 mg daily reduces the frequency of morbid skeletal events by more than one fourth, whereas monthly [Aredia] infusions of 90 mg … reduce by more than one third the frequency of all skeletal-related events'

This claim appeared on page 8 of the detail aid and was referenced to Body *et al* (1998).

COMPLAINT

Boehringer Ingelheim stated that although this was a quotation from a review paper, it was based on two separate studies rather than a direct comparison of clodronate with pamidronate. It might be the authors' opinion, but Novartis should be able to substantiate the claim; this it had been unable to do from a direct comparison and Boehringer Ingelheim therefore alleged a breach of Clause 7.2.

RESPONSE

Novartis stated that it had made no claim in the detail aid that the data presented was derived from a head-to-head comparison. The claim was clearly designated as a quotation, which represented the opinion of the author of the review article. Novartis noted that in point A2 above Boehringer Ingelheim had stressed the importance of a clinician's opinion. In this case Novartis submitted that it would be inappropriate to diminish the importance of a world renowned bisphosphonate researcher / user's opinion.

PANEL RULING

The Panel noted that the claim was a quotation from the review by Body *et al* (1998). The data for oral clodronate and for Aredia had come from different trials. Although the trials had separately reported a bigger percentage reduction in skeletal morbidity rate for Aredia compared with that reported for clodronate there was no way of knowing if the observed differences between the two medicines were statistically significant. The study authors noted that it 'was difficult to compare the trials of pamidronate and clodronate. Most of the pamidronate studies have been performed over a relatively short course (1 year) whereas the studies with clodronate have generally been performed over the lifetime of the patients'. The Panel considered that most readers would assume that the claim came from a head-to-head trial of Aredia and clodronate which was not so. The quoted figures were not directly comparable. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

5 Statements 'Oral clodronate has demonstrated no impact on time to first skeletal event, requirement for radiotherapy or overall survival'
'Attempts to use oral bisphosphonates have produced fewer clinical benefits in these patients'

These statements appeared on page 8 of the detail aid. The second statement appeared as a quotation from Berenson (1999).

COMPLAINT

Boehringer Ingelheim stated that these 'negative' claims for a competitor should be unacceptable as they implied that Aredia had been shown to be

effective in these variables. The statement on overall survival was particularly inappropriate and Boehringer Ingelheim believed that this was a breach of Clause 7.2.

Furthermore, the statements were factually incorrect as Kristensen *et al* (1999) had demonstrated an overall survival benefit with oral clodronate.

RESPONSE

Novartis stated that critical references to other companies' products were acceptable if they were accurate, balanced (Novartis stated the positive effect of clodronate on the skeletal morbidity on the same page), objective (this was clinical trial data) and unambiguous. The quotations from respected opinion leaders in this area were not taken out of context and were not inappropriate.

With specific regard to Boehringer Ingelheim's claim that Novartis had been 'negative' with regard to overall survival data of oral clodronate, Novartis noted that it was aware of Kristensen *et al* at the time of creating the detail aid. It should, however, be noted that the trial referred to in this paper had been conducted in patients who fell outside the current licensed indications for Bonefos (it included patients with solely sclerotic lesions). On this basis Novartis considered that it was inappropriate for it to use this data. Furthermore, the mean survival time between the two groups in this small trial did not reach significance (p=0.97). Novartis submitted that this trial clearly did not support an overall survival claim for clodronate, contrary to Boehringer Ingelheim's assertion.

Novartis did not accept that this represented a breach of Clause 7.2.

PANEL RULING

The Panel noted that the two statements appeared under the headline 'Once started, stay with the most effective treatment' which ran across pages 8 and 9. The two pages featured claims for Aredia and statements about clodronate to substantiate the claim that Aredia was the most effective treatment. In this context the Panel considered that negative statements about a competitor would imply that the opposite was true for Aredia.

With regard to survival the Panel referred to the studies cited in support of the claims considered in point A2 above (Lipton *et al*, Theriault *et al* and Data on File). The data from those studies showed that overall survival with Aredia therapy was not statistically different to that with placebo. The Panel considered that in the context of pages 8 and 9 the statement 'Oral clodronate has demonstrated no impact on … overall survival' implied that Aredia had demonstrated an impact on overall survival which was not so. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that although Boehringer Ingelheim had referred to the statement 'Attempts to use oral bisphosphonates have produced fewer clinical benefits in these patients' it had not given any details as to why it considered that it was in breach of the Code. Novartis' response had concentrated on the statement regarding survival. The Panel decided that in the circumstances it could make no ruling on this matter.

6 Quotation 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions. Low oral bioavailability is the most likely reason for this difference. Oral dosing should not be substituted for intravenous administration in the treatment of malignant osteolysis'

This quotation appeared on page 8 of the detail aid and was referenced to Major *et al* 2000.

COMPLAINT

Boehringer Ingelheim stated that this quotation was taken from the American Society of Clinical Oncology (ASCO) guidelines and was in contradiction to the British Association of Surgical Oncology (BASO) guidelines which endorsed both oral and intravenous administration of bisphosphonates for continuing therapy once severe pain or hypercalcaemia was controlled. As this promotion was intended for clinicians in the UK, it was inappropriate to quote American guidelines and ignore British guidelines. Boehringer Ingelheim therefore alleged that this was in breach of Clause 7.2 of the Code.

RESPONSE

Novartis stated that the paragraph was clearly marked as a quotation and as such was referenced to Major *et al* and not the ASCO guidelines as Boehringer Ingelheim suggested. Major was a Canadian clinician internationally renowned for his work with bisphosphonates. Oral bisphosphonates were the topic of this author's review, including clodronate. Novartis argued that the opinions of this clinician, based on his review, were relevant to the UK.

Novartis noted that it made reference to the ASCO guidelines on page 7 of the detail aid. These guidelines had been produced by US physicians in consultation with European physicians with full knowledge of available clodronate data, which was cited extensively throughout the official ASCO publication and referenced in the guideline bibliography. This was supported by the following quotation from these guidelines: 'The judgement was made that the recommended agent should be pamidronate based on the availability of level 1 evidence with a grade A recommendation and approval by the US FDA. This position was taken with knowledge of the results from studies with clodronate, which were considered to be less compelling in terms of benefit as reviewed above....'.

Novartis stated that the British guidelines were not contradictory to the ASCO guidelines and had been quoted on the preceding page and had thus hardly been ignored.

Novartis stated that oncology was an international discipline and to the best of its knowledge the influence of ASCO was tremendously important to the

UK which was perhaps best witnessed by the number of UK oncologists visiting its annual meetings.

Novartis therefore saw no breach of Clause 7.2.

PANEL RULING

The Panel noted that the quotation had been taken from a review by Major *et al*, not the American guidelines as submitted by Boehringer Ingelheim. The quotation had been correctly cited.

The Panel noted that the British guidelines recommended the use of intravenous bisphosphonates for the acute treatment of both hypercalcaemia and severe bone pain. Oral clodronate could then be given to prevent/treat recurrent hypercalcaemia or as continuing therapy once severe bone pain was controlled. With regard to the use of bisphosphonates to decrease skeletal morbidity in the presence of skeletal metastases, the guidelines made no distinction between the efficacy and use of either intravenous or oral agents.

The Panel considered that although the quotation was not an exact reflection of the British guidelines, it was not contradictory to them as alleged. No breach of Clause 7.2 was ruled.

7 Statement 'Gastrointestinal toxicity and poor oral bioavailability have limited the use of oral bisphosphonates to treat bone metastases'

This quotation appeared on page 9 of the detail aid and was referenced to Lipton (1998).

COMPLAINT

Boehringer Ingelheim stated that this quotation from a physician in America did not accurately reflect the situation in the UK where oral bisphosphonates were licensed for, and widely used in, the treatment of bone metastases. Boehringer Ingelheim therefore believed that this was in breach of Clause 7.2.

RESPONSE

Novartis stated that this statement was again clearly marked as a quotation and did not refer to any oral bisphosphonate in particular but the general acknowledgement that oral bisphosphonates had low bioavailability and problematic gastrointestinal side-effects which could compromise compliance.

Lipton was an international opinion leader and well aware of the European practice and availability of oral clodronate in the UK. He was also a member of the ASCO expert committee which reviewed bisphosphonate use.

Novartis did not therefore accept that this represented a breach of Clause 7.2.

PANEL RULING

The Panel noted that the statement appeared on the double page spread of pages 8 and 9 of the detail aid; these two pages contained several specific references to clodronate. The Panel noted Novartis' submission in point A3 above that pages 8 and 9 illustrated the differences between Aredia and oral clodronate. The Panel considered that within the context of the two pages readers would assume that the statement also applied to clodronate. The Panel noted that the Bonefos (clodronate) SPC stated 'Side-effects include gastrointestinal disturbances, for example nausea, vomiting and diarrhoea may occur during oral treatment, but these are usually mild'.

The Panel considered that, in the context in which it appeared, the statement was misleading with regard to the gastrointestinal tolerability of clodronate. A breach of Clause 7.2 was ruled.

B Leavepiece

COMPLAINT

Boehringer Ingelheim drew attention to the statement: 'Intravenous administration of bisphosphonates appears to be more effective than oral bisphosphonates'. This statement was referenced to the review by Major *et al* (2000), which stated, 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions'.

The statement in the leavepiece, Boehringer Ingelheim believed, breached Clause 7.2 of the Code as it not only misquoted but misled.

RESPONSE

Novartis pointed out that the statement to which Boehringer Ingelheim referred was further expanded by the full quotation from the article in the same piece.

Novartis made the clear assumption that if oral bisphosphonates did not appear to be as effective as intravenous administration, as stated by Major *et al*, then necessarily intravenous administration was more effective than oral delivery. This could not be seen as misleading as it clearly reflected the authors' meaning.

PANEL RULING

The Panel noted that the statement in question was not presented as a quotation; it could therefore not be a misquote.

The Panel noted that the review by Major *et al* stated 'Oral bisphosphonates do not appear to be as effective as intravenous administration in reducing skeletal complications in patients with metastases to bone lesions'. The Panel therefore considered that if oral bisphosphonates appeared not to be as effective as intravenous administration then intravenous administration must appear to be more effective than oral dosing as stated in the leavepiece.

The Panel did not consider that the statement was misleading or a misquote as alleged. No breach of Clause 7.2 was ruled.

Complaint received **26 January 2001**

Case completed **11 May 2001**

MERCK SHARP & DOHME v YAMANOUCHI PHARMA and GLAXOSMITHKLINE

Flomax MR journal advertisement

Merck Sharp & Dohme complained about a journal advertisement for Flomax MR (tamsulosin) placed by Yamanouchi Pharma and Glaxo Wellcome. The advertisement was headed 'Relief all round' beneath which were three bullet points. The claim at issue, 'Delays the need for surgery', appeared as the third bullet point.

Flomax MR was licensed for the 'treatment of functional symptoms of benign prostatic hyperplasia (BPH)'; there was no mention within the summary of product characteristics (SPC) that it could decrease the requirement for surgery. Merck Sharp & Dohme alleged that the claim 'Delays the need for surgery' was not consistent with the licence. The reference given was to data on file regarding an epidemiological study utilising the General Practice Research Database (GPRD). The limitations of such studies were well recognised, in particular confounding. Whilst attempts had been made in the analysis to adjust for some recognised confounding factors, all confounders could not be allowed for because of inadequate information in the database eg prostate size, severity of symptoms and compliance rates. The authors of the published paper acknowledged this and that 'this confounding and its effects are the subjects of further research'. There would also have been geographic variation in surgery rates, watchful waiting and extent of the use of the different products, each of which would be influenced by local urology practice to differing extents. It was simply impossible to estimate what effect these factors would have had on the results. Even for age, no data was provided on the profiles of patients taking the different medicines for the reader to make their own considered judgement. There had been marked changes in clinical practice over the period considered in the study, and the place of various treatments in BPH had become clearer. For example, in the early 90s many would have reserved medical treatment to those unsuitable for surgery. When the published randomised controlled trials for Flomax were reviewed there was no indication that it reduced the risk of surgery in comparison to placebo, even in the largest long-term studies. Given all the significant reservations about the nature of the GPRD data, together with the absence of high quality randomised control trial evidence, Merck Sharp & Dohme believed that the claim 'Delays the need for surgery' was inadequately substantiated and was not a fair reflection of the evidence.

Whilst the claim made in the advertisement was not comparative, the data on file provided as the reference did compare different treatments. Merck Sharp & Dohme believed it was completely inappropriate to compare its product Proscar (finasteride) with α-adrenoreceptor blockers in the way done in this study because of differing mechanisms of action and use in clinical practice. The mechanism of action of Proscar was completely different to the other medicines compared. It inhibited 5α-reductase rather than blocking α-adrenoreceptors, and treatment for six months might be necessary to assess whether a beneficial response had been achieved. Also, in contrast to α-adrenoreceptor blockers, the efficacy of Proscar in reducing the incidence of surgery and acute urinary retention had been well documented in randomised placebo-controlled studies and meta-analyses, and was reflected in its licensed indications which included reducing the need for surgery. Over time, it had become clear that the response to Proscar was greater the larger the prostate, and therefore its recommended place in practice had evolved to reflect this. In contrast, α-adrenoreceptor blockers might be used in those with lower urinary tract symptoms but small prostates, who had a lower risk of surgery and acute urinary retention. Such confounding by indication would bias in favour of Flomax. It could not be adjusted for in the analysis since prostate size was not recorded in GPRD. Merck Sharp & Dohme believed the reference provided in support of the claim intended to suggest that Flomax had similar efficacy to Proscar did not represent a balanced, fair and objective evaluation of all the evidence.

The Panel noted that Proscar was indicated for the treatment and control of BPH in patients with an enlarged prostate *inter alia* to reduce the incidence of acute urinary retention and the need for surgery. Flomax MR was indicated to treat the functional symptoms of BPH. In the Panel's view a delay in the need for surgery might be a benefit of treatment with Flomax MR, but such a delay was not the primary reason to use it; the reason to use Flomax MR, and its licensed indication, was to treat the functional symptoms of BPH. The Panel noted that a review (Clifford and Farmer) stated that '... upon evaluation of the risks associated with symptomatic BPH patients progressing to surgery or AUR [acute urinary retention], finasteride has been shown to offer beneficial effects that are as yet unproven with any α-blocker therapy, as no appropriate outcome analyses have been published. However, preliminary results from the PREDICT (Prospective European Doxazosin in Combination Therapy) study suggest that not only finasteride but also α-blocker therapy may reduce both AUR and surgery in BPH'.

The Panel noted that the data provided to support the claim came from the GPRD. Yamanouchi had submitted that the GPRD data was fully consistent with the expected efficacy of all licensed products. The Panel noted the comments from both parties with regard to potential confounders. There were no randomised controlled trials to support the claim for Flomax MR. There was such data for Proscar. The Clifford and Farmer review stated that large placebo effects (resulting in up to 40% symptom improvement) could persist for up to two years of therapy emphasising the importance of properly

designed double-blind placebo-controlled studies in evaluating the outcome of medical therapy for BPH.

The Panel considered that the claim that Flomax 'Delays the need for surgery' was inconsistent with the SPC, was not a fair reflection of the evidence and was not capable of substantiation. Breaches of the Code were ruled.

Upon appeal by Yamanouchi and GlaxoSmithKline, the Appeal Board noted the submission that current management of BPH was driven by both patients and their partners and their desire to have the patient's symptoms relieved and to delay surgery for as long as possible. The decision as to whether to operate or not was based on the need to relieve symptoms not, as in the past, on an assessment of urodynamic parameters. The Appeal Board considered that, given the way in which BPH was managed, a medicine which treated the symptoms of the disease would delay a patient's need for surgery. The SPC for Proscar stated that it reduced the incidence of acute urinary retention and the need for surgery. Flomax MR was licensed to treat functional symptoms of BPH and its SPC stated that it relieved obstruction; relief of obstruction was also a reason for surgery. The Appeal Board thus did not consider that the claim 'Delays the need for surgery' was inconsistent with the particulars listed in the Flomax SPC. The Appeal Board considered that the GPRD data substantiated the claim in question and that the data itself was representative of the balance of the evidence. No breaches of the Code were ruled.

With regard to the alleged inappropriate comparison with Proscar, the Panel noted that Merck Sharp & Dohme accepted that the claim 'Delays the need for surgery' was not comparative. The complaint related to the comparison of Proscar with α-adrenoceptor blockers in the data on file. The reference suggested that Proscar and Flomax MR had similar efficacy. The Panel noted that the advertisement made no comparative claim. The data on file compared the α-blockers with Proscar, a product that had an indication for delaying surgery. The Panel considered that as there was no claim in the advertisement in relation to the comparative efficacy, there was no breach of the Code.

Merck Sharp & Dohme Limited complained about a journal advertisement (ref Yam 62474B / WBR / AUG 2000) for Flomax MR (tamsulosin). The advertisement bore the names of Yamanouchi Pharma Ltd and Glaxo Wellcome and the complaint was taken up with both companies. The advertisement had appeared in the British Journal of Urology, Doctor, Geriatric Medicine, Guidelines in Practice, Health and Ageing, Hospital Doctor, Prescriber and Pulse. Merck Sharp & Dohme supplied Proscar (finasteride).

The advertisement was headed 'Relief all round' beneath which there were three bullet points. The claim at issue, 'Delays the need for surgery', appeared as the third bullet point.

COMPLAINT

Merck Sharp & Dohme stated that it had had correspondence with Yamanouchi about the claim 'Delays the need for surgery' but the response did not deal satisfactorily with the company's concerns.

Tamsulosin was licensed for the 'treatment of functional symptoms of benign prostatic hyperplasia (BPH)'. 'Functional' was defined as affecting physiological or psychological functions but not organic structure. There was no mention within the summary of product characteristics (SPC) that tamsulosin could decrease the requirement for surgery either in the indication or pharmacodynamics sections. Merck Sharp & Dohme alleged that the claim 'Delays the need for surgery' was not consistent with the licence for tamsulosin and was in breach of Clause 3.2 of the Code.

The reference quoted to support the claim was data on file regarding an epidemiological study utilising the General Practice Research Database (GPRD). This had not been published as a peer reviewed paper, but had appeared in a journal supplement (Clifford *et al* 2000). The limitations of such studies were well recognised, in particular confounding. Whilst attempts had been made in the analysis to adjust for some recognised confounding factors, all confounders could not be allowed for because of inadequate information in the database eg prostate size, severity of symptoms, compliance rates. The authors of the published paper acknowledged this, and that 'this confounding and its effects are the subjects of further research'. There would also have been geographic variation in surgery rates, watchful waiting and extent of the use of the different products, each of which would be influenced by local urology practice to differing extents. Indeed, there were likely to be marked differences between the various local management strategies, which might have had profound effects on the apparent efficacy of the different products on surgery rates. Whilst Yamanouchi argued that these would work against medical treatment, Merck Sharp & Dohme believed it was simply impossible to estimate what effect these factors would have had on the results. Even for age, no data was provided on the profiles of patients taking the different medicines for the reader to make their own considered judgement. There had been marked changes in clinical practice over the period considered in the study, and the place of various treatments in BPH had become clearer. For example in the early 90s many would have reserved medical treatment to those unsuitable for surgery.

Merck Sharp & Dohme stated that clinical trials regarding symptoms of BPH were subject to a marked placebo response, and 'controlled comparison studies are considered essential to evaluate a drug's efficacy' (Clifford and Farmer 2000). Since the majority of prostatectomies were carried out for symptoms, following Yamanouchi's arguments in its response, placebo would be expected to delay surgery in comparison to no treatment. The GPRD database, of course, had no placebo group. It was by no means certain that the delay in surgery was real. Indeed, when the published randomised controlled trials for tamsulosin were reviewed there was no indication that it reduced the risk of surgery in comparison to placebo, even in the largest long-term studies.

Given all the significant reservations about the nature of the GPRD data, together with the absence of high

quality randomised control trial (RCT) evidence, Merck Sharp & Dohme believed that the claim 'Delays the need for surgery' was inadequately substantiated, was not a fair reflection of the evidence, and was therefore in breach of Clauses 7.2 and 7.3.

Whilst the claim made in the advertisement was not comparative, the data on file provided as the reference did compare different treatments. Notwithstanding the reservations stated above with regard to the study, Merck Sharp & Dohme believed it was completely inappropriate to compare finasteride with α-adrenoreceptor blockers in the way done in this study because of differing mechanisms of action and use in clinical practice. The mechanism of action of finasteride was completely different to the other medicines compared. It inhibited 5α-reductase rather than blocking α-adrenoreceptors, and treatment for six months might be necessary to assess whether a beneficial response had been achieved. Also, in contrast to α-adrenoreceptor blockers, the efficacy of finasteride in reducing the incidence of surgery and acute urinary retention had been well documented in randomised placebo controlled studies and meta-analyses, and was reflected in its licensed indications which included reducing the need for surgery. As mentioned above, the place of medical treatments in the treatment of BPH had become clearer over time. This applied particularly to finasteride. Over time, it had become clear that the response to finasteride was greater the larger the prostate, and therefore its recommended place in practice had evolved to reflect this. In contrast, α-adrenoreceptor blockers might be used in those with lower urinary tract symptoms but small prostates, who had a lower risk of surgery and acute urinary retention. Such confounding by indication would bias in favour of tamsulosin. It could not be adjusted for in the analysis since prostate size was not recorded in GPRD. As stated above, there was an absence of high quality RCT data to show a benefit of α-adrenoreceptor blockers on surgery. Therefore, Merck Sharp & Dohme believed the reference provided in support of the claim intended to suggest that tamsulosin had similar efficacy to finasteride did not represent the balanced, fair and objective evaluation of all the evidence for both products required under Clause 7.2.

RESPONSE

Yamanouchi Pharma responded on behalf of both itself and GlaxoSmithKline.

Yamanouchi noted that one of the references provided by Merck Sharp & Dohme had larger patient numbers than in the data on file (61, 364 versus 58, 260 respectively). The reason was that the GPRD study cohort increased with time as data continued to be collected and new information or presentations of the data were published. However, to date, each publication or presentation had drawn the same conclusions.

1 'Delays the need for surgery' – alleged breach of Clause 3.2

Yamanouchi stated that Flomax MR was licensed for 'the treatment of functional symptoms of BPH'. Merck Sharp & Dohme had alleged that the Flomax MR licensed clinical particulars made no direct reference to the claim that the product delayed the need for surgery and, therefore, it was in breach of Clause 3.2. Yamanouchi refuted this. In addressing this allegation, it was necessary to understand the disease area and treatment options.

Symptomatic BPH was a chronic disease caused by increased smooth muscle tone of the prostatic urethra and enlargement of the prostate. The disease was insidious, non-life threatening, and was associated with an ageing male population. It was essentially a symptomatic disease and patients presented to their GP with a variety of urinary symptoms, varying in severity. The term 'bothersomeness,' which was now commonly used in urology to describe the impact of symptoms on patients, reinforced the fact that it was the symptoms which troubled patients, interfering with their normal pattern of life.

Commonly recognised symptoms were nocturia, frequency, intermittency, terminal dribbling and hesitancy. Others include dysuria (burning sensation), poor flow and sensation of incomplete emptying of the bladder.

Any combination of these might adversely affect patients' life styles, such that, for example, driving long distances and hobbies such as golf became difficult and anxiety riddled, because of the potential lack of accessible lavatory facilities. Without intervention (medical therapy or surgery), patients who experienced an unacceptable degree of bothersomeness would have to adapt their life styles and habits to avoid potentially embarrassing accidents occurring.

The management of BPH included the following three choices – watchful waiting, ie no treatment; medical therapy (alpha-blockers and finasteride); or elective surgery (prostatectomy). One of the key objectives of intervention was to improve patients' bothersome urinary symptoms and hence quality of life. As Merck Sharp & Dohme stated, 'the majority of prostatectomies are carried out for symptoms'.

Prostatectomy, an invasive procedure, was the only effective intervention available to patients with symptomatic BPH in the UK before the advent of effective medical treatment. Until the establishment of medical therapy over the past decade as an alternative to elective surgery, patients with mild, moderate or severe symptoms, would otherwise have had to endure ongoing suffering, anxiety and potential embarrassment due to accidents, with little or no chance of symptom relief, unless they opted for surgery. In fact, for those patients who were not considered suitable for surgery, there was often little hope of symptom improvement.

It could thus be seen that symptom relief afforded by licensed medical therapy was inextricably linked to the requirement or not for surgical prostatectomy. By reducing or ameliorating the disabling symptoms of BPH, all licensed medical therapies which treated symptoms (including Flomax MR) would delay the requirement for surgery. Therefore, the claim, Flomax MR 'Delays the need for surgery', was consistent with the benefits that an effective product could be

expected to produce and this applied to all products licensed for this indication.

Therefore, Yamanouchi did not consider that the claim was in breach of Clause 3.2.

2 'Delays the need for surgery' – alleged breach of Clauses 7.2 and 7.3

Merck Sharp & Dohme alleged that this claim was inadequately substantiated, not a fair reflection of the evidence, and therefore in breach of Clauses 7.2 and 7.3.

Yamanouchi did not consider that the claim was in breach of either Clause 7.2 or Clause 7.3.

It was not a requirement for all references that could substantiate a claim to be quoted. What was required was that any quoted references must be accurate, balanced, not mislead and could be substantiated.

Firstly, Yamanouchi contended that the claim was inherently capable of substantiation as a consequence of the terms of the product licence as detailed in point 1 above. The statement could be equally applied to all products licensed for the treatment of the symptoms of BPH. There was no implication in the statement that Flomax MR was the only product to delay the need for surgery, nor that it did so to any greater or lesser extent than other products. It was a pure statement of fact about Flomax MR, consequent upon the licensed indications, and no comparison was implied or made.

Secondly, the fact that effective (ie licensed) treatments for BPH delayed the need for surgery was acknowledged prior to the launch of Flomax MR in September 1996 (ie independent of Flomax MR *per se*). Some examples which made specific reference to this were: 'But the use of alpha blocker[s] … for those who desire to postpone surgery'; 'alpha$_1$-Adrenoceptor antagonists have a place … for those awaiting or wishing to delay surgery'; 'We considered [the] pharmacologic approach as a treatment that may delay the need for surgery for BPH'; 'Medication as treatment should be reserved for patients … who wish to delay surgery'.

The recent data from the GPRD analysis was fully consistent with the expected efficacy of all licensed products. GPRD was a reputable and representative database detailing the clinical outcomes that reflected everyday clinical experience as recorded by over 2,000 GPs working in primary care.

Yamanouchi therefore considered that doctors would be interested to know that 'their' database (GPRD) contained confirmatory evidence of this statement. The fact that, although the statement had been in constant use since April 2000 (10 months), Yamanouchi had not received a single request for the data on file from any health professional outside of the industry, indicated that neither GPs nor urologists found the claim discordant with their current thinking.

The referenced data on file described the results of a retrospective, observational, case control study investigating the management of BPH over the period 1992-1998. The study investigated the impact of medical therapy on BPH and survival time to surgery compared to a control group, ie no treatment group.

GPRD was managed by the Medicines Control Agency and contained high quality data from over 4.6 million patients as recorded by GPs in primary care. These numbers were substantial. The study underwent ethical approval before implementation and the Scientific and Ethical Advisory Group (SEAG) approved the study aim, methodology and study design, and statistical rationale to be of an acceptable and robust scientific standard before allowing the group to commence the GPRD observational study. SEAG also approved the abstracts presented at EAU 2000 (European Association of Urology), AUA 2000 (American Urological Association), BAUS 2000 (British Association of Urological Surgeons) and the manuscripts submitted to the European Journal of Urology prior to publication.

The aim, methodology and design of the GPRD study were provided.

The data were used to calculate the age-specific incidence rates of urinary symptoms due to BPH and prostatic surgery. Survival analyses were conducted examining the intervals between first diagnosis, treatment and surgery. A number of confounding factors were taken into consideration by using the Cox regression model.

Merck Sharp & Dohme had taken the statement regarding potential confounders out of context. Its reference was to a publication discussing the GPRD study results, not to the data on file. The contributors in both cases were the same. In the publication the authors clearly stated in their conclusion that 'treated patients come to surgery significantly later than those untreated; hazard ratio 0.76'. They drew attention to the only confounder they considered had any real potential to affect the study conclusion as a consequence of potential differences between untreated and medically treated groups. This was the potential of confounding by indication, ie according to symptom severity. They stated that this existed in both directions ie both in favour of and against medical treatments. To quote 'It is acknowledged that treated and untreated men may be dissimilar, thus introducing the potential of confounding by indication. However, the confounding exists in both directions; men with mild symptoms are less likely to be treated either medically or surgically, and men presenting with very severe symptoms are candidates for surgical intervention only'.

In terms of confounding by mild symptoms, both good clinical practice and medical logic would dictate that it was patients with milder symptoms, rather than those with more severe symptoms, who would be 'treated' by watchful waiting, ie the 'no treatment' group. It was, therefore, these patients who would logically require surgical intervention at a later date because they had mild symptoms not requiring either medical or surgical intervention. It would be illogical and inappropriate medical practice for the converse to be true. Therefore, any bias introduced into the study in respect of patients with mild but unrecorded symptoms would be in favour of the untreated group and against the medically treated group, which in this

respect would strengthen the statistical conclusion drawn from the study.

Turning now to the potential of confounding in the other direction from patients who had the most severe symptoms, this could be checked to see what, if any, effect there was on the hazard ratios when these patients were excluded from the analysis. If the hazard ratios remained statistically significant for each product compared with the no treatment group, then the statement that medical therapies delayed the need for surgery remained valid and the confounding would not have affected the original conclusion.

Therefore, hazard ratios were calculated for each group having excluded patients who had surgery within one month of entering the study, then again for those who had surgery within 2 months. The rationale for these analyses was that 'men presenting with very severe symptoms are candidates for surgical intervention only.' ie the patients with very severe symptoms would have surgery soon after their first GP visit for BPH as initiating medical therapy would not be warranted. This rationale would be validated if the data showed that the untreated group had a higher referral rate for surgery than those commencing medical therapy within the first month or so. The data confirmed this showing that within the first month after diagnosis 9.9% of untreated patients required surgery compared with, for example, 2% of tamsulosin patients, 1.3% of prazosin patients etc. In the second month, these figures changed noticeably, such that only 3.9% of untreated patients required surgery compared with approximately 1% on medical therapy.

When these patients were removed from the database at one and two months, the hazard ratios remained highly statistically significant for all products compared with no treatment. Exclusion of the patients having surgery in both the first and second months, whilst reducing the treatment/no treatment differences, had a similar effect on all products. Therefore, when confounding by severity of symptoms was taken into account by exclusion of patients having surgery within one or two months following entry to the study, all medical therapies had hazard ratios showing clearly statistically significant longer delays to surgery than the untreated patients.

The fact that medical therapies had similar numbers of patients who were lost to surgery in the first or second months, further supported the homogeneity of the treatment groups versus the untreated group, against which the comparisons were being made.

As discussed earlier, the data on file had been used to complement the Flomax MR licensed particulars and it acknowledged the consensus held by practising urologists and physicians in primary care that all medical therapies, including Flomax MR, delayed the need for surgery.

In conclusion, Yamanouchi considered that the claim was an inherent benefit associated with all licensed medical therapies and the data on file referenced in the advertisement was both consistent and supportive of this fact. Therefore, Yamanouchi did not agree that there had been a breach of Clauses 7.2 or 7.3.

3 'Delays the need for surgery' – alleged breach of Clause 7.2

Yamanouchi was pleased to note that Merck Sharp & Dohme, quite categorically, acknowledged that the claim in the advertisement was not comparative. It appeared, however, that Merck Sharp & Dohme considered it inappropriate to compare products of different classes for the same condition. This was, in fact, normal practice in both registration and post-marketing studies, eg ACE inhibitors versus beta-blockers for hypertension, tricyclic antidepressants versus SSRIs for depression. Whilst no comparison was made in the claim, it was not inappropriate to undertake a study that compared all products for the same condition regardless of their mode of action. The data on file clearly demonstrated that all products statistically significantly delayed the need for surgery. 'For all products, treated patients come to surgery significantly later than those receiving no medical therapy (hazard ratio 0.69, 95% confidence interval 0.67-0.71)'.

The final objection from Merck Sharp & Dohme was that, according to its interpretation of the data on file, Flomax MR and finasteride had similar efficacy and Yamanouchi had not provided balanced, fair and objective evidence to support the claim for both products. Merck Sharp & Dohme alleged that whilst the claim made in the advertisement was not comparative, the data on file did compare different treatments.

At no time was any comparison drawn between products to treat BPH, either within the claim itself as it appeared in the advertisement (as acknowledged by Merck Sharp & Dohme), nor within the data on file reference. The data on file reflected the presentations at the urology symposia, but specifically drew attention to the untreated comparison chart. The table below, using the data on file referenced, confirmed the study conclusion that all medical treatments significantly delayed the need for surgery.

Adjusted survival from first diagnosis to surgery by product 1992-1998 in patients with urinary symptoms due to BPH (untreated as reference).

	HR	***P***	***95% conf.int.***	
Untreated	**1.0**		**Reference**	
Alfuzosin	**0.46**	<0.001	0.38	0.55
Doxazosin	**0.70**	=0.001	0.56	0.87
Finasteride	**0.31**	<0.001	0.25	0.39
Indoramin	**0.51**	<0.001	0.41	0.64
Prazosin	**0.48**	<0.001	0.37	0.62
Tamsulosin	**0.35**	<0.001	0.28	0.44
Terazosin	**0.34**	<0.001	0.27	0.43

Yamanouchi was interested to note that Merck Sharp & Dohme considered that 'Over time, response to finasteride is greater the larger the prostate, and so its recommended place in practice has evolved to reflect this'. The finasteride SPC made no mention of this

fact. Yamanouchi had reviewed a selection of Merck Sharp & Dohme finasteride sales aids and advertisements over a number of years, which also made no reference to prostate size and symptom improvement or response. Therefore, Yamanouchi concluded that prostate size as a confounding factor was irrelevant in this case.

As Merck Sharp & Dohme had acknowledged, the claim was not comparative and the claim itself had already been justified in 1 and 2 above of this response. Therefore, Yamanouchi concluded that the data on file did represent a balanced, fair and objective evaluation of all medical therapies and was not in breach of the Code.

PANEL RULING

The Panel noted that the SPC for Merck Sharp & Dohme's product, Proscar (finasteride), stated that the product was indicated for the treatment and control of BPH in patients with an enlarged prostate *inter alia* to reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy. The Flomax MR SPC stated that the product was indicated to treat the functional symptoms of BPH.

In the Panel's view a delay in the need for surgery might be a benefit of treatment with Flomax MR but such a delay was not the primary reason to use the product; the reason to use Flomax MR, and its licensed indication was to treat the functional symptoms of BPH. The Panel noted that Clifford and Farmer stated that '... upon evaluation of the risks associated with symptomatic BPH patients progressing to surgery or AUR [acute urinary retention], finasteride has been shown to offer beneficial effects that are as yet unproven with any α-blocker therapy, as no appropriate outcome analyses have been published. However, preliminary results from the PREDICT (Prospective European Doxazosin in Combination Therapy) study suggest that not only finasteride but also α-blocker therapy may reduce both AUR and surgery in BPH'.

The Panel noted that the data provided to support the claim came from the GPRD. Yamanouchi submitted that the GPRD data was fully consistent with the expected efficacy of all licensed products. The Panel noted the comments from both parties with regard to potential confounders. There were no randomised controlled trials to support the claim for Flomax MR. There was such data for Proscar. The Panel noted that the Clifford and Farmer review stated that large placebo effects (resulting in up to 40% symptom improvement) could persist for up to 2 years of therapy emphasising the importance of properly designed double-blind placebo-controlled studies in evaluating the outcome of medical therapy for BPH.

The Panel considered that the claim that Flomax 'Delays the need for surgery' was inconsistent with the SPC and a breach of Clause 3.2 of the Code was ruled. The Panel also considered that the claim was not a fair reflection of the evidence and was not capable of substantiation Breaches of Clauses 7.2 and 7.3 of the Code were ruled. These rulings were appealed by Yamanouchi Pharma and GlaxoSmithKline.

With regard to the alleged inappropriate comparison with Proscar, the Panel noted that Merck Sharp & Dohme accepted that the claim 'Delays the need for surgery' was not comparative. The complaint related to the comparison of Proscar with α-adrenoceptor blockers in the data on file. The reference suggested that Proscar and Flomax MR had similar efficacy. The Panel noted that the advertisement made no comparative claim. The data on file compared the α-blockers with Proscar, a product that had an indication for delaying surgery. The Panel considered that as there was no claim in the advertisement in relation to the comparative efficacy, there was no breach of Clause 7.2 of the Code and ruled accordingly. This ruling was not appealed.

APPEAL BY YAMANOUCHI PHARMA AND GLAXOSMITHKLINE

Yamanouchi submitted an appeal on behalf of both companies. With regard to the Panel's ruling of a breach of Clause 3.2, Yamanouchi explained that BPH was a common, usually non-life threatening condition, for men, especially the elderly. Whilst there were a number of presenting symptoms, the commonest reason for presentation by patients to their GP was because they were distressed or disturbed by their symptoms. 'Bothersomeness' was the term currently used by urologists to sum up the impact of symptoms on the patient. Patients were seeking from their GP effective relief of their symptoms preferably with minimal side effects or morbidity, no matter whether the intervention was surgical or medical. Effective symptom relief was a goal for managing BPH patients in clinical practice.

Yamanouchi agreed that functional could be defined as affecting physiological or psychological functions but not organic structure. The company had never made any claim that organic structure was affected by tamsulosin. The reason why tamsulosin delayed the need for surgery was not through an effect on the organic structure of the prostate (which it did not have), but through its effect on the functional symptoms, by reducing the muscle tone of the prostatic urethra and bladder neck.

Prior to the advent of effective medical therapies the only effective treatment for patients' symptoms was surgery but surgery was invasive and associated with significant morbidity, for example infections, bleeding and urethal stricture. However, patients now had a choice in the management of their disease and where it was an appropriate option, would for many reasons often prefer to choose medical therapy instead of surgery.

Providing that the medical therapy was satisfactory in relieving the patients' symptoms (and was well tolerated) patients would 'put-off' having surgery for their symptoms ie surgery was delayed. As stated in an expert report '… medical therapies lead to the relief of troublesome symptoms in over 70% of patients. In my experience when these patients are reviewed they no longer wish or require surgical intervention' and '… from my own practical clinical experience, supports the principle that medical therapies delay the need for surgery …'.

This was reinforced in a second expert report in which it was stated 'Logically it follows that any drug that is effective in reducing the symptoms of BPH should delay the need for surgery'.

These statements applied to all effective medical therapies ie to all licensed BPH treatments.

Yamanouchi noted that it had been acknowledged for a number of years that licensed (ie effective) treatments for BPH delayed the need for surgery. Some examples of such articles which made specific reference to this were: 'But the use of alpha blocker[s] … for those who desire to postpone surgery' (Von-Heland and Casale 1994), 'alpha$_1$-Adrenoceptor antagonists have a place … for those awaiting or wishing to delay surgery' (Chapple 1996), 'We considered [the] pharmacologic approach as a treatment that may delay the need for surgery for BPH' (Di-Silverio *et al* 1995) and 'Medication as treatment should be reserved for patients … who wish to delay surgery' (Yamamoto and Miyake 1996).

Yamanouchi noted that the Panel had made, in part, this connection between medicines that relieved symptoms and a consequent delay in the need for surgery for symptom relief. To quote, '… a delay in the need for surgery might be a benefit of treatment with Flomax MR …'. However, the Panel went on to say '… but such a delay was not the primary reason to use the product …'. Yamanouchi submitted that doctors did not necessarily distinguish between primary and secondary reasons to use products, the two were inextricably linked. This was confirmed in the second expert report in which it was stated 'It is doubtful whether doctors in normal clinical practice can distinguish between a benefit of a particular medicine and a primary reason to use a medicine when the desired outcome, namely the relief of symptoms, is the prime motive for treatment'.

Yamanouchi stated that the advertisement was obviously drawing attention to the efficacy of Flomax MR in terms of symptom relief. The heading of 'Relief all round' related to relief across the spectrum of BPH symptoms and that the patient might have an improved urinary flow. Symptom relief was reinforced with the first bullet point 'Rapid and sustained relief of symptoms', leading the eye down to the third bullet point which occurred as a consequence of the 'Relief all round'. The advertisement did not suggest that Flomax MR should be used solely to delay surgery, ie it did not suggest this as a primary indication for the use of the product.

Yamanouchi noted that the breach was ruled on the grounds that 'the statement was inconsistent with the SPC'. The definition of the word 'inconsistent' in the New Shorter Oxford English Dictionary was 'not in keeping, discordant, at variance … of two or more things, incompatible, incongruous'. Delaying the need for surgery could not be 'not in keeping' nor 'discordant' nor 'at variance' with an effect which 'might be a benefit of treatment'. Equally the statement and the SPC could not be 'incompatible' or 'incongruous'. This issue of inconsistency was entirely separate from the breaches of Clauses 7.2 and 7.3 which related to whether the data supported such a claim as opposed to the claim being the natural outcome of effectively treating the symptoms.

Yamanouchi stated that it was particularly important to note the claim did not state that surgery was avoided. The company had never made this suggestion and it was quite clear from the advertising material in question that the claim made was a delay to surgery, not its avoidance.

In conclusion, as the first expert report stated 'medical therapies delay the need for surgery by their effects on patients' bothersome symptoms' and 'I understand this to be the opinion of consultant urologists and the majority of general practitioners …'. Therefore the claim could not be inconsistent with the licensed particulars for Flomax MR and was not in breach of Clause 3.2.

With regard to the Panel's ruling of a breach of Clause 7.2 and 7.3 Yamanouchi stated that it considered that the use of the GPRD analysis was a fair reflection of the evidence and that it substantiated a claim which applied to all medical therapies for BPH. In support of its position the company submitted a second expert report jointly written by a professor of epidemiology and a consultant urologist. This report dealt with specific points raised by Merck Sharp & Dohme and the Panel.

Even prior to the GPRD analysis it had been acknowledged for several years that licensed (ie effective) treatments for BPH delayed the need for surgery. Some examples of such articles which made specific reference to this had been given above.

The GPRD analysis was further confirmatory evidence of a fact which had been recognised for some time and which, as could be seen from both expert reports, was an outcome that urologists and GPs expected as a consequence of effective medical therapy.

GPRD was an extensive and reputable database, representative of primary care practices in England and Wales. It reflected every day clinical practice as recorded by over 2,000 GPs. It was managed by the MCA and contained high quality data from over 4.6 million patients.

Yamanouchi submitted data on file which described the aim, methodology, design and the results of a case control study using GPRD, which investigated the management of BPH over the period 1992-1998. The study investigated the impact of medical therapy on BPH and survival time to surgery compared to a control group ie no treatment group. The study underwent ethical approval before implementation and the Scientific and Ethical Advisory Group for GPRD (SEAG) approved the study aim, methodology and study design, and considered the statistical rational to be of an acceptable and robust scientific standard before allowing the group to commence the GPRD observational study. SEAG also approved the abstracts presented at the EAU 2000 (European Association of Urology), AUA 2000 (American Urological Association), BAUS 2000 (British Association of Urological Surgeons) and the manuscripts submitted to the European Journal of Urology prior to publication. The data were used to

calculate the age-specific incidence rates of urinary symptoms due to BPH and prostatic surgery. Survival analyses were conducted examining the intervals between first diagnosis, treatment and surgery. A number of confounding factors were taken into consideration by using the Cox regression model.

Yamanouchi noted that three major issues were raised in the Panel's ruling, namely the quote from the Clifford and Farmer review, confounders and lack of randomised controlled trials.

1 Quotation from Clifford and Farmer review

The Panel noted that Farmer *et al* stated '… finasteride has been shown to offer beneficial effects that are as yet unproven with any alpha-blocker therapy, as no appropriate outcome analyses have been published …'. Yamanouchi noted that this paper was submitted to the European Urology Journal in mid 1999 and accepted after revision in October 1999; it was published in July 2000. The data from the GPRD observational study in question was first published at the EAU in April 2000 and hence these statements in the review submitted to this Journal in 1999 had since been superseded and were therefore out of date. This was possibly why Merck Sharp & Dohme made no reference to this quotation.

2 Confounders

Yamanouchi noted that in Farmer's report, it was not disputed that observational studies, in particular database studies, could be limited as it was often not possible to adjust for confounding in the analysis. Merck Sharp & Dohme recognised that 'attempts have been made in the analysis to adjust for some recognised confounding factors', however it continued to raise concern that 'all confounders cannot be allowed for because of inadequate information in the database, eg prostate size, severity of symptoms, compliance rates'. These issues were addressed in the second expert report and the adjustments that had been made to counteract this argument explained.

a) ***Prostate size***
Prostate size was not generally assessed prior to initiation of medical therapy in general practice and therefore could not be a confounder for prescriptions generated by GPs. However, prostate size might influence prescriptions in secondary care as rectal examinations, and sometimes more sophisticated assessments of prostate size, were undertaken routinely. This could be taken into account by either partitioning, according to whether or not the patient had been referred to a specialist before the start of a medical treatment, or the outcome data could be *adjusted* for prior specialist referral. In the GPRD analysis the latter technique was used. The outcome was unchanged.

b) ***Symptom severity***
There were two possible proxies for symptom severity (or relative symptom severity) available from GPRD data: the initial presenting symptom eg urinary frequency, urinary incontinence, and the interval between the first symptom and the initiation of first treatment. Both of these had now been incorporated in the analytical model and had made no difference to the conclusion.

c) ***Compliance***
With respect to compliance rates, Yamanouchi stated that Merck Sharp & Dohme was not correct when it stated that compliance could not be measured by GPRD. As the expert report explained all prescriptions were included in the database along with the dosage and quantity prescribed. Treatments for BPH were usually taken long-term and therefore the sequence of prescriptions could be used as a proxy measure of compliance, particularly for symptomatic diseases. The sequence of prescriptions were investigated for all products licensed for the treatment of BPH and no differences were found.

d) ***Geographical variations***
Yamanouchi noted that Merck Sharp & Dohme commented on geographical variation in surgery rates, watchful waiting and extent of use of different products. GPRD, covering 4.6 million people, was considered representative of the population of England and Wales. The University of Surrey had worked extensively with the GPRD database as it considered it representative of primary care practice in England and Wales. Additionally, the representative nature of the database had been specifically validated by reference to prostatectomy rates in the NHS Hospital Episode Statistics (HES), and in terms of BPH therapies, against both International Medical Statistics (IMS) and Prescription Pricing Authority (PPA) statistics.

e) ***Age***
The age range for each of the products (including the no therapy group) was irrelevant as age had been taken into account as a confounder and therefore the groups could be compared. The hazard ratios quoted in the data on file had been adjusted for age and the year in which the patients first presented with lower urinary tract symptoms. These adjustments were carried out to compensate for any variations that could have been attributable to either age or secular trends in treatment policy.

3 Randomised/placebo-controlled trials

Yamanouchi noted that the Panel ruling stated that there were no randomised controlled trials to support the claim for Flomax MR, whereas there was such data for Proscar. The Panel's comments were, in themselves, true. The Panel also commented on placebo effects. However, randomised controlled trials including placebo-controlled studies, were not the only method of demonstrating efficacy, effectiveness or other outcomes. Whilst in the majority of situations, randomised controlled trials might be the gold standard, this did not preclude the use of other study designs, provided they were robust and statistically sound. The analysis of the GPRD was one such example and was used here to support the claim. The fact that this was not a randomised controlled study should not be the issue here. The issue should be whether the GPRD analysis

substantiated the claim. Yamanouchi considered that it did and that the questions concerning its robustness had been satisfactorily answered in this response.

The placebo effect referred to in the Panel's ruling was irrelevant in this situation as all medical therapies would have essentially similar placebo responses. Medical therapies were licensed because they had demonstrated efficacy and there would be a response (be that symptom relief or the delay to surgery) that would be over and above the response to placebo.

Yamanouchi stated that the evidence cited above showed clearly that the claim, based on a robust analysis of GPRD data, was a fair reflection of all available evidence. There was no up-to-date evidence nor any quotations that refuted the findings of this comprehensive study and therefore there was no breach of Clause 7.2. The claim was soundly substantiated by the thorough methodology and statistical handling of an extensive, highly credible and representative database of real life primary care practice and therefore there was no breach of Clause 7.3.

In conclusion, Yamanouchi considered that the evidence presented demonstrated that there had been no breaches of Clauses 3.2, 7.2 or 7.3.

GlaxoSmithKline confirmed that it supported Yamanouchi's appeal.

At the appeal hearing the representatives confirmed that although the prevalence of BPH had increased over the past 4-5 years because patients were living longer, the incidence of the disease had stayed constant. Data was presented which showed that over the same time period prostatectomy rates in the UK had fallen and that the time interval from first diagnosis to surgery had increased.

APPEAL BOARD RULING

The Appeal Board noted the submission that current management of BPH was driven by both patients and their partners and their desire to have the patient's symptoms relieved and to delay surgery for as long as possible. The decision as to whether to operate or not was based on the need to relieve symptoms not, as in the past, on an assessment of urodynamic parameters. The Appeal Board considered that, given the way in which BPH was managed, a medicine which treated the symptoms of the disease would delay a patient's need for surgery. The Appeal Board noted that the SPC for Proscar, Merck Sharp & Dohme's product, stated that the product reduced the incidence of acute urinary retention and the need for surgery. The Appeal Board noted that Flomax MR was licensed to treat functional symptoms of BPH. The SPC stated that the product relieved obstruction; relief of obstruction was also a reason for surgery. The Appeal Board thus did not consider that the claim 'Delays the need for surgery' was inconsistent with the particulars listed in the Flomax SPC and no breach of Clause 3.2 was ruled.

The Appeal Board considered that the GPRD data substantiated the claim in question and that the data itself was representative of the balance of the evidence. No breaches of Clauses 7.2 and 7.3 were ruled.

The appeal was successful.

Complaint received **26 January 2001**

Case completed **13 June 2001**

CASE AUTH/1134/2/01

CHUGAI PHARMA v AMGEN

Neupogen mailing

Chugai Pharma complained about a mailing for Neupogen (filgrastim) sent by Amgen to about 400 pharmacists in the UK. Chugai alleged that the mailing was highly unethical as it suggested that in the past oncology healthcare professionals had been treating seriously ill cancer patients with a sub-therapeutic dose of its product lenograstim (Granocyte).

The claim 'A survey containing cancer patient weights showed that the proportion of patients covered by ONE injection at 5µg would be: *† ● 97% Neupogen ● < 10% lenograstim' appeared beneath the heading 'Reduced injection burden'. The asterisk led to the statement 'The recommended dose of lenograstim is 150µg/m^2/day, therapeutically equivalent to 5µg/kg/day'. The obelus led to the reference 'ISIS Survey 1998'.

Chugai alleged that this comparison was unfair, ambiguous and designed to mislead. The licensed dose of lenograstim in the summary of product characteristics (SPC) was 150µg/m^2. The SPC also clearly stated that the 33.6MIU vial could be used in patients with a body surface area of up to 1.8m^2. The Cytotoxics Handbook stated that the dosage of lenograstim was 150mcg/m^2 per day and that a 33.6MIU vial was sufficient to treat patients with a body surface area of up to 1.8m^2. The data quoted in the Amgen mailing was a market research survey titled 'ISIS survey 1998'. Amgen had provided Chugai with the ISIS Cancer in Europe 1998 survey showing the cancer patient weight distribution in 1144 UK patients. Amgen had stated that the database was purchased in electronic database format to allow it to interrogate the data to understand more about the target patient population. Chugai had then contacted ISIS research and found out that the patient information collected included not only the weight of the patient but also the patient's body surface area in m^2. The body surface area data from this survey clearly showed that 75% of patients were less than or equal to 1.8m^2 which confirmed that 75% of cancer patients could be treated from a single 33.6MIU injection. It would be noted that this body surface area data referred to the identical patient group used in Amgen's mailing. Chugai therefore concluded that Amgen had access to this data but deliberately ignored it and made a highly misleading and inaccurate claim.

The Panel noted that the SPC for Granocyte stated that the recommended dose was 150mcg/m^2/day, therapeutically equivalent to 5mcg/kg/day. Amgen had compared the products on a mcg/kg/day basis as its product, Neupogen, did not have a recommended dose based on surface area. Amgen had referred to Cases AUTH/714/5/98 and AUTH/725/6/98 which concerned, *inter alia*, a table which depicted, according to patient weights, the amounts of Neupogen and lenograstim required to achieve a dose of 5mcg/kg of each. The Panel had considered that the expression of the dose of both products in mcg/kg would be less confusing to the reader than using two dosage units. The dose of lenograstim had been correctly expressed as 5mcg/kg. No breach of the Code had been ruled. The Panel considered that the present case was different to that previously considered. The basis of the comparison was not the same. In Cases AUTH/714/5/98 and AUTH/725/6/98 no mention had been made by the parties of the effect of the wide difference in the dosing requirement of lenograstim depending on whether it was mcg/kg or mcg/m^2 and thus the Panel had not previously considered this point. The ISIS data used to calculate the number of patients for whom one 33.6 MIU vial of lenograstim was sufficient varied depending on whether the patient's weight or surface area was used to calculate the dose. It was true to state that from the survey one vial of lenograstim would be sufficient for <10% of patients if body weight was used to calculate the dose. If the surface area was used instead, then one vial would be sufficient for 75% of patients. The Panel considered that given this difference the claim was misleading. The Granocyte SPC stated the dose of lenograstim according to either the patient's surface area or body weight, but the claim in question was only true if body weight had been used to calculate the dose. The Panel therefore ruled a breach of the Code.

Upon appeal by Amgen, the Appeal Board's view was that the matter was similar, but not identical, to that considered in Cases AUTH/714/5/98 and AUTH/725/6/98. One of the points at issue had been a table which depicted, according to the theoretical weight of patients, the amount of Neupogen and lenograstim required to achieve a 5mcg/kg dose of each. There had been no mention of patients' body surface area. In the circumstances the Panel had considered that it was acceptable to express the dose of both medicines in terms of mg/kg. The Panel's subsequent ruling of no breach of the Code was not appealed. No mention had been made of the effect of the wide difference of the dosing requirement of lenograstim depending on whether it was calculated according to mcg/kg or mcg/m^2. In the present case, the Appeal Board noted that the claim at issue was based on real patient data from which it had been possible to obtain both weight and body surface area data. The Granocyte SPC gave details of dosing according to either body weight or body surface area. The Appeal Board noted that if body surface area was the basis of the calculation then one vial of Granocyte would have been sufficient for 75% of patients included in the ISIS survey as opposed to less than 10% if body weight was used. The Appeal Board noted that the dose of Granocyte when calculated by body surface area was usually less than when calculated by body weight. Given that the Granocyte SPC gave two ways of calculating the dose, and that real patient data which had included body surface area was available, the Appeal Board considered that the claim in question was too simplistic. The claim was only true for dosing by body weight. The Appeal Board considered that in the circumstances the claim was misleading and upheld the Panel's ruling of a breach of the Code.

The claim 'Reduced risk of dosing errors' appeared as one of five bullet points under the heading 'The benefits of the Neupogen pre-filled syringe'. Chugai stated that the licensed dose of Neupogen was 5mcg/kg for post bone marrow transplantation and chemotherapy induced neutropenia. Therefore, for example, an 80kg patient would require a dosage volume of 1.33ml. The pre-filled syringe illustrated in the mailing was graduated in intervals of 0.4, 0.8, 1.2 and 1.6ml. It was therefore not possible to accurately dose patients between these intervals (a volume of 0.4ml corresponded to a patient weight difference of 24kg). This claim was therefore inaccurate and misleading. The Panel queried whether there was data to show a reduced risk of dosing errors with prefilled syringes. The Panel accepted that there were advantages for prefilled syringes over vials, etc, but was unsure whether there was a reduced risk of dosing errors compared to vials and syringes, particularly as the prefilled syringe was graduated in intervals of 0.4ml. Injecting 1.33ml from a syringe graduated in 0.4ml would be difficult regardless of whether or not the syringe was prefilled. On balance the Panel considered that the claim 'Reduced risk of dosing errors' overstated the data. It implied that there was a quantifiable reduction in risk and that was not so. The claim was misleading and a breach of the Code was ruled.

Chugai Pharma UK Limited complained about a mailing for Neupogen (filgrastim) sent by Amgen Limited to about 400 pharmacists in the UK.

Chugai Pharma alleged that the mailing was highly unethical as it suggested that in the past oncology healthcare professionals had been treating seriously ill cancer patients with a sub-therapeutic dose of its product lenograstim (Granocyte) which would have caused them great concern. Furthermore Chugai believed that the claim might have been damaging to its business in the UK.

Amgen stated that it had made every effort to resolve the matter with Chugai.

1 Claim 'A survey containing cancer patient weights showed that the proportion of patients covered by ONE injection at 5µg/kg would be: *† ● 97% Neupogen ● < 10% lenograstim

The claim appeared beneath the heading 'Reduced injection burden'.

The asterisk led to the statement 'The recommended dose of lenograstim is 150µg/m^2/day, therapeutically equivalent to 5µg/kg/day'. The obelus led to the reference 'ISIS Survey 1998'.

COMPLAINT

Chugai alleged that this comparison was unfair, ambiguous and designed to mislead in breach of Clause 7.2 of the Code.

The licensed dose of lenograstim in the summary of product characteristics (SPC) was 150µg/m^2. This was stated in the posology Section 4.2, and again in Section 4.2.1 in the individual indication sections.

Section 4.2 of the SPC also clearly stated that the 33.6MIU vial could be used in patients with a body surface area of up to 1.8m^2. This was irrespective of patient weight as body surface area calculations took this parameter into consideration.

The Cytotoxics Handbook, a widely used reference book for oncology pharmacists, contained a monograph on lenograstim and stated that the dosage of lenograstim was 150mcg/m^2 per day and that a 33.6MIU vial was sufficient to treat patients with a body surface area of up to 1.8m^2. This confirmed that 150mcg/m^2 was the accepted dosage of lenograstim in clinical practice.

The data quoted in the Amgen mailing was a market research survey titled 'ISIS survey 1998'. Chugai had contacted Amgen and requested a copy of this data. Amgen responded by sending the ISIS Cancer in Europe 1998 survey showing the cancer patient weight distribution in 1144 UK patients. A brief synopsis of the methodology used to obtain this data was provided. Amgen had stated that the database was purchased in electronic database format to allow it to interrogate the data to understand more about the target patient population.

Chugai had then contacted ISIS research which provided it with the 1998 Cancer Diary Study form that was used in the fieldwork to collect the data. Chugai noted that the patient information collected included not only the weight of the patient but also the patient's body surface area in m^2.

The body surface area data from this survey clearly showed that 75% of patients were less than or equal to 1.8m^2 which confirmed that 75% of cancer patients could be treated from a single 33.6MIU injection. It would be noted that this body surface area data referred to the identical patient group used in Amgen's mailing. Chugai therefore concluded that Amgen had access to this data but deliberately ignored it and made a highly misleading and inaccurate claim in clear breach of Clause 7.2.

RESPONSE

Amgen stated that the validity of the ISIS survey was not disputed by Chugai. Amgen believed that the comparison was fair, compared like with like and accurately reflected the data, and that it was not in breach of Clause 7.2.

Section 4.2 of the SPC for lenograstim clearly stated that the 'recommended dose of Granocyte is 150µg (19.2 MIU) per m^2 per day, therapeutically equivalent to 5µg (0.64 MIU) per kg per day'.

Amgen stated that although dosing by surface area took weight into consideration, it was generally accepted that dosing by body weight was a more simple and common practice. The lenograstim publications by Gisselbrecht *et al* 1994, Chevallier *et al* 1995 and Gisselbrecht *et al* 1997, all referred to a dose of 5mcg/kg/day. Moreover, the lenograstim drug evaluation review by Dunn and Goa 2000 referred to phase 2 and phase 3 work recommending a dose of 5mcg/kg/day.

In comparing two products Amgen believed that it

was essential to compare like with like, and as the Neupogen SPC recommended only mcg/kg dosing, this was used for both products.

A comparison between Neupogen and lenograstim, based on mcg/kg dosing, had previously been found not in breach of Clause 7.2 – Cases AUTH/714/5/98 and AUTH/725/6/98. The Panel concluded: 'The Panel noted that the table expressed the dose of both lenograstim and filgrastim in terms of micrograms per kg. The Panel considered that this would be less confusing to the reader than using two dosage units ie mcg/kg for filgrastim and mcg/m^2 for lenograstim. According to the Granocyte SPC the recommended dose of lenograstim, 150mcg (19.2 MIU) per m^2 daily, had been correctly expressed as 5mcg/kg. No breach of Clause 7.2 was ruled.'

Chugai had claimed that Amgen deliberately chose to use mcg/kg rather than mcg/m^2 as the comparator because the results showed fewer patients covered by one vial. While it was interesting, and somewhat perplexing, that there was such a wide difference between the dosing requirement of lenograstim, depending on whether it was dose by mcg/kg or mcg/m^2, Amgen chose to use mcg/kg because it was the unit that was referred to in the Neupogen SPC, and because the comparison was supported by the previous ruling of the Panel.

PANEL RULING

The Panel noted that the SPC for Granocyte stated that the recommended dose was 150mcg/m^2/day, therapeutically equivalent to 5mcg/kg/day. Amgen had compared the products on a mcg/kg/day basis as its product, Neupogen, did not have a recommended dose based on surface area.

The Panel noted that Amgen had referred to Cases AUTH/714/5/98 and AUTH/725/6/98 which concerned, *inter alia*, a table which depicted, according to patient weights, the amounts of Neupogen and lenograstim required to achieve a dose of 5mcg/kg of each together with corresponding costs. The Panel considered that the expression of the dose of both products in mcg/kg would be less confusing to the reader than using two dosage units. The dose of lenograstim had been correctly expressed as 5mcg/kg. No breach of Clause 7.2 was ruled.

The Panel considered that the present case was different to that previously considered. The basis of the comparison was not the same. The Panel noted that in Cases AUTH/714/5/98 and AUTH/725/6/98 no mention had been made by the parties of the effect of the wide difference in the dosing requirement of lenograstim depending on whether it was mcg/kg or mcg/m^2 and thus the Panel had not previously considered this point.

The Panel noted that the ISIS data used to calculate the number of patients for whom one 33.6 MIU vial of lenograstim was sufficient varied depending on whether the patient's weight or surface area was used to calculate the dose. It was true to state that from the survey one vial of lenograstim would be sufficient for <10% of patients if body weight was used to calculate the dose. If the surface area was used instead then one vial would be sufficient for 75% of patients. The Panel considered that given this difference the claim was misleading. The Granocyte SPC stated the dose of lenograstim according to either the patient's surface area or body weight but the claim in question was only true if body weight had been used to calculate the dose. The Panel therefore ruled a breach of Clause 7.2 of the Code.

APPEAL BY AMGEN

Amgen considered that the basis of this case, ie the comparison of mcg/kg to mcg/kg rather than mcg/m^2, was identical to the previous case. Dosing of lenograstim in the UK was predominantly calculated by the mcg/kg route. As the Granocycte SPC stated that 150mcg/m^2 was clinically equivalent to 5mcg/kg, Amgen considered that the comparison was like with like.

APPEAL BOARD RULING

In the Appeal Board's view the matter was similar, but not identical, to that considered in Cases AUTH/714/5/98 and AUTH/725/6/98. In the previous cases one of the points at issue had been a table which depicted, according to the theoretical weight of patients, the amount of Neupogen and lenograstim required to achieve a 5mcg/kg dose of each. There had been no mention of patients' body surface area. In the circumstances the Panel considered that it was acceptable to express the dose of both medicines in terms of mcg/kg. The Panel's subsequent ruling of no breach of the Code was not appealed. No mention had been made of the effect of the wide difference of the dosing requirement of lenograstim depending on whether it was calculated according to mcg/kg or mcg/m^2.

Turning to the case now before it, the Appeal Board noted that the claim at issue was based on real patient data from which it had been possible to obtain both weight and body surface area data. The Appeal Board noted that the Granocyte SPC gave details of dosing according to either body weight or body surface area. The Amgen representative had explained that the dose of Granocyte when calculated by body surface area was usually less than when calculated by body weight. Reference was also made to the various methods of calculating surface area. There was no one universally accepted method of calculation. An example of an 80kg patient of three heights, 158cm, 169cm and 182cm was used to illustrate how the calculated dose could vary. Calculating the dose according to body weight always gave a dose of 400mcg. By calculating the dose according to body surface area, using two different methods of determining body surface area, the dose for the 158cm patient could be 240 or 282mcg, for the patient of height 169cm the dose could be 285 or 291mcg but in both instances was 300mcg for the patient who was 182cm tall. The Appeal Board noted that if body surface area was the basis of the calculation, then one vial of Granocyte would have been sufficient for 75% of patients included in the ISIS survey as opposed to less than 10% if body weight was used.

Given that the Granocyte SPC gave two ways of calculating the dose, and that real patient data which had included body surface area was available, the Appeal Board considered that the claim in question was too simplistic. The claim was only true for dosing by body weight. Dosing by surface area gave a figure of 75% for Granocyte. The Appeal Board considered that in the circumstances the claim was misleading as alleged and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

2 Reduced risk of dosing errors

This claim appeared as one of five bullet points under the heading 'The benefits of the Neupogen pre-filled syringe'.

COMPLAINT

Chugai stated that the licensed dose of Neupogen was 5mcg/kg for post bone marrow transplantation and chemotherapy induced neutropenia. Therefore, for example, an 80kg patient would require a dosage volume of 1.33ml. The pre-filled syringe illustrated in the mailing was graduated in intervals of 0.4, 0.8, 1.2 and 1.6ml. It was therefore not possible to accurately dose patients between these intervals (a volume of 0.4ml corresponded to a patient weight difference of 24kg). This claim was therefore inaccurate and misleading in breach of Clause 7.2.

RESPONSE

Amgen stated that to its knowledge, no syringe had graduations that allowed 100% accuracy of dosing at every weight level. However, the graduations allowed consistent dosing and guidance, such that once the dose was determined the patient or nurse would be able to reproduce that dose by expelling fluid until the plunger reached the appropriate point.

Dosing by the Neupogen pre-filled syringe reduced the risk of dosing error because there were fewer steps involved in the administration, and therefore less chance of an error occurring at any one of those steps. It was often the patient who self-administered Neupogen (or lenograstim) instead of experienced healthcare professionals. Any reduction in complexity of administration would greatly reduce risk of error.

To prepare a dose of Neupogen from a pre-filled syringe took only one step – expelling the contents until the plunger was at the required point.

To prepare a dose of lenograstim, the patient must carry out a number of steps as described below, each of them with the potential for error (lenograstim SPC).

'Preparation of subcutaneous injection solution.

Aseptically add the extractable contents of one ampoule or of one pre-filled syringe of solvent (Water for Injection) to the Granocyte vial: 1.05ml for Granocyte.

Agitate gently until complete dissolution (about 5 seconds). Do not shake vigorously.

Withdraw the required volume from the vial.

Administer immediately by SC injection.'.

Detournay *et al* 1998 studied the use of prefilled disposable syringes versus conventional injection systems and stated: 'Standard dosages used in prefilled syringes and prelabelling during manufacturing may help to reduce medication errors.' Detournay *et al* 1998 concluded: 'Despite the general adoption of disposables in hospitals and efforts to inform and educate health professionals, the use of conventional injection systems (drug packaging in ampoules or vials and disposable syringes and needles) still raises safety problems for both patients and healthcare staff. The use of prefilled syringes may solve these difficulties in part. Moreover, qualitative data show that prefilled syringes are very much appreciated by nurses and pharmacists for their ease of use, safety and associated time savings.'

Amgen believed that the statement 'reduced risk of dosing errors' was supported by the above and therefore was not inaccurate or misleading and was not in breach of Clause 7.2.

PANEL RULING

The Panel queried whether there was data to show a reduced risk of dosing errors with prefilled syringes. The Panel accepted that there were advantages for prefilled syringes over vials, etc, but was unsure whether there was a reduced risk of dosing errors compared to vials and syringes particularly as the prefilled syringe was graduated in intervals of 0.4ml. Injecting 1.33ml from a syringe graduated in 0.4ml would be difficult regardless of whether or not the syringe was prefilled. The contents of the filled syringe would be more likely to vary given the steps for preparation. Detournay *et al* stated that standard dosages used in prefilled syringes and prelabelling during manufacture might help to reduce medication errors. On balance the Panel considered that the claim 'Reduced risk of dosing errors' overstated the data, it implied that there was a quantifiable reduction in risk and that was not so. The statements in Detournay *et al* 1998 were more cautious. The claim was misleading as alleged. A breach of Clause 7.2 of the Code was ruled.

Complaint received **1 February 2001**

Case completed **16 May 2001**

PATIENT v ASTRAZENECA

Sponsored asthma nurse

A patient complained about a letter which she had received from her general practitioner's surgery. This stated that to improve patient care, patients with asthma would be reviewed to ensure that they were receiving the best possible treatment. A specialist nurse would be running clinics at the surgery on a regular basis.

The complainant stated that upon enquiry she had found that the nurse came from AstraZeneca and she considered that the nurse would prescribe AstraZeneca's products. The local pharmacy had confirmed that usage of AstraZeneca products had gone up greatly. In the complainant's view, the nurse was a medical representative, nurse or not, and alleged that this was a new and rather aggressive method of selling.

The Panel noted that an audit protocol document set out the arrangements. Practices that had agreed to conduct an audit and participate in the programme were advised to establish an audit team with an identified leader. The document stated that all clinical and prescribing decisions must continue to be the responsibility of the GPs and practice nurse and set out points to be discussed at a meeting to agree the audit process.

The section on developing a management strategy suggested that clinical efficacy, compliance, tolerability and cost-effectiveness were considered prior to the medicine and device selection. No medicine was mentioned by either brand or generic name. Information and advice was given with regard to the prescribing of inhaled steroids together with examples of strategies to avoid their side effects. Examples of criteria that could be used for patient selection were also given.

It was intended that each patient consultation would last approximately 30 minutes. Patients were to be fully informed and a consent form was to be completed. Patients would be offered further appointments as necessary. Patients registered on the programme would be reviewed at three and six months. The programme was also evaluated for its effectiveness and a final report would be provided to the practice.

The Panel noted AstraZeneca's submission that its sponsored nurses did not prescribe or recommend either its products or those of other companies. The GP retained clinical responsibility for the management of patients including all prescribing decisions. The AstraZeneca nurse might refer patients back to the GP for re-evaluation of treatment as dictated by the agreed management strategy.

At the complainant's request the location of the GP practice in question had not been made known to AstraZeneca. The Panel could only make a ruling on the arrangements in general. Overall the Panel considered that the AstraZeneca Asthma Evaluation Programme was not unacceptable. It was a service that would benefit the NHS and enhance patient care. There was no link to any specific products. The Panel did not consider that the programme was an inducement to prescribe, supply, buy or administer any medicine. No breach of the Code was ruled.

A patient complained about a letter which she had received from her general practitioner's surgery.

The letter stated, *inter alia*:

'As part of our efforts to improve patient care, we have decided to review patients who have asthma, to try to ensure that they are receiving the best possible treatment.

A specialist nurse will be running clinics at the surgery on a regular basis, and you are invited to attend. The initial assessment (approximately 30 minutes) will include taking a detailed history of your asthma and its treatment and there will be time for discussion and advice.

If you choose to attend, it would be very helpful if you could bring along your inhalers, peak flow diaries and other medications'.

COMPLAINT

The complainant said that luckily for her she had chanced upon someone who had already participated and, besides being given AstraZeneca inhalers/turbohalers, one thing that struck the complainant was that her friend said that she didn't know where she (the nurse) came from because she did not know 'X'. The complainant's friend had had bad asthma for years.

The complainant rang up the surgery since she had once had a bad 'medical experience' which ensured that she asked the right questions and checked everything out now.

On learning that the nurse came from a pharmaceutical company, the complainant immediately cancelled her appointment and went to work investigating. People did not ask questions, as was borne out by the responses of the people she encountered. People did not think it strange to be asked to sign consent for a nurse to look at their medical records. After all, anything impinging on the NHS or the GP's surgery had to be kosher and that is what such a practice would trade on. One could give the simile of lambs to the slaughter and, if anything was questioned, well the nurse had a consent signature to show, had she not?

So the nurse made an appointment to see a certain number of patients and probably gave out a company inhaler and suggested another product of AstraZeneca and, in three months' time, no doubt the patient could be persuaded they were better then come what may, until after six months, it was established medication.

The local pharmacy had confirmed that AstraZeneca products had gone up greatly. Well the nurse had not unnaturally prescribed the company products. That being so the time spent had been well worth it.

The complainant's fear was that outlandish village surgeries were very vulnerable with less likelihood of the practice being noticed. Without somebody like the complainant being there things didn't get picked up, didn't get uncovered, and the local area had a good sprinkling of such surgeries.

The nurse was qualified. The complainant had checked with the UKCC but she was a Grade 1 nurse with no specialist training. However, if she worked for a pharmaceutical company she was a medical representative, nurse or no nurse, and this was just a new and rather aggressive method of selling.

As to what the GP got out of the situation one could only guess, but it was not ethical.

The complainant considered the whole affair very unethical and felt so strongly that she intended to submit letters to three local papers.

When taking the matter up with AstraZeneca UK Limited, the Authority drew attention to Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

AstraZeneca stated that, as would be appreciated, it was unable to respond to the specifics of the complaint in relation to a particular surgery, as it could not be identified from the information provided. However, general information in respect of its existing asthma nurse programme was provided.

AstraZeneca Clinical Nursing Service

The AstraZeneca Clinical Nursing Service had been in place for a number of years. The service was currently constituted as a department within the External Affairs and Strategic Planning Directorate. This directorate was separate from AstraZeneca's Sales and Marketing and Commercial Directorates. The Clinical Nurse Specialists worked locally.

All nurses recruited for these positions were required to be Registered General Nurses (part 1 of the UKCC register) and registration status had to be maintained as a condition of employment in this role. Nurses were also required to have a minimum of three years' post registration experience. Unless they had already undertaken additional asthma related training, those nurses who formed part of the respiratory nurse team were sponsored by the company to take such training.

It was optional to include additional qualifications on the Nursing Register, the onus being on the nurse herself to inform the UKCC accordingly. Thus, the full extent of the particular nurse's qualifications pertinent to this case might well not have been evident to the complainant. Part 1 of the register comprised those nurses who were Registered General Nurses, Part 2 comprised those with a midwifery qualification and Part 3 those who were qualified as health visitors. The complainant appeared to have misconstrued the nature of these separate parts of the register. It was perfectly feasible for a highly experienced nurse to be included on Part 1 of the register only.

All AstraZeneca Respiratory Clinical Nurse Specialists also participated in an internal training programme that included general training on asthma and on the implementation of the Asthma Evaluation Programme. The internal training, in common with the external training, naturally covered asthma treatments; however the range of available options was covered, training was not confined to AstraZeneca products. The training materials were provided.

Asthma Evaluation Programme

The overall purpose of the programme was to support the delivery of high quality care for asthma patients in the primary care sector. It provided a systematic assessment of asthma management via a process of audit and incorporated current best practice as represented by the British Thoracic Society (BTS) guidelines. The anticipated benefits for the practice included the construction of an accurate disease register of asthma patients, evaluation of asthma management throughout the period of the programme, production of personalised patient self-management plans and the opportunity for review of treatment. In addition, an extensive report of the audit outcome data was provided. For the patient, the programme provided confirmation of diagnosis, ongoing clinical assessment and the opportunity to develop a personalised management plan.

Full documentation on the programme 'The Asthma Evaluation Programme Audit Protocol' was provided. The documentation comprised a folder, the contents of which outlined the process, together with various appendices illustrating forms and documents used throughout the programme and some enclosures. The Clinical Nurse Specialist used the folder for reference whilst discussing the details of the programme with practices. The contents of the folder were also supplied in booklet form to the practice for its information and retention.

Identification of practices for the Asthma Evaluation Programme

Practices that wished to review their management of asthma patients, but which might not have the internal resource available to achieve this, were identified by the clinical nursing department as potential recipients of the service. There were a number of possible routes by which such practices became known to the department, these included: referral via another practice that had been a previous recipient of the service; response to proactive contact made by the Clinical Nurse Specialist based on local knowledge; following a request made by the surgery, either directly to the clinical nursing department, or via a sales representative.

The nurse initially telephoned the practice and outlined the programme, commonly to the practice nurse, GP interested in asthma or the practice manager, and established their interest in participating in the programme. The practice nurse, GP or manager would explain the programme to the other GPs in the practice, after which a meeting would be arranged for the Clinical Nurse Specialist to discuss the process in greater depth.

Initial stages in the Asthma Evaluation Programme

The nurse firstly introduced the concept of audit to

the practice and, if it was decided to proceed, the nurse guided the practice in the identification of a practice audit leader and facilitated the setting up of a practice audit team. The practice audit team would then be responsible, with guidance from the Clinical Nurse Specialist, for identifying the criteria and standards for the audit and for developing an agreed asthma management policy. A pre-audit meeting would take place at which this information would be formally documented using the pre-audit meeting form. The form documented the audit criteria, the method of data collection, the method by which patients were invited to attend clinics and referral to doctor criteria. The form included an agreement for the AstraZeneca nurse to have access to patient records and was signed by the responsible doctor and the Clinical Nurse Specialist; it also included a confidentiality statement in line with relevant legislation. In addition, a legal contract for provision of a nurse was signed by representatives of the practice and by the relevant AstraZeneca personnel and this incorporated a confidentiality clause.

Identification of patients for inclusion in the audit

Patients for the audit were identified using clear criteria as requested by the practice audit team, via a computer search undertaken by the practice. Following identification, patients were invited to attend a clinic. The audit documentation included copies of example letters that could be used for this purpose. The letter enclosed by the complainant differed in some respects from these proposed examples and AstraZeneca assumed it was produced by the practice in question, as was its prerogative. All patients who attended for clinic appointments received a patient information leaflet and were asked to sign a consent form to indicate agreement to participate in the process and for the nurse to have access to their notes.

Implementation of the programme

Implementation of the audit and of the management policy would fall within the remit of the Clinical Nurse Specialist via a number of clinics that she would run, in some cases with the involvement of the practice nurse as agreed at the pre-audit meeting. The nature and objectives of the clinics were outlined in the documentation.

During clinics, the nurse assessed the patient's current asthma status and level of control, assessed inhaler technique where appropriate and provided education and advice. Those patients who required re-evaluation of treatment were referred to the doctor in accordance with the management strategy as initially agreed by the practice audit team. All data collected were recorded on the relevant forms and, in addition, a final report was provided to the practice. A template for this report was provided.

The AstraZeneca nurse did not prescribe or recommend products, whether those of AstraZeneca or of other companies. This was in accordance with the nurse's role as written in to the legally binding contract. Clause 6.4 of the contract stated 'At all times the Doctor will retain clinical responsibility for the management of patients in his care, including all prescribing decisions and patient management'. Clause 6.5 stated that 'The nurse will not actively promote AstraZeneca products'.

Patients were only referred for re-evaluation of treatment as dictated by the agreed management strategy. Forms for this purpose were included in the protocol.

Summary

In summary, AstraZeneca's Clinical Nurse Specialists were employed in their capacity as qualified health professionals, to provide a bona fide service to medicine which was quite distinct from any promotional activity for medicines. AstraZeneca believed that this service provided assistance to primary care practices in reviewing asthma patients and ensuring management in line with current best practice. AstraZeneca's nurses were subject to the UKCC Code, which precluded any involvement in promotional activity.

AstraZeneca submitted that the materials relating to the programme had been meticulously prepared to appropriately reflect the nature of the service and they unambiguously denoted AstraZeneca's involvement with it. There was no implicit or explicit connection to any specific product and the service was in no way an inducement to a doctor to prescribe specific products. In conclusion, AstraZeneca did not believe that the Asthma Evaluation Programme could be considered to breach Clauses 2, 9.1 or 18.1 of the Code of Practice.

PANEL RULING

The Panel examined the arrangements for the AstraZeneca Asthma Evaluation Programme; the audit protocol document set out the arrangements. Practices that had agreed to conduct an audit and participate in the Asthma Evaluation Programme were recommended to establish a practice audit team with an identified leader. Such a team might include the Clinical Nurse Specialist, GPs, the practice nurse and practice manager / administrator. The documentation stated that all clinical and prescribing decisions must continue to be the responsibility of the GPs and practice nurse. The process of the implementation of change would be agreed by the practice audit team at the onset of the audit when considering the overall management strategy. The document set out points to be discussed at a meeting to agree the audit process. This included developing a management strategy for the practice to include treatment review, treatment referrals to the GP and practice nurse, urgent or emergency referrals to the GP and practice nurse, reversibility and nebulisation policies. The documentation included an example of a management strategy. The computer operator or receptionist would be asked to set up a computer search for the names of patients in the practice who met the criteria set by the practice audit team. It was advised that names of medicines and devices should be identified by the practice audit team via Chapter 3 Category 3.1 of a current British National Formulary.

The section on developing a management strategy suggested that the following factors: clinical efficacy, compliance, tolerability and cost-effectiveness were

considered prior to the medicine and device selection. Further detail was given about each factor. No medicine was mentioned by either brand or generic name. Reference was made to the recommendation in the BTS guidelines that the dose of an inhaled steroid should be adjusted to the minimum that would achieve control. With regard to tolerability it was stated that high dose steroids had a greater potential for systemic side effects. Advice was given about avoiding such side effects including use of an inhaler with low systemic bioavailability.

As an example of criteria that could be used for patient selection the document stated 'All patients who are between the ages of 2 and 65 years, currently taking inhaled beta2 medication, have required 2 or more prescriptions within the last six months and who are able to attend the clinic would be offered a consultation with a Clinical Nurse Specialist' and 'All patients who have attended the clinic and have a documented diagnosis of asthma in their notes, or who have proven reversibility of 15% or more, or who have demonstrated a diurnal variation of 20% or more over two weeks will be entered into the programme and referred to the doctor if a treatment review is required'. The documents stated that it was possible that many patients would be identified for a full assessment by the Clinical Nurse Specialist.

It was intended that each patient consultation would last approximately 30 minutes. Patients were to be fully informed of the nature and purpose of the clinic and a consent form was to be completed. An information leaflet was to be given to each patient. The assessment included taking a history etc. Peak flow was to be measured and an inhaler assessment and specific asthma symptom assessment was also undertaken. Patients would be offered further appointments as necessary. Patients registered on the programme would be reviewed at three months and six months. The programme was also evaluated for its effectiveness and a final report would be provided to the practice.

The Panel noted the submission from AstraZeneca that the AstraZeneca nurse did not prescribe or recommend products whether those of AstraZeneca or of other companies. Section 6.5 of the agreement for the provision of a nurse stated that the nurse would not actively promote AstraZeneca products. The doctor retained clinical responsibility for the management of patients including all prescribing decisions and patient management. The AstraZeneca nurse might refer patients back to the GP for re-evaluation of treatment as dictated by the agreed management strategy.

The Panel noted the submission that the UKCC Code precluded any involvement in promotional activity.

The Panel noted that the location of the complainant's practice had not been made known to AstraZeneca. The complainant had requested that this be kept confidential. The Panel could only make a ruling on the arrangements in general.

The Panel noted that the supplementary information to Clause 18.1 of the Code stated that it was not unacceptable for companies to provide medical and educational goods and services to enhance patient care or benefit the National Health Service. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. Further guidance had also been issued.

Overall the Panel considered that the AstraZeneca Asthma Evaluation programme was not unacceptable. It was a service that would benefit the NHS and enhance patient care. There was no link to any specific products. The Panel did not consider that the programme was an inducement to prescribe, supply, buy or administer any medicine. No breach of Clause 18.1 of the Code was ruled. The Panel also ruled no breach of Clauses 9.1 and 2 of the Code.

Complaint received **7 February 2001**

Case completed **31 May 2001**

CASE AUTH/1137/2/01

UCB PHARMA v SCHERING-PLOUGH

Promotion of NeoClarityn

UCB Pharma complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough. The items were a journal advertisement, an abbreviated advertisement and a leavepiece.

The claims 'Your old friend. With jaws' and 'Clarityn with extra clout' appeared in the journal advertisement and the leavepiece, both of which bore an illustration of a goldfish with a shark's fin strapped to it. UCB stated that these claims were designed to imply a clinical superiority of desloratadine (NeoClarityn) over loratadine (Clarityn). This was misleading as there were no comparative clinical trials and whilst desloratadine had only a limited licence, for seasonal allergic rhinitis, comparing the two products was intentionally misleading. The claim 'Clarityn with extra clout', within the clinical setting, was not supported by comparative trials. The summary of product characteristics (SPC) stated that the clinical relevance of antiallergic properties demonstrated *in vitro* remained to be confirmed. Using results from different clinical trials versus placebo was not a valid way to directly compare the effects of different products. The claim was exaggerated and all embracing for a product that had only enough evidence to support the single indication of seasonal allergic rhinitis.

The Panel noted that NeoClarityn was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Clarityn was indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis and also for the relief of symptoms associated with idiopathic chronic urticaria. In the Panel's view, the claims at issue would be read as clinical claims and that NeoClarityn had advantages over Clarityn. The Panel noted the differences in the indications for the products and that there was no direct comparison of the two. The Panel also noted that the NeoClarityn European public assessment report (EPAR) stated that 5mg desloratadine was not superior to 10mg loratadine. The Panel considered that the claims were misleading, exaggerated and had not been substantiated. Breaches of the Code were ruled.

The claim 'New NeoClarityn gives you the same confidence as Clarityn' appeared in the journal advertisement and the claim 'New NeoClarityn. Clarityn confidence…but with extra clout' appeared in the leavepiece. UCB stated that again it believed that a prescriber would consider the claim to be a comparison of at least equivalent products with equal indications. Confidence for a prescriber meant efficacy, safety and ease of use. This term was therefore intended to mislead, by inferring that NeoClarityn could be used in the same conditions as Clarityn. There were insufficient data to support the use of NeoClarityn in all of the indications for which Clarityn was approved. The Panel considered that its ruling above was relevant and that the claims relating to NeoClarityn giving the same confidence as Clarityn were not sufficiently qualified. The products had different indications and there was no comparative data. The claims were misleading and not capable of substantiation and breaches of the Code were ruled.

The claim 'New NeoClarityn gives you the same confidence as Clarityn, but with 40 times more potency' appeared in the journal advertisement and the claim '40 times more potent than Clarityn' appeared in the leavepiece. UCB stated that the claims were based on *in vitro* data. The use of this information was intended to extrapolate this *in vitro* effect to the clinical setting. In the absence of clinical data supporting the claims they became irrelevant and misleading. There was conflicting data. The study referenced was a recent one and did not reflect the balance of evidence that had been collected previously. Earlier studies found a relative potency of 2.5–4 times in animals. In the light of this evidence a general statement of 40 times more potent was unsubstantiated by the body of evidence. The claim was also exaggerated and, more importantly, was clinically irrelevant. Subsequent to making the complaint, UCB referred to the EPAR which reinforced its view that the potency claims made by Schering-Plough were exaggerated, designed to mislead and unsubstantiated. The Panel noted that the claim for potency was based on *in vitro* data. The claim was referenced to a study which was the only one using the cloned human H1 receptor. The Panel noted that the claims at issue did not made it clear that they were referring to *in vitro* data. Further, the Panel queried the relevance to the clinical situation, noting that no relevant clinical data had been supplied by Schering-Plough. Breaches of the Code were ruled.

UCB alleged that the claim 'The first antihistamine with significant anti-allergic and anti-inflammatory properties *in vitro*' in the leavepiece was untrue. Data supporting this effect with Zirtek (cetirizine – UCB's product) had been publicly available since the late 1980s. It was therefore intended to mislead by implying a new effect with NeoClarityn. Furthermore, the NeoClarityn SPC stated that the clinical relevance of these results was unclear. Even with Schering-Plough's assurance that the unique nature of this claim had been removed, UCB still believed that the use of such *in vitro* data in promotion to GPs was intended to mislead prescribers. NeoClarityn was not the first to show this effect. The Panel noted that the SPC for Zirtek stated that it was an antihistamine with anti-allergic properties; it inhibited the histamine-mediated 'early' phase of the allergic reaction and also reduced the migration of inflammatory cells and the release of mediators associated with the 'late' allergic response. Zirtek was indicated for the treatment of perennial rhinitis, seasonal allergic rhinitis, chronic idiopathic urticaria in adults and seasonal rhinitis in children aged between 2 to 6 years. The NeoClarityn SPC stated that desloratadine had demonstrated anti-allergic properties from *in vitro* studies and that the clinical relevance remained to be confirmed. The Panel considered that the claim in question was misleading. The clinical relevance still had to be

confirmed. Schering-Plough had accepted that NeoClarityn was not the first product to show anti-allergic and anti-inflammatory effects *in vitro*. The claim was not capable of substantiation. Breaches of the Code were ruled.

UCB alleged that the claim in the leavepiece 'Offers effective relief from nasal congestion' was misleading, suggesting a property that was not fully supported by the available evidence. Schering-Plough referred to a number of clinical papers but the Panel noted that it was not possible to establish from the limited data provided whether the pooled data described were from the same or different studies. The Panel noted Schering-Plough's submission that when the studies which had the same patient populations were pooled, the difference was statistically significant. The NeoClarityn SPC stated that it was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Section 5.1 stated that NeoClarityn was effective in relieving symptoms such as sneezing, nasal discharge and itching as well as ocular itching, tearing and redness and itching of palate. The Panel considered that nasal congestion was a symptom of hayfever. Schering-Plough had some data to support the effect of NeoClarityn on nasal congestion. Given the generality of the SPC indication and the data supplied the Panel considered that on balance the claim was not unreasonable and no breach of the Code was ruled.

The claim 'New NeoClarityn extends hay fever relief to cover even nasal congestion' appeared in the abbreviated advertisement. UCB stated that this claim was that NeoClarityn now offered an effect that had previously been unavailable in the treatment of hay fever. This was exaggerated and blatantly untrue; this feature had already been proven and accepted with cetirizine. Furthermore, as there were no comparative data, it could not be stated categorically that NeoClarityn offered an extension to the treatment of seasonal allergic rhinitis, beyond that already offered by cetirizine. Even if NeoClarityn was in the position to only claim top parity, within the antihistamine field, then this claim would still be misleading. The effect on nasal congestion had always been accepted as being the major benefit with topical steroids. The claim was therefore alleged to be inaccurate and misleading. The Panel considered that the claim implied that prior to NeoClarityn there was no product that could be used to relieve nasal congestion. This was not so. Nasal steroids were available for treating the problem. The Panel considered that the claim was misleading and exaggerated and breaches of the Code were ruled.

UCB proposed that with this style of advertising, where the new product was compared to a well established product, there was a genuine suggestion that the products could be used like for like. This was clearly not true for these two products. The licensed indications for NeoClarityn were limited when compared to Clarityn, as was the age range for use. This advertising encouraged off-licence prescribing and was alleged to breach Clause 2 of the Code. The Panel considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. The position was compounded as the indications for the products were not the same. The licensed indications for NeoClarityn were more restricted than for Clarityn. In the Panel's view Schering-Plough had not made sufficient effort to distinguish between the products. The Panel noted that Clause 2 was used as a sign of particular censure and was reserved for such use. On balance the Panel considered that the circumstances warranted a ruling of a breach of Clause 2 and a breach of that clause was ruled.

UCB Pharma Limited complained about promotional material used by Schering-Plough Ltd for its product NeoClarityn (desloratadine). The items at issue were a journal advertisement (ref NCL/00-005K), an abbreviated advertisement which had appeared in the classified section in GP journals (ref NCL/00-001C) and a leavepiece (ref NCL/00-015). Correspondence between the parties about the matter was provided by UCB. Even with Schering-Plough's assurances, UCB considered that breaches of the Code remained.

Schering-Plough stated that if UCB had taken up its offer to view Schering-Plough's amended material, it would have found that appropriate steps had already been taken to address the issues raised.

1 Claims 'Your old friend. With jaws' 'Clarityn with extra clout'

These claims appeared in the journal advertisement and the leavepiece, both of which bore an illustration of a goldfish with a shark's fin strapped to it.

COMPLAINT

UCB Pharma stated that these claims were designed to imply a clinical superiority of desloratadine (NeoClarityn) over loratadine (Clarityn). This was misleading as there were no comparative clinical trials and whilst desloratadine had only a limited licence, for seasonal allergic rhinitis, comparing the two products was intentionally misleading. A breach of Clause 7.2 of the Code was alleged.

The claim 'Clarityn with extra clout', within the clinical setting, was not supported by comparative trials. Schering-Plough's defence of this statement using animal and *in vitro* data was not clinically relevant, as admitted to in the summary of product characteristics (SPC). This stated 'Desloratadine has demonstrated antiallergic properties from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8 and IL-13 from human endothelial cells. The clinical relevance of these observations remains to be confirmed'. Also the defence using results from different clinical trials versus placebo was not a valid way to directly compare the effects of different products. A breach of Clause 7.3 was alleged.

The statement 'Clarityn with extra clout' was also alleged to breach Clause 7.8 as it was exaggerated and all embracing for a product that had only enough evidence to support the single indication of seasonal allergic rhinitis. Schering-Plough had assured UCB that the indication 'seasonal allergic rhinitis' would be

given a prominent position and this had relieved some of its concerns.

Subsequent to submitting the complaint, UCB referred to the European Public Assessment Report (EPAR). UCB stated that the overall conclusions (section 5) of the EPAR supported its position that desloratadine did not offer any real clinical advantage over loratadine. The following statements were particularly relevant: 'However, it seems from the percentage of improvement in Total Symptom Score that the clinical efficacy of 5mg desloratadine is probably not superior to 10mg loratadine' and 'The efficacy of desloratadine has not been studied in active comparator trials'.

RESPONSE

Schering-Plough stated that desloratadine was the active metabolite of loratadine. The claims were designed to succinctly inform the prescriber of the characteristics of a product that was, *in vitro*, a more active metabolite of a well-known parent compound. No claims regarding clinical efficacy were made.

Nevertheless, it was correct that desloratadine had activity in areas which loratadine did not. It had been shown, *in vitro*, as stated in the SPC, that desloratadine had the properties of 'inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8 and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells'. While the SPC stated 'The clinical relevance of these observations remains to be confirmed', previous work on loratadine had not shown the same antiallergic effect.

In addition, with respect to clinical data, while many of the current desloratadine publications were against placebo, in all trials examined desloratadine had at least a numerical advantage over placebo (and in several, a statistically significant advantage) in terms of treating the symptom of nasal congestion. A review of the loratadine literature showed a relative lack of efficacy of loratadine on nasal congestion. This consistent result, over a number of trials, demonstrated that, for at least this significant symptom, desloratadine had more 'clout' than loratadine.

While Schering-Plough believed it relevant to bring this data to the Authority's attention now, it would like to reiterate that it did not intend to, and believed that it had not, made a claim of clinical superiority for desloratadine compared to loratadine. In fact, in all Schering-Plough's material where it discussed the pre-clinical data related to desloratadine, it clearly stated this was *in vitro* data.

It was not Schering-Plough's intention to mislead its customers, deliberately or otherwise. The prescribing information included in the materials clearly indicated the product's approved indication. Nevertheless, Schering-Plough had adapted its current material to make it clearer that the pieces related to desloratadine in seasonal allergic rhinitis only.

With regard to the statements in the EPAR, Schering-Plough considered that the position could be argued in relation to the statement that the clinical efficacy of 5mg desloratadine was probably not superior to 10mg loratadine. It was perhaps sufficient to point out that the promotional material did not make any claims of clinical superiority or non-superiority of desloratadine over loratadine.

Schering-Plough was unsure of the relevance of the quotation 'The efficacy of loratadine has not been studied in active comparator trials'. It did not refer to comparative clinical data in the materials in question.

PANEL RULING

The Panel noted that the NeoClarityn SPC stated that it was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Clarityn was indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis such as sneezing, nasal discharge and itching and ocular itching and burning. Clarityn was also indicated for the relief of symptoms associated with idiopathic chronic urticaria.

In the Panel's view the claims at issue would be read as clinical claims and that NeoClarityn had advantages over Clarityn. The Panel noted the differences in the indications for the products and that there was no direct comparison of the products. The Panel also noted that the NeoClarityn EPAR stated that 5mg desloratadine was not superior to 10mg loratadine. The Panel considered that the claims were misleading, exaggerated and had not been substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code were ruled.

2 Claims 'New NeoClarityn gives you the same confidence as Clarityn' (journal advertisement) 'New NeoClarityn. Clarityn confidence…but with extra clout' (leavepiece)

COMPLAINT

UCB stated that again it believed that a prescriber would consider the claim to be a comparison of at least equivalent products with equal indications. Confidence for a prescriber meant efficacy, safety and ease of use. This term was therefore intended to mislead, by inferring that NeoClarityn could be used in the same conditions as Clarityn. A breach of Clause 7.2 was alleged. A breach of Clause 7.3 was also alleged as the statement was clearly insupportable. There were insufficient data to support the use of NeoClarityn in all of the indications for which Clarityn was approved.

As detailed above, the statement 'Clarityn confidence… but with extra clout' was also insupportable in the clinical setting and in breach.

RESPONSE

Schering-Plough stated that the statement 'NeoClarityn gives you the same confidence as Clarityn' was intended to reassure the prescriber that desloratadine had the same safety profile as loratadine. It was never intended to imply, and Schering-Plough believed did not imply, that desloratadine was licensed for the same range of indications as loratadine. In the context of both the advertisement and the leavepiece, 'confidence' clearly alluded to safety. The similarity of the safety profiles

of NeoClarityn and loratadine was attested to by the similar 'undesirable effects' section 4.8 of the SPCs of the two products, and the preclinical safety data of section 5.3 of the NeoClarityn SPC, which stated: 'Preclinical studies conducted with desloratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratidine'.

Schering-Plough did not agree that the average reader would take 'confidence' to refer to licensed indications other than seasonal allergic rhinitis, particularly as the prescribing information which contained the indication was clearly given on the same page.

As discussed, however, Schering-Plough had already amended its material to strengthen the message that desloratadine was currently only licensed for seasonal allergic rhinitis. In addition, as shown in the current leavepiece which had been provided, it had removed this statement from that material.

PANEL RULING

The Panel considered that its ruling in point 1 above was relevant. In the Panel's view the claims that NeoClarityn gave the same confidence as Clarityn would be read as being more than a reference to the products' safety profiles. It might be read as a reference to the products' indications. The journal advertisement mentioned increased potency of NeoClarityn as a difference. One page of the leavepiece was headed 'New NeoClarityn. Clarityn confidence ...' followed by four bullet points: 'Lack of clinically relevant cardiovascular effects', 'Lack of clinically relevant interactions', 'No sedation or impairment of performance' and 'Quick and effective relief'. This was followed by '... but with extra clout' followed by three bullet points: 'The first antihistamine with significant anti-allergic and anti-inflammatory properties *in vitro*', '40 times more potent than Clarityn' and 'Offers effective relief from nasal congestion'.

The Panel considered that the claims relating to NeoClarityn giving the same confidence as Clarityn were not sufficiently qualified. The products had different indications and there was no comparative data. The claims were misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 were ruled.

3 Claims 'New NeoClarityn gives you the same confidence as Clarityn, but with 40 times more potency' (journal advertisement) '40 times more potent than Clarityn' (leavepiece)

COMPLAINT

UCB stated that the data to support the claims, if truly representative, was based on *in vitro* evidence. The use of this type of information, in promoting the product to prescribers, was intended to extrapolate this effect to the clinical setting. In the absence of clinical data supporting the claims they became irrelevant and misleading. A breach of Clause 7.2 was alleged.

There was conflicting data. The study referenced was a recent study and did not reflect the balance of evidence that had been collected previously. Earlier studies found a relative potency of 2.5–4 times in animal studies. In the light of this evidence a general statement of 40 times more potent was unsubstantiated by the body of evidence. A breach of Clause 7.3 was alleged.

The claim was also alleged to be in breach of Clause 7.8 because it was exaggerated and, more importantly, was clinically irrelevant.

Subsequent to making the complaint, UCB referred to the EPAR which reinforced its view that the potency claims made by Schering-Plough were exaggerated, designed to mislead and unsubstantiated. With regard to potency, page 2 of the report stated 'Desloratadine is the major active metabolite of loratadine and possesses qualitatively similar pharmacodynamic activity with a relative potency of 10 to 20 times that of loratadine *in vitro*, and 2.5 to 4 times that of loratadine in animals'.

RESPONSE

Schering-Plough stated that the claims at issue were a factual description of a fundamental property of desloratadine. Schering-Plough did not see how informing prescribers of this property could be considered 'irrelevant and misleading'. Schering-Plough's references made clear that this statement was based on *in vitro* data and had not claimed increased clinical efficacy.

Nevertheless, to remove any ambiguity, the material had been amended to highlight more prominently the point that the data was derived from *in vitro* experiments with the cloned human H1 receptor.

The data that Schering-Plough had referred to was the most relevant. The earlier study to which UCB referred used older and less specific tests for antihistaminic potency. The tests were performed in H1 receptors in species other than man (rat, guinea pig, mouse and monkey) using organs that were not the prime target of H1 blockers (brain, lung and ileum) in models which did not necessarily represent the most accurate measurement of the potency of a medicine, in man, in seasonal allergic rhinitis (histamine induced lethality in the guinea pig, histamine induced increases in nasal microvascular permeability in the guinea pig, histamine induced changes in pulmonary resistance and compliance in the monkey).

The target of an antihistamine for clinical use was the human H1 receptor. The study referenced in Schering-Plough's materials was the only one using the cloned H1 receptor and, thus, was the most appropriate study. Moreover, Schering-Plough had amended its materials to state that the figure of 40 times greater potency referred specifically to relative potency at the human H1 receptor.

Following the additional information from UCB, Schering-Plough stated that its potency claims were not questionable. The current material clearly stated that the relative potency of 40 came from experiments using the cloned H1 receptor. As the target of an antihistamine for clinical use was the human H1 receptor this was the best model to use for reasons given above.

PANEL RULING

The Panel noted that the claim for potency was based on *in vitro* data. The claim was referenced to a study which was the only one using the cloned human H1 receptor.

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

The Panel noted that the claims at issue did not made it clear that they were referring to *in vitro* data. Further, the Panel queried the relevance to the clinical situation, noting that no relevant clinical data had been supplied by Schering-Plough. The Panel noted Schering-Plough's reasons for not using the data referred to in the SPC by UCB.

The Panel ruled breaches of Clauses 7.2 and 7.3 of the Code. The Panel considered that the alleged breach of Clause 7.8 was covered by its ruling of a breach of Clause 7.2.

4 Claim 'The first antihistamine with significant anti-allergic and anti-inflammatory properties *in vitro*' (leavepiece)

COMPLAINT

UCB alleged that the claim was untrue. Data supporting this effect with Zirtek (cetirizine – UCB's product) had been available in the public domain since the late 1980s. It was therefore intended to mislead by implying a new effect with NeoClarityn. Furthermore, the NeoClarityn SPC stated that the clinical relevance of these results was unclear. Even with Schering-Plough's assurance that the unique nature of this claim had been removed, UCB still believed that the use of such *in vitro* data in promotion to GPs was intended to mislead prescribers. A breach of Clause 7.2 of the Code was alleged.

A breach of Clause 7.3 was also alleged. NeoClarityn was not the first to show this effect. Schering-Plough had accepted its error of judgement in making this statement and had assured UCB that 'the first' would be removed from any further promotional material.

RESPONSE

Schering-Plough stated that it was correct that desloratadine was the first antihistamine to show these effects *in vitro* at concentrations similar to those achieved *in vivo* by a therapeutic dose. Prescribers were entitled to information on the characteristics of the compounds they prescribed both *in vitro* and *in vivo*. Schering-Plough did not believe that general practitioners were incapable of differentiating between *in vitro* and clinical data.

Nevertheless, to avoid future debate on this issue, Schering-Plough had removed the word 'first' from its amended material.

PANEL RULING

The Panel noted UCB's statement that there was data to show that Zirtek had anti-allergic and anti-inflammatory properties. The SPC for Zirtek stated that it was a potent antihistamine with a low potential for drowsiness at pharmacologically active doses and with additional anti-allergic properties. Cetirizine inhibited the histamine-mediated 'early' phase of the allergic reaction and also reduced the migration of inflammatory cells and the release of mediators associated with the 'late' allergic response. Zirtek was indicated for the treatment of perennial rhinitis, seasonal allergic rhinitis (hay fever), chronic idiopathic urticaria in adults and seasonal rhinitis (hay fever) in children aged between 2 to 6 years.

The Panel noted that the NeoClarityn SPC stated that desloratadine had demonstrated anti-allergic properties from *in vitro* studies. The SPC stated that the clinical relevance remained to be confirmed.

The Panel considered that the claim in question was misleading. The clinical relevance still had to be confirmed. Schering-Plough had accepted that NeoClarityn was not the first product to show anti-allergic and anti-inflammatory effects *in vitro*. The Panel ruled a breach of Clause 7.2 of the Code. The claim was not capable of substantiation and a breach of Clause 7.3 was also ruled.

5 Claim 'Offers effective relief from nasal congestion' (leavepiece)

COMPLAINT

UCB alleged that the claim was misleading. It would certainly be clarified by demonstrating the single indication seasonal allergic rhinitis on the leavepiece, but it remained in breach. Again it suggested a property that was not fully supported by the available evidence. Even the NeoClarityn SPC stated 'NeoClarityn was effective in relieving symptoms such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness and itching of the palate'. There was no mention of nasal congestion and this suggested insufficient evidence to support the licence application. The claim was therefore misleading, as Schering-Plough was claiming an effect that did not have the body of evidence to support its use. A breach of Clause 7.2 of the Code was alleged.

Subsequent to making the complaint, UCB referred to the EPAR and stated that the conclusions of the EPAR cast doubt on the claim that desloratadine improved nasal congestion. UCB referred to the following 'The symptom cough was evaluated in 3 out of 4 studies. In none of these studies did the change between mean baseline and mean post-treatment values attain statistical significance compared to placebo. This was also the case for the symptom of nasal congestion'.

RESPONSE

Schering-Plough stated that as UCB had not stated which of the available evidence did not support this claim, it was only able to describe the studies which it was aware of – all of which supported the claim.

All clinical trials with desloratadine had demonstrated an at least numerical, and in several studies statistical, superiority of desloratadine over placebo in treating nasal congestion.

For example Nayak *et al* (2000) reported on 661 patients given placebo who were compared to 659 patients given 5mg desloratadine and 662 given 7.5mg desloratadine. The authors reported 'Patients receiving desloratadine reported superior improvements in nasal congestion severity scores compared with those receiving placebo (P=0.02 for 5mg versus placebo; P=0.01 for 7.5mg versus placebo)'.

Similarly Lorber *et al* (2000) reported the results of three placebo-controlled trials in patients with seasonal allergic rhinitis. These studies had, respectively, 166, 140 and 171 patients on desloratadine. All three studies demonstrated a statistically significant improvement in severity of nasal congestion / stuffiness compared to placebo.

In individuals with seasonal allergic rhinitis and concurrent asthma, desloratadine similarly improved symptoms of nasal congestion. A recent paper (Nathan *et al* 2000) summarised this. A pooled analysis of five identical multicentre, double-blind, placebo-controlled trials randomised 613 patients with concurrent seasonal allergic rhinitis and asthma to receive desloratadine or placebo once daily for four weeks. Compared with placebo, desloratadine produced significant improvements from baseline in the average AM / PM reflective and AM instantaneous nasal congestion scores.

In a controlled pollen challenge study conducted by Horak *et al* (2000) the authors reported that 'nasal stuffiness scores decreased by –22% and –50%, at 20 and 90 minutes, respectively, among the 2-point responder group.

Other studies, currently in press, demonstrated the same finding, namely, desloratadine improved nasal congestion in individuals with seasonal allergic rhinitis.

The use of the phrase 'such as', used in the SPC in the sense of 'for example', implied that the following list made no claim to be comprehensive.

In addition, the SPC stated in section 4.1, Therapeutic indications, 'NeoClarityn is indicated for the relief of symptoms associated with season allergic rhinitis'. No qualifications, exclusions or provisos were made here.

As the existing and emerging body of evidence, described earlier, conclusively demonstrated, desloratadine had an anticongestant effect.

With regard to comments about the EPAR, Schering-Plough stated that selective quotation by UCB gave the false impression that desloratadine was not active in nasal congestion. This was not so.

All clinical trials with desloratadine had demonstrated an at least numerical superiority of desloratadine over placebo in treating nasal congestion. In each of the studies mentioned by the EPAR desloratadine was numerically superior to placebo in relieving the symptoms of nasal congestion. When the studies which had the same patient populations were pooled together to give sufficient numbers the difference was statistically significant. Schering-Plough referred to the details of various studies as above.

PANEL RULING

The Panel examined the data provided by Schering-Plough. Nayak *et al*, presented as an abstract, referred to the effects of desloratadine on data pooled from randomized, parallel-group, double-blind, placebo controlled studies. Desloratadine significantly decreased nasal congestion / stuffiness (p=0.02 and 0.01 for 5mg and 7.5mg respectively of desloratadine v placebo).

Lorber *et al* described three studies; in all the reduction from baseline congestion score was significantly greater with desloratadine than with placebo at 14 days. Two studies ran for 28 days and the reduction from baseline was significantly greater with desloratadine than with placebo.

Nathan *et al* reported on pooled data. Desloratadine was associated with significantly greater improvement from baseline than placebo in the average morning / evening reflective and morning instantaneous total symptom score over weeks 1-2 and 1-4 ($p<0.001$). The authors concluded that desloratadine had a significant decongestant effect.

Horak *et al* was an open label study on 28 patients which concluded that nasal stuffiness scores decreased by around 22% and around 50% at 20 and 90 minutes.

The Panel noted that it was not possible to establish from the limited data provided whether the pooled data described were from the same or different studies. The Panel noted Schering-Plough's submission that when the studies which had the same patient populations were pooled, the difference was statistically significant.

The Panel noted that the NeoClarityn SPC stated that it was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Section 5.1 stated that NeoClarityn was effective in relieving symptoms such as sneezing, nasal discharge and itching as well as ocular itching, tearing and redness and itching of palate.

The Panel considered that nasal congestion was a symptom of hayfever. Schering-Plough had some data to support the effect of NeoClarityn on nasal congestion. Given the generality of the SPC indication and the data supplied the Panel considered that on balance the claim was not unreasonable. No breach of Clauses 7.2 and 7.3 was ruled.

6 Claim 'New NeoClarityn extends hay fever relief to cover even nasal congestion' (abbreviated advertisement)

COMPLAINT

UCB stated that this claim was that NeoClarityn now offered an effect that had previously been unavailable in the treatment of hay fever. This was exaggerated and blatantly untrue and thus breached Clauses 7.8 and 7.2 of the Code.

When one just considered the antihistamine market this feature had already been proven and accepted with cetirizine. Furthermore, as there were no comparative data, it could not be stated categorically

that NeoClarityn offered an extension to the treatment of seasonal allergic rhinitis, beyond that already offered by cetirizine.

Even if NeoClarityn was in the position to only claim top parity, within the antihistamine field, then this claim would still be misleading.

The effect on nasal congestion had always been accepted as being the major benefit with topical steroids. The claim was therefore alleged to be inaccurate and misleading as the effect on nasal congestion had always been available, with steroids, in the treatment of seasonal allergic rhinitis.

To suggest this was a new benefit with NeoClarityn was obviously misleading.

RESPONSE

Schering-Plough stated that the claim was not for a unique effect for desloratadine. While the claim was supported by the body of data cited above, there was no attempt to imply that NeoClarityn was unique in its ability to treat nasal congestion, simply that it had activity in nasal congestion.

Many hay fever sufferers found nasal congestion a symptom resistant to treatment, including treatment with some antihistamines. A postal survey of patients with seasonal allergic rhinitis demonstrated that patients 'strongly agreed that nasal congestion was an irritating and uncomfortable symptom which was a constant problem during the hay fever season'. The authors concluded 'Nasal congestion clearly remains a problem despite use of antihistamine treatments; many patients (58%) were taking additional treatments specifically for this symptom'.

Not only did patients perceive that nasal congestion was a significant problem, but the medical community had, in the past, believed that antihistamines were ineffective in dealing with this condition. A quote from a review article 'Both first – and second – generation antihistamines…are effective in reducing the annoying symptoms of allergic rhinitis except congestion' (Hadley 1999) demonstrated the perceived difficulty of treating this condition.

It was therefore appropriate to make clinicians aware of the data regarding desloratadine in treating nasal congestion.

As stated above, the claim simply brought the attention of the prescriber to the information regarding NeoClarityn's impact on nasal congestion. There was no intent to compare it with cetirizine, and indeed, there was no mention of cetirizine. Nor was there a claim that this property was unique to desloratadine. At most, given the context of the statement, the reader might conclude that there was data supporting desloratadine in this area that was not available for loratadine, which would be an accurate conclusion.

Schering-Plough certainly agreed that topical steroids had an effect on nasal congestion. The statement in no way refuted or denied that.

PANEL RULING

The Panel considered that the claim implied that prior to NeoClarityn there was no product that could be used to relieve nasal congestion. This was not so. Nasal steroids were available for treating the problem.

The Panel considered that the claim was misleading and exaggerated and breaches of Clauses 7.2 and 7.8 were ruled.

7 Alleged breach of Clause 2

COMPLAINT

UCB proposed that with this style of advertising, where the new product was compared to a well established product, that there was a genuine suggestion that the products could be used like for like.

This was clearly not true for these two products. The licensed indications for NeoClarityn were limited when compared to Clarityn, as was the age range for use. Furthermore, the encouragement of prescribing NeoClarityn, for all patients previously using Clarityn or one of the other second generation antihistamines, would result in prescriptions of NeoClarityn outside of the approved indication of seasonal allergic rhinitis.

As there was no evidence to support the use of NeoClarityn for any other indication than seasonal allergic rhinitis, then this line of advertising encouraged off-licence prescribing and as such breached Clause 2 of the Code.

UCB believed the promotional material amounted to the strategic use of ambiguity and some statements were obviously untrue.

RESPONSE

Schering-Plough stated that its new materials gave increased prominence to the current licensed indication. It believed this should be enough to make it clear to prescribers that NeoClarityn was licensed only for the treatment of seasonal allergic rhinitis.

PANEL RULING

The Panel considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. The position was compounded as the indications for the products were not the same. The licensed indications for NeoClarityn were more restricted than for Clarityn. In the Panel's view Schering-Plough had not made sufficient effort to distinguish between the products.

The Panel noted that Clause 2 was used as a sign of particular censure and was reserved for such use. On balance the Panel considered that the circumstances warranted a ruling of a breach of Clause 2 and a breach of that clause was ruled.

Complaint received **14 February 2001**

Case completed **22 May 2001**

CASES AUTH/1139/2/01 and AUTH/1140/2/01

CHAIRMAN OF TRUST PHARMACY & THERAPEUTICS COMMITTEE v PHARMACIA and PFIZER

Promotion of Celebrex outside its licence

The Chairman of the Pharmacy and Therapeutics Committee at an NHS Trust complained about the promotion of Celebrex (celecoxib) by a Searle representative. The matter was taken up with Pharmacia, of which Searle was now part. It was also taken up with Pfizer, which co-promoted the product, but as Pfizer had had no connection with the events at issue the Director determined that there was no *prima facie* case for it to answer.

The complainant stated that celecoxib had been placed on the Trust formulary in August 2000. Following a recent promotional meeting within the orthopaedic department, however, when the benefits of 'less bleeding when used with Clexane' were stressed, the product was used for both peri- and post-operative analgesia. The Trust formulary pharmacist spoke with Searle's medical department and was informed that the company had no intention of applying for a peri- or post-operative analgesia licence and that there was no peri-operative beneficial outcome data. In January the local representative met pharmacists and reassured them 'that there was no intention to promote for peri-operative use' and that the intention was to issue a memorandum and meet the orthopaedic department to correct any misinterpretation.

The memorandum sent by the representative to orthopaedic department medical staff was alleged to be misleading, inaccurate and had not been verified by the pharmacy department.

The Panel noted that Celebrex was indicated for symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis. The product was on the Trust formulary but only for those patients who had three or more defined risk factors for serious gastrointestinal complications if NSAIDs were used. Following a promotional meeting within the orthopaedic department, it appeared that there was some confusion as to whether or not the product could be used for peri- and/or post-operative analgesia. It was agreed that the representative should write a memorandum to the department to clarify the situation. Given the original confusion over the licensed indications for Celebrex, the Panel did not consider that the memorandum made the position sufficiently clear. The memorandum consisted of three sentences, the first sentence of which ended by stating that post-operative pain or treatment was not a licensed indication; the second sentence inferred that such use was acceptable as long as the patient had osteoarthritis, rheumatoid arthritis or was at risk.

In the Panel's view, the memorandum also compounded the original confusion as it stated that Celebrex could be initiated in patients with osteoarthritis, rheumatoid arthritis or at risk, whereas hospital policy stated that it could only be initiated in patients with osteoarthritis or rheumatoid arthritis who were also at risk. The Panel noted that Pharmacia had acknowledged that 'or at risk' should have read 'and at risk'. The memorandum ended with the statement 'For any other issues please refer to the Hospital Formulary'. The Panel considered that this implied that the formulary was a secondary document – only to be referred to if the information required was not in the memorandum. Given the content of the rest of the memorandum this was not adequate.

The Panel was concerned that the representative had written to a hospital department in an effort to clarify local policy with regard to the use of Celebrex. The memorandum had been written by an employee of the company responsible for marketing Celebrex and had stated the product name and its indications; it was therefore a piece of promotional material. In this regard it was irrelevant as to whether the pharmacy department had approved the wording of the memorandum before it had been issued. The Panel was concerned about the conflict of evidence in this regard. The formulary pharmacist clearly stated that he had not seen the memorandum until after it had been issued. Pharmacia submitted that the formulary pharmacist had been informed and involved with the wording of the memorandum.

The Panel considered that the memorandum was misleading and as such promoted Celebrex outside of its licensed use. The representative had not maintained a high standard of ethical conduct and had failed to comply with the Code. The Panel ruled breaches of the Code on the part of Pharmacia.

The Chairman of the Pharmacy and Therapeutics Committee at an NHS Trust complained about the promotion of Celebrex (celecoxib) by a representative of Searle. The major point of concern was a memorandum issued by the representative to medical staff within the orthopaedic department. The memorandum, distributed to nineteen recipients, read:

'Reminder:

Celebrex 200mg is only licensed for osteoarthritis and rheumatoid arthritis pain, **not post-op pain or treatment**.

If the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk, then Celebrex can be initiated.

For any other issues please refer to the Hospital Formulary.'

The complainant had written direct to Searle and had copied his letter to the Authority. The matter was taken up with Pharmacia Limited, of which Searle was now a part. It was also taken up with Pfizer Limited, which co-promoted the product, though it was not clear whether Pfizer was involved or not in the events at issue.

COMPLAINT

The complainant wrote to Searle to express his concern as Chairman of the Trust Pharmacy and Therapeutics Committee with regard to the inappropriate local promotion of Celebrex.

The complainant explained that celecoxib was placed on the Trust formulary of recommended products at the last annual revision (August 2000). The relevant entry was provided. This local policy was derived following consultation with local specialists.

Following a recent promotional meeting within the orthopaedic department, however, when the benefits of 'less bleeding when used with Clexane' were stressed, the product was used for both peri- and post-operative analgesia. The Trust formulary pharmacist spoke with Searle's medical department and was informed that the company had no intention of applying for a peri- or post-operative analgesia licence, that there was no peri-operative beneficial outcome data, and that the company agreed that this was probably 'overenthusiastic promotion'.

In January the local representative met pharmacists and reassured them 'that there was no intention to promote for peri-operative use' and that the intention was to issue a memorandum and meet the orthopaedic department to correct any misinterpretation.

The complainant stated that the memorandum issued raised several concerns:

1 even though the pharmacy department sought to verify the content, this was not done prior to issue;

2 recognising that the first paragraph with regard to licence was correct the subsequent information was inaccurate;

3 the statement 'If the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk, then Celebrex can be initiated' was inaccurate and misleading;

3.1 stating that the product might be used for operative pain in osteo and rheumatoid patients because it had a licence for osteo and rheumatoid pain was palpable nonsense; these were separate pains and separate issues;

3.2 whereas the product might be licensed in these conditions in non peri-operative cases, the agreed local hospital policy was that it was only approved for at risk patients – which was defined in the policy;

4 the statement 'For any other issues please refer to the Hospital Formulary' was misleading – the local hospital formulary policy was applicable to all use of the product, not as a peripheral issue as implicated.

Correction of these inaccuracies had taken a considerable amount of professional time.

When writing to the companies, the Authority drew attention to Clauses 3.2, 7.2, 9.1 and 15.1 of the Code.

Case AUTH/1139/2/01

RESPONSE FROM PHARMACIA

Pharmacia confirmed that Pfizer, its UK marketing colleague for Celebrex, was not involved in any contact made with the Trust.

The memorandum, sent on 19 January, followed a meeting between the representative and staff in the orthopaedic department on 21 November. At and following this meeting, two questions were raised:

1 Whether the use of Celebrex, presumably in an operative setting, resulted in less bleeding when used with Clexane, compared to the bleeding seen with the use of other non-steroidal anti-inflammatory drugs (NSAIDs).

Having no information on this issue, the representative contacted the company's medical information department and was advised that no data on the use of Celebrex with Clexane was available, but that reference was made to the use of the product with warfarin in the clinical monograph. This information was conveyed to the member of staff concerned.

2 The representative was informed by the Trust's formulary pharmacist that Celebrex was used in the department for both peri- and post-operative analgesia.

The representative assured the member of staff who had raised the issue that such use was 'off-licence'.

It was agreed with the formulary pharmacist that the representative should issue a memorandum to staff in the orthopaedic department, highlighting the fact that such use was 'off label'. At no time was Celebrex promoted by the representative for peri- or post-operative analgesia.

Pharmacia addressed the Trust's concerns.

1 *'Even though the pharmacy sought to verify the content (of the memorandum) this was not done prior to issue'.*

The formulary pharmacist was informed and involved in the wording of the memorandum. Apparently the memorandum was typed by one of the Trust's secretaries and distributed the same day. The complaint was factually incorrect in that the pharmacy had verified the content of the memorandum.

2 *'Recognising that the (memorandum's) first paragraph with regard to (the) licence was correct, the subsequent information was inaccurate.*

3 *The statement 'If the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk, then Celebrex can be initiated' was inaccurate and misleading.*

3.1 *Stating the product might be used for operative pain in osteo and rheumatoid patients because it had a licence for osteo and rheumatoid pain was palpable nonsense. These were separate pains and separate issues.*

3.2 *Whereas the product might be licensed in these conditions in non-peri operative cases, the agreed local hospital policy was that the product was only approved for at risk patients, which were defined in the policy.*

As stated by the complainant, the indications for Celebrex were correctly stated in the first paragraph of the memorandum, with the wording 'not post-op pain or treatment' printed in bold. The licensed

indications were reiterated in the second sentence, with the addition of the statement 'or is at risk'. The risk factors referred to were those highlighted in the Trust's local formulary. Quoted from Bandolier (no 52, June 1998) these were stated risk factors for serious GI complications with all NSAIDs: age greater than 75 years; history of peptic ulcer; history of GI bleeding; history of heart disease.

The formulary stated that

'Patients at high risk (3 or more risk factors) who **need** NSAIDs should be considered for:

– Celecoxib

– or concurrent gastro-protectants

Arthrotec (Diclofenac and Misoprostol)

NSAIDs + Lansoprazole 15 mg or 30 mg.'

Pharmacia stated that the word 'or' in the second sentence of the memorandum ('if the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk …') should have read 'and'. This was a typographical error following the memorandum's dictation, and it was not intended that clinical staff be misled. Reference to the risk factors highlighted above was incorporated to reflect the recommendations of the Trust's local formulary and to draw attention to those factors. Pharmacia contended that except for the unintentional presence of the typographical error, the memorandum was neither inaccurate nor misleading.

The memorandum plainly stated that Celebrex was not licensed for the treatment of post-operative pain.

4 *The statement 'For any other issues refer to the Hospital Formulary.' was misleading. The local hospital's formulary policy was applicable to all use of the product, not as a peripheral issue as implicated.*

Pharmacia apologised for any misunderstanding that appeared to have occurred following the issue of this memorandum, but it reiterated that the wording was agreed with the Trust's formulary pharmacist, prior to distribution.

FURTHER COMMENTS FROM THE COMPLAINANT

As Pharmacia had specifically referred to the formulary pharmacist the complainant forwarded Pharmacia's response to him for further comment.

The formulary pharmacist noted a number of statements made by Pharmacia in its response.

a) 'It was agreed with the formulary pharmacist that the representative should issue a memorandum to staff in the orthopaedic department, highlighting the fact that such use was off label'.

The formulary pharmacist stated that it was not agreed. He was aware of the representative's intention to do so.

b) 'The formulary pharmacist was informed and involved in the wording of the memorandum'.

This was incorrect. As stated by the complainant 'Even though the pharmacy department had sought to verify the content, this was not done prior to issue'. The formulary pharmacist stated that the first sight he had of the memorandum was several days later, after it had been issued.

c) 'The complaint was factually incorrect in that pharmacy had verified the content of the memorandum'.

The formulary pharmacist stated that this was incorrect, as at no time did pharmacy verify the content of the memorandum. He would not have agreed to the wording. The fact that the wording, particularly of the second paragraph, encouraged outside licence use, was a major reason for the complaint.

The formulary pharmacist stated that as the memorandum was issued to the orthopaedic department where significant use of NSAIDs was peri-operative, and celecoxib had already been noted as being outside licence, it should be considered inaccurate and misleading. In particular the second paragraph encouraged 'off-licence' use.

The formulary pharmacist noted that the second paragraph of the memorandum read 'If the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk then Celebrex can be initiated'. As stated, significant NSAID use was peri-operative, even if the patient had osteo or rheumatoid arthritis, if Celebrex was used peri-operatively it was 'off-licence'.

The formulary pharmacist stated that unfortunately the apology given at the end of Pharmacia's response was hollow as Pharmacia perpetuated its misunderstanding of events. The formulary pharmacist emphasised the facts were as stated in the complaint ie 'even though the pharmacy department had sought to verify the contents of the memorandum, this was not done prior to issue'. The pharmacist reiterated that the first sight he had of the memorandum was several days later, after it had been issued.

PANEL RULING

The Panel noted that the Celebrex summary of product characteristics stated that it was indicated for symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis. The product was available for use on the Trust formulary but only for those patients who had three or more risk factors for serious gastrointestinal complications if NSAIDs were used. These were age greater than 75, history of peptic ulcer, gastrointestinal bleeding or heart disease. Following a promotional meeting within the orthopaedic department it appeared that there was some confusion as to whether or not the product could be used for peri- and/or post-operative analgesia; it was agreed that the representative should write a memorandum to the department to clarify the situation.

The Panel noted that the memorandum stated that Celebrex was only licensed for osteoarthritis and rheumatoid arthritis pain, not post-operative pain or treatment. The memorandum went on to state 'If the patient is known to have osteoarthritis, rheumatoid arthritis or is at risk, then Celebrex can be initiated'. Given the original confusion over the licensed

indications for Celebrex, the Panel did not consider that the memorandum made the position sufficiently clear. Although the first sentence ended by stating that post-operative pain or treatment was not a licensed indication, the second sentence inferred that such use was acceptable as long as the patient had osteoarthritis, rheumatoid arthritis or was at risk. In the Panel's view the memorandum compounded the original confusion.

The Panel also noted that the memorandum stated that Celebrex could be initiated in patients with osteoarthritis, rheumatoid arthritis or at risk whereas hospital policy stated that it could only be initiated in patients with osteoarthritis or rheumatoid arthritis who were also at risk. The Panel noted that Pharmacia had acknowledged that 'or at risk' should have read 'and at risk'.

The memorandum ended with the statement 'For any other issues please refer to the Hospital Formulary'. The Panel considered that this implied that the formulary was a secondary document – only to be referred to if the information required was not in the memorandum. Given the content of the rest of the memorandum this was not adequate.

The Panel was concerned that the representative had written to a hospital department in an effort to clarify local policy with regard to the use of Celebrex. The memorandum had been written by an employee of the company responsible for marketing Celebrex and had stated the product name and its indications; it was therefore a piece of promotional material. The Panel noted that in this regard it would have been irrelevant as to whether the pharmacy department had approved the wording of the memorandum before it had been issued. The Panel was concerned about the conflict of evidence in this regard. The formulary pharmacist clearly stated that he had not seen the memorandum until after it had been issued. Pharmacia had submitted that the formulary pharmacist had been informed and involved with the wording of the memorandum.

The Panel considered that the memorandum was misleading and as such promoted Celebrex outside of its licensed use. The representative had not maintained a high standard of ethical conduct and had failed to comply with the Code. The Panel ruled breaches of Clauses 3.2, 7.2 and 15.2 of the Code.

Case AUTH/1140/2/01

Pfizer stated that Pfizer had had no involvement with either the promotional meeting held within the orthopaedic department or the memorandum. The Director therefore decided that there was no *prima facie* case to answer under the Code in relation to Pfizer.

Complaint received **15 February 2001**

Case completed **14 May 2001**

CASE AUTH/1141/2/01

UCB PHARMA v SCHERING-PLOUGH

Promotion of NeoClarityn

UCB Pharma complained about a leavepiece and a 'Dear Pharmacist' letter for NeoClarityn (desloratadine) issued by Schering-Plough.

The leavepiece bore the claim 'NeoClarityn is more potent than all available 2nd generation antihistamines at the human H1-receptor'. UCB alleged that the claim was misleading as the page did not reveal that the human H1 receptor in this study was actually expressed in Chinese Hamster ovary cells *in vitro*. The reference did not reflect the balance of evidence and was not capable of substantiation. It was alleged to be exaggerated and all embracing. The Panel noted that a similar claim had been considered in Case AUTH/1137/2/01. The Panel considered that the nature of the data on which the claim at issue was based had not been made clear. The Panel also queried the relevance of the *in vitro* data to the clinical situation. The Panel considered that the claim would be read as applying to the clinical situation, particularly given that the sub-heading to this section of the leavepiece was 'Forty times more clout than Clarityn (loratadine)'. The Panel considered that the claim was misleading, exaggerated and not capable of substantiation and ruled breaches of the Code.

UCB alleged that the statement in the 'Dear Pharmacist' letter '… with the result that it [Clarityn] has become the most popular prescription therapy in its field' was misleading and untrue and as it was not referenced it was unclear from where this data arose or what was actually meant by 'most popular'. UCB's product Zirtek (cetirizine) had globally the highest number of standard daily doses sold. The Panel noted that UCB had referred to IMS Health Data Unit sales, July 1999 – June 2000, with regard to global sales which showed that Zirtek had the highest number of standard daily doses sold. Schering-Plough had referred to more recent global data, 12 months to September 2000, showing a difference in favour of Clarityn. Neither party had provided the Panel with the global sales data. The UK data to December 2000 was in favour of Clarityn. The Panel noted Schering-Plough's submission that globally the most up-to-date evidence was that more Clarityn was prescribed and dispensed than any other second generation antihistamine. The Panel considered that the term 'most popular' had not been adequately explained; it was unclear whether it referred to total sales, sales over a particular time period, or some other means of measuring popularity. The claim was too general and breaches of the Code were ruled.

In relation to the claim in the letter 'NeoClarityn is desloratadine – a purified development of Clarityn', UCB stated that this breached the Code because it was not a purified development. It was a development of the active metabolite of desloratadine and as such a new molecular entity. The Panel noted that desloratadine was a metabolite of loratadine. The development of desloratadine had the effect of removing other mostly inactive metabolites. In the circumstances, the Panel did not consider that it was unreasonable to describe NeoClarityn as a purified development of Clarityn. No breach of the Code was ruled.

The statement in the letter '… with so many antihistamines available – both POM and OTC …' was completed with '– is there really a need for another one?'. UCB stated that this again was misleading as it suggested a feature that NeoClarityn did not have. At present its legal category was POM and therefore to mention OTC was again misleading. The Panel did not accept that it was misleading to mention that OTC antihistamines were available. There was no suggestion that NeoClarityn was an OTC medicine. No breach of the Code was ruled.

In relation to the claim 'NeoClarityn heralds the advent of the next generation of anti-allergy therapy', UCB stated that there was no evidence to suggest that NeoClarityn offered any advantages over existing antihistamines. The Panel did not consider there was sufficient evidence to demonstrate that the difference between Clarityn and NeoClarityn was such as to justify the claim at issue. The product was only licensed for the symptoms of seasonal allergic rhinitis. The Panel considered that the claim 'the next generation' implied that there had been a significant development in anti-allergy therapy. Breaches of the Code were ruled.

The claim 'Even with 2nd generation antihistamines, there is <u>still</u> an unfulfilled need for a truly effective therapy' appeared in bold near to the end of the letter. UCB stated that this disparaged all currently available second generation antihistamines. It did not clarify what was meant by 'truly effective' and therefore suggested that the current treatments did not fulfil the need of patients. Patient satisfaction had been considered within clinical trials with Zirtek and was generally accepted as high. The Panel noted the submission from Schering-Plough that the claim at issue referred to the patient satisfaction survey discussed in the preceding paragraphs. The claim at issue comprised a separate paragraph in emboldened blue text. The prominence of the claim at issue was such that it was immediately apparent to the reader and might not be considered in light of the preceding paragraphs. The claim implied that none of the second generation antihistamines were truly effective. The Panel considered that the claim was disparaging. The medicines were licensed treatments. The Panel ruled a breach of the Code.

In relation to the leavepiece and the letter, UCB stated that once again it believed the use of strategic ambiguity supported its previous concerns about Schering-Plough's promotional campaign for NeoClarityn. UCB alleged that the extent of this misrepresentation also breached Clause 2. The Panel noted that in the previous case, Case AUTH/1137/2/01, it had considered that on balance the circumstances warranted a ruling of a breach of Clause 2 and a breach of that clause had been ruled.

The Panel noted that the allegations now before it were different to those in the previous case. Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel did not accept that the circumstances of this case warranted a ruling of a breach of Clause 2.

UCB Pharma Limited complained about a 'Dear Pharmacist' letter (NCL/01-022) and leavepiece (ref NCL/01-020) for NeoClarityn (desloratadine) issued by Schering-Plough Ltd.

UCB Pharma had previously complained about NeoClarityn promotional materials (Case AUTH/1137/2/01). UCB stated that this new material extended the strategic use of ambiguity to pharmacists. Statements already complained about were used but there was additional material which UCB alleged was in breach of the Code. Schering-Plough had confirmed that there was no comparative human data.

Subsequent to submitting the complaint, UCB referred to the European Public Assessment Report (EPAR). UCB stated that the overall conclusions (section 5) of the EPAR supported its position that desloratadine did not offer any real clinical advantage over loratadine.

The following statements on page 21 of the report were particularly relevant: 'However, it seems from the percentage of improvement in Total Symptom Score that the clinical efficacy of 5mg desloratadine is probably not superior to 10mg loratadine' and 'The efficacy of desloratadine has not been studied in active comparator trials'.

With regard to the statements in the EPAR, Schering-Plough considered that the position could be argued in relation to the statement that the clinical efficacy of 5mg desloratadine was probably not superior to 10mg loratadine. It was perhaps sufficient to point out that the promotional material did not make any claims of clinical superiority or non-superiority of desloratadine over loratadine. Schering-Plough was unsure of the relevance of the quotation 'The efficacy of loratadine has not been studied in active comparator trials'. It did not refer to comparative clinical data in the materials in question.

A Leavepiece (ref NCL/01-020)

Claim 'NeoClarityn is more potent than all available 2nd generation antihistamines at the human H1-receptor'

This claim was referenced to Anthes *et al* (2000).

COMPLAINT

UCB Pharma stated that this might be a true quotation from the referenced paper but placed into this setting it became irrelevant.

It was misleading as the page did not reveal that the human H1 receptor in this study was actually expressed in Chinese Hamster ovary cells *in vitro.* As such it was misleading and breached Clause 7.2 of the Code. If further studies were considered that looked at *in vitro* or other potency measures in animals or healthy volunteers, then this reference did not reflect the balance of evidence and was not capable of substantiation. As such it also breached Clause 7.3. It was alleged to be exaggerated and all embracing in breach of Clause 7.8.

RESPONSE

Schering-Plough noted that the claim appeared on a page devoted to discussing the *in vitro* properties of desloratadine. It was clear that the statements made referred to *in vitro* data. No attempt was made to mislead the reader and specifically no clinical claims were derived from this claim.

Schering-Plough did not believe that educating health professionals about the properties of a new medicine could be considered irrelevant.

The target of an antihistamine for clinical use was the human H1 receptor, and thus, studies based on the cloned H1 receptor were the most appropriate to use. Schering-Plough was not aware of other data regarding the relative potency of antihistamines at the human H1 receptors. In the absence of any other published data, then surely the reference must be considered to reflect the consensus of opinion related to potency at the human receptor. Schering-Plough again noted that no claims for clinical efficacy were made from this description data regarding a property of the desloratadine molecule.

PANEL RULING

The Panel noted that a similar claim had been considered in Case AUTH/1137/2/01. The Panel considered that it had not been made clear that the claim at issue in the present case related to the human H1 receptor expressed in Chinese Hamster ovary cells *in vitro.* The Panel also queried the relevance of the *in vitro* data to the clinical situation. The Panel considered that the claim would be read as applying to the clinical situation, particularly given that the sub-heading to this section of the leavepiece was 'Forty times more clout than Clarityn (loratadine)'.

The Panel considered that the claim was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.8 of the Code.

B 'Dear Pharmacist' letter

B1 Claim '... with the result that it [Clarityn] has become the most popular prescription therapy in its field'

COMPLAINT

UCB alleged that this statement was misleading and untrue and as it was not referenced it was unclear from where this data arose or what was actually meant by 'most popular'. Zirtek (cetirizine) [UCB's product] had globally the highest number of standard daily doses sold. This was referenced to IMS Health Data Unit Sales, July 1999 – June 2000. Therefore, Schering-Plough could not claim that Clarityn was the most popular. This statement breached Clauses 7.2, 7.3 and 7.8 of the Code.

RESPONSE

Schering-Plough stated that it was unsure why UCB did not quote the more recent IMS data. This confirmed that Clarityn had, globally or in the UK, the largest number of unit doses sold. The more recent MAT for Q3/00 – reflecting sales from September 1999 – September 2000 gave a different and more accurate picture to that portrayed in the complaint. Out of the total number of units of Zirtek and Clarityn sold, 61% were of Clarityn, and 39% were of Zirtek.

Globally, the most up-to-date evidence was that more loratadine was prescribed and dispensed than any other second generation antihistamine. It could therefore be legitimately called 'more popular'.

This mailing was sent to pharmacists in the UK. The UK situation with respect to sales was very similar to that globally. More packs of Clarityn were dispensed than packs of Zirtek. Data for the 12-month period to December 2000 were provided which reinforced the accuracy of the claim.

PANEL RULING

The Panel noted that the 'Dear Pharmacist' letter had been sent to pharmacists in the UK. The letter was undated but bore a date of preparation of January 2001. Within the UK the Panel noted that in the 12 month period finishing December 2000 more units of Clarityn were sold compared to units of Zirtek.

The Panel noted that UCB had referred to IMS Health Data Unit sales, July 1999 – June 2000, with regard to global sales which showed that Zirtek had the highest number of standard daily doses sold. Schering-Plough referred to more recent global data, 12 months to September 2000, showing a difference in favour of Clarityn. Neither party had provided the Panel with the global sales data. The Panel noted Schering-Plough's submission that globally the most up-to-date evidence was that more Clarityn was prescribed and dispensed than any other second generation antihistamine.

The Panel considered that the term 'most popular' had not been adequately explained; it was unclear whether it referred to total sales, sales over a particular time period, or some other means of measuring popularity. The claim was too general. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code were ruled.

B2 Claim 'NeoClarityn is desloratadine – a purified development of Clarityn'

COMPLAINT

UCB stated that this again breached Clause 7.2, because it was not a purified development. It was a development of the active metabolite of desloratadine and as such a new molecular entity. The suggestion that it was purified was not substantiated in any way and as such this breached Clauses 7.2 and 7.3 of the Code. UCB suggested that it also breached Clause 7.8.

RESPONSE

Schering-Plough stated that loratadine was the parent compound of desloratadine, as such desloratadine could justifiably be considered a development of loratadine.

The breakdown of loratadine produced a mixture of metabolites. With the exception of desloratadine, these metabolites were of weaker potency than loratadine. They therefore had little contribution to the activity of Clarityn at the histamine receptor. The development of desloratadine had the effect of removing these mostly inactive metabolites.

The Collins English Dictionary definition of pure was 'not mixed with extraneous or dissimilar materials'.

By removing these 'extraneous' metabolites, then NeoClarityn might be considered a purer version of Clarityn.

In addition Schering-Plough doubted anyone would disagree that as part of the manufacturing process desloratadine was further purified.

PANEL RULING

The Panel noted that desloratadine was a metabolite of loratadine. Other metabolites were also produced from Clarityn. The development of desloratadine had the effect of removing these mostly inactive metabolites. In the circumstances, the Panel did not consider that it was unreasonable to describe NeoClarityn as a purified development of Clarityn. No breach of Clauses 7.2, 7.3 and 7.8 was ruled.

B3 Statement '... with so many antihistamines available – both POM and OTC ...'

This statement was completed with '– is there really a need for another one?'

COMPLAINT

UCB stated that this again was misleading as it suggested a feature that NeoClarityn did not have. At present its legal category was POM and therefore to mention OTC was again misleading and breached Clause 7.2 of the Code.

RESPONSE

Schering-Plough stated that the statement made no attempt to claim, directly or indirectly, that NeoClarityn had any other than POM status. It was a fact that some antihistamines had OTC status. The question raised was 'is there really a need for another one?'.

Having asked this rhetorical question the letter then went on to answer why there was a continued need to develop new and more effective antihistamines. Evidence was given, from a survey conducted in the UK, that many patients were not receiving full relief from their current hayfever therapy. This survey included patients taking antihistamines that were available over-the-counter.

It was surely appropriate to include, in a discussion of a new therapy, all alternatives to that therapy, whether those alternatives were prescription only or over-the-counter. By mentioning these alternatives no claim was being made as to the legal status of NeoClarityn.

PANEL RULING

The Panel did not accept that it was misleading to mention that OTC antihistamines were available. There was no suggestion that NeoClarityn was an OTC medicine. No breach of Clause 7.2 of the Code was ruled.

B4 Claim 'NeoClarityn heralds the advent of the next generation of anti-allergy therapy'

COMPLAINT

UCB alleged that this breached Clauses 7.2, 7.3 and 7.8. There was no evidence to suggest that NeoClarityn offered any advantages over existing antihistamines. Schering-Plough's lack of comparative data in the clinical setting should prohibit it from making such claims.

RESPONSE

Schering-Plough stated that there was no question that loratadine, an established anti-allergy therapy, was the parent compound of desloratadine. As such desloratadine could be considered a daughter compound, or the 'next' generation.

PANEL RULING

NeoClarityn contained desloratadine which was a metabolite of Clarityn. There was no comparative clinical data. The Panel did not consider there was sufficient evidence to demonstrate that the difference between Clarityn and NeoClarityn was such as to justify the claim at issue. The product was only licensed for the symptoms of seasonal allergic rhinitis. The Panel considered that the claim 'the next generation' implied that there had been a significant development in anti-allergy therapy. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.8 of the Code.

B5 Claim 'Even with 2nd generation antihistamines, there is <u>still</u> an unfulfilled need for a truly effective therapy'

The claim appeared in bold near to the end of the letter.

COMPLAINT

UCB stated that this introduced a new breach of Clause 8.1. In one statement Schering-Plough was disparaging to all currently available second generation antihistamines. It did not clarify what was meant by 'truly effective' and therefore suggested that the current treatments did not fulfil the need of patients.

Patient satisfaction had been considered within clinical trials with Zirtek and was generally accepted as high. Approximately, 70-80% of patients treated with Zirtek would be happy to take it again.

RESPONSE

Schering-Plough stated that the three paragraphs preceding this statement, following the rhetorical question 'But with so many antihistamines available – both POM and OTC – is there really a need for another one?', discussed a recent UK survey which described the dissatisfaction of individuals on currently existing antihistamines.

This survey, which was provided, quantified the level of satisfaction of patients with their existing therapy. Key efficacy parameters were rated on a scale of 1 to 10, where 10 = extremely satisfied and 1 = not at all satisfied.

In none of the parameters measured was satisfaction greater than 8.3. As examples relief of itchy / watery eyes was rated as 6.6; relief of sneezing 6.8; lack of drowsiness 7.7 and lack of side effects (other than drowsiness) 8.3.

The answer from this survey was unequivocal. Existing therapies did not provide full relief for patients with hayfever. New therapies were needed.

Schering-Plough suggested that the point that 70-80% of patients on Zirtek would be happy to take it again further strengthened the claim that there was still an unfulfilled need. On the figures given it would suggest that up to 20 or 30% of patients in the controlled environment of a clinical trial were not happy to take Zirtek again. At least some of these would be patients unwilling to take it again due to lack of efficacy.

Until 100% of patients obtained 100% relief from their medication there was still an unfulfilled need.

PANEL RULING

The Panel noted the submission that the claim at issue referred to the patient satisfaction survey discussed in the preceding paragraphs. The Panel noted that the claim at issue comprised a separate paragraph emboldened blue text. The prominence of the claim at issue was such that it was immediately apparent to the reader and might not be considered in light of the preceding paragraphs.

The Panel considered that the claim implied that none of the second generation antihistamines were truly effective. The Panel considered that the claim was disparaging. The medicines were licensed treatments. The Panel ruled a breach of Clause 8.1 of the Code.

C Leavepiece and 'Dear Pharmacist' letter alleged breach of Clause 2

COMPLAINT

UCB stated that once again it believed the use of such strategic ambiguity supported its previous concerns about Schering-Plough's promotional campaign for NeoClarityn and supported its view that it was in breach of Clauses 7.2, 7.3, 7.8 and 8.1.

UCB alleged that the extent of this misrepresentation also breached Clause 2.

RESPONSE

Schering-Plough said that it had already responded to the earlier allegations and had modified its promotional materials.

When UCB informed Schering-Plough of its concerns, in a attempt to avoid protracted dispute it took the step of amending its material and further offered UCB, in the spirit of openness, an opportunity to view its amended material before release. Had it viewed Schering-Plough's current material, Schering-Plough believed it would have agreed that appropriate steps had already been taken to resolve these issues.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/1137/2/01, it had considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. The position was compounded as the indications for the products were not the same. The licensed indications for NeoClarityn were more restricted than for Clarityn. In the Panel's view Schering-Plough had not made sufficient effort to distinguish between the products. On balance the Panel had considered that the circumstances warranted a ruling of a breach of Clause 2 and a breach of that clause had been ruled.

The Panel noted that the allegations now before it were different to those in the previous case. Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2.

Complaint received **16 February 2001**

Case completed **16 May 2001**

CASE AUTH/1142/2/01

CONSULTANT PHYSICIAN v TAKEDA

Meetings about Actos

A consultant physician complained about two meetings relating to the promotion of pioglitazone (Actos) to which she had been invited by Takeda.

The complainant believed that the offer to pay her £250 to attend an evening meeting in Northern Ireland was in direct contravention of the Code. This was not the first time she had been offered a direct financial inducement to attend a local promotional meeting. Unfortunately she had not retained documentation relating to previous examples of this malpractice. Takeda had also invited her to Juan les Pins but she felt that there was excessive and inappropriate hospitality associated with this offer and did not accept. Her general impression was that many companies were currently flouting the Code guidance on inappropriate hospitality to health professionals and this had the potential to become yet another health service 'scandal'. The specific example she drew attention to was the most blatant instance she had encountered.

The Panel noted that the meeting in Belfast was an advisory board meeting to discuss and receive feedback on the introduction of thiazolidinediones to the UK market and the impact of NICE guidance. New clinical data and the future development programme for Actos would also be discussed. The meeting ran from 6 to 9pm. According to the Chairman's notes the presentation from the marketing director would last 15 minutes followed by 30 minutes of feedback. The medical director would give four presentations, two lasting 10 minutes, one lasting 15 minutes and one lasting 20 minutes, followed by feedback sessions of 25 minutes, 5 minutes, 15 minutes and 10 minutes respectively. The Chairman was asked to encourage feedback and questions from all attendees. The meeting in question was one of a series of eight regional meetings planned around the expected timing of the release of the NICE pioglitazone guidance. The Panel considered that although the invitation mentioned the interactive nature of the meeting in very general terms, it was not sufficiently clear about the precise role of the invitees. The Panel queried whether there was sufficient justification for all of meetings held, particularly given the relevance of NICE guidance outside England and Wales.

The Panel noted that Takeda had aimed to involve 6-8 physicians on each advisory board; potential delegates had been identified by the unit business managers or the marketing department. Such a selection process might be open to criticism. Nineteen potential delegates had been contacted with regard to the meeting in question and eight had accepted the invitation. The delegates were being 'employed' as consultants and as such their inclusion should stand up to independent scrutiny. The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. It was difficult in such cases to decide precisely where the boundary lay. The Panel was concerned that the delegates were not asked to do a sufficient amount of work to justify the fee. The meeting only lasted three hours, less than half of which, according to the Chairman's brief, was allocated to feedback and discussion. The meeting included a presentation from the marketing director and an update on the development of Actos. The cost of the buffet at £20 per head was not unreasonable. Nevertheless, on balance the Panel considered that the arrangements for the meeting meant that it constituted one in a series of

promotional meetings. It was not appropriate to pay doctors to attend such meetings and a breach of the Code was ruled.

Upon appeal by Takeda, the Appeal Board was concerned that the invitation only mentioned the interactive nature of the meeting in very general terms. It was not sufficiently clear about the expected pro-active role of the invitees. Invitees were told that an honorarium was available for their attendance. The invitees were diabetologists and a small number of general practitioners. No health authority staff such as prescribing advisers were invited. The Appeal Board considered that such people would have useful and relevant information about the impact of NICE guidelines. The Chairman's notes gave more details than the agenda did particularly with regard to the shorter presentations indicating that each session would start with a presentation from a Takeda member of staff followed by time for feedback from the group. A number of the short sessions started with a list of questions to be answered by the attendees and the whole of the meeting was very interactive. On balance the Appeal Board decided that the arrangements for the meeting, particularly the invitation and the agenda, created the impression that it was one in a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Appeal Board upheld the Panel's ruling of a breach of the Code.

With regard to the meeting in Juan les Pins (south coast of France) the Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK but there had to be valid and cogent reasons for so doing. The Panel noted that following selection by regional business managers, representatives verbally invited physicians. This was followed up with a written invitation if the physician expressed interest in attending. The meeting was entitled 'New advances in the management of insulin resistance in type 2 diabetes – a European perspective'. The meeting was on a Saturday and was to start at 9am and finish at 6pm. Delegates were to arrive on the Friday and leave on the Sunday. There were to be four presentations with time for questions. In the afternoon 2½ hours were to be spent on breakout sessions.

The Panel considered that with regard to meetings held outside the UK attended by UK doctors, the content had to apply to all countries, a reasonable proportion of participants from each country should attend, the costs and logistics should be reasonable and the meeting should be consistent with the requirements of the Code as to educational content and the balance between that and the hospitality provided. The Panel considered that the expected cost (£625) per UK delegate was high and this would exceed the level that some recipients would normally adopt when paying for themselves. The meeting was a joint meeting for physicians from all countries in Europe where Takeda had a subsidiary. The Panel queried whether the educational content justified two nights' accommodation. There was no educational programme on the Sunday. It was not unreasonable to provide accommodation for the evening prior to a meeting starting at 9am. The second night's accommodation had been provided because of the location of the venue and possible difficulties for delegates to return home on the Saturday evening. In that regard the Panel queried Takeda's submission that the location of the meeting was chosen because it had good rail, road and air links to the UK, France, Germany and Italy. The Panel was concerned that the choice of venue had not been sufficiently justified and that the cost per delegate was more than delegates would pay if they were paying for themselves. The Panel considered that the arrangements for the meeting were unacceptable and a breach of the Code was ruled.

Upon appeal by Takeda, the Appeal Board noted that the meeting in question involved delegates and speakers from the UK, France, Germany, Italy and Switzerland. The arrangements were such that the delegates arrived on the Friday afternoon or evening and returned home on the earliest convenient flight on the Sunday. The Appeal Board noted that a venue had to be chosen that had good links with the various countries. The Appeal Board did not consider that the final cost of the accommodation and meals at £218.71 per person was excessive. The average travel costs for the UK delegates was £300. The Appeal Board did not consider that in these circumstances it was unreasonable to offer two nights' accommodation. The educational content was reasonable. It considered that in the context of a meeting attended by delegates from a number of European countries the choice of venue was not inappropriate. The Appeal Board ruled that there had been no breach of the Code.

A consultant physician complained about two meetings relating to the promotion of pioglitazone (Actos) to which she had been invited by Takeda UK Limited.

COMPLAINT

The complainant stated that she had recently received an invitation from Takeda to attend a meeting to promote its new medicine, pioglitazone. A copy of the letter she had received, and the proposed programme for the meeting, were provided. The meeting, to be held in Belfast in March, started at 5.30pm and finished at 9pm. The complainant believed that the offer to pay her £250 to attend this meeting was in direct contravention of the Code. This was not the first time she had been offered a direct financial inducement to attend a local promotional meeting. Unfortunately she had not retained documentation relating to previous examples of this malpractice. A few weeks ago, Takeda had also invited her to Juan les Pins, again for the promotion of pioglitazone. She felt that there was excessive and inappropriate hospitality associated with this offer and did not accept. Her general impression was that many companies were currently flouting the Code guidance on inappropriate hospitality to healthcare professionals and this had, she believed, the potential to become yet another health service 'scandal'. The specific example she drew attention to was the most blatant instance she had encountered.

When writing to Takeda the Authority drew attention to Clauses 2, 9.1 and 19.1 of the Code. The advisory board meeting and the international meeting were considered separately.

1 Advisory Board Meeting

RESPONSE

Takeda was very concerned that the complainant had misunderstood the purpose of this meeting, as it believed that the invitation did make the advisory nature clear.

Background to the need for regional advisory boards

Takeda stated that there were large regional variations in a number of factors which were affecting the uptake of the thiazolidinediones, a new class of medicines for diabetes. These included the population of patients with diabetes in the region, which was affected by ethnic variations, the arrangements of health care and, most recently, the attitude to the National Institute of Clinical Excellence (NICE). There had been enormous controversy surrounding the publication of each guidance produced by NICE and it had not been possible to predict the response from any region. While awaiting the guidance from NICE, some regions had produced interim guidelines on the usage of the thiazolidinediones and these had varied in content.

Takeda believed that it needed to establish quickly the local views in each region in response to the two NICE guidance documents for the thiazolidinediones to understand how this would affect the development of the uptake of this class of medicines, and in particular of pioglitazone.

Takeda was in a unique position with respect to the effect that NICE had and would have on prescribing and the effect was expected to be different across the UK. In each other appraisal completed by NICE, guidance had been issued for a class of medicines. However, for the thiazolidinediones NICE had conducted separate reviews. This had meant that one medicine in the class received a guidance from NICE within one month of being made available in the UK whereas for pioglitazone there had been a period of 5 months after launch before guidance had been made available. This had created a unique position, with some uncertainty among physicians, which Takeda believed had been viewed differently across the country. Takeda needed to gain accurate opinions from key opinion leaders throughout the UK on how to deal with the publication of the NICE guidance.

Advisory board meeting in Belfast

This meeting was one of a series of eight regional meetings and the primary aims were for Takeda to gain insight into local issues affecting the adoption of new medicines, and in particular the potential varied responses to a NICE guidance throughout the UK. The other meetings would be held in Cambridge, Newcastle, London, Birmingham, Newport, Leeds and Glasgow to allow information on the opinions on NICE to be evaluated from most health regions.

Although NICE guidance did not strictly govern the usage of new medicines outside England and Wales, Takeda had had feedback that the absence of NICE guidance was a barrier to prescribing in Northern Ireland and that physicians were waiting for the NICE review in Scotland. The meetings were planned around the expected timing of the release of the pioglitazone guidance (early March). Unfortunately the final publication of the NICE guidance on 9 March was one week later than Takeda had anticipated and the meeting planned in Belfast had been postponed to a later date.

The meeting in Northern Ireland was the first advisory meeting that Takeda had ever had including doctors from this region. The meeting to which this physician had been invited was a small closed advisory board meeting in which Takeda would give confidential information to the small group of advisors and receive feedback and advice from this group on how to move forward in Northern Ireland. Each advisor would be asked to sign a confidentiality agreement before attending the meeting and, as the physician would be giving advice, an honorarium was payable. Takeda believed that the honorarium was appropriate for a senior physician to attend and offer advice at a meeting lasting four hours.

The letter inviting the physician to the meeting clearly stated that the purpose was advisory and that Takeda wished to discuss and receive feedback.

The physician had suggested that the hospitality associated with the meeting was excessive. However, the only hospitality offered was a 'working evening buffet' at a cost of £20 per head. No overnight stay or dinner was included. Takeda believed that this working buffet was appropriate for this type of meeting. The total cost of this meeting would be:

Room: £200

Buffet: £160

Honoraria: £2000 (£250 per advisor and £500 for the chairman)

The physician had suggested that this meeting was promotional. However, no sales personnel would be at the meeting. Sales people had not been involved in the distribution or follow up of invitations or any of the administration of the meeting.

The meeting was deliberately divided into two sections. During the first part of the meeting the marketing director would outline the current usage of the thiazolidinediones (both throughout the UK and in the region), providing data on dosage distribution, and prescribing practice to date. Takeda hoped to obtain feedback from the clinicians on the local issues which were facilitating or preventing the use of new medicines, with particular reference to the thiazolidinediones eg acceptance of liver function test monitoring and the development of local protocols for prescribing groups.

The second part of the meeting would discuss particular issues that were related to NICE and the introduction of the thiazolidinediones. In addition, as the NICE appraisal included a section relating to recommendations for future clinical trials, Takeda

would exchange information on the ongoing development programme. This would include information about PROACTIVE, a large study due to start soon to investigate the long-term effects of pioglitazone on cardiovascular outcomes, which was one of the areas highlighted by NICE. The discussion would focus around new suggestions for and feedback on future avenues to explore. The UK principal investigator would attend the meetings (where possible) to outline the large outcome study and to discuss the study with the advisory panel. If he was not attending the meeting the UK medical director would lead this discussion.

Formal presentations would take up only a small part of the meeting, as most of the time would be for discussion. Copies of the letters sent to the chairman of the meeting were provided which emphasised that although there would be some presentations the objective of the meeting was to receive feedback from the board.

The feedback received from the advisors at this meeting would be used to input into local business unit plans to disseminate information about NICE and help with selection of suitable investigators for the future clinical trial programme.

Distribution of meetings and physicians invited

The physicians invited were selected based on information suggesting that he/she had a special interest in new treatments eg feedback from the unit business managers or the marketing department that the physician had a special expertise with or interest in new agents for treatment of type 2 diabetes, and physicians who had been in discussion with Takeda's medical department about clinical trials. In total 19 physicians had been contacted about the meeting in Belfast and eight had accepted the invitation. Each advisory board aimed to involve 6-8 physicians making up the eight regional advisory boards. The physicians were invited because Takeda believed that they would have special awareness and understanding of their own region. They were consultant physicians or leading general practitioners with a special interest in treating type 2 diabetes and in most cases had formed a good relationship with Takeda.

In light of the complaint made by this physician Takeda would put in place new checks on the interests of the physicians invited.

Of the physicians contacted Takeda had had very positive feedback on the nature of the meeting with many physicians expressing regret that they could not attend the advisory board as they would have liked to be involved in this initiative. Takeda had however had one physician who sent feedback stating that she felt that the meeting was inappropriate. One other physician telephoned to question the content of the meeting as he had been invited to other meetings where there were scores of physicians. He was reassured on hearing that it was a small closed meeting and he had accepted the invitation to become a member of the regional advisory board.

Takeda believed that this meeting was a true advisory board and it would act on the advice received as a result of each meeting. The locations of the meetings had been selected to give an overall picture of the influence of NICE throughout the UK reflecting the views of each health region.

Takeda believed that the meetings included appropriate hospitality for the physicians and was not in breach of Clause 19.1 of the Code. In addition Takeda believed that it recognised the professional standing of the physician invited to the advisory board meeting by offering the honorarium as appropriate payment for advice given. Takeda did not believe that the honorarium offered was an inducement to attend the meeting but would be an appropriate payment for a physician attending a meeting lasting four hours and giving advice. Takeda believed that this had not been a breach of Clauses 9.1 or 19.2 of the Code.

Takeda believed that this meeting did not bring discredit to the pharmaceutical industry but was appropriate and of a high standard and so not in breach of Clause 2 of the Code.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. The arrangements had to comply with the Code.

The Panel noted that the purpose of the meeting was to discuss and receive feedback on the introduction of thiazolidinediones to the UK market and the impact of NICE guidance. New clinical data and the future development programme for the product would also be discussed. The meeting started with arrivals and light refreshments from 5.30pm to 6pm. The meeting ran from 6 to 9pm. According to the Chairman's notes the presentation from the marketing director would last 15 minutes followed by 30 minutes of feedback. The medical director gave four presentations, two lasting 10 minutes, one lasting 15 minutes and one lasting 20 minutes, followed by feedback sessions of 25 minutes, 5 minutes, 15 minutes and 10 minutes respectively. The Chairman was asked to encourage feedback and questions from all attendees.

The meeting in question was one of a series of eight regional meetings planned around the expected timing of the release of the NICE pioglitazone guidance. The Panel considered that although the invitation mentioned the interactive nature of the meeting in very general terms, it was not sufficiently clear about the precise role of the invitees. The Panel queried whether there was sufficient justification for all of the meetings held, particularly given the relevance of NICE guidance outside England and Wales. The Panel noted that Takeda had aimed to involve 6-8 physicians on each advisory board. The Panel also noted that the potential delegates had been identified by the unit business managers or the marketing department. Such a selection process might be open to criticism. Nineteen potential

delegates had been contacted with regard to the meeting in question and eight had accepted the invitation. The delegates were being 'employed' as consultants and as such their inclusion should stand up to independent scrutiny.

The Panel considered that it was difficult in such cases to decide precisely where the boundary lay. The Panel was concerned that the delegates were not asked to do a sufficient amount of work to justify the fee. The meeting only lasted three hours less than half of which, according to the Chairman's brief, was allocated to feedback and discussion. The meeting included a presentation from the marketing director and an update on the development of the product. The Panel considered that the cost of the buffet at £20 per head was not unreasonable. Nevertheless, on balance the Panel considered that the arrangements for the meeting meant that it constituted one in a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Panel ruled a breach of Clause 18.1 of the Code.

The Panel did not accept that the circumstances warranted rulings of a breach of Clause 9.1 or of Clause 2 which was used as a sign of particular censure.

APPEAL BY TAKEDA

Takeda stated that it maintained that the meetings were of an advisory nature and that these meetings were not promotional so it was appropriate to offer payment to the doctors for their time and advice.

The meeting in Northern Ireland was one of a series of small closed advisory board meetings, in which Takeda discussed confidential information with a group of advisors. As the physicians were asked to give advice, an honorarium was paid. The company considered that the honorarium of £250 was appropriate for a senior physician to attend and offer advice at a meeting lasting a full three hours. (The current BMA rate for pharmaceutical work was £142.50 per hour). The company submitted that for the chairman, who prepared for the meeting beforehand, the payment of £500 was also appropriate.

The series of eight regional advisory boards had the primary aims for the company of gaining insight into local issues affecting the adoption of new medicines and in particular the potential varied responses to a NICE guidance throughout the UK, to receive feedback on new clinical data and guidance on new research avenues to be explored. The meetings were held in Cambridge, Newcastle, London, Birmingham, Belfast, Newport, Leeds and Glasgow to allow information on the opinions on NICE to be evaluated from most health regions.

Takeda anticipated that there would be some controversy surrounding the publication of the guidance produced by NICE for pioglitazone as this had happened with most completed guidances. In some areas the company had an indication that trusts were not concerned about the guidance issued by NICE, as pioglitazone had already been added to hospital formularies. In other areas there were clear signs that prescription of pioglitazone would be severely restricted until after the guidance was issued. Examples were provided. Takeda stated that it believed that it needed to establish quickly the local views in response to the two NICE guidances for the glitazones, to understand how this would affect the development of the uptake of the glitazones, and in particular for pioglitazone. Takeda was in a unique position with respect to the effect that NICE had had on the prescribing of a new medicine as in each other appraisal completed by NICE, guidance has been issued for a class of medicines. However, for the glitazones NICE had conducted separate reviews. This had created a unique position, with uncertainty among physicians and the effect had varied from one region to another.

Takeda stated that its expectation of the level of controversy surrounding the publication of the NICE guidance, and need for advice from groups of experts, was confirmed when the company learned of an open letter written by Novo Nordisk to NICE. A copy of the letter was sent to a large number of diabetologists in England, Wales and Scotland questioning the NICE guidance for the glitazones. At the last two of the advisory meetings Takeda was given the diabetologists' views on this letter.

Takeda stated that the physicians were invited because the company considered that they would have special awareness and understanding of their own region. They were consultant physicians or leading general practitioners with a special interest in treating type 2 diabetes and in most cases had formed a good relationship with Takeda.

Takeda noted that the complainant had suggested that this meeting was promotional. However, no sales personnel were at the meetings. Sales people were not involved in the distribution or follow up of invitations or any of the administration of the meeting. Takeda did not believe that the content of the meeting was promotional.

During the first part of the meeting the marketing director outlined the current usage of the oral antidiabetic agents included the glitazones (both throughout the UK and in the region), and provided data on dosage distribution and regional variation in uptake of the glitazones. The clinicians gave feedback on the local issues, which patients were being started on this class of medicine and factors which were facilitating or preventing the use of this class of medicines. There was discussion of the acceptance of liver function test monitoring, who should take responsibility for this and the development of local protocols for prescribing groups.

The second part of the meeting discussed the process of NICE and the guidances for the glitazones with a presentation from the medical director. Takeda had received very valuable feedback from the panel on which parts of the NICE guidance were the most important for the physicians and the local response to NICE guidances. In some areas there was a strict application of the NICE guidance, whereas in others it was assumed that any positive endorsement would allow use within the licensed indications. The meetings took place in the month following the

release of the pioglitazone guidance to allow the company to tailor its response within different business units.

Takeda stated that although NICE guidance did not strictly govern the usage of new medicines outside England and Wales, it had had feedback that the absence of NICE guidance was a barrier to prescribing in Northern Ireland and that physicians were waiting for the NICE review in Scotland so it was appropriate to discuss the NICE guidance in these areas. This view was confirmed in the meetings held in Scotland and Northern Ireland.

Takeda stated that as the company was currently discussing the future development of pioglitazone it was vital that it understood the views of practising clinicians on the future place of the glitazones in the management of type 2 diabetes and related conditions. After discussion of the data currently available the company had open debate on the future direction to take with the medicine and the diabetologists gave very valuable advice.

Takeda explained that whilst discussing the future development it had included information about PROACTIVE, a large study due to start soon to investigate the long-term effects of pioglitazone on cardiovascular outcomes. The UK principal investigator attended two of the meetings. When he did not attend the meeting the UK medical director led this discussion.

The presentations were informal and the data shown was discussed throughout. This could not be reflected on the agenda.

Takeda submitted that the feedback received from the advisors at this meeting would be used to input into local business unit plans to disseminate information about NICE and help with selection of suitable investigators for the future clinical trial programme.

Takeda stated that it had had very positive feedback on the nature of the meeting. Many physicians had voiced how open and honest the company had been for presenting the market data and requesting the views of the panel in a way that allowed free and frank discussion on all aspects of the development of the glitazones with physicians. No members of the advisory board had suggested that this was a promotional meeting.

Takeda stated that it believed that this meeting was a true advisory board and it was acting on the advice received as a result of each meeting. The company did not consider that the honorarium offered was an inducement to attend the meeting but would be an appropriate payment for a physician attending a meeting lasting 3 hours and giving advice. Takeda considered that there had been no breach of Clause 18.1 of the Code.

APPEAL BOARD RULING

The Appeal Board accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. All the arrangements had to comply with the Code.

The Appeal Board was concerned about the invitation and the impression given. The invitation mentioned the interactive nature of the meeting in very general terms. It was not sufficiently clear about the expected pro-active role of the invitees. Invitees were told that an honorarium was available for their attendance at the meeting. The invitees were diabetologists and a small number of general practitioners. No health authority staff such as prescribing advisers were invited. The Appeal Board considered that such people would have useful and relevant information about the impact of NICE guidelines.

The Chairman's notes gave more details than the agenda did about timings, indicating that each session would start with a presentation from a Takeda member of staff. The marketing director presented the first session and the other sessions were presented by the medical director. Each presentation was followed by time for feedback from the group although this was not clearly stated on the agenda with regard to the shorter presentations. At the appeal the medical director explained that a number of short sessions started with a list of questions to be answered by the attendees and that the whole of the meeting was very interactive. The Appeal Board was concerned, however, that by not including sufficient details the invitation and the agenda gave the impression that the meeting was a promotional meeting.

On balance the Appeal Board decided that the arrangements for the meeting, particularly the invitation and the agenda, created the impression that it was one in a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1 of the Code. The appeal was unsuccessful.

2 International Meeting

RESPONSE

A copy of the agenda for this Takeda International meeting was provided. Takeda stated that it was arranged in support of the launch of pioglitazone in Europe where a number of renowned international speakers would discuss the recent data on pioglitazone. The audience for this meeting would include key opinion leaders from all countries in Europe where Takeda had a subsidiary. The site of the meeting was selected for convenience for all the key Takeda subsidiaries in a central location with good road, rail or flight access to UK, France, Germany and Italy.

It was expected that approximately 75 people would attend this meeting with 10 physicians from the UK.

No honorarium had been offered for attending this meeting, as it was not an advisory meeting. The selection of physicians to be invited to this meeting had been from the regional business managers. Representatives initially verbally invited the physicians and this was followed with a written invitation if the physician expressed interest in

attending the meeting. The selection was based on the personal knowledge of the sales person of the interests of the physician.

The meeting had a formal agenda from 9am to 6pm with balanced presentations on insulin resistance and pioglitazone. The hospitality offered included lunch, dinner and overnight accommodation for one or two nights depending on the flight availability. It was not possible to avoid an overnight stay for a meeting of this length when physicians from a number of different countries were involved.

Takeda believed that only appropriate hospitality had been included. The venue and agenda had been chosen to allow renowned speakers to present and allowed time for the speakers to be available for questions to an audience of diabetologists with special interest in new treatments for type 2 diabetes.

A similar meeting was held in February and copies of the summary feedback from all physicians who completed the meeting assessment forms were provided.

The cost of the meeting was expected to be £625 per UK physician (this consisted of accommodation and meals £325; transport £300). Although the cost of flights from the UK was relatively high the overall cost to Takeda per head would be considerably less than this estimate with the significantly lower costs of transport from Italy and France to the meeting.

Takeda believed that the meeting included appropriate hospitality for the physicians and so was not in breach of Clause 19.1 of the Code. It believed that there had not been a breach of Clause 9.1 or 19.2 of the Code.

Takeda believed that this meeting did not bring discredit to the pharmaceutical industry but was appropriate and of a high standard and so not in breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that the venue for the international meeting, Juan les Pins, was in France between Nice and Cannes. The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK. There had to be valid and cogent reasons for so doing. When considering whether a meeting and associated hospitality contravened the Code, all the circumstances had to be considered including cost, location, educational content, level of hospitality and the overall impression created by the arrangements. Each case had to be considered on its own merits. The programme should attract delegates and not the venue or associated activities.

The Panel noted that following selection by regional business managers, representatives verbally invited physicians. This was followed up with a written invitation if the physician expressed interest in attending. The selection was based on the personal knowledge of the sales person and the interests of the physician.

The Panel examined the documentation provided by Takeda. The meeting was entitled 'New advances in the management of insulin resistance in type 2 diabetes – a European perspective'. The meeting was to start at 9am and finish at 6pm on Saturday, 24 March. Delegates were to arrive on the Friday and leave on the Sunday. There were to be four presentations with time for questions. In the afternoon **2½** hours were to be spent on panel breakout sessions. The written invitation referred to by Takeda was a delegate registration form. Takeda referred to a similar meeting held in February whereby the UK delegates had commented on the arrangements. The comments were generally complimentary although one attendee noted that it would have been interesting if the small groups had not been held on a country basis. Takeda had invited 75 people to include 10 physicians from the UK to the meeting to be held in March. No details had been provided about the company personnel expected to attend.

The Panel considered that with regard to meetings held outside the UK attended by UK doctors, the content had to apply to all countries, a reasonable proportion of participants from each country should attend, the costs and logistics should be reasonable and the meeting should be consistent with the requirements of the Code as to educational content and the balance between that and the hospitality provided.

The Panel considered that the expected cost (£625) per UK delegate was high and this would exceed the level that some recipients would normally adopt when paying for themselves. The meeting was a joint meeting for physicians from all countries in Europe where Takeda had a subsidiary.

The Panel noted Takeda's submission that a similar meeting had been held in February. At that meeting the breakout sessions were on a country basis. The Panel queried whether there was an educational advantage to having delegates from Europe when the majority of discussions appeared to be on a country basis.

The Panel queried whether the educational content justified two nights' accommodation. There was no educational programme on the Sunday. It was not unreasonable to provide accommodation for the evening prior to a meeting starting at 9am. The second night's accommodation had been provided because of the location of the venue and possible difficulties for delegates to return home on the Saturday evening. In that regard the Panel queried Takeda's submission that the location of the meeting was chosen because it had good rail, road and air links to the UK, France, Germany and Italy.

The Panel considered that this was a difficult case. It was concerned that the choice of venue had not been

sufficiently justified and that the cost per delegate was more than delegates would pay if they were paying for themselves.

The Panel considered that the arrangements for the meeting were unacceptable. The Panel therefore ruled a breach of Clause 19.1 of the Code. The Panel did not consider that there had been a breach of Clause 9.1 nor of Clause 2 which was used as a sign of particular censure.

APPEAL BY TAKEDA

Takeda submitted that the meeting was an international meeting bringing together delegates from four key European countries to allow exchange of information and ideas. The speakers were all well respected international speakers. The company considered that the format and location of the meeting were appropriate for a meeting with high calibre international speakers.

Takeda stated that the meeting had a formal agenda from 9am to 6pm with balanced presentations on insulin resistance and pioglitazone. The hospitality offered included lunch, dinner and overnight accommodation for one or two nights depending on the flight availability. It was not possible to avoid an overnight stay for a meeting of this length when physicians from a number of different countries were involved. The company considered that the cost for the meeting offered appropriate hospitality for the level of physician invited.

Takeda stated that had the meeting been staged in the UK its overall cost would have been considerably higher. The cost of delegate travel from the other countries would have been higher and the cost of accommodation in a hotel of acceptable standard for the calibre of the attendees would have been considerably greater.

Feedback from the attendees confirmed that the meeting was of a high standard. The breakout sessions allowed the delegates from each country to put questions in a small group setting to the panel of speakers and to discuss areas of particular interest locally.

Takeda stated that it considered that only appropriate hospitality had been included. The venue and agenda were chosen to allow renowned speakers to present and allowed time for the speakers to be available for questions to an audience of diabetologists with special interest in new treatments for type 2 diabetes. Overall 46 people attended the meeting. A minority of the attendees was from the UK with just 9 British delegates. The other participants were from Italy, France, Germany and Switzerland. The final cost for each delegate was £218.71 (this consisted of hotel accommodation £62.08 / person / night (including breakfast) and cost for meals of £94.55). Takeda stated that it considered that this hospitality was appropriate for the physicians and so not in breach of Clause 19.1 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the meeting in question involved delegates and speakers from the UK, France, Germany, Italy and Switzerland. The meeting had been held on the Saturday from 9am to 6pm. The Appeal Board noted the submission made at the appeal hearing. The arrangements were such that the delegates arrived on the Friday afternoon or evening and returned home on the earliest convenient flight on the Sunday. The Appeal Board noted that a venue had to be chosen that had good links with the various countries.

The Appeal Board did not consider that the final cost of the accommodation and meals at £218.71 per person was excessive. The average travel costs for the UK delegates was £300. The Appeal Board did not consider that in these circumstances it was unreasonable to offer two nights' accommodation. The educational content was reasonable. It considered that in the context of a meeting attended by delegates from a number of European countries the choice of venue was not inappropriate. The Appeal Board did not consider that there had been a breach of Clause 19.1 of the Code and accordingly ruled no breach of that clause. The appeal was successful.

Complaint received **21 February 2001**

Case completed **6 July 2001**

CASE AUTH/1147/2/01

WYETH v ORGANON LABORATORIES

Promotion of Zispin

Wyeth alleged that a journal advertisement for Zispin (mirtazapine), which had been placed by Organon Laboratories, made a false comparison between the costs of Zispin and venlafaxine (Wyeth's product Efexor). The advertisement stated 'Did you know ZISPIN is over 25% cheaper than venlafaxine?' in large print suggesting that Zispin was usually 25% cheaper than venlafaxine. In the majority of patients this was not so. Market research data confirmed that approximately 70% of prescriptions for venlafaxine XL were for 75mg daily which cost £23.97 per month. The cost of 30mg Zispin (the most commonly prescribed dose) was £22.92 per month, making it 4% cheaper than venlafaxine, not 25% as stated. The claim was neither balanced nor fair.

The Panel noted that the data came from DIN-LINK and the 25% difference in cost was stated to be 'Based on average monthly cost of treatment (28 days at current NHS prices MIMS January 2001) and average daily dosage of Zispin 30mg and venlafaxine 107.8mg'. The Panel considered that most readers would assume that the claim meant that for the typical patient Zispin was over 25% cheaper than venlafaxine. The Panel did not consider that the claim would be read as comparing weighted average costs and weighted average doses as submitted by Organon. A 107.8mg dose of venlafaxine was not a dose which would typically be prescribed. The Panel noted that the average (mean) dose of a product would be dependent on its dose range and the weighted average cost would be dependent upon the price structure of the product range. The dose of Efexor could vary from 75mg a day, in two divided doses, up to 375mg a day; tablets were available containing 37.5mg, 50mg or 75mg venlafaxine. The dose of Efexor XL could range from 75mg once daily to 225mg once daily; capsules were available as 75mg or 150mg. Treatment with Zispin could vary from 15mg/day to 45mg/day; only 30mg tablets were available. The Panel considered that to compare the cost of Zispin 30mg with venlafaxine 107.8mg was unfair and misleading. It was too simplistic to claim that Zispin was 25% cheaper than venlafaxine. The Panel ruled a breach of the Code.

Upon appeal by Organon, the Appeal Board considered that using the weighted average cost of a medicine was not unacceptable *per se*. It would be relevant in some circumstances. In any comparison the basis must be made clear and must be fair. The Appeal Board was concerned that Organon was unable to provide information about the patient population upon which the DIN-LINK data was based or provide details about the methodology by which the data was collated. It also noted that venlafaxine had broader licensed indications than Zispin. The advertisement was aimed at GPs, who, in the Appeal Board's view, would consider that the cost saving related to the price of the product for an individual patient. That was not so. This view was compounded by the phrase '… by prescribing Zispin rather than venlafaxine, you can save more than £8 per patient per month' which also appeared in the advertisement. The Appeal Board considered that the claim 'Did you know that Zispin is over 25% cheaper than venlafaxine?' was misleading. It was not sufficiently qualified given the method of calculation. A breach of the Code was ruled.

Wyeth stated that the claim 'When SSRI treatment fails, another class of antidepressant, like Zispin, is now recommended' suggested that guidelines recommended Zispin, or another antidepressant of the same class. Zispin was to all intents and purposes the only available medicine in its class, which would imply that the guidelines recommended only Zispin when SSRI treatment failed. The guidelines said nothing of the sort. Most guidelines recommended switching (to any other) class after initial treatment. The specific guidelines referenced in the advertisement were referring to venlafaxine and mirtazapine and stated that both might be valuable in depression which had not responded to other antidepressants. The claim was therefore both exaggerated and unbalanced.

The Panel noted the submission from Wyeth that Zispin was the only available medicine in its class. The guidelines referenced in the advertisement referred to 'newer combined action antidepressant drugs (venlafaxine and [Zispin].....' whereas the claim in the advertisement referred to 'another class of antidepressant like Zispin'. The Panel noted that venlafaxine and mirtazapine were both combined action antidepressants but that each belonged to a different class of medicine. The Panel considered that the claim was not a fair reflection of the advice given in the guidelines, it implied that Zispin was the only product recommended when SSRIs were not effective. The Panel also considered that the claim was exaggerated. Breaches of the Code were ruled.

Upon appeal by Organon, the Appeal Board considered that the use of the word 'recommended' in the advertisement was less equivocal than that used in the actual guidelines which stated that the newer combined action antidepressant medicines (venlafaxine and mirtazapine) 'should not be used as first line antidepressants, but may be valuable in depression that has not responded to other antidepressants. These should be included as an option…'. The Appeal Board considered that the claim at issue was not a fair reflection of the guidelines and also implied that only Zispin was recommended which was not so. Breaches of the Code were ruled.

Wyeth complained about a journal advertisement (ref 02907F) for Zispin (mirtazapine) which had been placed by Organon Laboratories Ltd in GP, 23 February, 2001.

1 Cost Comparison

COMPLAINT

Wyeth alleged that the advertisement made a false comparison between the costs of Zispin and venlafaxine (Wyeth's product Efexor).

The advertisement stated 'Did you know ZISPIN is over 25% cheaper than venlafaxine?' in large print suggesting that Zispin was usually 25% cheaper than venlafaxine. In the large majority of patients this was simply not the case.

Market research data confirmed that the majority (approximately 70%) of prescriptions for venlafaxine XL were for 75mg daily which cost £23.97 per month. The cost of 30mg Zispin (the most commonly prescribed dose) was £22.92 per month, making it 4% cheaper than venlafaxine, not 25% as stated in the advertisement. As the claim was neither balanced nor fair it contravened Clause 7.2 of the Code.

RESPONSE

Organon Laboratories stated that the claim was clearly referenced to calculations on data that were derived from DIN-LINK. Approval for the use of these data, and indeed approval of the calculations based upon the data, was obtained (as stipulated in its guidelines) from the owner of the DIN-LINK database.

Organon noted that the use of DIN-LINK data in promotional materials was in general considered to be acceptable. For example, in Wyeth's Premique detail aid ZHRT03/0101.

The claim was referenced to, and supported by, calculations that compared the 'average' monthly cost of treatment for Zispin and venlafaxine formulations based on: 28 days at current NHS prices as published in MIMS January 2001, 'Average' daily dosage of Zispin of 30mg and 'Average' daily dosage of venlafaxine formulations of 107.8mg

The prescription data used were the most recent available at the time of calculation (MAT October, 2000), and they showed that the following presentations were prescribed in the UK: Zispin 30mg tablets, venlafaxine 37.5mg, 50mg, 75mg tablets, and venlafaxine 75mg and 150mg capsules

DIN-LINK showed that the average daily dosage of Zispin 30mg tablets, the only presentation available, was exactly one tablet per day. The NHS cost of 28 days of 30mg Zispin treatment was £22.92. However since several presentations of venlafaxine were prescribed in the UK it was necessary to devise a fair method of representing typical usage of the products. The DIN-LINK data showed that venlafaxine was prescribed at various doses in a variety of presentations. Taking each of the venlafaxine presentations in turn, the distribution of prescriptions, and the mean prescribed daily dose of that presentation, allowed calculation of a weighted average dose, and consequently a weighted average cost. The various contributions of these presentations were then aggregated to arrive at the overall totals. In the interest of clarity, Organon had simplified the term 'weighted average dose' to 'average dose'.

From a weighted average dose of 107.77mg, a weighted average cost for 28 days of £31.23 for all venlafaxine presentations was calculated.

Therefore comparing 28 days' treatment costs of the average prescribed dosage, the weighted average cost for venlafaxine was £31.23 versus a cost of £22.92 for Zispin. Thus the claim: '25% cheaper' was entirely justified, and was actually conservative as Zispin was in fact 26.6% cheaper.

Organon believed that its calculation was the most well adjusted way of comparing a product that had one presentation, with one that had several (five) different presentations.

On the other hand Wyeth's remark in its letter of complaint: 'Market research data confirms that the majority (approximately 70%) of prescriptions for venlafaxine XL are for 75mg daily which costs £23.97' was misleading in three respects: Firstly it only referred to prescriptions of venlafaxine XL capsules which represented in total only 52.4% of the prescriptions of venlafaxine. Secondly, the cited cost of £23.97, as Wyeth indeed admitted, related only to 70% of prescriptions for XL capsule formulations (ie 70% of 52.4% = 36.68% of venlafaxine prescriptions). And thirdly, the majority of patients using venlafaxine were prescribed doses in excess of 75mg daily. Indeed more than 75% of prescriptions were for a mean daily dose greater than 75mg. This compared with the previously mentioned average daily dose of Zispin of 30mg.

Consequently Organon did not consider that Wyeth's cost comparison was well-founded. Indeed it could be argued that Wyeth's statement was one that was unbalanced, unfair and misleading.

In summary Organon believed that its price comparison was accurate, balanced and fair, and therefore it did not believe that it was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that in the advertisement reference 1 was cited in support of the claim. In the list of references, given in small print before the prescribing information, it was explained that the data for reference 1 came from DIN-LINK and that the 25% difference in cost was 'Based on average monthly cost of treatment (28 days at current NHS prices MIMS January 2001) and average daily dosage of Zispin 30mg and venlafaxine 107.8mg'.

The Panel considered that most readers would assume that the claim in question meant that for the typical patient Zispin was over 25% cheaper than venlafaxine. The Panel did not consider that the claim would be read as comparing weighted average costs and weighted average doses as submitted by Organon.

The claim was based on a 107.8mg dose of venlafaxine which was not a dose which would typically be prescribed. The Panel noted that the average (mean) dose of a product would be dependent on its dose range and the weighted average cost would be dependent upon the price structure of the product range.

The dose of Efexor could vary from 75mg a day, in two divided doses, up to a maximum of 375mg a day. Tablets were available containing 37.5mg, 50mg or 75mg venlafaxine. The dose of Efexor XL could range from 75mg once daily to a maximum of 225mg once daily. Efexor XL capsules were available as 75mg or 150mg. Treatment with Zispin could vary from 15mg/day to 45mg/day; only 30mg tablets were available.

The Panel considered that to compare the cost of Zispin 30mg with venlafaxine 107.8mg was unfair and misleading. It was too simplistic to claim that Zispin was 25% cheaper than venlafaxine. The Panel ruled a breach of Clause 7.2 of the Code.

APPEAL BY ORGANON LABORATORIES

Organon stated that it appeared that the Panel had taken a different interpretation of the DIN-LINK data presented above. It was precisely because venlafaxine was prescribed in a variety of formulations and doses, that an averaging process must take place to determine usage among a cohort of patients. The DIN-LINK calculations took into account the totality of patients, and the totality of prescriptions. A table was provided which showed the distribution of all prescriptions across the full range of venlafaxine formulations. For example venlafaxine 75mg capsules comprised 36.1% of all prescriptions, and were prescribed at a mean dose of 82.5mg a day. The table also showed that doses of 150mg and 165mg a day were prescribed for a total of 37.7% of prescriptions. Therefore over one third of all prescriptions were for a dose of 82.5mg a day (75mg capsules) and over one third of all prescriptions were for doses in excess of 150mg a day.

While the prescription data showed the actual mean daily doses prescribed for each formulation, Organon (with the approval of DIN-LINK) sought to be scrupulously fair in its price comparison by calculating the weighted average dose for venlafaxine. This led to the figure of 107.8mg a day, a value below the simple arithmetic mean daily dose (112.75mg), and therefore more flattering to venlafaxine.

It was clear from all of the available data that venlafaxine was prescribed in a range of doses, and GPs were well aware of this. Indeed dose titration to an effective dose was recommended in the product's summary of product characteristics.

Organon stated that it was difficult to identify what the Panel called a typical patient. Nevertheless it was clear that in today's climate, GPs and others would attempt to quantify spending on particular medicines. If that was to be done for medicines such as venlafaxine then some form of averaging must take place. In its most simple form, the total number of mg per day, prescribed to each and every patient could be collated. The daily dose for the average (or typical) patient could then be derived. Thus the concept of average daily cost per patient must be very familiar to GPs, and this was basically all that Organon's calculations showed.

Organon re-iterated that its calculations were approved by the owners of the data, DIN-LINK, as being an appropriate strategy for comparing the costs of two products available in a variety of formulations / presentations.

By comparison, although the Panel pointed out that Zispin was recommended in a range of doses from 15 to 45mg a day, the DIN-LINK data showed that in spite of this, the average daily dose was 30mg a day. Indeed 96% of all Zispin prescriptions were for 30mg a day.

In conclusion Organon believed that its price comparison was fully justified on the basis of prescribing patterns for both products. Furthermore its comparison was fair and was not misleading. Finally it did not agree that its comparison was 'too simplistic'.

For the avoidance of doubt, it repeated that when the prescribed dose for each patient of each formulation of venlafaxine was taken into account, the weighted average daily dose was 107.8mg. This indeed represented the 'typical patient' for the purposes of cost calculations. It failed to see how else such cost comparisons could be made.

APPEAL BOARD RULING

The Appeal Board considered that using the weighted average cost of a medicine was not unacceptable *per se*. It would be relevant when describing overall cost differences in the NHS patient population to, for instance, certain NHS audiences. In any comparison the basis must be made clear and must be fair as required by Clause 7.2 of the Code.

The Appeal Board was concerned that Organon was unable to provide information about the patient population upon which the DIN-LINK data was based or provide details about the methodology by which the data was collated. It also noted that venlafaxine had broader licensed indications than Zispin.

The Appeal Board noted that the advertisement was aimed at GPs, who, in the Appeal Board's view, would consider that the cost saving related to the price of the product for an individual patient. That was not so. This view was compounded by the phrase '… by prescribing Zispin rather than venlafaxine, you can save more than £8 per patient per month' which also appeared in the advertisement. The Appeal Board considered that the claim 'Did you know that Zispin is over 25% cheaper than venlafaxine?' was misleading. It was not sufficiently qualified given the method of calculation. A breach of Clause 7.2 was ruled. The appeal on this point was unsuccessful.

2 Claim 'When SSRI treatment fails, another class of antidepressant, like Zispin, is now recommended'

COMPLAINT

Wyeth stated that the claim suggested that guidelines recommended Zispin, or another antidepressant of the same class. Zispin was to all intents and purposes the only alpha-2 presynaptic antagonist available, which would imply that the guidelines recommended only Zispin when SSRI treatment failed. The guidelines said nothing of the sort. Most guidelines, such as the Maudsley 2001 prescribing guidelines, recommended switching (to any other) class after initial treatment. The specific guidelines from Manchester referenced in the advertisement were referring to venlafaxine and mirtazapine and stated that both might be valuable in depression which had not responded to other antidepressants. The claim was therefore both exaggerated and unbalanced contravening Clauses 7.8 and 7.2.

RESPONSE

Organon stated that the claim was derived from a prescribing guideline and was referenced. The referred page from the guideline provided by Wyeth was not disputed. It advised:

'The newer combined action antidepressant drugs (venlafaxine and mirtazapine – which operate on both the serotonin and noradrenaline systems) should not be used as first line anti-depressants, but may be valuable in depression which has not responded to other antidepressants. These should be included as an option in a primary care formulary as they may reduce the need for referral'.

Organon submitted that the advertisement simply paraphrased the advice from the above-mentioned guideline whilst acknowledging that the class of antidepressants known as SSRIs was a first line treatment choice: Organon believed that the claim was a balanced recapitulation of the original text.

Clearly Zispin was 'another' class of antidepressant from SSRIs. It had a dual mode of action rather than the single mode typified by SSRIs. Organon did not claim that Zispin was alone in having a dual mode of action. Rather this was a characteristic shared by other classes of antidepressant.

Wyeth proposed that the claim suggested that the guideline recommended Zispin, or another antidepressant of exactly the same class. It argued that since Zispin was the only antidepressant that existed in its class, the claim would imply a recommendation to use only Zispin when SSRI treatment failed, a claim that would not be consistent with the cited prescribing guidance.

The complaint appeared to hinge on the interpretation of the words 'like Zispin'. A thesaurus provided alternatives for the word 'like', including similar to, akin to, or in the vein of. All of these alternative wordings exactly conveyed Organon's intended meaning. The claim and the cited prescribing guidelines, advised that combined action antidepressants might be valuable when single action antidepressants (like, similar to, akin to, or in the vein of SSRIs) were not effective.

The intended meaning of the claim was further emphasised by the use of commas (...antidepressant, like Zispin, is.....). Organon did not state 'Zispin is now recommended', 'only Zispin is now recommended' or 'the only other class of anti-depressant, Zispin, is now recommended', wordings that would indeed imply a unique claim. The rather unusual interpretation of the statement that Wyeth sought to introduce did not represent common English usage. Therefore Organon did not believe that the claim was either exaggerated or unbalanced, or that it breached Clauses 7.2 or 7.8 of the Code.

PANEL RULING

The Panel noted that Zispin was a presynaptic alpha 2 antagonist increasing central noradrenergic and serotonergic neurotransmission. Efexor was a serotonin and noradrenaline reuptake inhibitor (SNRI).

The Panel noted the submission from Wyeth that Zispin was the only alpha 2 presynaptic antagonist available.

The Panel noted that the guidelines referenced in the advertisement were as quoted by Organon in its response. The guidelines referred to 'newer combined action antidepressant drugs (venlafaxine and [Zispin].....' whereas the claim in the advertisement referred to 'another class of antidepressant like Zispin'. The Panel noted that venlafaxine and mirtazapine were both combined action antidepressants but that each belonged to a different class of medicine. The Panel considered that the claim was not a fair reflection of the advice given in the guidelines, it implied that Zispin was the only product recommended when SSRIs were not effective. The Panel also considered that the claim was exaggerated. Breaches of Clauses 7.2 and 7.8 were ruled.

APPEAL BY ORGANON LABORTORIES

Organon referred to the arguments in its original response to the complaint. The claim used the wording 'another class of antidepressant, like Zispin…'. Organon did not believe that this wording could be reasonably construed to mean 'the only other class Zispin ...' as implied by the Panel ruling.

Organon believed the interpretation of its claim construed by Wyeth and supported by the Panel was quite frankly ludicrous. Whilst accepting that wording could often be open to alternative interpretation, it seemed perverse that every phrase should be scrutinised for every possible alternative meaning. It believed that common sense should prevail. All the more so since as an industry, it was dedicated to providing information to patients in language that was easy to understand. Organon very strongly contended that extreme interpretations of simple language could do nothing but harm the reputation of the industry and the Authority.

APPEAL BOARD RULING

The Appeal Board considered that the use of the word 'recommended' in the advertisement was less equivocal than that used in the actual guidelines which stated that the newer combined action antidepressant medicines (venlafaxine and mirtazapine) 'should not be used as first line antidepressants, but may be valuable in depression that has not responded to other antidepressants. These should be included as an option…'. The Appeal Board considered that the claim at issue was not a fair reflection of the guidelines and also implied that only Zispin was recommended which was not so. Breaches of Clauses 7.2 and 7.8 were ruled. The appeal on this point was unsuccessful.

Complaint received **28 February 2001**

Case completed **14 June 2001**

CASE AUTH/1149/2/01

PARAGRAPH 16/DIRECTOR v GLAXOSMITHKLINE

Engerix B poster

An Engerix B (hepatitis B vaccine) poster issued by SmithKline Beecham was the subject of Case AUTH/1108/11/00. During its consideration of that case, the Panel noted that in a corner of the poster was the statement 'Best choice for late presenting travellers'. The claim 'Best choice …' was a superlative. It was also noted that the only date on the poster was 28 June 1999 at the end of the prescribing information. Three references published in 2000 had, however, been cited in the poster. The Panel asked that these matters be taken up in accordance with Paragraph 16 of the Constitution and Procedure.

The Panel noted that the Code stipulated that superlatives must not be used except for those limited circumstances where they related to a clear fact about a medicine. The supplementary information stated that a claim that a product was 'the best' treatment for a particular condition could not be substantiated as there were too many variables to enable such a sweeping claim to be proven. The use of a superlative which could be substantiated was a simple statement of fact which could be very clearly demonstrated. The Panel noted GlaxoSmithKline's submission that, because Engerix B was the only vaccine that could be used for travellers presenting late, it was the best treatment. The Panel accepted that the submission had some merit. In the Panel's view, however, the claim implied that for late presenting travellers, ie those presenting within one month of travel, there was a choice of which hepatitis B vaccine to use and that Engerix B was the best one to use. The other products, however, were not licensed for use in such circumstances and so the Panel considered that such a comparison was not justified. On balance, the use of the superlative 'best' was not acceptable. A breach of the Code was ruled.

Upon appeal, the Code of Practice Appeal Board noted that the section of the poster in question was headed '… when your patients need it!' (this was the continuation of a claim appearing elsewhere in the poster that Engerix B 'Delivers unbeaten long term protection against hepatitis B …'). Beneath the claim '… when your patients need it!', reference was made to the choice of 3 schedules, these being: 0, 1, 6 months; 0, 1, 2 months (+12 month booster) and 0, 7, 21 days (+ 12 month booster). The final schedule was highlighted and next to this was the claim in question 'Best choice for late presenting travellers'. Noting that superlatives could only be used where they related to a simple statement of fact which could be very clearly demonstrated, the Appeal Board considered that the context was important. The claim 'Best choice for late presenting travellers' was referring to the choice of dosage regimen not Engerix B *per se*. Out of the three dosing schedules, the third schedule, 0, 7, 21 days plus 12 month booster, was the best choice for late presenting travellers. In the circumstances the Appeal Board considered that the use of the superlative was not unacceptable and no breach of the Code was ruled.

In relation to the date of preparation, GlaxoSmithKline submitted that the poster bore a reference number from which this could be determined, but the Panel considered that the purpose of the requirement was to enable the reader of the promotional material to determine the date on which it was drawn up or last revised. The number was insufficient in this regard. The date had not been included and a breach of the Code was ruled.

A promotional poster (ref EBLP/00/36) for Engerix B (hepatitis B vaccine) issued by SmithKline Beecham Pharmaceuticals had been the subject of Case AUTH/1108/11/00.

COMPLAINT

During its consideration of Case AUTH/1108/11/00 the Panel noted that in the bottom right hand corner of the poster was the statement 'Best choice for late presenting travellers'. The claim 'Best choice …' was a superlative. The Panel queried whether the requirements of Clause 7.8 of the Code had been met. The Panel also noted that the only date on the poster was 28 June 1999, which appeared at the end of the prescribing information. Three references published in 2000 had, however, been cited in support of some of the claims. The Panel queried whether the poster met the requirements of Clause 4.7 of the Code. The Panel requested that these matters be taken up in accordance with Paragraph 16 of the Constitution and Procedure of the Authority.

RESPONSE

GlaxoSmithKline stated that the statement that Engerix B was the 'Best choice for late presenting travellers' was justified as Engerix B was the only hepatitis B vaccine with a licence for a very rapid schedule of immunisation at days 0, 7 and 21. Other hepatitis B vaccines had licences for schedules at months 0, 1 and 2 or months 0, 1 and 6. Thus a traveller who presented for immunisation within 4 weeks of travel could receive three doses (the full primary course) of Engerix B, but only one dose of other hepatitis B vaccines. The summary of product characteristics (SPC) for Engerix B was provided.

The number at the bottom right hand corner of the poster indicated the date of revision (in this case EBPL/00/36).

FURTHER LETTER TO GLAXOSMITHKLINE

The Authority noted that under Paragraph 16.3, if the company did not accept that there was a breach of the Code the procedures under Paragraph 6 had to be followed. This meant that the claim 'Best choice for late presenting travellers' and the date of preparation or revision would be considered by the Code of Practice Panel and a formal ruling would be made. The relevant clauses were 4.7 and 7.8.

GlaxoSmithKline was asked to confirm the date upon which the poster was drawn up or last revised and invited to provide any further information which it wished to submit to the Panel.

FURTHER RESPONSE

GlaxoSmithKline stated that it did not consider that the claim 'Best choice for late presenting travellers' constituted a breach of Clause 7.8, as the statement related to a clear fact about Engerix B.

Engerix B was the only hepatitis B vaccine with a licence for a primary immunisation schedule at days 0, 7 and 21, with a fourth dose at 12 months. The only other licensed hepatitis B vaccine in the UK was HB-Vax II (Aventis Pasteur) which was licensed for a schedule of primary immunisation at months 0, 1 and 6 or months 0, 1 and 2 with a fourth dose at 12 months.

For a traveller who presented to a health professional within four weeks of travelling, and for whom hepatitis B vaccine was indicated, it was, in GlaxoSmithKline's view, a clear fact that the best protection could be afforded by giving Engerix B, as three doses of Engerix B could be given before travel compared to only one dose of HB-Vax II. The seroprotection rate (anti-HBs titre 10mIU/ml or greater) one month after three doses of Engerix B given at days 0, 7 and 21 was 65% whereas one month after a single dose of HB-Vax II in the licensed 10 microgram formulation it was only 11%.

The other issue concerned the date the poster was drawn up or revised. The poster was drawn up on 18 July 2000. This was indicated at the bottom of the poster by the letters EBPL/00/36. This number was recorded on a central register held by the company, from which the date a poster was drawn up or revised could be determined. GlaxoSmithKline did not consider that this constituted a breach of Clause 4.7 of the Code.

PANEL RULING

The Panel noted that Clause 7.8 of the Code stated that superlatives must not be used except for those limited circumstances where they related to a clear fact about a medicine. The supplementary information to Clause 7.8 of the Code stated that a claim that a product was 'the best' treatment for a particular condition could not be substantiated as there were too many variables to enable such a sweeping claim to be proven. The use of a superlative which could be substantiated was a simple statement of fact which could be very clearly demonstrated.

The Panel noted the submission that, because Engerix B was the only vaccine that could be used for travellers presenting late, it was the best treatment. The Panel accepted that the submission had some merit. In the Panel's view, however, the claim implied that for late presenting travellers ie those presenting within one month of travel, there was a choice of which hepatitis B vaccine to use and that Engerix B was the best one to use. The other products, however, were not licensed for use in such circumstances and so the Panel considered that such a comparison was not justified. Given the general prohibition on the use of superlatives and the guidance in the supplementary information, on balance the use of the superlative 'best' was not acceptable. A breach of Clause 7.8 of the Code was ruled.

The Panel considered that the purpose of Clause 4.7 was to enable the reader of promotional material to determine the date on which it was drawn up or last revised. The letters EBPL/00/36 were insufficient in this regard. The date had not been included on the poster. A breach of Clause 4.7 of the Code was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline wished to defend the claim 'Best choice for late presenting travellers' and appealed the ruling of a breach of Clause 7.8 on the grounds that the claim was a factual statement.

The poster clearly showed a choice of three schedules for Engerix B. All three schedules shown were licensed for the use in travellers and could all potentially be used in late presenting travellers. Until the exceptional schedule for Engerix B (0, 7, 21 days and 12 month booster) was introduced last year, the other two primary immunisation schedules for Engerix B would have been and were still used in late presenting travellers.

The Panel stated that other products were not licensed in such circumstances and therefore the claim was not justified. However, the poster only compared the dosing schedules of Engerix B and did not include comparisons with other company's products.

In addition, the exceptional schedule provided the highest seroprotection rates at one month. The company provided details of the protection rates at various time points following the three recommended schedules.

APPEAL BOARD RULING

The Appeal Board noted that the section of the poster in question was headed '… when your patients need it!' (this was the continuation of a claim appearing elsewhere in the poster that Engerix B 'Delivers unbeaten long term protection against hepatitis B …'). Beneath the claim '… when your patients need it!' reference was made to the choice of 3 schedules, these being: 0, 1, 6 months; 0, 1, 2 months (+ 12 month booster) and 0, 7, 21 days (+ 12 month booster). The final schedule was highlighted and next to this was the claim in question 'Best choice for late presenting travellers'.

The Appeal Board noted the requirements of Clause 7.8 of the Code and its supplementary information. Noting that superlatives could only be used where they related to a simple statement of fact which could be very clearly demonstrated, the Appeal Board considered that the context was important. The claim 'Best choice for late presenting travellers' was referring to the choice of dosage regimen not Engerix B *per se*. Out of the three dosing schedules, the third schedule, 0, 7, 21 days plus 12 month booster, was the best choice for late presenting travellers. In the circumstances the Appeal Board considered that the use of the superlative was not unacceptable. The Appeal Board ruled no breach of Clause 7.8 of the Code. The appeal was successful.

Proceedings commenced 9 February 2001

Case completed 18 April 2001

CONTINENCE ADVISER v NORGINE

Promotion of Nocutil

A continence adviser complained about statements made by a representative from Norgine at a regional meeting of the Association of Continence Advisors. Norgine marketed Nocutil (desmopressin) nasal spray. The product was licensed for the short term treatment of nocturnal enuresis in children over five years of age following exclusion of organic causes, and for the treatment of central diabetes insipidus. The complainant raised concerns regarding conflicting advice given by the representative about the therapeutic indications for Nocutil. The impression given was that Nocutil could be given to patients suffering from multiple sclerosis although it did not appear to be licensed for that particular use. The complainant was concerned that as nurse prescribing was on the increase, and many nurses relied on representatives for up-to-date information, any misinformation could cause problems.

The Panel noted that the Norgine representative had attended the meeting in question to promote another Norgine product, Movicol. During a break at the meeting a group of nurses were discussing whether or not Desmospray (a Ferring brand of desmopressin) could be used in multiple sclerosis. The Ferring representative had already left the meeting. The Panel noted Norgine's submission that the nurses were aware that it promoted Nocutil. According to its summary of product characteristics Desmospray was indicated for, *inter alia*, 'The treatment of nocturia associated with multiple sclerosis where other treatments have failed'. Conversely, Nocutil nasal spray was not licensed for use in multiple sclerosis. The Panel noted Norgine's submission that the nurses had asked its representative whether Desmospray could be used in multiple sclerosis. The Norgine representative had stated that he thought it could, although as it was not a Norgine product he could not speak about it. The complainant had alleged that the impression was given that Nocutil could be given to patients with multiple sclerosis. The parties' accounts differed. The complainant had declined to comment on the company's response. In such circumstances it was difficult to determine where the truth lay. The Panel was thus obliged to rule no breach of the Code.

A continence adviser complained about statements made by a representative from Norgine Limited at a regional meeting of the Association of Continence Advisors (ACA). Norgine marketed Nocutil (desmopressin 0.1mg/ml) nasal spray. The product was licensed for the short term treatment of nocturnal enuresis in children over 5 years of age following exclusion of organic causes, and for the treatment of central diabetes insipidus.

COMPLAINT

The complainant raised concerns regarding conflicting advice given by the representative about the therapeutic indications for Nocutil.

The complainant stated that the impression given was that Nocutil could be given to patients suffering from multiple sclerosis. However, on checking the literature, it did not appear to be licensed for that use.

The complainant was concerned that as nurse prescribing was on the increase, and many nurses relied on representatives for up-to-date information, any misinformation could cause problems.

When writing to the company the Authority drew attention to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

Norgine submitted that there had been a misinterpretation of events. The medical director had interviewed the representative in question.

The Norgine representative was one of several from various pharmaceutical companies who attended the regional ACA meeting. The representative attended in a capacity to promote Movicol, a treatment for chronic constipation.

During one of the breaks, however, a group of nurses were discussing whether or not Desmospray (a Ferring brand of desmopressin) could be used in multiple sclerosis (MS). The Ferring representative had already left the meeting by this time and had only left limited information. As the nurses were aware that Norgine promoted Nocutil (a nasal spray for nocturnal enuresis, also containing desmopressin), they asked the company's representative whether Desmospray could be used in MS. The representative replied that he thought it could, although as it was not a Norgine product he could not speak about it.

Norgine stated that its representative did not possess, show or distribute any material relating to Nocutil at the above meeting; he was only promoting Movicol. Norgine referred to the Nocutil summary of product characteristics (SPC) and the representative briefing material for Nocutil, which made it clear that the product was only licensed for nocturnal enuresis and diabetes insipidus.

The representative concerned had many years' experience as a pharmaceutical representative. He was fully aware of the Code. On being questioned about his recollection of this incident he was very clear that at no time in the discussion did he claim that Nocutil could be used in MS.

Norgine was satisfied that this representative did not promote Nocutil outside the indications covered by its marketing authorization. He provided accurate information about Norgine's product, and, in doing so, complied with all relevant requirements of the Code and maintained a high standard of ethical conduct in the discharge of his duties.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant did not wish for the case to go further. The point had been raised regarding the importance of representatives giving accurate information and the complainant did not feel that there would be any advantage in pursuing the matter further.

The complainant did not want to be identified to the company as it would make future working relationships very difficult.

PANEL RULING

The Panel noted that the complainant declined to comment further and sought to withdraw the complaint. The Panel noted that in accordance with Paragraph 14.1 of the Constitution and Procedure it was not possible to withdraw the complaint as the respondent's response had been received; the Panel thus made its ruling on the information before it.

The Panel noted that the Norgine representative had attended the meeting in question to promote Movicol. During a break at the meeting a group of nurses were discussing whether or not Desmospray, produced by Ferring, could be used in multiple sclerosis. The Ferring representative had already left the meeting.

The Panel noted the submission that the nurses were aware that Norgine promoted Nocutil.

The Panel noted that according to its SPC, Desmospray was indicated for, *inter alia*, 'The treatment of nocturia associated with multiple sclerosis where other treatments have failed'. Conversely, the Panel noted that Nocutil nasal spray was not licensed for use in MS.

The Panel noted Norgine's submission that the nurses had asked the representative whether Desmospray could be used in multiple sclerosis. The Norgine representative had stated that he thought it could, although as it was not a Norgine product he could not speak about it. The Panel noted the complainant had alleged that the impression was given that Nocutil could be given to patients suffering from multiple sclerosis. The Panel noted that the parties' accounts differed. The complainant had declined to comment on the company's response. In such circumstances it was difficult to determine where the truth lay. The Panel was thus obliged to rule no breach of Clauses 3.2, 7.2 and 15.2 of the Code.

Complaint received **5 March 2001**

Case completed **10 May 2001**

CASE AUTH/1152/3/01

LUNDBECK v GLAXOSMITHKLINE

Promotion of Seroxat

Lundbeck complained about the promotion of Seroxat (paroxetine) by SmithKline Beecham, the items at issue being a leavepiece entitled 'Seroxat or citalopram, what's the difference? Your questions answered', and letters sent by representatives. Lundbeck supplied Cipramil (citalopram).

A page in the leavepiece headed 'How do their dosages in depression compare?' featured three stab points for Seroxat which detailed the licensed dose of the product, 20mg up to 50mg/day, the percentage of UK prescriptions written for the lowest licensed dose, 20mg/day, and a statement that this dose was accepted globally as the most appropriate for mild/moderate depression. Three comparable stab points followed for citalopram; the third one read 'Data Sheets in the USA and France raise the possibility that most depressed patients should receive 40mg/day'. Lundbeck complained about this stating that information from other regulatory bodies in this context was not relevant for UK promotional material. The summary of product characteristics (SPC) for Cipramil stated that, in the management of depression, the initial dose was 20mg daily with the possibility of upwards titration to 60mg/day according to patient response; there was no mention of an optimum dose. This section of the leavepiece was likely to raise doubts in the prescriber's mind about the efficacy of the 20mg dose of Cipramil. This was misleading and disparaging.

With regard to citalopram, the Panel noted that in the USA the product labelling stated that it should be administered at an initial dose of 20mg once daily, generally with an increase to a dose of 40mg/day. The French and Spanish equivalents of the SPC both referred to 20mg as the minimum effective dose and 40mg daily as 'the optimum dose'. The Panel considered that the statement 'Data Sheets in the USA and France raise the possibility that most depressed patients should receive 40mg/day' was true. This statement had been balanced by dosage information from the UK SPC and the statement '78% UK prescriptions written for 20mg/day'. The Panel did not consider that the statement was misleading or that it disparaged Cipramil. No breach of the Code was ruled.

The lower portion of the same page featured a highlighted box of text which read:

'However:

- **Opinion is divided over whether these two SSRIs have comparable efficacy at this 20mg dose.**
- **Although 10mg citalopram is licensed as the initiation dose in the treatment of panic disorder,**

this dose is not licensed for the treatment of depression.

- The minimum effective dose of both Seroxat and citalopram in depression has been found to be 20mg/day'.

Lundbeck alleged that the first and third stab points appeared to contradict each other and that this was ambiguous. The implication of the second stab point was that paroxetine was licensed for depression at a dosage of 10mg which would contradict the SPC. This was misleading. By highlighting the 'However: .....' section, Lundbeck considered that the page supported the implication that citalopram was less efficacious than paroxetine in the treatment of depression without presenting a controlled clinical comparison. The Panel did not consider that the first and third stab points contradicted each other; they meant that, while some patients might respond to 20mg of either Seroxat or citalopram, a greater proportion would be controlled on this dose of Seroxat. The Panel did not consider that the stab points were ambiguous and no breach of the Code was ruled. With regard to the second stab point, the Panel considered that given the layout of the page in question the statement would not be read in isolation. Two other stab points on the same page clearly stated that in depression the lowest licensed dose/minimum effective dose of Seroxat was 20mg/day. Given the context in which the statement appeared, the Panel did not consider that doctors would be misled into thinking that 10mg of Seroxat was licensed for use in depression. No breach of the Code was ruled. The Panel did not consider that, on the page in question, use of a highlighted box of text meant that the presentation of the data was unbalanced or unfair.

The claim 'No clinically significant effects on ECG reported during clinical trials' appeared on a page headed 'How do they compare in terms of safety in overdose?'. Lundbeck stated that this claim was referenced to the Seroxat SPC and presumably referred to the statement: 'Cardiac conditions: Seroxat does not produce clinically significant changes in ..... ECG'. There was no mention of the wording 'reported in clinical trials'. Lundbeck alleged that the claim was factually inaccurate. Furthermore Lundbeck stated that instances of ECG changes of clinical significance associated with paroxetine use had been reported and the claim was therefore an inaccurate reflection of current data. The Panel noted that the relevant SPC statement referred to the use of Seroxat in patients with cardiac conditions; it did not refer to clinical trials. The SPC statement referred to the safety of Seroxat when used clinically in a particular patient group, whereas the claim at issue referred to the effects of Seroxat generally when taken in overdose. The Panel considered that, given the context in which it appeared, the claim was misleading and a breach of the Code was ruled.

Lundbeck alleged that the claim'Patients who have ingested up to 2000mg of Seroxat experienced no ECG changes' inaccurately reflected the paper to which it was referenced (Barbey and Roose). The Panel noted from that paper that with SSRIs in general there was a potential for ECG changes to occur following large overdoses. The Panel considered that from the claim in question readers would assume that ECG changes had not been reported at all following paroxetine overdose. This was not so. The Panel considered that the claim was misleading and did not accurately reflect the whole of the data presented by Barbey and Roose. A breach of the Code was ruled.

The statement 'Published reports have shown citalopram overdose to cause ECG changes, including QTc prolongation, QRS complex widening and severe bradycardia' was one of three stab points in a highlighted box of text in the lower portion of the page and was referenced to Personne *et al* (1997) and Grundemar *et al* (1997). QTc prolongation could, in association with severe bradycardia, lead to the potentially fatal condition torsades de pointes. In neither paper however was there a mention of severe bradycardia in association with citalopram overdose. The use of 'severe bradycardia' in this statement was therefore not only factually inaccurate but also likely to imply, wrongly, a connection between citalopram overdose and torsades de pointes. Furthermore, in a subsequent publication Personne *et al* stated 'Our conclusions about the severity of citalopram intoxication are that most cases have an uneventful course. Serious symptoms such as generalised convulsions can develop when the dose exceeds 600mg, but clinically significant arrhythmias are very rare'. When one also reviewed the paper by Barbey and Roose, the lack of balance in this whole page could be seen. Barbey and Roose concluded that 'In general, overdoses with SSRIs alone very rarely result in fatality, and most patients recover without sequelae' and.....'the very few instances of fatalities suggest that SSRIs generally share the favourable safety in overdose profile observed with fluoxetine and citalopram'. Lundbeck alleged that the statement was inaccurate and disparaged citalopram.

The Panel noted that although published cases of citalopram overdose had included reports of prolonged QT intervals (Grundemar *et al*), QRS complex widening (Personne *et al*) and severe bradycardia (Rothenhäusler *et al*) such irregularities had not occurred simultaneously in one patient. Personne *et al* noted that tachycardia, widened QRS complexes, moderate CNS depression, muscular hyperexcitability and generalised convulsions dominated the symptom complex and that while widened QRS complexes occurred more often than expected, at doses higher than 600mg, no malignant arrhythmias appeared in cases of pure citalopram overdose. The Panel noted that the risk of drug-induced torsades de pointes increased when QT interval prolongation, hypokalaemia and sinus bradycardia simultaneously appeared (Rothenhäusler *et al*). The Panel considered that the claim, by referring to QTc prolongation and severe bradycardia, raised the possibility of torsades de pointes although it did not state that this had never been reported. The Panel considered that the claim was misleading in this respect and disparaged citalopram and breaches of the Code were ruled.

The statement 'Citalopram's SmPC mentions the theoretical possibility of QTc prolongation in the presence of high levels of the didemethyl metabolite in susceptible individuals' was one of three stab points in a highlighted box of text in the lower portion of the page. Lundbeck noted that the Seroxat SPC stated that caution was advised when treating patients with cardiac conditions. SmithKline Beecham had only stated the caution in the Cipramil SPC and ignored cautions in the Seroxat SPC and had failed to take into consideration current published data as to the cardiovascular safety in routine use of Cipramil. SmithKline Beecham had presented an unbalanced view of the cardiac safety of citalopram, which was designed to disparage and reduce confidence in it. Once again, the formatting of this section involving the highlighting of the 'However:' section had been done to present an unbalanced view of the latter section by drawing readers to it rather than the section above.

The Panel noted that the Cipramil SPC stated that while increased levels of didemethylcitalopram could theoretically prolong the QTc interval in susceptible individuals, ECG monitoring of 2500 patients including 277 with pre-existing cardiac conditions had not detected any clinically significant changes. The Panel noted that the statement in the leavepiece reflected the first half of the SPC statement and so the theoretical cardiovascular effects of citalopram had not been put into a clinical context. The Panel considered that the statement was misleading and disparaged Cipramil as alleged and breaches of the Code were ruled. The Panel noted that this point was similar to one ruled in breach in a previous case, Case AUTH/966/1/00. An allegation had been made in the current case that GlaxoSmithKline had failed to comply with the undertaking given in Case AUTH/966/1/00. This is dealt with below. The Panel considered that overall the impression given was that in overdose ECG changes did not occur with Seroxat but that they were a problem with citalopram. The Panel noted that Barbey and Roose stated that 'There is no apparent difference among SSRIs with respect to overdose safety'. The Panel considered that the page in question was misleading with regard to the comparative safety in overdose of Seroxat and citalopram and, notwithstanding the ruling made above, in this instance the use of a highlighted box of text to draw attention to the statements made about citalopram was unfair. A breach of the Code was ruled.

The claim "Seroxat' 20mg is only 2p more, per day, than citalopram 20mg' appeared on a page headed 'Is there any difference in the cost of treatment?'. Lundbeck stated that the price quoted compared a 20mg tablet of paroxetine and a 20mg tablet of Cipramil (citalopram). Both paroxetine and Cipramil were licensed for use at doses from 10mg - 60mg (for various indications). The cost of treatment was dependent on a number of factors and not just the cost of a single tablet. This claim was therefore inaccurate as it only took into account tablet price differences. The Panel considered that the claim only referred to the difference in the price of the two medicines, there was no implication that the claim related to the cost effectiveness of Seroxat and paroxetine. The Panel did not consider that prescribers would be misled in this regard and ruled no breach of the Code.

Lundbeck alleged that the use of the superlative 'the logical' in the claim "Seroxat' is the logical choice for first time new patients because:' implied a special merit that was not warranted as could be observed from usage data from all the SSRIs. The Panel considered that the claim 'the logical choice' implied that Seroxat was the only choice. The Panel considered that this was an exaggerated all embracing claim and a breach of the Code was ruled. This had already been accepted by GlaxoSmithKline.

Lundbeck also complained about two representatives' letters. The content of the letters was similar. Paragraph 2: 'Firstly, Seroxat is indicated to lift mood and treat the underlying anxiety symptoms of depression, whereas citalopram is not'. Lundbeck alleged that this statement suggested an unlicensed indication as paroxetine had no licence 'to lift mood'. Paragraph 3: 'Secondly, 'Seroxat' has a well established safety profile having been used to treat more than 70 million patients worldwide. Evidence suggests that citalopram could cause cardiovascular side effects in overdose'. Lundbeck stated that these consecutive statements presented an unbalanced view as they compared the safety profile of paroxetine in routine use with data on citalopram in overdose. An up-to-date review in overdose should also include the reviews by Barbey and Roose and the updated publication from Personne, amongst others. The overall conclusion of these reviews was that all SSRIs shared a favourable profile in overdose, and most cases of cardiovascular adverse effects in citalopram overdose recovered fully and were of no clinical significance. The object of the letter, apart from its obvious imbalance, was to further disparage Cipramil.

The Panel noted that Seroxat was licensed to treat the symptoms of depressive illness of all types including depression accompanied by anxiety. Cipramil was licensed for the treatment of depressive illness. The Panel considered that as a natural consequence of treating depression a patient's mood would lift. The Panel therefore considered that the claim '.....Seroxat is indicated to lift mood and treat the underlying anxiety symptoms of depression....' promoted the product within its licensed indication and no breach of the Code was ruled. With regard to the claim 'Seroxat has a well established safety profile having been used to treat more than 70 million patients worldwide. Evidence suggests that citalopram could cause cardiovascular side effects in overdose', the Panel considered that comments made above applied here. In the Panel's view the claim implied that there was a significant difference, in favour of Seroxat, with regard to the safety in overdose of it and citalopram but the review by Barbey and Roose had not established this. The Panel considered that the claim was misleading and disparaged citalopram as alleged and breaches of the Code were ruled.

Lundbeck stated that there appeared to be a consistent thread of inaccuracy, attempts to mislead and disparagement throughout the promotional materials and activities of the sales force; this suggested inadequate procedures were in place for copy approval and training of the salesforce. Lundbeck had raised the issues of use of non-UK regulatory references and presentation of unbalanced cardiac safety data concerning Cipramil in Case AUTH/966/1/00. The use of such references and the unbalanced presentation of cardiac safety data were found to be misleading and disparaging and in breach of the Code, both in an original ruling and on appeal by SmithKline Beecham. Lundbeck alleged that the disregard of the undertaking given in the previous case was a breach of Clause 21 of the Code. Lundbeck contented that the continued use of such material to disparage Cipramil, and the flagrant disregard of a previous ruling and undertaking, constituted behaviour likely to bring discredit upon the pharmaceutical industry in breach of Clause 2.

The Panel noted that Case AUTH/966/1/00 concerned a 'Dear Doctor' letter issued by SmithKline Beecham which compared Seroxat with citalopram. Two paragraphs of the letter discussed the adverse events associated with the two medicines although it dealt, in the main, with the adverse cardiovascular effects of citalopram referring to the theoretical risk of QTc prolongation in susceptible patients and ECG abnormalities in overdose. The Panel noted that the theoretical cardiovascular effects of citalopram had not been put into clinical context. Breaches of the Code were ruled which were upheld upon appeal by SmithKline Beecham. The case had been completed in June 2000. Turning to the case now before it, the Panel noted that one matter above, and the rulings made, were almost identical to those made in the previous case. Again the theoretical risk of QTc prolongation had not been put into a clinical context. The leavepiece included a date of preparation of November 2000. It appeared to the Panel that when the leavepiece was prepared no attempt had been made to comply with the undertaking which had been given in June 2000 with regard to statements about the theoretical cardiovascular effects of citalopram. In Case AUTH/966/1/00, both the Panel and the Appeal Board had noted that such statements had not been put into a clinical context. A breach of Clause 21 was now ruled. The Panel also considered that this brought discredit upon the pharmaceutical industry and ruled a breach of Clause 2.

Lundbeck Ltd complained about the promotion of Seroxat (paroxetine) by SmithKline Beecham Pharmaceuticals. The items at issue were a leavepiece (ref ST:LP0064) and letters sent by representatives (ref LMS:POST-CALL/SXT/VERSATILITY). Lundbeck supplied Cipramil (citalopram).

A Leavepiece: entitled 'Seroxat or citalopram, what's the difference? Your questions answered'

A1 Page headed 'How do their dosages in depression compare?'

A1a The top portion of this page featured three stab points for Seroxat which detailed the dose of the product as stated on the summary of product characteristics (SPC), 20mg up to 50mg/day, the percentage of UK prescriptions written for the lowest licensed dose, 20mg/day and a statement that the lowest licensed dose was accepted globally as the most appropriate dose for mild/moderate depression. Three comparable stab points followed for citalopram; the third one read 'Data Sheets in the USA and France raise the possibility that most depressed patients should receive 40mg/day'.

COMPLAINT

Lundbeck complained about the third citalopram stab point and noted that the references cited were the Physicians Desk Reference 2000 (a text containing US approved product labelling) and the citalopram SPC from France.

Lundbeck stated that the UK SPC for Cipramil represented the approved prescribing details about citalopram in the UK. Information from other regulatory bodies in this context was not relevant for UK promotional material. The SPC for Cipramil stated that, in the management of depression, the initial dose was 20mg daily with the possibility of upwards titration to 60mg/day according to patient response; there was no mention of an optimum dose.

This section of the leavepiece was likely to raise doubts in the prescriber's mind about the efficacy of the 20mg dose of Cipramil. This was not only misleading but also disparaged Cipramil and was in breach of Clauses 7.2 and 8.1 of the Code.

RESPONSE

GlaxoSmithKline, which SmithKline Beecham had now become, stated that the leavepiece factually recorded SPC dosage ranges in depression for both Seroxat and citalopram as well as the market data that showed that 78% of citalopram prescriptions and 74% of paroxetine prescriptions were written for 20mg/day. It went on to point out that there was a relevant difference between the two antidepressants in that 20mg/day of citalopram, unlike 20mg/day of paroxetine, was not universally accepted as the most appropriate therapeutic dose for the majority of depressed patients.

To substantiate this contention, GlaxoSmithKline noted the following:

Montgomery *et al* (1992), in a placebo-controlled trial of 20mg and 40mg of citalopram, concluded 'The dose response relationship seen in this study indicates that the 40mg dose is associated with a better response than the lower 20mg dose and would therefore be the appropriate dose for major depression'. The same paper, commenting on the initial studies of paroxetine in depression conducted with 40-50mg, stated '...20mg is the more appropriate dose'.

In a placebo-controlled fixed dose study of 10mg, 20mg, 40mg and 60mg daily doses of citalopram in 650 depressed patients, Feighner and Overø (1999) found that while the 40mg and 60mg arms showed statistically significant differences from placebo on all

efficacy measures tested, the 10mg and 20mg dose arms only showed significant differences on some of the measures.

A meta-analysis of studies of the acute therapy of depression by Bech (1993) found, with regard to doses, that 'For fluvoxamine 100mg/day seems most appropriate, and for citalopram, 40mg/day'.

An eight week flexible dose study by Mendels *et al* (1997) reported that citalopram at doses of 20 to 80mg/day was effective in the treatment of depression, with an average dose at endpoint of 52mg/day.

In a review article, Tan and Levin (1999) quoted the above Montgomery *et al*, Feighner and Overø and Mendels *et al* references and included the dosing advice 'Dosing should start at 20mg/day, generally with an increase to 40mg once/day after 1 week....Most patients should respond to 40mg/day, but the dosage should be titrated to individual response'.

This advice was consistent with the recommended dosing regime given in the official product labelling for citalopram in a number of countries, such as the USA, France and Spain.

Thus, several published articles and the prescribing information in a number of other countries supported the contention that 20mg of paroxetine and 20mg of citalopram were not necessarily therapeutically equivalent. However, this was not inconsistent with the citalopram SPC, nor did it contradict the fact that 20mg citalopram was an effective dose for a proportion of depressed patients.

GlaxoSmithKline therefore rejected the accusation that this section was misleading or disparaging to citalopram. Breaches of Clauses 7.2 and 8.1 of the Code were therefore denied.

PANEL RULING

The Panel noted that the information given in the three stab points for Seroxat was comparable with that given in the stab points for citalopram. The first stab point for each product detailed the licensed doses as given on the respective SPCs, the second stated the percentage of prescriptions written for the lowest licensed dose and the third commented on the global acceptability of the lowest licensed dose 20mg in relation to Seroxat and the reference to the 40mg dose in the American and French data sheets in relation to citalopram.

With regard to citalopram the Panel noted that in the USA the product labelling for Celexa (citalopram) stated that it should be administered at an initial dose of 20mg once daily, generally with an increase to a dose of 40mg/day. The French and Spanish equivalents of the SPC for Seropram (citalopram) both referred to 20mg as the minimum effective dose and 40mg daily as 'the optimum dose'.

The Panel considered that the statement 'Data Sheets in the USA and France raise the possibility that most depressed patients should receive 40mg/day' was true. This statement had been balanced by dosage information from the UK SPC and the statement '78% UK prescriptions written for 20mg/day'. The Panel did not consider that the statement was misleading as alleged or that it disparaged Cipramil. No breach of Clauses 7.2 and 8.1 was ruled.

A1b Highlighted box of text

The lower portion of the page featured a highlighted box of text which read:

'However:

- Opinion is divided over whether these two SSRIs have comparable efficacy at this 20mg dose.
- Although 10mg citalopram is licensed as the initiation dose in the treatment of panic disorder, this dose is **not** licensed for the treatment of depression.
- The minimum effective dose of both Seroxat and citalopram in depression has been found to be 20mg/day'.

COMPLAINT

Lundbeck complained that the first and third stab points appeared to contradict each other. The company alleged that this was ambiguous in breach of Clause 7.2.

Lundbeck stated that the implication of the second stab point was that paroxetine was licensed for depression at a dosage of 10mg which would contradict the SPC. This was misleading and was in breach of Clause 7.2.

Lundbeck stated that the format of the page with a highlighted 'However' section was intended to focus the reader on that section rather than the whole page. By highlighting the 'However: .....' section the page supported the implication that citalopram was less efficacious than paroxetine in the treatment of depression without presenting a controlled clinical comparison.

Lundbeck alleged that this method of data presentation was in breach of Clause 7.6.

RESPONSE

GlaxoSmithKline stated that there was no contradiction in the statements 'Opinion is divided over whether these two SSRIs have comparable efficacy at this 20mg dose' and 'The minimum effective dose of both Seroxat and citalopram in depression has been found to be 20mg/day'. The point was that while some patients might respond to 20mg of either product, a greater proportion might be adequately treated at this dose of Seroxat than at the same dose of citalopram. GlaxoSmithKline denied this was ambiguous to a medical audience and that it breached Clause 7.2.

GlaxoSmithKline stated the purpose of the statement 'Although 10mg citalopram is licensed as the initiation dose in the treatment of panic disorder, this dose is **not** licensed for the treatment of depression' was to remind prescribers that, as was clearly stated above on the same page, the minimally [sic] effective dose of citalopram for depression was 20mg/day.

GlaxoSmithKline had received reports from the marketplace that the ratio of sales of 10mg tablets to 20mg tablets of citalopram was increasing in the UK and that some GPs were using this dose to treat depressed patients.

As the 10mg/day dose had been shown to be sub-therapeutic in clinical trials in depression, this point was a legitimate one for a competitor to make. GlaxoSmithKline denied that it was trying to imply that Seroxat was licensed to treat depression at this dose, as it had also clearly indicated on the same page that the Seroxat SPC stated that dosage in this indication was 20-50mg/day. In addition, Seroxat was not even available in a 10mg dosage form.

GlaxoSmithKline stated that this stab point was not misleading and thus was not in breach of Clause 7.2 of the Code.

GlaxoSmithKline further denied Lundbeck's allegation that this highlighted section implied citalopram was less efficacious than paroxetine. GlaxoSmithKline's point was to do with the therapeutic equivalence of the 20mg doses, not that paroxetine was a more efficacious product overall. This point was not inconsistent with the two products' SPCs.

GlaxoSmithKline denied that this section of the leavepiece breached Clause 7.6 (which it anyway understood to refer to illustrations, graphs and tables).

PANEL RULING

The Panel did not consider that the first and third stab points contradicted each other. The Panel accepted GlaxoSmithKline's submission that together the stab points meant that while some patients might respond to 20mg of either Seroxat or citalopram, a greater proportion would be controlled on this dose of Seroxat than on this dose of citalopram. The Panel did not consider that the stab points were ambiguous. No breach of Clause 7.2 was ruled.

With regard to the second stab point the Panel considered that on a page headed 'How do [Seroxat and citalopram] dosages in depression compare?', the statement 'Although 10mg citalopram is licensed as the initiation dose in the treatment of panic disorder, this dose is **not** licensed for the treatment of depression' might imply that a 10mg dose of Seroxat was so licensed. The Panel considered, however, given the layout of the page in question, that the statement would not be read in isolation. Two other stab points on the same page clearly stated that in depression the lowest licensed dose/minimum effective dose of Seroxat was 20mg/day. Given the context in which the statement appeared the Panel did not consider that doctors would be misled into thinking that 10mg of Seroxat was licensed for use in depression. No breach of Clause 7.2 was ruled.

The Panel did not consider that, on the page in question, use of a highlighted box of text meant that the presentation of the data was unbalanced or unfair as alleged. No breach of Clause 7.6 was ruled.

A2 Page headed 'How do they compare in terms of safety in overdose?'

A2a Claim 'No clinically significant effects on ECG reported during clinical trials'

COMPLAINT

Lundbeck stated that this claim was referenced to the Seroxat SPC and presumably referred to a statement in section 4.4: 'Cardiac conditions: Seroxat does not produce clinically significant changes in ..... ECG'. There was no mention of the wording 'reported in clinical trials'. Lundbeck alleged that the claim was factually inaccurate in breach of Clause 7.2.

Lundbeck stated that furthermore, there were instances of ECG changes of clinical significance associated with paroxetine use that had been reported. Erfurth *et al* (1998) reported three cases of ECG changes in patients treated with paroxetine, in therapeutic doses, necessitating withdrawal of therapy. Barbey and Roose (1998) cited reports of ECG changes and cardiovascular events in patients overdosing with paroxetine. Lundbeck alleged that the claim was therefore an inaccurate reflection of current data and in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline stated that it was important to note that the introductory text of this page included the statement '.....all SSRIs are considered to have a wide margin of safety in overdose.....'. This obviously applied to citalopram as well as Seroxat.

GlaxoSmithKline had used the SPCs of both Seroxat citalopram to reference the identical claim for both products that 'No clinically significant effects on ECG reported during clinical trials'. It was true that the SPC wording did not contain the words 'in clinical trials' but GlaxoSmithKline denied that this had any material effect on the message being conveyed. Even if it did, this effect would not benefit Seroxat over citalopram in the minds of the reader. If 'in clinical trials' was left off the claim, it would not alter the message that neither product reported significant ECG changes in humans during their pre-marketed development phase (if they had, this could have been reflected in their SPCs).

GlaxoSmithKline denied that this minor referencing issue amounted to a breach of Clause 7.2, as the meaning was not altered by the inclusion of the 'in clinical trials'.

GlaxoSmithKline noted that although Lundbeck alleged that the claim was factually inaccurate, in breach of Clause 7.2, it produced no relevant evidence to demonstrate this. The references cited by Lundbeck in support of its allegation had no bearing on the claim. Inspection revealed the Erfurth paper to be a poor quality report of three alleged cases of ECG alteration during routine post-marketing clinical use and the Barbey and Roose paper actually contained the statement, referring to paroxetine clinical trials, 'No ECG abnormalities, coma or convulsions were reported following pure paroxetine overdose', which would seem to contradict Lundbeck's argument.

A breach of Clause 7.2 was denied.

PANEL RULING

The Panel noted that the claim 'No clinically significant effects on ECG reported during clinical trials' was referenced to the Seroxat SPC. The relevant statement from the SPC came from section 4.4 'Special warnings and precautions for use' and referred to the use of Seroxat in patients with cardiac conditions. The statement in the SPC did not refer to clinical trials.

The Panel noted that the statement in the SPC referred to the safety of Seroxat when used clinically in a particular patient group whereas the claim at issue referred to the effects of Seroxat generally when taken in overdose. The Panel considered that, given the context in which it appeared, the claim was misleading. A breach of Clause 7.2 was ruled.

A2b Claim 'Patients who have ingested up to 2000mg of Seroxat experienced no ECG changes'

COMPLAINT

Lundbeck noted that this claim was referenced to the paper by Barbey and Roose and had been quoted out of context with the rest of the same section that dealt with paroxetine in an overdose situation. In the paper, under the section headed 'Paroxetine', paragraphs entitled 'Published reports' and 'FDA reports' described the reporting of one ECG abnormality; tachycardia, cardiac arrest and cardiogenic shock associated with paroxetine overdose. Lundbeck alleged that the claim inaccurately reflected the paper referenced, in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline stated that inspection of the relevant section of the Barbey and Roose paper revealed only one possible case of actual ECG abnormality coming from the FDA's post-marketing spontaneous reporting database. Tachycardia, cardiac arrest and cardiogenic shock could not be considered primary ECG abnormalities in the context of SSRI overdose safety. Thus, one possible case, from a very large database of adverse events where causality was not proven, did not contradict the more reliable data coming from the closely regulated environment of clinical trials.

A breach of Clause 7.2 was denied.

PANEL RULING

The Panel noted that the claim was referenced to Barbey and Roose, a review of SSRI safety in overdose. Data for the review was taken from the published literature, case reports from the American Association of Poison Control Centres and from the United States Food and Drug Administration (FDA) adverse event database. With regard to paroxetine the authors stated that in clinical trials no ECG abnormalities, coma, or convulsions were reported following pure paroxetine overdose. All patients recovered fully, including those who ingested up to 2000mg of paroxetine. This was in turn referenced to the Physicians Desk Reference. Barbey and Roose noted, however, that one possible pure paroxetine overdose which caused ECG abnormalities, followed by full recovery, had been reported to the FDA.

The Panel noted that with SSRIs in general there was a potential for ECG changes to occur following large overdoses (Barbey and Roose). The Panel considered that from the claim in question readers would assume that ECG changes had not been reported at all following paroxetine overdose. This was not so. The Panel considered that the claim was misleading and did not accurately reflect the whole of the data presented by Barbey and Roose. A breach of Clause 7.2 was ruled.

A2c Statement 'Published reports have shown citalopram overdose to cause ECG changes, including QTc prolongation, QRS complex widening and severe bradycardia.'

This statement was one of three stab points in a highlighted box of text in the lower portion of the page.

COMPLAINT

Lundbeck noted that this statement had been referenced to Personne *et al* (1997) and Grundemar *et al* (1997). QTc prolongation could, in association with severe bradycardia, lead to the potentially fatal condition known as torsades de pointes. In neither paper however was there a mention of severe bradycardia in association with citalopram overdose. The use of the terminology 'severe bradycardia' in this statement was therefore not only factually inaccurate but also likely to imply, wrongly, a connection between citalopram overdose and torsades de pointes. Furthermore, Personne *et al*, in a letter published by The Lancet in 1997, supplied additional data to that contained in their already published paper (referenced, above). The numbers of cases reported in the respective publications were as follows – total cases of citalopram ingestion 108 vs 44; citalopram ingestion >600mg 34 vs 18; citalopram ingestion >1900mg 19 vs 5. The authors stated 'Our conclusions about the severity of citalopram intoxication are that most cases have an uneventful course. Serious symptoms such as generalised convulsions can develop when the dose exceeds 600mg, but clinically significant arrhythmias are very rare'.

When one also reviewed the paper by Barbey and Roose, the lack of balance in this whole page in the promotional item could be seen. Barbey and Roose concluded that 'In general, overdoses with SSRIs alone very rarely result in fatality, and most patients recover without sequelae' and '… the very few instances of fatalities suggest that SSRIs generally share the favourable safety in overdose profile observed with fluoxetine and citalopram'.

Lundbeck alleged that the statement was inaccurate and disparaged citalopram in breach of Clauses 7.2 and 8.1.

RESPONSE

GlaxoSmithKline stated that it accepted that a reference had been accidentally omitted from this stab

point. The missing reference was 'Suicide Attempt by Pure Citalopram Overdose Causing Long-lasting Severe Sinus Bradycardia, Hypotension and Syncopes: Successful Therapy with a Temporary Pacemaker'. Rothenhäusler *et al* (2000).

A further report of severe bradycardia in association with citalopram was contained in the publication by Favre *et al* (1999).

GlaxoSmithKline noted that it made no mention of torsades de pointes nor implied that citalopram caused this in overdose. Lundbeck chose to quote from the Personne paper 'Serious symptoms such as generalised convulsions can develop when the dose exceeds 600mg, but clinically significant arrhythmias are very rare'. Nothing in this leavepiece contradicted this contention and GlaxoSmithKline was pleased that Lundbeck recognised the importance of the Personne data.

Also, the extracts Lundbeck highlighted from the Barbey and Roose paper; 'In general, overdoses with SSRIs alone very rarely result in fatality, and most patients recover without sequelae' and 'the very few instances of fatalities suggest that SSRIs generally share the favourable safety in overdose profile observed with fluoxetine and citalopram' were not contradicted by the text of the leavepiece.

The stab point was not inaccurate, merely inadequately referenced, and GlaxoSmithKline denied that it was attempting to disparage citalopram. The leavepiece only presented, in a necessarily brief form, the major relevant published data on the known effects of overdose with these two products.

GlaxoSmithKline denied a breach of Clauses 7.2 and 8.1.

PANEL RULING

The Panel noted that although published cases of citalopram overdose had included reports of prolonged QT intervals (Grundemar *et al*), QRS complex widening (Personne *et al*) and severe bradycardia (Rothenhäusler *et al*) such irregularities had not occurred simultaneously in one patient. Personne *et al* noted that tachycardia, widened QRS complexes, moderate CNS depression, muscular hyperexcitability and generalised convulsions dominated the symptom complex and that while widened QRS complexes occurred more often than expected, at doses higher than 600mg, no malignant arrhythmias appeared in cases of pure citalopram overdose.

The Panel noted that the risk of drug-induced torsades de pointes increased when QT interval prolongation, hypokalaemia and sinus bradycardia simultaneously appeared (Rothenhäusler *et al*). The Panel considered that the claim, by referring to QTc prolongation and severe bradycardia, raised the possibility of torsades de pointes occurring, although it did not state that this had never been reported. The Panel considered that the claim was misleading in this respect and disparaged citalopram as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

A2d Statement 'Citalopram's SmPC mentions the theoretical possibility of QTc prolongation in the presence of high levels of the didemethyl metabolite in susceptible individuals'

This statement was one of three stab points in a highlighted box of text in the lower portion of the page.

COMPLAINT

Lundbeck noted that in section 4.4 of the Seroxat SPC 'Cardiac conditions' it was stated that 'Nevertheless, as with all psychoactive drugs, caution is advised when treating patients with cardiac conditions'.

Lundbeck stated that SmithKline Beecham had only stated the caution in the Cipramil SPC and ignored cautions in the Seroxat SPC and had failed to take into consideration current data as to the cardiovascular safety in routine use of Cipramil including:

Elsborg (1991): from a study in elderly patients 'No cardiovascular side effects of clinical importance have been demonstrated during treatment with citalopram'.

Labatte and Rubey (1999): 'didemethylcitalopram forms in minuscule concentrations in man and is not clinically relevant'.

Rasmussen *et al* (1999) which was a review of over 6000 ECGs prospectively and retrospectively from 1978-1996 assessing the cardiac safety of citalopram in clinical trials: 'There were no significant effects on PQ, QRS or QTc intervals, indicating that citalopram has no effect on cardiac conduction and repolarisation during short- or long-term treatment'.

Tan and Levin (1999): 'No serious cardiovascular adverse events in humans have been associated with [Cipramil]'.

SmithKline Beecham presented an unbalanced view of the cardiac safety of citalopram, which was designed to disparage and reduce confidence in the compound. This had obviously been done to show citalopram in a very negative way in respect to cardiac safety in routine and overdose situations as compared to paroxetine. This lack of balance, factual inaccuracy, selective use of data and disparaging tone was in breach of Clauses 7.2 and 8.1.

Once again, the formatting of this section involving the highlighting of the 'However:' section had been done to present an unbalanced view of the latter section by drawing readers to it rather than the section above. This was in breach of Clause 7.6 of the Code.

RESPONSE

GlaxoSmithKline stated that Lundbeck quoted a section of the Seroxat SPC, which read 'Seroxat does not produce clinically significant changes in blood pressure, heart rate and ECG. Nevertheless, as with all psychoactive drugs, caution is advised when treating patients with cardiac conditions'. Lundbeck went on to complain that GlaxoSmithKline had 'ignored' this wording from its own SPC and then failed to take into account 'current data as to the cardiovascular safety in routine use of Cipramil.....'.

Firstly, the leavepiece was not intended as comparison of the wording of the two products' SPCs so the charge of 'ignoring' wording in the Seroxat SPC was irrelevant (and as GlaxoSmithKline's 'cardiac' wording applied to all antidepressants, there would seem little point in including it on a brief leavepiece designed to highlight differences between products).

Secondly, GlaxoSmithKline failed to see how quoting the Cipramil SPC could be considered as failing to take into account current data on that product's cardiac safety. Was Lundbeck suggesting the Cipramil SPC was out-of-date? If so, it should take this up with the Medicines Control Agency. Nowhere in this leavepiece did GlaxoSmithKline state or imply that at routine therapeutic doses, citalopram presented a cardiac risk to patients.

Thirdly, situations where the didemethyl metabolite might be raised were exceptional (e.g. overdose) and were therefore not relevant to the 'routine use of Cipramil'.

GlaxoSmithKline denied that the leavepiece presented an unbalanced, inaccurate or disparaging view of the cardiac safety of citalopram and so also denied that it had breached Clauses 7.2, 7.6 and 8.1.

PANEL RULING

The Panel noted that the Cipramil SPC stated 'Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted'. The Panel noted that the statement in the leavepiece only reflected the first half of the SPC statement and so the theoretical cardiovascular effects of citalopram had not been put into a clinical context. The Panel considered that the statement was misleading and disparaged Cipramil as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

The Panel noted that this point was similar to one ruled in breach in a previous case, Case AUTH/966/1/00. An allegation had been made in the current case that GlaxoSmithKline had failed to comply with the undertaking given in Case AUTH/966/1/00. This matter is dealt with under point C below.

The Panel noted that at the top of the page in question was the statement 'Although all SSRIs are considered to have a wide margin of safety in overdose, the toxicity of any drug prescribed to depressed patients is a very important consideration'. Beneath this were three claims for Seroxat two of which detailed a lack of ECG changes in clinical trials and overdose respectively. These claims had been considered in points A2a and A2b above. Beneath the Seroxat claims were four statements regarding citalopram, three of which were in a highlighted box of text and detailed the medicine's adverse cardiovascular effects. Two of the claims were those considered in points A2c and A2d above. The Panel considered that overall the impression given was that in overdose ECG changes did not occur with Seroxat but that they were a problem with citalopram. The Panel noted that Barbey and Roose stated that 'There is no apparent difference among SSRIs with respect to overdose safety'.

The Panel considered that the page in question was misleading with regard to the comparative safety in overdose of Seroxat and citalopram. In this regard the Panel considered that notwithstanding the ruling made in point A1b above, in this instance the use of a highlighted box of text to draw attention to the statements made about citalopram was unfair. A breach of Clause 7.6 was ruled.

A3 Page headed 'Is there any difference in the cost of treatment?'

A3a Claim "Seroxat' 20mg is only 2p more, per day, than citalopram 20mg'

COMPLAINT

Lundbeck stated that the price quoted was for the comparison between a 20mg tablet of paroxetine and a 20mg tablet of Cipramil (citalopram). Both compounds, paroxetine and Cipramil, were licensed for use at doses from 10mg-60mg (for various indications).

The cost of treatment was dependent on a number of factors and not just the cost of a single tablet. In individual patients both dose and duration of therapy would vary along with other factors such as consultation rates, compliance due to adverse effects etc, and so the overall cost of treatment per day would also vary and not just be the price of a tablet. This claim was therefore inaccurate as it only took into account tablet price differences, and was therefore in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline stated that the leavepiece did not state that the cost of treating depression with Seroxat was 2p more per day that citalopram but simply pointed out the slight difference in cost of the 20mg tablets of each. GlaxoSmithKline believed that prescribers were not being misled by these claims and were not aware of independent evidence that treatment costs, excluding drug costs, were lower for one particular SSRI used in depression compared to any other.

GlaxoSmithKline denied a breach of Clause 7.2.

PANEL RULING

The Panel considered that the claim only referred to the difference in the price of the two medicines, there was no implication that the claim related to the cost effectiveness of Seroxat and paroxetine. The Panel did not consider that prescribers would be misled in this regard and ruled no breach of Clause 7.2.

A3b Claim "Seroxat' is the logical choice for first-time success with new patients, because:'

COMPLAINT

Lundbeck stated that use of the superlative 'the logical' implied a special merit that was not warranted as could be observed from usage data for all the SSRIs. This statement was in breach of Clause 7.8.

RESPONSE

GlaxoSmithKline stated that the use of the word 'the' instead of 'a' was an oversight. It accepted that this mistake put the item in breach of Clause 7.8.

PANEL RULING

The Panel considered that the claim 'the logical choice' implied that Seroxat was the only choice. The Panel considered that this was an exaggerated all embracing claim as alleged. A breach of Clause 7.8 was ruled as acknowledged by GlaxoSmithKline.

B Representatives' letters

COMPLAINT

Lundbeck also complained about two representatives' letters from different regions in the UK and at two different time points (29 June 2000 and 6 February 2001).

The content of the letters was similar.

Paragraph 2:

'Firstly, 'Seroxat' is indicated to lift mood *and* treat the underlying anxiety symptoms of depression, whereas citalopram is not'.

This claim was referenced to the SPCs for Seroxat and citalopram.

Lundbeck stated that although paroxetine had a licence to treat 'the symptoms of depressive illness' there was no specific indication 'to lift mood'. This statement suggested an unlicensed indication and was in breach of Clause 3.2.

Paragraph 3:

'Secondly, 'Seroxat' has a well established safety profile having been used to treat more than 70 million patients worldwide. Evidence suggests that citalopram could cause cardiovascular side effects in overdose'.

These statements were referenced to Data on File SB and papers by Östrom *et al* (1996), Grundemar *et al* (1997) and Personne *et al* (1997).

Lundbeck stated that these consecutive statements presented an unbalanced view in that they attempted to compare the safety profile of paroxetine in routine use with various data on citalopram in overdose. This was in breach of Clause 7.2.

An up-to-date review in overdose should also include the reviews by Barbey and Roose (as per seroxat promotional item ST:LP0064) and the updated letter by Personne (The Lancet), amongst others.

The overall conclusion of these reviews was that all SSRIs shared a favourable profile in overdose, and most cases of cardiovascular adverse effects in cases of citalopram overdose recovered fully and were of no clinical significance. The object of the letter, apart from its obvious imbalance, was to further disparage, Cipramil, and this item was therefore also in breach of Clause 8.1.

RESPONSE

GlaxoSmithKline stated that these brief letters were used by sales representatives as reminders of their detailing call to individual doctors. With regard to the claim 'Firstly, 'Seroxat' is indicated to lift mood and treat the underlying anxiety symptoms of depression, whereas citalopram is not', GlaxoSmithKline stated that if a product had received marketing authorization to treat depression it must necessarily lift the patient's mood. GlaxoSmithKline considered that Lundbeck was being disingenuous to claim that this statement represented an attempt to promote an unlicensed indication. The statement merely pointed out the fact that citalopram, unlike Seroxat, did not have marketing authorization for the indication 'depression accompanied by anxiety'. Thus, GlaxoSmithKline denied a breach of Clause 3.2.

GlaxoSmithKline refuted the allegation that the statement 'Secondly, 'Seroxat' has a well established safety profile, having been used to treat more than 70 million patients worldwide. Evidence suggests that citalopram could cause cardiovascular side effects in overdose' was unbalanced. As a small proportion of the 70 million treated patients had overdosed on Seroxat, its 'well established safety profile' included its record in overdose as well as at therapeutic doses. Therefore, it was not the case that GlaxoSmithKline was comparing Seroxat's profile at therapeutic doses with citalopram's in overdose. The three references quoted pointed out valid concerns about the cardiovascular overdose safety of citalopram. These concerns did not extend to paroxetine. Despite wide scale usage since launch ten years ago, such cardiovascular side effects were not accepted as being part of paroxetine's overdose side effect profile.

A GlaxoSmithKline representative's brief follow-up letter was not an appropriate place for a 'review of overdose', despite Lundbeck's apparent claim to the contrary. GlaxoSmithKline felt the content of the letter was appropriate to its context and capable of substantiation.

GlaxoSmithKline denied that this statement breached Clause 7.2. It further denied the letter disparaged citalopram and thus also denied a breach of Clause 8.1.

PANEL RULING

The Panel noted that Seroxat was licensed to treat the symptoms of depressive illness of all types including depression accompanied by anxiety. Cipramil was licensed for the treatment of depressive illness. The Panel considered that as a natural consequence of treating depression a patient's mood would lift. The Panel therefore considered that the claim '.....'Seroxat' is indicated to lift mood and treat the underlying anxiety symptoms of depression....' promoted the product within its licensed indication. No breach of Clause 3.2 was ruled.

With regard to the claim '...'Seroxat' has a well established safety profile having been used to treat more than 70 million patients worldwide. Evidence suggests that citalopram could cause cardiovascular side effects in overdose', the Panel considered that its comments made in point A2d above applied here. In the Panel's view the claim implied that there was a significant difference, in favour of Seroxat, with regard to the safety in overdose of it and citalopram. The Panel noted that the review by Barbey and Roose had not established this. The Panel considered that the claim was misleading and disparaged citalopram as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

C Alleged breaches of Clauses 2 and 21 of the Code

COMPLAINT

Lundbeck stated that there appeared to be a consistent thread of inaccuracy, attempts to mislead and disparagement throughout the promotional materials and activities of the sales force. This would suggest inadequate procedures were in place for review of promotional material and training of the salesforce.

Lundbeck had raised the issues of use of non-UK regulatory references and presentation of unbalanced cardiac safety data concerning Cipramil with SmithKline Beecham before, and the matter was ultimately referred to the Authority (see ruling Case AUTH/966/1/00).

The use of such references and the unbalanced presentation of cardiac safety data were found to be misleading and disparaging and in breach of Clauses 7.2, 7.7 and 8.1 both in an original ruling and on appeal by SmithKline Beecham. Presumably an undertaking was made by SmithKline Beecham accepting the ruling and its subsequent disregard of this undertaking was a breach of Clause 21 of the Code.

It was Lundbeck's contention that the continued use of such material to disparage its compound, Cipramil, and the flagrant disregard of a previous ruling and undertaking constituted behaviour likely to bring discredit upon the pharmaceutical industry. Such activity was therefore also in breach of Clause 2.

Lundbeck realised that this was a lengthy complaint; however, the continued promotional activities of GlaxoSmithKline in this area, despite previous contact and rulings, raised serious issues.

RESPONSE

GlaxoSmithKline denied that that its activity in relation to this or any other promotional item was in breach of either Clause 21 or Clause 2. Specifically, it felt that it had not contravened its undertakings following Case AUTH/966/1/00 as both the wording and context of the information given had been altered to take into account the comments of the Panel and the Code of Practice Appeal Board on that case.

GlaxoSmithKline strenuously refuted the implication that within the company 'inadequate procedures were in place for review of promotional material and training of the salesforce' and it was disappointed that Lundbeck did not do it the courtesy of informing it of its concerns about this promotional item before approaching the Authority.

In view of the accepted breach of Clause 7.8, using the word 'the' instead of 'a' in the stab point 'Seroxat is the logical choice for first-time success with new patients, because....', the leavepiece had been withdrawn from use.

PANEL RULING

The Panel noted that Case AUTH/966/1/00 concerned a 'Dear Doctor' letter issued by SmithKline Beecham which compared Seroxat with citalopram. Two paragraphs of the letter discussed the adverse events associated with the two medicines although it dealt, in the main, with the adverse cardiovascular effects of citalopram referring to the theoretical risk of QTc prolongation in susceptible patients and ECG abnormalities in overdose. The Panel noted that the theoretical cardiovascular effects of citalopram had not been put into clinical context. Breaches of the Code were ruled which were upheld upon appeal by SmithKline Beecham. Case AUTH/966/1/00 had been completed in June 2000.

Turning to the case now before it, the Panel noted that the matter considered in point A2d above, and the rulings made, were almost identical to those made in the previous case; again the theoretical risk of QTc prolongation had not been put into a clinical context. The leavepiece included a date of preparation of November 2000. It appeared to the Panel that when the leavepiece was prepared no attempt was made to comply with the undertaking which had been given in June 2000 with regard to statements about the theoretical cardiovascular effects of citalopram. In Case AUTH/966/1/00 both the Panel and the Appeal Board had noted that such statements had not been put into a clinical context. A breach of Clause 21 was now ruled. The Panel also considered that this brought discredit upon the pharmaceutical industry and ruled a breach of Clause 2 of the Code.

Complaint received **5 March 2001**

Case completed **11 May 2001**

GENERAL PRACTITIONER v SANOFI-SYNTHÉLABO

Conduct of representatives

A general practitioner complained about the conduct of a medical representative and a regional sales manager from Cardinal. The representatives were employed by Ashfield Healthcare but contracted to Sanofi-Synthélabo to promote Aprovel. Sanofi-Synthélabo was accordingly responsible for them under the Code.

It was alleged that the medical representative had asked too many questions, to which the complainant objected, rather than giving any information about Aprovel. The regional sales manager had then intervened and was rude to the complainant. He would not stop and went on arguing with the complainant. The regional sales manager had not had permission to enter the complainant's room. He just entered with the medical representative who asked 'Is it alright that [my colleague] can come?'.

The Panel noted the submission that the representative and the regional sales manager had visited the complainant's surgery early one morning with a view to getting an appointment to see him later that morning. They were asked to return at 11am and on their return they had been shown into the complainant's consulting room by one of the receptionists. The Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The parties' account of events differed. It was difficult to know exactly what had transpired between the representatives, the practice staff and the complainant. Although the Panel appreciated that the complainant had been very upset by the regional manager's presence and by the medical representative's style of promotion, it considered that there was no evidence to show that either had not maintained a high standard of ethical conduct. The Panel ruled no breach of the Code.

A general practitioner complained about the conduct of a medical representative and a regional sales manager from Cardinal. The complainant had written direct to Cardinal and had copied his letter to the Authority with a covering letter stating that he wished to draw the matter to its attention.

The complainant provided copies of the visiting cards of the two representatives. These bore the Ashfield logo and the matter was accordingly taken up with Ashfield Healthcare Limited. Ashfield advised that the representatives in question were contracted to promote Aprovel on behalf of Sanofi-Synthélabo. The supplementary information to Clause 15 of the Code provided that companies employing or using contract representatives were responsible for their conduct and compliance with the Code. Sanofi-Synthélabo was thus responsible for the activities of the representatives and the matter was taken up with that company.

COMPLAINT

The complainant stated that he did not appreciate the way the representative promoted his product. Rather than giving any information about it, he asked too many questions to which the complainant objected. At this stage the regional sales manager intervened and was very rude to the complainant. He would not stop and went on and on arguing with the complainant for nothing. In the complainant's opinion both of these representatives needed further training before they made any further contact with general practitioners.

RESPONSE

Sanofi-Synthélabo confirmed that the representatives concerned were employed by Ashfield Healthcare and were contracted to promote Aprovel on behalf of Sanofi-Synthélabo. Sanofi-Synthélabo deeply regretted that the complainant had cause to complain about the behaviour of the representatives and was confident that the full inquiry carried out by Ashfield Healthcare, and the actions proposed by it, would ensure no repetition of what appeared to be a regrettable one-off incident resulting from a misunderstanding.

Under the terms of Sanofi-Synthélabo's agreement with Ashfield Healthcare, Ashfield Healthcare undertook full Code of Practice training of its representatives. Although not the subject of complaint, Sanofi-Synthélabo could verify that it undertook full product training which met the same standard as the training for its in-house representatives and included an end of course examination with an 80% pass mark.

In summary, Sanofi-Synthélabo explained that both representatives entered the complainant's surgery with the knowledge and consent of the practice staff. During the discussion the questions asked did not appear offensive. However, it was clear that the complainant took offence to the questions asked, and the representatives apologised unreservedly for that.

Sanofi-Synthélabo stated that on a more general note, the correspondence submitted to the Authority demonstrated Ashfield Healthcare's commitment to Code of Practice training for its staff, together with updated information. Both Sanofi-Synthélabo and Ashfield Healthcare diligently reinforced appropriate behaviour within the Code.

Sanofi-Synthélabo was sure that both representatives would be very sensitive to such issues in future but, having demonstrated the steps taken by Ashfield Healthcare to maintain high standards of conduct, Sanofi-Synthélabo trusted that this regrettable, isolated incident would not require censure under the Code.

Adding to the above response, Ashfield Healthcare stated that the regional sales manager had passed the ABPI examination with distinction. The medical representative would be sitting the examination in May this year.

Ashfield Healthcare stated that it was extremely sorry for any offence that might have been inadvertently caused by these two representatives. From the information they had provided, it seemed as though it was the questions they asked the complainant which resulted in the complaint. These questions related to the complainant's views on the therapy area and current prescribing habits, in order that they could relate their product messages to his needs. They denied either being rude, or indeed arguing with the complainant, and they left the surgery immediately that they were asked.

Ashfield Healthcare stated that it had further updated and trained both representatives as a result of this complaint. Whilst the regional sales manager did not have an appointment to see the complainant, he was shown in to the surgery by the receptionist and was invited to sit down by the complainant himself. The representatives admitted that they asked the complainant several questions to establish which element of the product they were promoting would be of most benefit to him and his patients. If, in asking those questions, they offended the complainant they apologised profusely; however they felt that they were acting both in the complainant's interests and in a highly professional and ethical manner. When they were asked to leave they did so immediately and they would not return to that surgery unless invited to do so.

A memorandum from the regional sales manager stated that at approximately 8.45am he and the representative visited the medical centre and asked permission to return later that morning to see the complainant. They were instructed to return at 11.00am with a view to seeing him. They discussed the plan of the call and how the representative was going to approach it. On their return they were instructed to wait outside the complainant's consulting room as the receptionist would call them in when appropriate. After about five minutes wait a receptionist appeared from the complainant's consulting room and ushered them into the room.

The representative introduced himself to the complainant and introduced the regional sales manager as a colleague. After a brief introduction as to the reason for the visit, the medical representative asked 'There appears to be a lot of Aprovel used in this area and I was wondering if there were any particular patient groups you would like to use it for?'. The complainant responded with 'That is no way to conduct yourself, just do your job'. The representative responded with 'OK, I'll take you through the current information if that is alright with you'. The complainant responded 'This interview has ended, give me your card and I will complain to the company and the ABPI'. At this point the representative passed his card to the complainant and the regional sales manager offered his card as a sign of support for his colleague. They left the consulting room immediately, approximately one minute after their entrance.

The representative had been particularly shaken by the meeting, and was concerned as to what the doctor might do as a result; he and his regional sales manager discussed at length the exact course that the meeting had taken and concluded that there was nothing more they could have done in the situation, and that there was nothing in the meeting that warranted such a response. A later discussion with a representative of another company revealed that they were not the first people who had met with such a response.

Interestingly, they also met with another GP in the centre and proceeded to have a fruitful and interesting discussion on and around the subject area. The representative had also contacted other doctors in the centre and had found them to be polite and courteous.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant emphasised that the regional sales manager did not have his prior permission to enter his room; he just entered with the representative who asked 'Is it alright that [my colleague] can come?'. The complainant stated that in his opinion the representative should not promote his product by asking question after question. The complainant noted that the representative had apologised to him but after some persuasion. The complainant stated that at this stage the regional manager came charging towards him showing his visiting card and said in a very unpleasant way that if he wanted his details as well which annoyed the complainant most.

PANEL RULING

The Panel noted that Ashfield Healthcare stated that both the representative and the regional sales manager had visited the complainant's surgery early one morning with a view of getting an appointment to see him later that morning. They were asked to return at 11am and on their return they had been shown into the complainant's consulting room by one of the receptionists. The complainant stated that the regional sales manager did not have his prior permission to enter his room. In addition the complainant had objected to the representative's style of promoting his product which had been to ask questions in the first instance to establish the complainant's views and current prescribing habits.

The Panel noted that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint. The Panel noted that the parties' account of events differed; it was difficult to know exactly what had transpired between the representatives, the practice staff and the complainant. Although the Panel appreciated that the complainant had been very upset by the regional manager's presence and by the representative's style of promotion, it considered that there was no evidence to show that either had not maintained a high standard of ethical conduct. On the balance of the information before it the Panel ruled no breach of Clause 15.2 of the Code.

Complaint received **13 February 2001**

Case completed **8 May 2001**

CASES AUTH/1160/3/01 and AUTH/1161/3/01

MERCK SHARP & DOHME v PHARMACIA and PFIZER

Celebrex leavepiece

Merck Sharp & Dohme complained about a leavepiece for Celebrex (celecoxib) issued by Pharmacia and Pfizer. Merck Sharp & Dohme supplied Vioxx (rofecoxib).

The claim 'Superior GI tolerability' appeared beneath the heading 'Use instead of diclofenac or naproxen'. Merck Sharp & Dohme stated that Pharmacia had suggested that this claim was now accepted by the clinical and scientific community. However, this was certainly not the case for the comparison with diclofenac. The claim did not reflect the balance of the available data. The frequency of abdominal pain was significantly more frequent for diclofenac than for celecoxib in the study by Emery *et al*. However, the authors stated 'Frequencies of other gastrointestinal adverse events were not significantly higher for diclofenac than for celecoxib'. This study did show a significantly lower rate of endoscopic ulcers for celecoxib compared with diclofenac. However, as stated in the summary of product characteristics (SPC), a second study did not. In the CLASS (Celecoxib Long-term Arthritis Safety Study) study, celecoxib did not have a significantly lower rate of symptomatic ulcers or complicated ulcers compared to diclofenac. Merck Sharp & Dohme did not believe that the claim made in relation to diclofenac accurately took into account all of the available evidence.

The Panel noted that Emery *et al* concluded that celecoxib had better GI safety and tolerability than diclofenac. The results suggested that the rate of ulcer complications with celecoxib might be lower than that noted with conventional NSAIDs. Pooled data that compared celecoxib with diclofenac in osteoarthritis showed that the composite endpoint (abdominal pain, nausea or dyspepsia) was statistically significantly worse for diclofenac than for celecoxib. The cumulative incidence of the composite endpoint at 6 weeks with diclofenac was 17.6% compared with 11.1% for celecoxib and 13.3% for placebo. A third study demonstrated that the GI tolerability of celecoxib was better than diclofenac and ibuprofen as measured by GI adverse events and rates of withdrawal due to GI adverse events. Over 12 weeks celecoxib was associated with a statistically significantly lower incidence of gastroduodenal ulcers than ibuprofen and a numerically (although not statistically significant) lower incidence of gastroduodenal ulcers than diclofenac. With regard to the CLASS data, the Panel noted that celecoxib was administered at twice the UK maximum licensed dose. In the Panel's view the results from CLASS were not directly relevant to the claim at issue. The Panel noted that the Celebrex SPC referred to data with regard to endoscopic ulcers. Two studies compared celecoxib and diclofenac. One study (6 months on treatment) showed a statistically significant lower incidence of endoscopic ulcers at the study endpoint for treatment with celecoxib. The other study (12 weeks) showed no statistically significant difference in endoscopic ulceration. The Panel considered that the claim with regard to diclofenac was a reasonable reflection of the available evidence regarding the GI tolerability of Celebrex at UK approved doses and ruled no breach of the Code.

In relation to the claim 'Lower hepatic toxicity versus NSAIDs, diclofenac and ibuprofen', Merck Sharp & Dohme stated that 97% of the liver function test abnormalities occurred in patients taking diclofenac. Whilst not presented in the referenced study, Silverstein *et al*, separate analyses were conducted for diclofenac and ibuprofen which were submitted to the FDA. Significantly lower hepatic toxicity was demonstrated for diclofenac but not for ibuprofen. It would have been far more appropriate to use this analysis as the reference. As it stood the claim suggested a difference vs. ibuprofen that could not be substantiated.

The Panel noted that in Silverstein *et al* results of the liver function tests were reported such that differences between celecoxib and diclofenac, and celecoxib and ibuprofen, could not be determined separately. For the comparison with celecoxib the NSAID data remained pooled. The Panel was concerned that the wording of the claim was confusing. It could be read that Celebrex had lower hepatic toxicity than all NSAIDs. No data had been provided to support such an interpretation. The data for ibuprofen and diclofenac were pooled. At the time the leavepiece was produced there was no data to support a claim for lower hepatic toxicity compared to ibuprofen. The Panel considered that the claim was misleading and had not been substantiated and breaches of the Code were ruled.

The claim 'Fewer moderate to severe upper GI adverse events' appeared beneath the right-hand column's heading 'Use instead of rofecoxib Superior tolerability'. The claim was followed by an obelus, the explanation was given via a footnote 'Dyspepsia, abdominal pain, nausea'. Merck Sharp & Dohme stated that the composite endpoint, dyspepsia, abdominal pain and nausea, was used for a comparison with rofecoxib in the right-hand column and was described as 'moderate to severe upper GI adverse events'. The reader was directed to a footnote. In contrast, the left-hand column headed 'Use instead of diclofenac or naproxen' cited Bensen *et al* to support 'Superior GI tolerability'. This had the same composite endpoint of dyspepsia, abdominal pain and nausea, but the reader was not directed to the footnote listing these adverse events. Merck Sharp & Dohme could not agree that severe and serious as defined by regulatory authorities was well recognised by clinicians and this claim would be misinterpreted as ulcers. Merck Sharp & Dohme believed the artificial distinction between the two claims in the left- and right-hand columns would mislead.

The Panel noted its comments above on the claim 'Superior GI tolerability' which appeared beneath 'Use instead of diclofenac or naproxen'. The gastrointestinal data went beyond a difference in dyspepsia, abdominal pain and nausea. The claim

'Fewer moderate to severe upper GI adverse events' was by way of an explanatory footnote related to dyspepsia, abdominal pain and nausea. The Panel considered that the claim at issue was more specific than the claim considered above. It appeared beneath the heading 'Superior tolerability' and the two claims taken together might be read as implying that Celebrex had superior GI tolerability to rofecoxib. There was no data to support this. The claim had been qualified by the footnote. It was not acceptable under the Code to qualify claims by use of footnotes. The Panel considered that some of the recipients might take the reference to moderate to severe adverse events to mean ulcers. Others would not. It appeared that there was no mention in the published data about the numbers of moderate to severe upper GI adverse events. Health professionals reading the material would be aware of the concerns about GI effects. The Panel considered that the claim was open to misinterpretation. This had been demonstrated by the companies' need to include a footnote. The Panel considered that the distinction between the data would mislead and a breach of the Code was ruled.

Merck Sharp & Dohme stated that the claim 'No significant change in existing blood pressure' was absolute rather than comparative. The SPC for celecoxib listed hypertension as an uncommon adverse effect and stated that NSAIDs might reduce the effect of antihypertensives. Two data on file references were provided for separate studies of celecoxib versus rofecoxib. One study stated that there were no clinically important differences in respect to changes in vital signs (which would include blood pressure). In a Merck Sharp & Dohme sponsored study comparing rofecoxib with celecoxib, rofecoxib 25mg did not increase mean blood pressure. Unfortunately, there was no placebo group for comparison, but there were still 11.2% of patients taking celecoxib who had aggravated hypertension as defined in this study. It was also of relevance to Pharmacia's suggestion that this was a comparative claim, that there was no significant difference between rofecoxib and celecoxib in the number of patients with raised systolic blood pressure over the whole six week study. Merck Sharp & Dohme alleged that the claim was inaccurate, did not reflect the balance of the available evidence, was an exaggerated claim and was inconsistent with the particulars listed in the SPC.

The Panel noted the differences in the SPCs. The Celebrex SPC stated that hypertension was an uncommon (0.1 - 1%) undesirable effect. The Vioxx (rofecoxib) SPC listed hypertension as a common side effect with an incidence of 1 - 10%. The Panel noted that the study to which the claim was referenced was a comparison of celecoxib and rofecoxib in hypertensive patients. This had not been made clear. The study showed that aggravated hypertension occurred in 8% of patients prescribed rofecoxib compared to 5.6% of those taking celecoxib. The proportion of patients reaching the systolic blood pressure endpoint as defined for aggravated hypertension was, at any time, significantly lower in the celecoxib group (11.2%) compared to the rofecoxib group (16.5%). No comparative data in normotensive patients had been supplied. There was a possibility of a change in existing blood pressure with Celebrex as stated in the SPC. The Panel considered that the claim was misleading, all embracing and not substantiated by the data and was inconsistent with the SPC. Breaches of the Code were ruled.

The claim 'Superior tolerability' immediately followed the statement 'Use instead of rofecoxib'. Merck Sharp & Dohme stated that whilst some specific points relating to tolerability were made, it believed that this claim was all-embracing. The Panel considered that the claim 'Superior tolerability' was a wide claim. It went further than the features mentioned in the three subsequent claims on the leavepiece. The data comparing the two products were limited. The Panel considered that the claim was all-embracing and a breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about a two-sided leavepiece for Celebrex (celecoxib) issued by Pharmacia Limited and Pfizer Limited. The piece bore the Pharmacia reference 83537-6000 January 2001 and the Pfizer reference A41989. Merck Sharp & Dohme supplied Vioxx (rofecoxib).

At the top of one side of the leavepiece, the following claims appeared 'New Celebrex', '200mg o.d. in OA', 'Use in a wide range of patients' and 'Licensed for OA and RA'. Following these the leavepiece was in effect divided into two columns. The left-hand column was headed 'Use instead of diclofenac or naproxen' followed by the claims 'Superior GI tolerability' and 'Lower hepatic toxicity versus NSAIDs, diclofenac and ibuprofen'. The right-hand column was headed 'Use instead of rofecoxib Superior tolerability:' followed by the claims 'Fewer moderate to severe upper GI adverse events', 'No significant change in existing blood pressure' and 'Fewer composite renal adverse events'.

Pharmacia and Pfizer submitted identical responses to the allegations.

1 Claim 'Superior GI tolerability'

The claim appeared beneath the heading 'Use instead of diclofenac or naproxen' and was referenced to Bensen *et al* (2000) and Emery *et al* (1999).

COMPLAINT

Merck Sharp & Dohme stated that this claim was made with reference to naproxen and diclofenac. Pharmacia had suggested that this '...is now accepted by the clinical and scientific community'. However, this was certainly not the case for the comparison with diclofenac. The claim did not reflect the balance of the available data. The frequency of abdominal pain was significantly more frequent for diclofenac than for celecoxib in the study of Emery *et al*. However, the authors stated 'Frequencies of other gastrointestinal adverse events were not significantly higher for diclofenac than for celecoxib'. This study did show a significantly lower rate of endoscopic

ulcers for celecoxib compared with diclofenac. However, as stated in the summary of product characteristics (SPC), and quoted by Pharmacia in its response to Merck Sharp & Dohme, a second study did not. In the CLASS (Celecoxib Long-term Arthritis Safety Study) study celecoxib did not have a significantly lower rate of symptomatic ulcers or complicated ulcers compared to diclofenac.

Merck Sharp & Dohme provided a graph from the Statistical Reviewer Briefing Document for the Advisory Committee celecoxib sNDA. The graph was entitled Kaplan-Meier Estimator for CSUGIE (clinically significant upper gastrointestinal events) Incidence. The summary of the CSUGIE incidence data provided by Merck Sharp & Dohme was from the same source.

In summary, Merck Sharp & Dohme did not believe that the claim made in relation to diclofenac accurately took into account all of the available evidence and alleged that it was in breach of Clause 7.2 of the Code.

RESPONSE

Pharmacia and Pfizer stated that they were surprised by Merck Sharp & Dohme's concern regarding this claim. The balance of the available data robustly supported celecoxib's superior GI tolerability over that of diclofenac. To make such a claim to the targeted audience, UK healthcare professionals, the evidence base must comprise data from trials fulfilling certain criteria. One essential prerequisite was that the doses used must be comparable. Both should be prescribed at doses relevant to clinical practice, and certainly within the licensed range. For Merck Sharp & Dohme to cite the CLASS study was frankly misleading. As it was well aware, CLASS was conducted for regulatory purposes, in a design driven by the FDA, in order to challenge a class labelling in the US. Celecoxib was administered at twice the maximum licensed dose (400mg bd) in order to assess its safety at supratherapeutic doses over the traditional NSAIDs diclofenac and ibuprofen, both prescribed at the maximum licensed dose (diclofenac 75mg bd).

In contrast, the reference used in this leavepiece, Emery *et al*, was relevant to the claim. It described the results of a large trial (N=655) in adult-onset rheumatoid arthritis (RA), comparing celecoxib 200mg bd with diclofenac 75mg bd for 24 weeks. GI safety was assessed by endoscopic detection of gastroduodenal ulcers and revealed a significant advantage in favour of celecoxib (4% vs 15% $p<0.001$). GI tolerability was also evaluated by collection of adverse event data. It too showed a clear advantage in favour of celecoxib. Firstly, the proportion of patients experiencing a GI adverse event (48%, 159/329, on diclofenac and 36%, 118/326, on celecoxib, $p=0.002$), and secondly, withdrawals due to GI related adverse events (16%, 51/329, on diclofenac and 6%, 18/326, on celecoxib $p<0.001$).

The sentence quoted in Merck Sharp & Dohme's letter, 'Frequencies of other gastrointestinal adverse events were not significantly higher for diclofenac than for celecoxib', related to individual adverse events. Again, this was misleading because the trial was not powered to show specific advantages in terms of, for example, 'nausea' *per se*. The difference for 'abdominal pain' did reach statistical significance, but to expect other individual adverse events to separate in a trial of this size was unrealistic. This did not, however, detract from the claim, which related to GI tolerability as a whole.

Further, Pharmacia and Pfizer were comfortable that this claim reflected the balance of evidence, including trials currently unpublished. In addition to the large RA trial reported by Emery, the company had conducted a pooled analysis of two osteoarthritis (OA) trials versus diclofenac. This was specifically to evaluate upper gastro-intestinal tolerability. This composite endpoint was defined as the cumulative incidence of abdominal pain, dyspepsia and nausea. Confidential data on file which was provided showed in summary that in OA the cumulative incidence of the composite endpoint at 6 weeks with diclofenac was 17.6% (95%CI:14.4-20.9%) compared with 11.1% (95%CI:8.4-13.8%) for celecoxib ($p=0.0002$).

Merck Sharp & Dohme had highlighted that the other GI endoscopy trial comparing celecoxib with diclofenac failed to show a statistically significant separation in terms of endoscopic ulcers. Pharmacia and Pfizer stated that: the claim was based on the balance of evidence, not one trial; the trend in endoscopic gastroduodenal ulceration was clearly in favour of celecoxib in this trial; a number of the secondary end-points relevant to GI tolerability revealed statistically significant advantages in favour of celecoxib eg the incidence of duodenal ulcers and duodenal erosions. The withdrawal rate due to GI adverse events was also lower on celecoxib (3%) versus diclofenac (6%) and ibuprofen (8%), although no statistics were undertaken because the trial was not powered for this analysis. Endoscopic ulcers were an important surrogate marker for GI safety. However, they were often not associated with symptoms. They were one of a number of relevant end-points used to evaluate GI tolerability, such as incidence of GI adverse events and withdrawals due to GI adverse events.

Pharmacia and Pfizer submitted that the broad claim of superior GI tolerability compared to diclofenac was accurate, balanced and fair.

PANEL RULING

The Panel noted that Bensen *et al* compared Celebrex with naproxen and placebo.

Emery *et al* was a study on 655 rheumatoid arthritis patients who were assigned to receive celecoxib 200mg twice daily or diclofenac SR 75mg twice daily for 24 weeks. The study concluded that celecoxib had better gastrointestinal safety and tolerability than diclofenac. The products had similar anti-inflammatory and analgesic activity. The study stated that the results suggested that the rate of ulcer complications with celecoxib might be lower than that noted with conventional NSAIDs.

Pooled data that compared celecoxib with diclofenac in osteoarthritis showed that the composite endpoint

(abdominal pain, nausea or dyspepsia) was statistically significantly worse for diclofenac than for celecoxib. The cumulative incidence of the composite endpoint at 6 weeks with diclofenac was 17.6% compared with 11.1% for celecoxib (p=0.002) and 13.3% for placebo (p=0.157). This data was stated to be company confidential. A third study compared the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200mg bd, diclofenac 75mg bd and ibuprofen 800mg tds in osteoarthritis or rheumatoid arthritis patients. The gastrointestinal tolerability of celecoxib was better than diclofenac and ibuprofen as measured by GI adverse events and rates of withdrawal due to GI adverse events. Over 12 weeks celecoxib was associated with a statistically significantly lower incidence of gastroduodenal ulcers than ibuprofen and a numerically (although not statistically significant) lower incidence of gastroduodenal ulcers than diclofenac.

With regard to the CLASS data, the Panel noted that in this study celecoxib was administered at 400mg bd. This was twice the UK maximum licensed dose. In the Panel's view the results from CLASS were not directly relevant to the claim at issue. In the CLASS study the week 52 crude rate of CSUGIE incidence was 0.43% for Celebrex and 0.50% for diclofenac (p=0.64).

The Panel noted that the Celebrex SPC referred to data with regard to endoscopic ulcers. Two studies compared celecoxib and diclofenac. One study (6 months on treatment) showed a statistically significant lower incidence of endoscopic ulcers at the study endpoint for treatment with celecoxib. The other study (12 weeks) showed no statistically significant difference in endoscopic ulceration.

The Panel considered that the claim with regard to diclofenac was a reasonable reflection of the available evidence regarding the GI tolerability of Celebrex at UK approved doses. The Panel ruled no breach of Clause 7.2 of the Code.

2 Claim 'Lower hepatic toxicity versus NSAIDs, diclofenac and ibuprofen'

This claim was referenced to Silverstein *et al* 2000.

COMPLAINT

Merck Sharp & Dohme stated that 97% of the liver function test abnormalities occurred in patients taking diclofenac. Whilst not presented in the publication of the referenced study, separate analyses were conducted for diclofenac and ibuprofen which were submitted to the FDA. Significantly lower hepatic toxicity was demonstrated for diclofenac but not for ibuprofen. It would have been far more appropriate to use this analysis as the reference. As it stood the claim suggested a difference versus ibuprofen that could not be substantiated. This was in breach of Clause 7.3 and was misleading in breach of Clause 7.2.

RESPONSE

Pharmacia and Pfizer stated that the title leading this piece made it clear that the products targeted for comparison were diclofenac and naproxen, not ibuprofen.

In the Silverstein paper, a composite statistical analysis was used to assess adverse events. The comparison was between celecoxib, as a representative of the 'coxib' class, and two commonly prescribed NSAIDs, representing NSAIDs. Whilst agreeing that, in this case (hepatic toxicity), it might have been more appropriate for the authors to analyse the data for diclofenac and ibuprofen separately, this was not done. It was, therefore, considered poor practice to report the results for diclofenac without supportive statistical data.

The analysis cited by Merck Sharp & Dohme, taken from the CLASS Advisory Committee Briefing Document, was not available at the time this leavepiece was designed. Neither was it mentioned in Merck Sharp & Dohme's letter of complaint to the companies dated 20 February. Now that the companies had this data on file they would proactively amend future material. In fact, this change would establish the target message with greater clarity. However, the companies refuted any suggestion that they had breached the Code and argued that they had gone out of their way to report the available data accurately. The take home message for clinicians remained clear: celecoxib was an appropriate alternative to diclofenac, one advantage being a lower incidence of hepatic toxicity.

PANEL RULING

The Panel was confused about the submission from Pharmacia and Pfizer that the products targeted for comparison were diclofenac and naproxen not ibuprofen. The subheading to the left-hand column was 'Use instead of diclofenac or naproxen'. The claim at issue was that Celebrex had lower hepatic toxicity versus NSAIDs, diclofenac and ibuprofen. The complaint was that the claim, in respect of Celebrex versus ibuprofen, could not be substantiated.

Silverstein *et al* was a study comparing celecoxib with NSAIDs based on data from CLASS. The dose of celecoxib was 400mg bd. Patients received either celecoxib or a NSAID (diclofenac or ibuprofen). With regard to liver function tests the authors reported that 97% of abnormalities occurred in patients taking diclofenac. Results of the liver function tests were not reported, however, such that the differences between celecoxib and diclofenac, and celecoxib and ibuprofen, could be determined separately. For the comparison with celecoxib the NSAID data remained pooled.

The Panel was concerned that the wording of the claim was confusing. It could be read that Celebrex had lower hepatic toxicity than all NSAIDs. No data had been provided to support such an interpretation. The data for ibuprofen and diclofenac were pooled. At the time the leavepiece was produced there was no data to support a claim for lower hepatic toxicity compared to ibuprofen.

The Panel considered that the claim was misleading as alleged and a breach of Clause 7.2 of the Code was ruled. The claim had not been substantiated and a breach of Clause 7.3 was also ruled.

3a Claim 'Fewer moderate to severe upper GI adverse events'

This appeared beneath the heading to the right-hand column 'Use instead of rofecoxib Superior tolerability'. The claim now at issue was followed by an obelus, the explanation was given via a footnote 'Dyspepsia, abdominal pain, nausea'. The claim was referenced to Pharmacia data on file 149.

COMPLAINT

Merck Sharp & Dohme stated that the composite endpoint, dyspepsia, abdominal pain and nausea, was used for a comparison with rofecoxib in the right-hand column and was described as 'moderate to severe upper GI adverse events'. The reader was directed to a footnote. In contrast, the left-hand column headed 'Use instead of diclofenac or naproxen' cited Bensen *et al* to support 'Superior GI tolerability'. This had the same composite endpoint of dyspepsia, abdominal pain and nausea but the reader was not directed to the footnote listing these adverse events. Merck Sharp & Dohme could not agree that severe and serious as defined by regulatory authorities was as well recognised by clinicians as Pharmacia would have everyone believe, and this claim would be misinterpreted as ulcers. Merck Sharp & Dohme believed the artificial distinction between the two claims in the left- and right-hand columns would mislead the reader and alleged that it was therefore in breach of Clause 7.2.

RESPONSE

With regard to the alleged inconsistency between the labelling in the right and left-hand columns, Pharmacia and Pfizer stated that the composite endpoint, 'dyspepsia, abdominal pain and nausea', was defined in a footnote on the right because it was the only robust GI tolerability data relevant to a comparison with rofecoxib. Study 149 was the only large trial in which a comparison of the tolerability of these products had been the primary objective. Conversely, on the left, celecoxib was widely accepted by the clinical and scientific community as exhibiting superior GI tolerability to naproxen. This appeared not to be contested by Merck Sharp & Dohme in the first part of its complaint. A footnote for the Bensen study was therefore deemed inappropriate because the data from this paper was an extremely robust example of that available to support the claim. Others, if required, included Simon *et al* (1999), Burr *et al* (1999) and the Celebrex SPC.

With regard to the potential for misinterpreting the qualifying terms 'moderate to severe', the companies stated that the predefined composite endpoint used in this large trial to assess 'upper GI tolerability' only included adverse events judged 'moderate to severe' by the investigator. It would have been inaccurate and misleading, warranting a referral for breach of Clause 7.2, if this qualification had not been included. The companies did not agree that clinicians would consider these adverse events all to be 'serious', as defined by ICH GCP (International Conference on Harmonisation, Good Clinical Practice), especially as the category included the words 'moderate to'. Those clinicians unfamiliar with clinical trial terminology would correctly interpret 'moderate to severe', from common parlance, to be a measure of intensity, reflecting the degree to which the patient had been incapacitated, usually temporarily, by the event. If Merck Sharp & Dohme considered that 'severe' would be misinterpreted as 'serious', then it assumed that 'serious' would be correctly understood to mean 'life-threatening or resulting in death, permanent disability or hospitalisation' (unlikely for a clinician who did not know what a 'severe' adverse event was). The word 'serious' reflected outcome and intensity of management. It was difficult to envisage how 'moderately serious' could be interpreted. Of course, there would be patients who had 'severe' adverse events that were also serious. Further, there could be patients who had 'moderate' adverse events that were also 'serious' eg some GI bleeds, particularly when sub-acute or chronic, required transfusion and investigation (hospitalisation), but the patient was not particularly incapacitated and was able to walk onto the ward. In summary, the companies considered this point a highly technical attempt to distort an accurate and unambiguous claim. The common usage of these terms was consistent with their meaning in this piece, and a full explanation of the differences was unnecessary and would be onerous in a piece of this size.

PANEL RULING

The Panel noted its comments on point 1 above which related to the claim 'Superior GI tolerability' which appeared beneath the claim 'Use instead of diclofenac or naproxen'. The gastrointestinal data went beyond a difference in dyspepsia, abdominal pain and nausea. The Panel noted that the claim 'Fewer moderate to severe upper GI adverse events' was by way of an explanatory footnote related to dyspepsia, abdominal pain and nausea. The quoted reference, Pharmacia data on file 149, was a double blind randomised, parallel group comparative study of the safety of celecoxib versus rofecoxib in hypertensive patients with peripheral osteoarthritis taking antihypertensive medications. Patients had to be aged 65 or over with a diagnosis of osteoarthritis of the hip, knee or hand. A total of 810 patients were entered in the study, 399 received rofecoxib, 411 received celecoxib. The study report stated that celecoxib demonstrated better upper gastrointestinal tolerability than rofecoxib predefined as the occurrence of moderate or severe upper gastrointestinal discomfort (abdominal pain, dyspepsia and nausea). The percentage of patients in the celecoxib group who had moderate or severe upper gastrointestinal discomfort was significantly smaller than in the rofecoxib group (3.2% v 6.5%; p=0.032).

The Panel considered that the claim at issue was more specific than the claim at issue in point 1 above. It appeared beneath the heading 'Superior tolerability' and the two claims taken together might be read as implying that Celebrex had superior GI tolerability to rofecoxib. There was no data to support this. The Panel noted that the claim had been qualified by the footnote. It was not acceptable under the Code to qualify claims by use of footnotes. The Panel

considered that some of the recipients might take the reference to moderate to severe adverse events to mean ulcers. Others would not. The Panel considered that on balance, given its context, the claim would be misinterpreted. The Panel considered that there was a difference between the data available comparing naproxen and diclofenac with Celebrex and the data comparing rofecoxib with Celebrex. The comparative data for rofecoxib and celecoxib was in a group of elderly patients with hypertension. There did not appear to be data in other patient populations. The data on file to which the claim was referenced was now published. It appeared that there was no mention in the published data about the numbers of moderate to severe upper GI adverse events. Health professionals reading the material would be aware of the concerns about GI effects. The Panel considered that the claim was open to misinterpretation. This had been demonstrated by the companies' need to include a footnote. The Panel considered that the distinction between the data would mislead and a breach of Clause 7.2 of the Code was ruled.

3b Claim 'No significant change in existing blood pressure'

The claim was referenced to Pharmacia data on file 149.

COMPLAINT

Merck Sharp & Dohme stated that this claim was absolute rather than comparative like the other two in the right hand column. The SPC for celecoxib listed hypertension as an uncommon adverse effect, and stated that NSAIDs might reduce the effect of antihypertensives (ie increase blood pressure). Two data on file references were provided, 149 and 152, for separate studies of celecoxib versus rofecoxib. Study 152 stated that there were no clinically important differences in respect to changes in vital signs (which would include blood pressure). In a Merck Sharp & Dohme sponsored study comparing rofecoxib with celecoxib, rofecoxib 25mg did not increase mean blood pressure. Unfortunately, there was no placebo group in study 149 for comparison, but there were still 11.2% of patients taking celecoxib who had aggravated hypertension as defined in this study. It was also of relevance to Pharmacia's suggestion that this was a comparative statement that there was no significant difference between rofecoxib and celecoxib in the number of patients with raised systolic blood pressure over the whole six week study. Merck Sharp & Dohme alleged that the claim was inaccurate in breach of Clause 7.2, did not reflect the balance of the available evidence in breach of Clause 7.3, was an exaggerated claim in breach of Clauses 7.7 and 7.8, and was inconsistent with the particulars listed in the SPC in breach of Clause 3.2.

RESPONSE

Pharmacia and Pfizer stated that the leavepiece clearly indicated that a comparison was being made between celecoxib and diclofenac or naproxen on the left, and celecoxib and rofecoxib on the right. All stab-points on the right were qualifying celecoxib's superior tolerability over rofecoxib. Study 149, which predefined the parameters used to assess changes in blood pressure and published data, clearly showed that differences existed between rofecoxib and celecoxib in respect to their effects on blood pressure. The differences noted in Study 149 were, firstly, that systolic blood pressure increased significantly in 17% of rofecoxib-treated patients compared to 11% of celecoxib-treated patients ($p=0.032$) and, secondly, at week six, the change from baseline in mean systolic blood pressure was +2.6mmHg for rofecoxib compared with –0.5mmHg for celecoxib ($p=0.007$).

To support its conviction that no evidence existed to separate these products, Merck Sharp & Dohme had cited two efficacy studies which were neither designed nor powered to show differences in this safety endpoint. Study 149 (now in press) was conducted in 810 elderly hypertensive patients with osteoarthritis. Of course, in a population of such patients, it was not surprising that some patients' blood pressures were reported as changed during the trial. This did not prove a causal association, and only data from large meta-analyses could provide any comfort in this regard (see below).

Should this be misconstrued as an absolute statement taken in isolation, and not in the context of the whole design of this piece, then the companies had the following comments. They did not dispute the fact that hypertension was listed as an undesirable effect (uncommon – 0.1-1%) on the SPC. However, hypertension was a common chance finding within a large population, especially an ageing population consistent with a condition like arthritis. New SPCs listed all adverse events reported, whether or not a causal association existed.

Whelton *et al* in an analysis of twelve North American controlled arthritis trials involving 9667 patients stated 'Celecoxib appears to have no clinically detectable effect on blood pressure. Even in the 40% of patients who were being treated for hypertension at the time of study entry, no clinically detectable changes in blood pressure were observed'.

The review also quoted the US product labelling for rofecoxib:

'It should be noted here that the product labelling for the recently approved COX-2 inhibitor rofecoxib, contains the following statement:

– In patients with mild to moderate hypertension, administration of 25mg daily of (rofecoxib) with the ACE inhibitor benazepril, 10-40mg for 4 weeks, was associated with an average increase in mean arterial blood pressure of about 3mmHg compared to ACE inhibitor alone.'

Similarly, hypertension had been more frequently reported in the rofecoxib trials and was quoted on the UK SPC as being a common side effect (an incidence of >1%, <10%).

The companies did not consider that this claim would be misinterpreted, and in this context did not consider it inconsistent with the evidence base.

PANEL RULING

The Panel noted the differences in the SPCs. The Celebrex SPC stated that hypertension was an uncommon (0.1 - 1%) undesirable effect. The Vioxx SPC listed hypertension as a common side effect with an incidence of 1 - 10%.

The Panel noted that the study to which the claim was referenced was a comparison of celecoxib and refecoxib in hypertensive patients. This had not been made clear. The study showed that aggravated hypertension occurred in 8% of patients prescribed rofecoxib compared to 5.6% of those taking celecoxib. The proportion of patients reaching the systolic blood pressure endpoint as defined for aggravated hypertension was, at any time, significantly lower in the celecoxib group (11.2%) compared to the rofecoxib group (16.5%) (p=0.032). No comparative data in normotensive patients had been supplied. There was a possibility of a change in existing blood pressure with Celebrex as stated in the SPC. The Panel considered that the claim was misleading, all embracing and not substantiated by the data. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code were ruled. The Panel considered that the claim was inconsistent with the SPC and a breach of Clause 3.2 was ruled. The Panel considered that the alleged breach of Clause 7.7 was covered by these rulings.

3c Claim 'Superior tolerability'

The claim immediately followed the statement 'Use instead of rofecoxib', forming the heading to the right-hand column. Two claims in the right-hand column were the subject of separate allegations (points 3a and 3b). A third claim 'Fewer composite renal adverse events' was not the subject of complaint.

COMPLAINT

Merck Sharp & Dohme stated that whilst some specific points relating to tolerability were made, it believed that this claim constituted an all embracing claim and a breach of Clause 7.8 was alleged.

RESPONSE

Pharmacia and Pfizer stated that this introductory title was followed by a colon which preceded three stab points, each qualifying the nature of the superiority. These stab points were substantiated in the referenced material.

PANEL RULING

The Panel considered that the claim 'Superior tolerability' was a wide claim. It went further than the features mentioned in the three subsequent claims on the leavepiece. The Panel noted that the data comparing the two products were limited. It also noted its rulings in points 3a and 3b above.

The Panel considered that the claim was all embracing as alleged and a breach of Clause 7.8 of the Code was ruled.

Complaint received **7 March 2001**

Case completed **31 May 2001**

CASE AUTH/1162/3/01

GLAXOSMITHKLINE v ASTRAZENECA

Promotion of Oxis 12 Turbohaler and Bricanyl Turbohaler

GlaxoSmithKline complained about the promotion of the Oxis 12 Turbohaler (eformoterol) and the Bricanyl Turbohaler (terbutaline) by AstraZeneca.

A leavepiece entitled 'Long-acting bronchodilators are not the same' gave details of two studies which examined the effect of adding a long-acting inhaled ß$_2$-agonist to therapy with inhaled corticosteroids in patients with asthma. The FACET study was a clinical study which examined the hypothesis that adding Oxis 12 to therapy with inhaled budesonide (AstraZeneca's Pulmicort) would improve symptoms of asthma without a long-term worsening of the disease. The salmeterol meta-analysis study was a retrospective data analysis to compare the efficacy and effect on long-term disease control of either adding salmeterol (GlaxoSmithKline's Serevent) or at least doubling the dose of inhaled steroid in asthma patients symptomatic on low to moderate doses of inhaled steroid alone.

When the leavepiece was fully extended, the study details were laid out side by side.

The FACET study showed that severe exacerbations of asthma were reduced compared with low dose Pulmicort 100mcg bd by 49% with Pulmicort 400mcg bd and by 63% with Oxis 12 and Pulmicort 400mcg bd. Mild exacerbations were reduced compared with low dose Pulmicort 100mcg bd by 37% with Pulmicort 400mcg bd and by 62% with Oxis 12 and Pulmicort 400mcg bd. The percentages referred to were absolute reductions and were presented in red triangles. In the salmeterol meta-analysis study the relative reduction for any exacerbation (mild, moderate, severe) was 2.73%, for moderate or severe exacerbation the relative reduction was 2.42%. The results were presented in black circles.

GlaxoSmithKline stated that the FACET and salmeterol meta-analysis studies were radically different and the details of differences in the studies were referred to in the text; however, the impression given throughout was that eformoterol had a greater effect on exacerbations than salmeterol when added to inhaled corticosteroids. This impression was enhanced by the downward pointing arrows bearing the percentage reductions in exacerbations for eformoterol and the circles bearing the percentage reductions in exacerbations for salmeterol. GlaxoSmithKline was unaware of any studies that had directly compared the effects of adding salmeterol or eformoterol on exacerbation of asthma. It was difficult to understand the rationale for placing two different studies side-by-side in the material if it was not to invite the reader to compare the studies. GlaxoSmithKline alleged that the artwork did not give a clear, fair or balanced view of the matters and the juxtaposition of the studies was misleading. In the Panel's view, the leavepiece would be opened out and read such that the details of the two studies were next to each other. The presentation of the results of the two studies, in red triangles (FACET) or black circles (salmeterol meta-analysis), caught the eye. The design was such that the reader would be drawn to the results of the FACET study and compare these directly with the results of the salmeterol meta-analysis study. The studies were not directly comparable. The juxtaposition of the studies would encourage such comparisons to be made. In the Panel's view the presentation was misleading and breaches of the Code were ruled.

GlaxoSmithKline stated that the presentation of the two studies in the leavepiece was intended to compare (or contrast) the salmeterol meta-analysis study and FACET. The salmeterol meta-analysis study compared the rate of exacerbations for salmeterol plus inhaled corticosteroids versus at least doubling the dose of inhaled corticosteroids. In the majority of the studies analysed the baseline dose of beclomethasone was 400mcg/day, and the 24-week exacerbation rates were reduced more by the addition of salmeterol than by increasing the steroid dose. In addition, one study used a dose of beclomethasone 200mcg/day (comparative to the dose of budesonide 100mcg bd). If the FACET and the salmeterol meta-analysis studies were to be juxtaposed, as in this leavepiece, the inclusion of the eformoterol versus increased dose of steroid data was critical to an understanding of the balance of evidence. GlaxoSmithKline alleged that the data, as shown, was unbalanced and misleading. The Panel considered that in essence this allegation was covered by its first ruling above. The Panel noted the different doses of budesonide used in FACET and that only some of the data had been provided in the leavepiece. The Panel noted that giving the higher dose of budesonide resulted in a greater reduction in the rate of severe exacerbations than did the addition of eformoterol to the lower dose of budesonide. The Panel considered that the omission of this data from the leavepiece was misleading and a breach of the Code was ruled.

GlaxoSmithKline alleged that the terms 'absolute reduction' and 'relative reduction', positioned below the triangles and circles for reduction in exacerbation rates, were misused, implying a greater real effect for eformoterol than salmeterol. The FACET study results were based on the difference in 12-month exacerbation rates divided by the low dose inhaled corticosteroid rate. This was a result relative to the low dose inhaled exacerbation rate and thus was a relative reduction and not an absolute reduction as stated. The salmeterol meta-analysis study results were based on the absolute differences in percentages of patients with exacerbations between the treatment arms ie one percentage minus the other and therefore these results were absolute reductions and not relative reductions as stated. It was alleged that the claims were inaccurate and misleading.

The Panel noted that the figures for the FACET study represented relative reduction rates. It was misleading to refer to them as 'absolute reduction' and a breach of the Code was ruled as accepted by

AstraZeneca. With regard to the salmeterol meta-analysis study, it was stated that for exacerbations the measure was the difference in the percentage of participants with one or more exacerbations in the group where salmeterol was added to a low moderate dose of inhaled steroid compared with the increased dose of inhaled steroids (at least double the dose). This was stated in the leavepiece. It appeared that the results were a simple subtraction and that the rate of exacerbations with the low to moderate dose of inhaled steroid was not taken into account in the calculated reductions. It was misleading to refer to the results as 'relative reduction' and a breach of the Code was ruled.

GlaxoSmithKline stated that the studies deliberately compared different patient types. The FACET study evaluated well-controlled patients. Only those patients whose asthma was stable at the end of a four week run-in period were randomised for entry to the study. By contrast, the salmeterol meta-analysis study analysed the pooled results from nine individual studies, which evaluated poorly controlled patients. The leavepiece failed to make this clear only stating 'Patient asthma control was not a prerequisite for entering the study'. However patients in the salmeterol meta-analysis study would have been ineligible for the FACET study. This difference was not made clear. The differences in definition of exacerbations and clinical identification of exacerbations significantly effected the primary outcomes of the studies. The omission of these details therefore reduced the ability of the reader to assess that comparisons could not be made between the studies. GlaxoSmithKline alleged that the lack of mention of these differences in study design and exacerbation criteria was misleading. The Panel noted that there were differences between the studies with regard to the entry criteria and the definition of exacerbations. Readers could not assess the data as insufficient detail had been given. The Panel considered that it was misleading not to give fuller details about the selection criteria and the definitions of exacerbations and a breach of the Code was ruled.

GlaxoSmithKline stated that reference 3 was an incorrect reference, as it referred to a paediatric study of salmeterol as monotherapy and beclomethasone, whereas eformoterol did not have a paediatric licence. It was also misleading as the impression given was that the quotation was from the Verberne study referenced, whereas it was in fact from the FACET study. The Panel noted that the quotation was from the FACET study and not from Verberne *et al* (1997). It was inaccurately referenced and a breach of the Code was ruled.

GlaxoSmithKline stated that its view of the promotional intention behind the leavepiece was reinforced by events that took place at a medical meeting at a hospital in February where an AstraZeneca representative and an honorary associate specialist, who was also a member of staff at GlaxoSmithKline, had discussed the leavepiece. The representative had said that AstraZeneca had a great deal of evidence showing the effectiveness of Oxis in reducing exacerbations, while Allen & Hanburys despite all its efforts was unable to produce such convincing evidence for salmeterol. The Panel noted that the parties' account of events differed; it was difficult to know exactly what had transpired between them. The Panel considered that the matter was covered by its rulings regarding the leavepiece.

A Bricanyl Turbohaler journal advertisement included a photograph of Turbohalers sitting in an aeroplane. The phrase 'Business class image' appeared top left and the phrase 'Economy class price' appeared bottom right. Beneath the photograph was 'turbohaler' in logo form followed immediately by the claim 'Performance you expect at a price you don't'. GlaxoSmithKline stated that it was clear that the reader was being invited to think of the Bricanyl Turbohaler as having an upper level image, which was provided at a bargain or economy price. A price comparison of all the reliever medications in all inhaler devices (MDI and DPI) was provided. It displayed the seventeen inhaler presentations available and gave a cost per dose and also a cost per dose range. This showed that the cost of the recommended dose range of nine inhalers was between 1.74 and 4.8p. Six fell within the range 5.4 to 6.4p (including the Turbohaler, which was towards the top of that range). Two cost more than 6.4p. Fifteen presentations cost less than the Turbohaler. GlaxoSmithKline stated that while the price of the Bricanyl Turbohaler might not be first class, it was clear that it was very much in the business class rather than the economy class. Given the comparative price data, GlaxoSmithKline alleged that the image/price comparisons were misleading The Panel noted that there were a number of products that were less expensive than the Turbohaler preparations. It was true that Bricanyl Turbohaler, whilst not the most expensive medication, was not the least expensive. The Panel considered that the advertisement implied that economy class was the cheapest flight price. This analogy was not true for Bricanyl Turbohaler. The impression from the advertisement was misleading; it implied that Bricanyl Turbohaler was one of the least expensive asthma medications and that was not so. It was a middle range priced product. A breach of the Code was ruled.

In relation to the claim 'Performance you expect at a price you don't',GlaxoSmithKline stated that it was unaware of any data detailing health professionals' expectations of the price of a Turbohaler. However, it considered that the reader was again being invited to expect that the Turbohaler cost less than would be anticipated. As the price of the Bricanyl Turbohaler was greater than the vast majority of $ß_2$ agonist inhalers, including dry powder inhalers, it alleged that the claim was misleading. The Panel noted the submission from AstraZeneca that US market research indicated that many prescribers considered that relative to other dry powder inhalers the Turbohaler was an expensive or premium price device. The Panel noted its previous ruling. On balance it considered that, in the context of an advertisement implying that Bricanyl Turbohaler was one of the least expensive treatments, the claim was misleading and a breach of the Code was ruled.

Another Bricanyl Turbohaler journal advertisement

featured a photograph of a Turbohaler sitting in a deckchair on a beach with the phrase 'Barbados image' and 'Bognor price' and the claim 'Performance you expect at a price you don't'. GlaxoSmithKline stated that the image of Barbados was clearly one of expense and luxury, whereas the Bognor price implied bottom of the market and cheap. In terms of costings provided, it was clear that the Turbohaler was very much in the Barbados (or at least the Canary Isles) price bracket rather than the Bognor category claimed. GlaxoSmithKline considered that the image/price comparisons were misleading. The Panel considered that this was similar to the previous point; the advertisement implied that Bognor was the cheapest holiday destination. This analogy was not true for Bricanyl Turbohaler which, although not the most expensive asthma medication, was not the least expensive either. The Panel considered that the advertisement was misleading and a breach of the Code was ruled.

GlaxoSmithKline complained about the promotion of Oxis 12 Turbohaler (eformoterol) and Bricanyl Turbohaler (terbutaline) by AstraZeneca UK Limited.

A Leavepiece 'Long acting bronchodilators are not the same'

The leavepiece (ref OXIS 00 7078) was folded into 8 pages. It was distributed by representatives and gave details of two studies which examined the effect of adding a long-acting inhaled $ß_2$-agonist to therapy with inhaled corticosteroids in patients with asthma. The FACET study was a clinical study which examined the hypothesis that adding Oxis 12 to therapy with inhaled budesonide (AstraZeneca's product Pulmicort) would improve symptoms of asthma without a long-term worsening of the disease. The salmeterol meta-analysis study was a retrospective data analysis to compare the efficacy and effect on long-term disease control of either adding salmeterol (GlaxoSmithKline's product Serevent) or at least doubling the dose of inhaled steroid in asthma patients symptomatic on low to moderate doses of inhaled steroid alone.

A1 Comparison of the FACET and salmeterol meta-analysis studies

When the leavepiece was fully extended, two pages (in yellow) on the left-hand side referred to the FACET Study; the following two pages (on the right-hand side) referred to the salmeterol meta-analysis study (in green). The study details were thus laid out side by side. For each study the method, dosages etc and results were given.

The FACET study results were that severe exacerbations of asthma were reduced compared with low dose Pulmicort 100mcg bd by 49% with Pulmicort 400mcg bd and by 63% with Oxis 12 and Pulmicort 400mcg bd. Mild exacerbations were reduced compared with low dose Pulmicort 100mcg bd by 37% with Pulmicort 400mcg bd and by 62% with Oxis 12 and Pulmicort 400mcg bd. The percentages referred to were absolute reductions and were presented in red triangles.

In the salmeterol meta-analysis study the relative reduction for any exacerbation (mild, moderate, severe) was 2.73%, for moderate or severe exacerbation the relative reduction was 2.42%. The results were presented in black circles.

COMPLAINT

GlaxoSmithKline stated that the FACET and salmeterol meta-analysis studies were radically different and the details of differences in the studies were referred to in the text; however, the impression given throughout was that eformoterol had a greater effect on exacerbations than salmeterol when added to inhaled corticosteroids. This impression was enhanced by the downward pointing arrows bearing the percentage reductions in exacerbations for eformoterol and the circles bearing the percentage reductions in exacerbations for salmeterol.

GlaxoSmithKline raised the issue with AstraZeneca which agreed that the intent of the leavepiece was to compare the FACET and the salmeterol meta-analysis studies, with the studies being presented 'in a comparative situation'. AstraZeneca replied to GlaxoSmithKline that 'The layout chosen to present both studies was consistent, with similar or identical headings being used to identify the study categories described above, enabling the reader to clarify more readily how the two studies differ'.

GlaxoSmithKline disagreed. It considered that the juxtaposition of the results on pages that faced each other when the leavepiece was opened highlighted the direct comparison, which was being made between the studies. In spite of disclaimers which appeared in the text, GlaxoSmithKline considered that the reader would be left with the impression that the studies were being compared and that eformoterol had a greater effect on exacerbations than salmeterol when added to inhaled corticosteroids.

GlaxoSmithKline was unaware of any studies that had directly compared the effects of adding salmeterol or eformoterol on exacerbation of asthma. It was difficult to understand the rationale for placing two different studies side-by-side in the material if it was not to invite the reader to compare the studies.

This belief was reinforced by representative activity (point A6).

GlaxoSmithKline alleged that the artwork did not give a clear, fair or balanced view of the matters.

Reference was made to Case AUTH/866/4/99 where the Panel considered that the data presented and the layout invited a direct comparison of the results of different studies, which was misleading. In that case breaches of Clauses 7.2 and 7.6 were ruled.

Although the study design was described in the text, the juxtaposition of these studies, where like was not compared with like, was misleading and was alleged to be in breach of Clauses 7.2 and 7.6 of the Code.

RESPONSE

AstraZeneca stated that the leavepiece was prepared to address some of the important differences between

a GlaxoSmithKline meta-analysis of salmeterol data and the FACET study evaluating eformoterol, which were unclear amongst health professionals.

The meta-analysis of salmeterol and FACET publications were important in that they reported the effect on asthma exacerbations of the addition of long-acting bronchodilators to inhaled steroids. The publications however differed greatly in their data sources and methodology. These differences were important for proper understanding of the results of the two studies.

Following publication of the salmeterol meta-analysis results, Allen and Hanburys sponsored the publication of supplements, which provided an overview of the data and the views of a specialist group that had considered the implication for clinical practice. In these supplements brief reference was also made to the FACET study but the level of detail was inadequate for readers to understand what was different about the studies. As a result the FACET study was poorly understood, either it was considered to be very similar to the salmeterol meta-analysis or it was known to be different but not how it differed.

The leavepiece was designed specifically to provide sufficient information on both studies to highlight the major differences between the studies, particularly to make it clear that they could not be considered comparable. It contained no statements or claims of a competitive nature but presented a factual overview of the methodology and findings from two very different pieces of work.

With regard to GlaxoSmithKline's view that the juxtaposition of the results on pages that faced each other when the leavepiece was opened out highlighted the direct comparison, AstraZeneca noted that the more normal way of reading the leavepiece might be to turn the pages like a book, in which case the studies were read separately. The leavepiece was designed in this way.

AstraZeneca disagreed that the layout of the studies in this leavepiece was misleading. The piece was developed specifically to communicate the differences between the studies. Differences between the studies were clearly presented in the text, and graphically different background colours and symbols emphasised non-comparability.

AstraZeneca noted that the complainant referred to a previous case (Case AUTH/866/4/99) where what were described as similar studies were compared in the absence of comparative data. The company submitted that this case was not relevant as the leavepiece in question made plain that these were different studies.

PANEL RULING

The Panel noted the layout of the leavepiece. In the Panel's view the leavepiece would be opened out and read such that the details of the two studies were next to each other. The presentation of the results of the two studies, in red triangles (FACET) or black circles (salmeterol meta-analysis), caught the eye. The design was such that the reader would be drawn to the results of the FACET study and compare these directly with the results of the salmeterol meta-analysis study. The studies were not directly comparable. The juxtaposition of the studies would encourage such comparisons to be made. In the Panel's view the presentation was misleading. Breaches of Clauses 7.2 and 7.6 of the Code were ruled.

A2 Severe exacerbation

COMPLAINT

GlaxoSmithKline stated that the leavepiece quoted a 63% reduction in exacerbation rate for patients on eformoterol 12mcg bd plus budesonide 400mcg bd compared with low dose inhaled corticosteroids (budesonide 100mcg bd).

The figure of a 63% reduction in exacerbations (achieved with eformoterol and the four-fold higher dose of inhaled corticosteroids compared with the lower dose of inhaled corticosteroids) was clearly intended to be compared and contrasted with the 2.73% reduction in exacerbations achieved with salmeterol and inhaled corticosteroids compared with at least double the dose of inhaled corticosteroids.

The most common comparison in clinical practice, endorsed by the British Guidelines on Asthma Management, was between long-acting $ß_2$ agonists plus low dose inhaled corticosteroids compared with high dose inhaled corticosteroids. For the FACET study this comparison for severe exacerbations showed that there was a 26% reduction for the eformoterol plus low dose budesonide group, but a 49% reduction for the high dose budesonide group. Hence high dose budesonide was more effective in reducing exacerbations.

In fact in the FACET study, the authors stated: 'Giving the higher dose of budesonide resulted in a greater reduction in the rate of severe exacerbations than did the addition of formoterol (p=0.03)'.

GlaxoSmithKline stated that the presentation of the two studies in the leavepiece was intended to compare (or contrast) the salmeterol meta-analysis study and FACET. The salmeterol meta-analysis study compared the rate of exacerbations for salmeterol plus inhaled corticosteroids versus at least doubling the dose of inhaled corticosteroids. In the majority of the studies analysed the baseline dose of beclomethasone was 400mcg/day, and the 24-week exacerbation rates were reduced more by the addition of salmeterol than by increasing the steroid dose. In addition, one study used a dose of BDP 200mcg/day (comparative to the dose of budesonide 100mcg bd).

If the FACET and the salmeterol meta-analysis studies were to be juxtaposed, as in this leavepiece, the inclusion of the eformoterol versus increased dose of steroid data was critical to an understanding of the balance of evidence.

GlaxoSmithKline alleged that the data, as shown, was unbalanced and misleading, in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that the data on exacerbations accurately represented the findings from the studies, and further demonstrated methodological differences between the studies. The FACET study included four treatment arms comprising low dose inhaled steroid (budesonide 100mcg bd), low dose steroid plus eformoterol 12mcg bd, high dose inhaled steroid (budesonide 400mcg bd) and high dose plus eformoterol 12mcg bd. The study showed that the addition of eformoterol to both low and high dose inhaled steroid reduced the number of both mild and severe exacerbations compared with that dose of inhaled steroid alone. Compared with low dose inhaled steroid, high dose alone significantly reduced both mild and severe exacerbations.

The data presented were selected to demonstrate that, compared to low dose inhaled steroid, both high dose steroid alone and high dose steroid plus eformoterol might substantially reduce both mild and severe exacerbations.

The salmeterol meta-analysis study compared only low to moderate doses of inhaled steroid plus salmeterol with 'at least double the dose of inhaled steroid' and the key findings were presented in the leavepiece. No combination of these doses was even broadly similar to the doses in FACET where there was a fourfold difference between low and high doses of inhaled steroid. Therefore it would be impossible to show comparable data – a further illustration of the differences between the studies.

AstraZeneca stated that the complainant seemed to suggest that a comparison of low dose budesonide plus eformoterol versus high dose budesonide would be more appropriate. Clearly this would be no more valid as the doses between the studies were not comparable. Furthermore, the comparison of low dose steroid plus eformoterol with high dose steroid alone was not a primary comparison in the FACET study. GlaxoSmithKline was correct that such a comparison would have shown that the reduction of severe exacerbations was greater with the four-fold higher dose steroids than low dose budesonide plus eformoterol. However, the reduction, in mild exacerbations, would have been 40% with low dose budesonide plus eformoterol compared with 37% with the much higher dose budesonide.

The presentation of the data was balanced and not misleading.

PANEL RULING

The Panel considered that in essence this allegation was covered by its rulings in A1 above. The Panel noted the different doses of budesonide used in FACET and that only some of the data had been provided in the leavepiece. The Panel noted that giving the higher dose of budesonide resulted in a greater reduction in the rate of severe exacerbations than did the addition of eformoterol to the lower dose of budesonide (p=0.03). The Panel considered that the omission of this data from the leavepiece was misleading. The Panel ruled a breach of Clause 7.2 of the Code.

A3 Use of the terms 'absolute reduction' and 'relative reduction'

COMPLAINT

GlaxoSmithKline alleged that the terms 'absolute reduction' and 'relative reduction', positioned below the triangles and circles for reduction in exacerbation rates, were misused, implying a greater real effect for eformoterol than salmeterol.

The FACET study results were based on the difference in 12-month exacerbation rates divided by the low dose inhaled corticosteroid rate. This was a result relative to the low dose inhaled exacerbation rate and thus was a relative reduction and not an absolute reduction as stated.

The salmeterol meta-analysis study results were based on the absolute differences in percentages of patients with exacerbations between the treatment arms ie one percentage minus the other and therefore these results were absolute reductions and not relative reductions as stated.

GlaxoSmithKline alleged that the claims were inaccurate and misleading and in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that it was unclear how these terms might imply a greater effect for eformoterol when the studies and the variables were so different that comparison was, in any case, inappropriate. The terms were applied because of the different way that percentage differences between treatments were derived in each study. In the FACET study, differences in the rate of exacerbation (rate treatment A – rate treatment B) were converted to percentages by dividing by the comparator rate (treatment B) and multiplying by 100. In the salmeterol meta-analysis study the measure was the difference in the percentage of patients with one or more exacerbations, as the measure was already a percentage, simple subtraction was sufficient to derive a percentage reduction.

AstraZeneca did not agree that the salmeterol meta-analysis study results were based upon absolute differences, however in retrospect it accepted that the term 'absolute reduction' was misapplied to the FACET data as these should also show relative reduction.

In the light of this new issue which was not previously raised in intercompany correspondence it had withdrawn the leavepiece.

PANEL RULING

The Panel noted that the figures in the leavepiece for the FACET study represented relative reduction rates. They were calculated as described by GlaxoSmithKline. It was misleading to refer to them as 'absolute reduction' and a breach of Clause 7.2 was ruled as accepted by AstraZeneca.

With regard to the salmeterol meta-analysis study it was stated that for exacerbations the measure was the difference in the percentage of participants with one or more exacerbations in the group where salmeterol

was added to a low moderate dose of inhaled steroid compared with the increased dose of inhaled steroids (at least double the dose). This was stated in the leavepiece. It appeared that the results were a simple subtraction and that the rate of exacerbations with the low to moderate dose of inhaled steroid was not taken into account in the calculated reductions. In the Panel's view the data was calculated as described in GlaxoSmithKline. It was misleading to refer to the results as 'relative reduction' and a breach of Clause 7.2 was ruled.

A4 Study Design

COMPLAINT

GlaxoSmithKline stated that the studies deliberately compared different patient types. The FACET study evaluated well-controlled patients. The study protocol required patients to enter a 4-week run-in period during which they were treated with budesonide at a dose of 800mcg twice daily (the maximum licensed dose in the UK). Only those patients whose asthma was stable at the end of this period were randomised for entry to the study. By contrast, the salmeterol meta-analysis study analysed the pooled results from nine individual studies, which evaluated poorly controlled patients. The leavepiece failed to make this clear only stating: 'Patient asthma control was not a prerequisite for entering the study'. However patients in the salmeterol meta-analysis study would have been ineligible for the FACET study. This difference was not made clear.

In view of the focus of the leavepiece the most important comparison might be taken to be exacerbations. However, the fact that the studies used different definitions of exacerbations was not stated.

In the salmeterol meta-analysis study, exacerbations were defined as:

Mild exacerbation – the requirement for an increase in rescue medication.

Moderate exacerbation – the requirement for an increase in inhaled steroid medication

Severe exacerbation – the requirement for oral steroids or admission to hospital.

The analysis looked at 'any exacerbation', and 'moderate or severe exacerbations'.

In the FACET study, a severe exacerbation was defined as requiring oral steroids or a decrease in peak expiratory flow (PEF) to more than 30% below baseline value on two consecutive days. A mild exacerbation was defined as a 20% decrease in PEF below baseline value, the use of more than three additional inhalations of short-acting $ß_2$ agonist or a night-time awakening.

GlaxoSmithKline stated that the differences in definition of exacerbations and clinical identification of exacerbations significantly affected the primary outcomes of the studies. The omission of these details therefore reduced the ability of the reader to assess that comparisons could not be made between the studies.

GlaxoSmithKline alleged that the lack of mention of these differences in study design and exacerbation criteria were misleading in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that the studies, as noted by GlaxoSmithKline and clearly presented in the leavepiece, did indeed involve different patient types, although not quite as outlined in the complaint. In FACET, for selection for the study, patients had to be treated with inhaled steroids and have persistent symptoms. During the 4-week run-in period they received budesonide 800mcg bd and were eligible for randomisation if at the end of the run-in they had complied with treatment and their asthma was stable.

The studies included in the salmeterol meta-analysis all randomised similar patients. These were patients who had symptoms (yes/no) or a minimum symptom score during the last seven days of the run-in period during which they continued their regular medication.

It was not correct to state that the patients from the salmeterol meta-analysis would have been ineligible for FACET as they would have met the criteria for selection. However, the difference between the studies in the run-in period ie high dose steroids to gain stability of asthma in FACET and continuance of existing treatment in the salmeterol meta-analysis, would by design lead to differences in the asthma control of the patients at the time of randomisation. Hence AstraZeneca believed that the statement in the leavepiece that 'asthma control was not a prerequisite for entry' in the salmeterol meta-analysis was a very accurate reflection of the difference. It was clear from the leavepiece that there were differences in patient inclusion criteria and it was not misleading.

The specific definitions of exacerbations used in the studies could have been included in the leavepiece, although in AstraZeneca's view the clinical differences resulting from the different definitions were of limited significance alongside the major differences in data sources and methodology. As it was quite clear that the data from these two studies were not comparable, it would not be helpful to include the definitions.

PANEL RULING

The Panel noted that there were differences between the studies with regard to the entry criteria and the definition of exacerbations. Readers could not assess the data as insufficient detail had been given. The Panel considered that it was misleading not to give fuller details about the selection criteria and the definitions of exacerbations. A breach of Clause 7.2 was ruled.

A5 References

COMPLAINT

GlaxoSmithKline stated that reference 3 was an incorrect reference, as it referred to a paediatric study of salmeterol as monotherapy and beclomethasone,

whereas eformoterol did not have a paediatric licence. AstraZeneca acknowledged that this reference was inaccurate. It was also misleading as the impression given was that the quotation was from the Verberne study referenced, whereas it was in fact from the FACET study. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

AstraZeneca stated that it had acknowledged the error in this reference in correspondence with GlaxoSmithKline. It accepted that the reference was inaccurate; it did not believe that this typographical error was misleading.

PANEL RULING

The Panel noted that reference 3 appeared beside a quotation that the FACET study demonstrated that 'It is important to emphasise that our conclusions may apply only when formoterol (Oxis Turbohaler 12) is given with an inhaled glucocorticoid'.

The quotation was from the FACET study and not from Verberne *et al* (1997). It was inaccurately referenced and a breach of Clause 7.2 of the Code was ruled.

A6 Statements made by a representative at a medical meeting

COMPLAINT

GlaxoSmithKline stated that its view of the promotional intention behind the leavepiece was reinforced by events that took place at a medical meeting at a hospital on Thursday, 22 February.

One of the company's associate medical directors was present in his position as associate specialist in the department of respiratory medicine. The lunchtime scientific meeting was sponsored by AstraZeneca. An AstraZeneca representative was looking after the stand. The leavepiece in question was on the stand. The representative, without prompting, told the associate medical director, while showing him the leavepiece, that AstraZeneca had a great deal of evidence showing the effectiveness of Oxis in reducing exacerbations, while Allen & Hanburys despite all its efforts was unable to produce such convincing evidence for salmeterol.

GlaxoSmithKline alleged that this activity was in breach of Clause 7.2 of the Code.

In view of the fact that the company was also receiving reports from customers that AstraZeneca representatives were talking about a 63% reduction in exacerbations with formoterol compared with 2.73% with salmeterol, GlaxoSmithKline stated that it would be grateful if the Authority would review the briefing materials given to the AstraZeneca field force on the FACET and salmeterol meta-analysis studies.

RESPONSE

AstraZeneca stated that it had identified the representative concerned who had been interviewed by her area manager.

The representative clearly recalled meeting the associate medical director as she recognised him from a previous meeting as a fellow industry employee working at that time, she believed, for Allen & Hanburys. However on speaking with him it became apparent that he also worked at the hospital part-time in the respiratory department. The representative was adamant that she did not initiate the conversation. Instead she remembered him informing her that, in his practice, he did not have any experience of using Oxis and would she list the main differences between Oxis and salmeterol.

AstraZeneca stated that the representative then correctly informed him that Oxis, compared with salmeterol, had a faster onset of bronchodilatory effect and that based on equivalent doses, Oxis was the cheaper long-acting bronchodilator.

The representative then, using the leavepiece to make reference to the FACET study, demonstrated the effect adding in Oxis to inhaled corticosteroid therapy had on reducing asthma exacerbations compared with inhaled corticosteroids alone. Throughout this conversation, she was fully aware that owing to the associate medical director's position and experience he was sure to have a great deal of knowledge about clinical trials in this area.

She then referred to the salmeterol meta-analysis, but not in terms of making a direct comparison to FACET, but to emphasise the fact that the salmeterol meta-analysis was so different from the FACET study in terms of inclusion criteria, treatment duration and dosages, that the results of FACET could not be extrapolated to infer a class effect. The representative then went on to point out that GlaxoWellcome had not yet reproduced the results that the FACET study had shown for Oxis, in terms of reducing asthma exacerbations, in a similar study with its long-acting bronchodilator, salmeterol. To this the associate medical director made no comment.

AstraZeneca firmly believed that, in this particular instance, the representative used the leavepiece in the manner it was intended and questioned whether the associate medical director's perception of the discussion reflected pre-existing concerns with the promotional piece in question. It did not accept that a breach of Clause 7.2 occurred.

* * * * *

AstraZeneca's response was sent to GlaxoSmithKline for comment.

FURTHER COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that its associate medical director had not previously attended a meeting in the postgraduate centre where there was representation from AstraZeneca. In fact his attendance at these meetings only commenced this year when he changed his clinic day.

It was possible that the representative recognised him from his time as a general practitioner but he did not recognise the representative and she showed no sign

of recognising him at any stage of the short discussion that took place.

He did not identify himself, but he was wearing his hospital badge which identified him as an honorary associate specialist.

There were many members of the hospital staff around the stand prior to the lunch-time lecture and when he arrived at the stand the representative was talking to another doctor. He picked up the leavepiece in question. The representative asked him whether she could tell him anything about it. He then asked what the comparison between the two medicines showed. The representative then stated that it showed Oxis to be effective at reducing exacerbations and that 'despite all its efforts' Allen & Hanburys had been unable to produce similar results for salmeterol. The associate medical director made no comment other than thanking her for the information and left the stand.

There were no discussions on cost or on onset of action of Oxis, although the associate medical director was aware that as there was in excess of 50 hospital staff at the meeting, discussions on these topics might have taken place between the representative and another member of staff.

PANEL RULING

The Panel noted that the parties' account of events differed; it was difficult to know exactly what had transpired between the parties.

The Panel noted that the representative and the member of staff from GlaxoSmithKline had discussed the leavepiece at issue. The Panel considered that the matter was covered by its rulings regarding the leavepiece. A breach of Clause 7.2 was ruled.

B 'Business Class Image' Bricanyl Turbohaler advertisement

The advertisement (ref TURB 00 7395) included a photograph of Turbohalers sitting in a aeroplane. The phrase 'Business class image' appeared top left and the phrase 'Economy class price' appeared bottom right. Beneath the photograph was 'turbohaler' in logo form followed immediately by a claim 'Performance you expect at a price you don't'.

B1 'Business Class Image' 'Economy class price'

COMPLAINT

GlaxoSmithKline stated that it was clear that the reader was being invited to think of the Bricanyl Turbohaler as having an upper level image, which was provided at a bargain or economy price.

A price comparison of all the reliever medications in all inhaler devices (MDI and DPI) was provided. It displayed the seventeen inhaler presentations available and gave a cost per dose and also a cost per dose range. This took into account the direction on some inhalers that '1 puff or 2 puffs' might be administered.

GlaxoSmithKline stated that where the probable equivalent dose of the seventeen preparations available was compared, in terms of cost, the products would seem to fall broadly into three categories. Nine fell within the cost range 1.74 to 4.8p (including the Bricanyl metered dose inhaler, which was less than half the price of the Bricanyl Turbohaler). Six fell within the range 5.4 to 6.4p (including the Turbohaler, which was towards the top of that range). Two cost more than 6.4p.

The cost differences shown in the cost table were further exaggerated if the cost of one inhalation from each of the preparations was compared. In this instance fifteen presentations cost less than the Turbohaler.

In terms of typical examples of the price differential between business and economy class travel, GlaxoSmithKline stated that while the price of the Bricanyl Turbohaler might not be first class, it was clear that it was very much in the business class rather than the economy class.

Given the comparative price data, GlaxoSmithKline alleged that the image / price comparisons were misleading and in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca referred to market research from which it became apparent that many prescibers considered that relative to other dry powder inhalers (DPI) the Turbohaler was an expensive or premium price device.

However, according to the price comparisons provided the cost per inhalation of all short-acting bronchodilators available in a dry powder inhaler (whether 1 or 2 puffs were recommended per day) was between 3 and 10 pence. Bricanyl Turbohaler cost 6.3 pence per dose and therefore, although not the cheapest short-acting device on the market, it was definitely not the most expensive.

Of course short-acting bronchodilators presented in a pMDI, particularly generics, were in many cases much less expensive than DPI devices but this was generally known and accepted. It was the relative cost of Turbohaler and other DPI devices that was commented upon.

AstraZeneca stated that it was this misconception that the advertisement was designed to address. Associating an image of an 'Economy class price' with the cost of Turbohaler was not inappropriate. An economy class air ticket implied one that was of an affordable and standard price. It did not imply that it was the cheapest, as was apparent from consideration of, for example, the cost of a scheduled airline economy ticket and a ticket from a budget airline. In the cost calculations provided, the Turbohaler could be seen to fall well within the average price range of dry powder inhalers.

To continue the theme of airline tickets and to make a suitable comparison, it associated the high standards and high level of service that one would expect when flying 'Business Class' with the high level of performance the Turbohaler delivered. The Turbohaler was well recognised for its performance in

terms of lung deposition, dose consistency, ease of use and patient preference.

The summary of an article in the European Respiratory Review, a peer-reviewed journal, stated:

> 'This article discusses the important attributes of an 'ideal inhaler', including portability, good deposition, ease of use, lower oropharyngeal side effects, minimal inspiratory effort and low cost. The author concludes that 'Some dry powder inhaler devices have many properties of the 'ideal' inhaler. For example, Turbohaler is portable, provides multiple doses (up to 200 without refilling), requires little co-ordination to use, achieves optimal lung deposition, contains no harmful additives, and is more efficient than other delivery devices, allowing lower dosing regimens to be prescribed with an equivalent antiasthmatic effect'.

The imagery and price comparisons used in the advertisement were appropriate for the message intended and not likely to mislead the reader. AstraZeneca did not believe it had breached Clause 7.2 of the Code.

PANEL RULING

The Panel noted that there were a number of products that were less expensive than the Turbohaler preparations. It was true that Bricanyl Turbohaler whilst not the most expensive medication, was not the least expensive. The Panel considered that the advertisement implied that economy class was the cheapest flight price. This analogy was not true for Bricanyl Turbohaler. The impression from the advertisement was misleading; it implied that Bricanyl Turbohaler was one of the least expensive asthma medications and that was not so. It was a middle range priced product. A breach of Clause 7.2 of the Code was ruled.

B2 Claim 'Performance you expect at a price you don't'

COMPLAINT

GlaxoSmithKline stated that it was unaware of any data detailing health professionals' expectations of the price of a Turbohaler. However, it considered that the reader was again being invited to expect that the Turbohaler costs less than would be anticipated.

As the price of the Bricanyl Turbohaler, as detailed in the cost comparison provided, was greater than the vast majority of $ß_2$-agonist inhalers including dry powder inhalers, it alleged that the claim was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that in the same vein, US market research indicated that many prescribers considered that relative to other DPIs the Turbohaler was an expensive or premium price device. It was also apparent that the Turbohaler was recognised for its high level of performance, as had also been referenced above. The advertisement was merely playing this back to the intended audience.

AstraZeneca considered that the claim was appropriate for the purpose of conveying the message and did not believe it to be either misleading or in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted the submission from AstraZeneca that US market research indicated that many prescribers considered that relative to other dry powder inhalers the Turbohaler was an expensive or premium price device.

The Panel noted its ruling in point B1 above. On balance it considered that in the context of an advertisement implying that Bricanyl Turbohaler was one of the least expensive treatments the claim was misleading. A breach of Clause 7.2 was ruled.

C 'Barbados Image' Bricanyl Turbohaler advertisement

The advertisement (ref TURB 00 7581) used a photograph of a Turbohaler sitting in a deckchair on a beach. The phrase 'Barbados image' appeared top left and the phrase 'Bognor price' appeared bottom right. As in B, above beneath the photograph was 'turbohaler' in logo form followed by a claim 'Performance you expect at a price you don't'.

C1 'Barbados Image' 'Bognor price'

COMPLAINT

GlaxoSmithKline stated that the image of Barbados was clearly one of expense and luxury, whereas the Bognor price would seem to be intended to convey bottom of the market and cheap.

In terms of costings provided, it was clear that the Turbohaler was very much in the Barbados (or at least the Canary Isles) price bracket rather than the Bognor category claimed.

Given the comparative price data, GlaxoSmithKline considered that the image/price comparisons were misleading and in breach of Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that as in the Turbohaler advertisement referred to in point B, the purpose behind this advertisement was again to address the misconception amongst prescribers that the Turbohaler relative to other DPIs was an expensive or premium price device.

Again it was this misconception AstraZeneca wanted to address and considered that associating 'Bognor prices' with the cost of the Turbohaler did so appropriately. This was from the point of view that a holiday in Bognor implied an affordable and economical price, which, similar to the airfare comparison, was not necessarily the cheapest. From the cost comparison provided the Turbohaler could be seen to fall within the average price range of DPIs.

To continue the theme of holiday destinations and to

make a suitable comparison, AstraZeneca associated the high quality and high level of standards that that one would expect a holiday in Barbados to offer with the high level of performance the Turbohaler delivered.

PANEL RULING

The Panel considered that this was similar to point B1 above. The Panel considered that the advertisement implied that Bognor was the cheapest holiday destination. This analogy was not true for Bricanyl Turbohaler which, although not the most expensive asthma medication, was not the least expensive either. It was a middle range priced product.

The Panel considered that the advertisement was misleading and a breach of Clause 7.2 of the Code was ruled.

C2 Claim 'Performance you expect at a price you don't'

COMPLAINT

GlaxoSmithKline repeated its allegation in B2 above.

RESPONSE

AstraZeneca referred to its response in B2 above.

PANEL RULING

The Panel considered that this allegation was covered by its ruling in point B2 above.

Complaint received **9 March 2001**

Case completed **21 June 2001**

CASE AUTH/1163/3/01 ***NO BREACH OF THE CODE***

MEDICAL SECRETARY TO LOCAL MEDICAL COMMITTEE v AVENTIS PASTEUR MSD

Local purchasing group

The medical secretary to a local medical committee complained about a letter sent to local practices by an Aventis Pasteur MSD representative which gave details of discounts on vaccines which were 'currently available to the local purchasing group for your area'. The representative had apparently been visiting practices saying that he could facilitate bulk vaccine purchasing through the group. Upon enquiry, the complainant could find no such group having been set up by local primary care groups, the health authority or any consortium of local general practitioners. His committee was concerned that the group seemed to have been created by the company, rather than by the doctors themselves, and by the fact that it was limited to one company. It seemed to the complainant that the whole point of a purchasing group was to be able to shop around amongst the various companies which supplied vaccines and other products to general practices, in such a way that they gained the best advantage in terms of price, delivery and quality of goods.

In the Panel's view, it was perhaps unfortunate that the name of the local purchasing group was such that it might imply that it was officially associated with the local medical committee. This was not so. Although the purchasing group had been established at the suggestion of the local representative, it had actually been set up by a practice manager who acted as the authorised group organiser. The representative had written to others inviting them to join the group and so benefit from the discounts available. A list from Aventis Pasteur MSD showed that, in addition to the original general practice, fifteen others and one pharmacy had joined the group. The Panel noted that a purchasing group had to agree to purchase a minimum quantity of vaccines to qualify for defined levels of discount. In the Panel's view linking discounts to volume was not an unacceptable trade practice. The group did not have to buy any or all of its vaccines from Aventis Pasteur MSD and the terms of its agreement with the company did not prevent it from approaching other companies to request similar group buying benefits. The Panel appreciated the concern of the complainant but did not consider that the representative had behaved unethically by facilitating the formation of the local purchasing group and no breach of the Code was ruled.

The medical secretary to a local medical committee complained about the activities of a representative of Aventis Pasteur MSD Ltd in relation to references to a local purchasing group. The complainant provided a copy of a letter sent to local general practitioners by a senior representative of Aventis Pasteur MSD which had attached to it details of discounts on vaccines which were 'currently available to the local purchasing group for your area'. The letter referred to the range of support materials and services which were available in relation to vaccines and gave a contact telephone number for those wishing to join the group or wanting information and advice. A sheet of paper showing potential buying group discounts, headed 'Sheet 1' showed the account name '— Buying Group'.

COMPLAINT

The complainant said that he was writing to express his committee's concern over a problem brought to its attention by some local general practitioners. The representative had been visiting practices apparently stating that he was able to facilitate bulk vaccine purchasing through the '– local purchasing group'. Upon enquiry, the complainant could find no such

group having been set up by local primary care groups, the health authority or any consortium of general practitioners. He wondered therefore whether the representative was conducting himself correctly. The complainant stated that he had also written direct to Aventis Pasteur MSD.

RESPONSE

Aventis Pasteur MSD stated that it offered discounts to general practitioners from the NHS price of its vaccines. These discounts were related to the volume purchased and might be related to daily orders, product orders over a 12 month period or, in the case of a buying group, its collective product usage over a 12 month period.

Aventis Pasteur MSD explained that a buying group:

- was defined as a group of surgeries which agreed to purchase a minimum quantity of vaccine to qualify for defined levels of discount;
- did not have to be based on official PCG, PCT, LMC or HA boundaries;
- did have to have an agreed non-company co-ordinator to authorise the inclusion of surgeries into the group;
- was set up and maintained by following a process that was defined by the company;
- was not responsible for payment of invoices; that remained with the individual surgery.

All surgeries within the buying group were individually invoiced and delivered to.

The company submitted that the setting up of buying groups was a legitimate business practice co-ordinated from its head office and governed by a clear set of internal procedures and paper work, copies of which were provided. This information demonstrated that these guidelines had been followed for the buying group in question and that Aventis Pasteur MSD and its vaccine representative had operated within its guidelines and within the Code.

Aventis Pasteur MSD stated that buying groups were an opportunity for a number of practices to combine their individual orders into a single order. This maximised the volume related discount available to them and reduced the cost of the vaccines to all the practices involved. Practices were invited 'Should you wish to benefit from joining this group …' to join the group, but there was no compulsion or pressure for anyone to join the group or for any members of the group to buy any or all of their vaccines through the group. In addition the buying group had no organisational, administrative or any other role other than the option of collective purchasing of vaccines.

The purchasing group in question had been set up through the practice manager at a local group practice and included sixteen further practices and pharmacies in the area. Details of these were provided.

Aventis Pasteur MSD stated that, unfortunately, the local sales representative of another pharmaceutical company had generated much of the concern over this buying group. Aventis Pasteur MSD had been contacted by two practice managers for reassurance after they were told by that company's sales representatives that buying groups were 'illegal'. In one instance the practice manager was told that if they joined the group they could be 'fined up to £3000 by the ABPI'. Aventis Pasteur MSD had received no other expressions of concern from anywhere else in the UK.

FURTHER LETTER FROM COMPLAINANT

The complainant provided the Authority with a copy of a further letter which he had sent to Aventis Pasteur MSD.

This stated that he had made enquiries amongst his general practitioner colleagues and had found that of the names listed on the paperwork submitted by Aventis Pasteur MSD, at least two practices were unaware that they were on the list, and one practice had definitely withdrawn. The complainant understood that other practices were quite happy to be part of this group. What concerned the committee was not that doctors should band together to gain the advantages of bulk purchasing, but that this group seemed to have been created by a representative of the company, rather than being created by the doctors themselves. Also the products that this group intended to purchase were limited to one company; Aventis Pasteur MSD. It seemed to the complainant that the whole point of a purchasing group was to be able to shop around amongst the various companies which supplied vaccines and other products to general practices, in such a way that they gained the best advantage in terms of price, delivery and quality of goods.

REPLY FROM AVENTIS PASTEUR MSD

Aventis Pasteur MSD provided the Authority with a copy of its reply to the further letter from the complainant. Aventis Pasteur MSD made the following points.

- Although the suggestion for the group did indeed come from the company representative, the group itself could only be set-up by a practice manager. In this case, the practice manager at a local group practice.
- There was absolutely no compulsion for any member of the buying group to buy all or indeed any of their vaccines from Aventis Pasteur MSD. The group simply offered members the opportunity to maximise the discount for any vaccines that they would normally purchase from the company.
- The terms of the buying group did not prevent its members from approaching any other company for a similar group buying agreement with its associated economies of scale.
- It was worth reiterating that the group did not seek to offer anything other than that described previously and above, and it was in no way intended or able to undermine the role of individual surgeries, primary care groups or local medical committees.

PANEL RULING

In the Panel's view it was perhaps unfortunate that the name of the local purchasing group was such that it might imply that it was officially associated with the local medical committee. This was not so. Although the purchasing group had been established at the suggestion of the local representative, it had actually been set up by a practice manager who acted as the authorised group organiser. The representative had written to others inviting them to join the group and so benefit from the discounts available. A list from Aventis Pasteur MSD showed that in addition to the original general practice fifteen others and one pharmacy had joined the group.

The Panel noted that a purchasing group had to agree to purchase a minimum quantity of vaccines to qualify for defined levels of discount. In the Panel's view linking discounts to volume was not an unacceptable trade practice. The group did not have to buy any or all of its vaccines from Aventis Pasteur MSD and the terms of its agreement with the company did not prevent it from approaching other companies to request similar group buying benefits.

The Panel appreciated the concern of the complainant but did not consider that the representative had behaved unethically by facilitating the formation of the local purchasing group. No breach of Clause 15.2 was ruled.

Complaint received **9 March 2001**

Case completed **18 May 2001**

CASE AUTH/1165/3/01

UNIVERSITY CLINICAL LECTURER v JANSSEN-CILAG

Conduct of representative

A university clinical lecturer complained about a Janssen-Cilag representative's brusque attempt to bully him into prescribing atypical [anti-psychotics] in general, and Risperdal (risperidone) in particular. The complainant stated that he was subjected to a prolonged, uncompromising and opinionated lecture about 'what psychotic patients are like', how 'olanzapine is a terrible drug, it causes patients to balloon', and how 'not prescribing atypical antipsychotics is negligent as they are obviously superior to typical antipsychotics'. The complainant strongly resented the suggestion that his predecessor's prescribing policy was uncaring and negligent in regard to not changing patients on depot antipsychotics to oral atypicals at all costs. In the hope that the representative might recognise that she had over-stepped the mark, the complainant asked her whether her strongly-held opinions were based on any actual contact with real patients. She smiled, said 'Oh, I see where you're going, no; but I've talked to a lot of nurses and doctors', and then continued to inform the complainant about what psychotic patients were like. Her manner was wholly inappropriate, suggesting an expertise in clinical psychiatry which was, at best, entirely second-hand. The complainant was concerned that less experienced clinicians than himself might take much of what was said at face value. It was a deeply unpleasant interview and the representative had demonstrated little awareness of just how irritating was her attitude that antipsychotic prescribing was very straightforward and that anyone prescribing typicals was negligent.

The Panel noted that the company had stated that it accepted the representative's assurances that the word negligence (or derivatives) were not used but could not refute the fact that this impression might have been given as the representative did not check the clinician's understanding of the intended message and thus could not clarify or qualify the initial impression. The company accepted that if this impression was given it did not reflect mainstream clinical opinion and further accepted that, on the balance of probability, the representative might have left the clinician with a misleading impression on this point. The complainant also alleged that the representative had stated that olanzapine was a terrible drug which caused patients to balloon; the representative denied describing olanzapine as such. It was not possible to determine where the truth lay. With reference to the word 'balloon', the representative could not remember using it on this occasion but it was a word she had used before. The company had therefore conceded that, on the balance of probability, the word was used and that it should not have been.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code and a breach of the Code was ruled. With regard to the allegation that olanzapine had been described as a terrible drug, the Panel noted that it was impossible to determine where the truth lay and no breach was ruled. In response to the allegation that the representative had suggested that the complainant's predecessor's prescribing policy was uncaring and negligent, Janssen-Cilag had stated that the representative denied referring to the complainant's predecessor. It was impossible to tell where the truth lay and no breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

A university clinical lecturer and honorary consultant psychiatrist complained about the conduct of a representative from Janssen-Cilag Ltd who was promoting Risperdal (risperidone). The complainant had written direct to Janssen-Cilag and copied his letter to the Authority.

COMPLAINT

The complainant stated that the representative was delivering a model brain, for which he was very grateful. Over the years his relationships with representatives of the pharmaceutical industry had on the whole been cordial and constructive, but this brusque attempt to bully him into prescribing atypical [anti-psychotics] in general, and risperidone in particular, was unique in his experience.

The complainant stated that he was subjected to a prolonged and opinionated lecture about 'what psychotic patients are like', how 'olanzapine is a terrible drug, it causes patients to balloon' and how 'not prescribing atypical antipsychotics is negligent as they are obviously superior to typical antipsychotics'. The representative's statements were uncompromising. Despite the occasional admission that there was some uncertainty in the field, the complainant stated that he would like to be as certain about any one thing that the representative mentioned, as she appeared certain about them all.

The complainant also strongly resented the representative's suggestion that his predecessor's prescribing policy was uncaring and negligent in regard to not changing patients on depot antipsychotics to oral atypicals at all costs. The complainant stated that his predecessor was a fine and caring clinician.

In the hope that the representative might recognise that she had over-stepped the mark, the complainant asked her whether her strongly-held opinions were based on any actual contact with real patients. She smiled, said 'Oh, I see where you're going, no; but I've talked to a lot of nurses and doctors', and then continued to inform the complainant about what psychotic patients were like. Her manner was wholly inappropriate, suggesting an expertise in clinical psychiatry which was, at best, entirely second-hand. The complainant was concerned that less experienced clinicians than himself might take much of what was said at face value.

The complainant stated that he was sure that the representative was entitled to hold any views she liked, and that some of this could be attributed to her manner. However, she represented Janssen-Cilag. The complainant wanted to know was Janssen-Cilag privy to clinical data that supported such black and white views of what were understood to be complex and hotly contested aspects of antipsychotic prescribing? Did Janssen-Cilag's training of its representatives put them in a position to know better than doctors how to manage patients?

The complainant stated that it was a deeply unpleasant interview and that the representative demonstrated little awareness of just how irritating was her attitude that antipsychotic prescribing was very straightforward and that anyone prescribing typicals was negligent.

When writing to Janssen-Cilag the Authority drew attention to Clauses 2, 7.2, 8.1, 8.2, 9.1 and 15.2 of the Code.

RESPONSE

Janssen-Cilag was very concerned to receive such a serious allegation about the behaviour of one of its representatives and the events in question had been carefully investigated with the individual and her manager.

The representative had had several previous contacts with the complainant, both face to face and at sponsored meetings and she considered their relationship prior to the meeting in question to be both constructive and cordial.

Janssen-Cilag noted that the complainant described the meeting on 7 March as a prolonged and opinionated lecture, but observed that at no point did the complainant directly express this opinion to the representative or seek to curtail the meeting. The representative recalled a two-way dialogue and did not consider the complainant's description of the meeting as a 'lecture' to be fair. In fact the representative specifically recalled not using her sales-aid during the meeting so as to engender and maintain a participative dialogue with the complainant. She attempted to give the complainant two leavepieces and a clinical paper to help illustrate some of the points made during the discussion but, according to the representative, the complainant placed the leavepieces straight in the bin. The complainant did keep the clinical paper however. The representative was unable to explain these actions but simply assumed that the clinician favoured 'independent' clinical papers over company promotional materials.

The complainant stated that the representative gave the clear impression that it was her view that the use of the older typical antipsychotics in preference to the newer atypicals was negligent. The representative absolutely refuted that the word negligent was ever used in these discussions and asserted that if this was the inference drawn from what was said then it was an unfortunate misunderstanding and certainly was not the intention. Janssen-Cilag accepted the representative's assurances that the word negligence (or derivatives) was never used but could not refute the fact that this impression might have been given as the representative did not check the clinician's understanding of the intended message and thus could not clarify or qualify the initial impression. The company accepted that if this impression regarding antipsychotics was given then it was misleading in that it did not reflect mainstream clinical opinion. This was also not a position supported by the company, which therefore accepted on the balance of evidence, albeit unintentional, that the representative might have left the clinician with a misleading impression on this point.

Janssen-Cilag noted that the complainant submitted that he challenged the representative about her assertions regarding psychotic patients by asking

whether her strongly held opinions were based on any actual contact with real patients. In response to this, the representative would freely admit to limited exposure to psychotic patients but the company noted that she made 2000 to 3000 separate contacts with psychiatric healthcare professionals per year, as well as attending seminars and symposia relating to this subject. Whilst she would never claim to know better than a doctor how to manage patients, she was not without sufficient knowledge to discuss therapeutic choices with a doctor, which was what she felt she had done on this occasion.

Janssen-Cilag noted that the complainant ended by expressing how deeply unpleasant he found the whole experience. The company could only observe again that at no time did he make this plain to the representative or attempt to curtail the interview. The representative left the interview unaware that she had caused offence and was genuinely shocked to have received this complaint. To this end Janssen-Cilag accepted from the accounts given that the representative could have better picked up on the non-verbal cues from this clinician and tailored her approach appropriately. Failure to do so had obviously compounded the situation adding to the complainant's displeasure.

Janssen-Cilag concluded that since offence was caused, albeit unintentionally, a breach of Clause 9.1 had taken place and this was conceded. Given this, the representative had failed to comply with the requirements of the Code and a breach of Clause 15.2 was also conceded.

Janssen-Cilag noted that the complainant alleged that the representative disparaged a competitor product by stating 'olanzapine is a terrible drug, it causes patients to balloon'. The representative refuted that this was said. She denied ever describing a competitor product as 'a terrible drug' and would never do so. She also did not recall talking about the propensity for olanzapine to cause weight gain at this meeting or saying specifically that 'it causes patients to balloon'. She conceded, however, that when discussing weight gain as a side effect of antipsychotics she had used olanzapine as an example of a medicine that had a potential to cause significant weight gain. Within this context she might have used phraseology similar to that above (i.e. 'it causes patients to balloon'). She noted, however, that such phraseology was not of her invention but was descriptive language she had heard many psychiatrists use in relation to this topic and was not meant to be disparaging.

Janssen-Cilag accepted that although the use of the word 'balloon' was meant to be descriptive and was not uncommonly used by psychiatrists, it was not a generally accepted medical phrase and might be seen as disparaging by some. Although the representative did not specifically remember using this phrase with this customer she admitted that she had used it and the company could not therefore refute with certainty that it was used on this occasion. Janssen-Cilag therefore conceded that on the balance of probability it was said and further conceded, despite the use of the term by some psychiatrists, that its representative should not have used this term and a breach of Clause 8.1 was conceded.

Janssen-Cilag noted that the complainant alleged that the representative had suggested that his predecessor was uncaring and negligent with regard to not changing patients from depots (long acting intramuscular typical antipsychotics) to atypicals at all costs. The representative absolutely refuted that the complainant's predecessor was mentioned or that the words negligent (or derivatives) or uncaring were ever used. The representative's relationship with the complainant's predecessor was extremely amicable and professional with the representative calling on him on several occasions. The representative would fully agree with the complainant that his predecessor was a fine and caring clinician. Although Janssen-Cilag had already conceded that the representative might have given a misleading impression of their general view regarding the prescription of typicals in preference to atypical, it did not believe that this view was specifically ascribed to the complainant's predecessor or could reasonably be ascribed to him even by inference. Given these facts Janssen-Cilag did not accept that the complainant's predecessor was disparaged and therefore denied a breach of Clause 8.2.

Janssen-Cilag believed that the representative did not set out to cause offence or mislead but had inadvertently done so due mainly to a failure to unearth and allay the clinician's concerns and a failure to adequately clarify and qualify her statements at this meeting. This was believed to be a single aberration on the part of this representative as her several previous contacts with this clinician had been uneventful. Thus, although Janssen-Cilag fully accepted that, on this occasion, this representative had fallen below the standard she would set for herself, and that expected by the company, it did not believe that she had brought the industry into disrepute. Additionally, it believed that the representative did not disparage the complainant's predecessor but might have disparaged olanzapine by repeating a descriptive word she had heard practising clinicians use. Janssen-Cilag considered that the inadvertent use of this word did not bring the industry into disrepute.

Janssen-Cilag stated that the severe censure of Clause 2 was not justified.

Janssen-Cilag stated that since it was also written to directly by the complainant, it had taken the opportunity to contact him directly and had made a full apology on behalf of the company and the representative for the distress caused by this incident.

The representative concerned had been reprimanded and the company would be taking appropriate further action to ensure that this was not repeated. It did not believe that this unfortunate incident was in any way reflective of the generally positive and constructive relationships fostered with healthcare professionals and it would continue to routinely reinforce the importance of compliance with the Code to all its representatives.

PANEL RULING

The Panel noted that the parties had provided differing accounts of the meeting. It was difficult in

such cases to determine exactly what had transpired. A judgement had to be made on the available evidence.

The Panel noted that the representative and complainant had discussed the use of newer atypicals versus older typical antipsychotics. The complainant stated that the representative commented that 'not prescribing atypical antipsychotics is negligent as they are obviously superior to typical antipsychotics'. The complainant described the representative's comments as uncompromising and black and white views of what were understood to be complex and hotly contested aspects of antipsychotic prescribing. The company stated that it accepted the representative's assurances that the word negligence (or derivatives) were not used but could not refute the fact that this impression might have been given as the representative did not check the clinician's understanding of the intended message and thus could not clarify or qualify the initial impression. The company accepted that if this impression was given it did not reflect mainstream clinical opinion and further accepted that, on the balance of probability, the representative might have left the clinician with a misleading impression on this point.

The Panel noted that the complainant alleged that the representative stated that olanzapine was a terrible drug which caused patients to balloon. The company stated that the representative denied describing olanzapine as a terrible drug. It was not possible to determine where the truth lay. With reference to the word 'balloon' the representative could not remember using it on this occasion but it was a word she had used before. The company had therefore conceded that, on the balance of probability, the word was used and that it should not have been.

The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and had failed to comply with all relevant requirements of the Code and a breach of Clause 15.2 was ruled.

The Panel noted with regard to the allegation that the representative had described olanzapine as a terrible drug it was impossible to determine where the truth lay. No breach of Clause 8.1 was ruled. The Panel noted that in response to the allegation that the representative had suggested that the complainant's predecessor's prescribing policy was uncaring and negligent Janssen-Cilag had stated that the representative denied referring to the complainant's predecessor with whom her relationship was described as extremely amicable and professional. It was impossible to tell where the truth lay. No breach of Clause 8.2 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure.

Complaint received **14 March 2001**

Case completed **16 May 2001**

CASE AUTH/1168/3/01

NOVO NORDISK v PHARMACIA

Polaroid camera for child patients

Novo Nordisk stated that some nurses had told it that Pharmacia was currently advertising the gift of Polaroid cameras to children who might be prescribed growth hormone. The cameras were being distributed along with height charts and videotapes to children who were prescribed Pharmacia's growth hormone (Genotropin). The nurses were uncomfortable about being involved in the distribution chain and had therefore alerted Novo Nordisk about the scheme. Novo Nordisk alleged that the distribution of the camera was in breach of the Code as it was clearly not inexpensive and did not add any value to the height chart, which was the medically accepted method of monitoring growth. Photographs taken by the camera were not a scientific means of monitoring growth and in no way related to the condition under treatment. Novo Nordisk understood that some paediatric centres which prescribed growth hormone offered patients a choice of devices and products. Clearly the offer of a Polaroid camera must encourage the patient to choose the Pharmacia product. Novo Nordisk believed that Pharmacia's campaign over-commercialised medicinal products and might reduce public confidence in the pharmaceutical industry and potentially bring disrepute upon it as a whole, in breach of Clause 2 of the Code.

The Panel noted that the Genotropin starter kit was in a large box, the wrapper of which stated 'Inside you will find Your Genotropin Pen, Camera, Stickers, User Guide and Height Chart'. The height chart had spaces presumably for children to put in photographs taken with the camera. The camera cost £15.38, came with batteries and a film, and produced instant mini-photographs (approximately 4 x 2.5cm). The Panel considered that the camera was an attractive item that children would be keen to receive. It was not unreasonable to assume that the supply of a Polaroid camera by the manufacturers of Genotropin would become known and this might lead to requests from new patients and/or their parents for Genotropin. There was no evidence before the Panel to indicate that the provision of the camera had led to requests from new patients.

The Panel noted that the Code allowed gifts to or for use by patients. Items made available to patients had to be inexpensive and related to either the condition under treatment or general health. No gift for use by patients must be given for the purpose of encouraging patients to request a particular medicine. The Panel did not accept Pharmacia's submission that the camera was a compliance aid. It would be difficult to monitor changes in height using the photographs. The camera was a gift to patients. It failed to meet the requirement of being inexpensive as it cost more than the permitted £5 (excluding VAT). The Panel did not consider relevant Pharmacia's submission that as the average length of treatment was eight years the camera was not excessive at a cost of less than £2 per year. In the Panel's view, the camera also failed to meet the second criteria of being related to the condition under treatment. A breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such circumstances.

Novo Nordisk Limited complained about the provision of a Polaroid camera by Pharmacia Limited in connection with the prescribing of Genotropin.

COMPLAINT

Novo Nordisk stated that it had been brought to its attention by some nurses working in paediatric centres that Pharmacia was currently advertising the gift of Polaroid cameras to children who might be prescribed growth hormone. The cameras were being distributed along with height charts and videotapes to children who were prescribed Pharmacia's growth hormone (Genotropin). The nurses were uncomfortable about being involved in the distribution chain and had therefore alerted Novo Nordisk about the scheme.

It was Novo Nordisk's view that the distribution of the Polaroid camera was in breach of Clause 18.2 of the Code which stated in the supplementary information, Gifts to or for use by Patients, that '… promotional aids … should be inexpensive and related to … the condition under treatment …'; it stated further that 'no gift or promotional aid for use by patients must be given for the purpose of encouraging patients to request a particular medicine'.

Novo Nordisk stated that absolute cost aside, the Polaroid camera was clearly not an 'inexpensive' gift to a child, and in its view did not add any value to the height chart, which was the medically accepted method of monitoring growth. Photographs taken by the camera were not a scientific means of monitoring growth and in no way related to the condition under treatment.

Novo Nordisk understood that some paediatric centres which prescribed growth hormone offered patients a choice of devices and products. Clearly the offer of a Polaroid camera must encourage the patient to choose the Pharmacia product, bearing in mind the attractiveness of such a gift to a young child. Some children might thus put undue pressure on their parents as well as the prescriber on the choice of growth hormone.

Novo Nordisk had written to Pharmacia which replied that 'the camera is … part of a compliance program and not a promotional item …'. Novo Nordisk did not accept this contention, as it believed the camera was an obvious promotional item aimed at the point of making the prescribing decision. Furthermore there was no evidence that it would aid compliance in the longer term.

Novo Nordisk believed by refusing to withdraw the promotional aid, Pharmacia's campaign over-commercialised medicinal products. Such commercialisation might reduce public confidence in the pharmaceutical industry and potentially bring

disrepute upon the pharmaceutical industry as a whole in breach of Clause 2 of the Code.

RESPONSE

Pharmacia stated that it strongly refuted the allegation for the following reason.

The Polaroid camera was contained in the Genotropin starter kit. The only mention of the camera occurred on the starter kit box itself and in the instructional video. The starter kit was given to patients following the decision to prescribe the Genotropin pen and not before. The video was an instructional one showing patients and carers the proper use of the Genotropin pen device and the use of such videos was standard industry practice. Pharmacia believed that the suggestion that these items were being 'distributed' was a distortion. As discussed above they formed part of a self-contained starter kit for patients for whom a decision had already been made to prescribe the Genotropin pen.

The starter kit was supplied as an aid to initiation of, and compliance with, ongoing Genotropin therapy. Standard clinical practice was for a growth hormone specialist to evaluate the patient and their requirements for treatment. They would then discuss growth hormone therapy with the patient and carers. This discussion was not related to a specific brand of growth hormone. When there was agreement for therapy the specialist prescribed whichever product was most appropriate based on the delivery (injection) system and related compliance issues likely to face the individual patient.

Pharmacia had heard anecdotal accounts that patient choice was offered in a small number of centres. The company's understanding was that this choice was restricted to the delivery device itself and that the starter kit was not shown to patients until final choice of device was made. Therefore it could not be claimed that the starter kit was an inducement for a child to put pressure on parents/carers to request Genotropin.

Adherence with daily growth hormone injections was a well-documented problem on which specialists sought Pharmacia's assistance in terms of product development. Whilst the cost of the camera, at £15.38, was outside the recommended cost for a gift, Pharmacia's position was that it was intended as an aid to compliance. There was a role for aids that motivated patients to view their treatment positively. As the average length of treatment for a child was 8 years, Pharmacia submitted that such an item was not excessive at a cost of under £2 per year. The role of the camera was to provide a photographic record, which gave positive feedback on the child's progress on therapy and was intended as a compliance aid. The development of the starter kit was discussed with endocrine nurses and its subsequent launch had been well received. Pharmacia provided copies of communications that had been sent from the specialist growth clinics around the country attesting to the value of this kit.

PANEL RULING

The Panel noted that the Genotropin starter kit was supplied in a bag together with three months' supply of needles, a sharps bin, swabs and a cool bag/ice pack for transporting growth hormone. The starter kit itself was in a large box the wrapper of which stated 'Inside you will find Your Genotropin Pen, Camera, Stickers, User Guide and Height Chart'. The height chart had spaces for children to put pictures. The Panel assumed that the spaces were designed to take the photographs produced by the Polaroid camera. The Panel noted there was no mention or space in the kit for the video. It assumed that the video (which referred to the Polaroid camera) was provided separately. Novo Nordisk's complaint was clearly about the provision of the Polaroid camera.

The camera cost £15.38 and came with batteries and a film. The camera produced instant mini-photographs (approximately 4 x 2.5cm).

The Panel considered that the camera was an attractive item that children would be keen to receive. It was not unreasonable to assume that the supply of a Polaroid camera by the manufacturers of Genotropin would become known and this might lead to requests from new patients and/or their parents for Genotropin. There was no evidence before the Panel to indicate that the provision of the camera had led to requests from new patients.

The Panel noted that the Code allowed gifts to or for use by patients. Such items had to meet the requirements of Clause 18.2. Further guidance was given in the supplementary information in that items made available to patients had to be inexpensive and related to either the condition under treatment or general health. No gift for use by patients must be given for the purpose of encouraging patients to request a particular medicine.

The Panel did not accept the submission that the camera was a compliance aid. It would be difficult to monitor changes in height using the photographs. The camera was a gift to patients. It failed to meet the requirement of being inexpensive as it cost more than the permitted £5 (excluding VAT). The Panel did not consider relevant Pharmacia's submission that as the average length of treatment was eight years the camera was not excessive at a cost of less than £2 per year.

In the Panel's view the camera also failed to meet the second criteria of being related to the condition under treatment. The camera failed to meet the requirements of Clause 18.2 of the Code and was therefore in breach of Clause 18.1. A breach of that clause was ruled.

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

Complaint received **21 March 2001**

Case completed **16 May 2001**

NOVO NORDISK v LILLY

Promotion of HumaPen

Novo Nordisk complained about an advertisement for HumaPen (a pen style syringe for injecting insulin) which had been placed in a patient magazine by Lilly. The advertisement was headed 'Are you using a HumaPen?', beneath which was stated 'If yes, there is now an upgrade available' followed by illustrations of the pen and the pen opened and a list of changed features. At the bottom was stated 'If you are an existing HumaPen user ask your Healthcare Professional or telephone [number stated] for your FREE UPGRADE PACK'.

Novo Nordisk believed that the HumaPen could only be used with Lilly's Humalog and Humalin insulin cartridges. Although the advertisement tried to target people already using a HumaPen, it was promoting the HumaPen upgrade in the public domain with product claims and hanging comparisons ('easier to see your insulin as you inject', 'tighter fitting cap' etc). Novo Nordisk stated that if Lilly truly wanted to target HumaPen users, it would have been more appropriate to have used other methods, which focused on HumaPen users only and not the general public. The advertisement encouraged people to use a HumaPen but in order to do this they would have to be switched to a Lilly insulin. Novo Nordisk alleged that this was in breach of the Code in line with rulings in Cases AUTH/1018/4/00 and AUTH/1079/9/00 which had established that a device should not be promoted to the public if it could take only one manufacturer's insulin. Any discussion of pen devices in the public domain that focused on the HumaPen only was not a balanced representation of information. The fact that the device only appeared to take Lilly cartridges meant that a patient attracted by this advertisement could request this device from their doctor who would then be pressured into prescribing a Lilly insulin.

The Panel noted that in Case AUTH/1018/4/00 it was alleged that a mailing to the general public about Novo Nordisk's NovoPen 3, an insulin injection device, constituted indirect advertising to patients of specific brands of insulin because the device was designed such that it could only be used with Novo Nordisk human insulins. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine. No other manufacturer's insulin cartridge could be used in the NovoPen system. Promotion of the NovoPen 3 system therefore constituted promotion of Novo Nordisk insulin cartridges. The Panel considered that the mailing constituted an advertisement to the public for a prescription only medicine. The mailing would encourage patients to ask their doctors to prescribe the NovoPen 3 and in effect a Novo Nordisk insulin cartridge. In Case AUTH/1079/9/00 a similar device from another manufacturer had been advertised in a patient magazine and was ruled in breach of the Code as constituting promotion of the company's insulins to the public.

The Panel considered that there were similarities between the two previous cases referred to above and the case now before it. The advertisement had appeared in a patient magazine its purpose being to alert users of HumaPen that the device had been upgraded. The advertisement provided details of the improvements and a telephone number to obtain a free upgrade pack. The insulins that fitted the pen were prescription only medicines. The Panel considered that readers of the advertisement who were not users of HumaPen might be tempted to find out what was new about the upgraded HumaPen. This would lead to discussions about the device with health professionals. The Panel did not accept Lilly's submission that because the advertisement did not make any claims for the insulin to be used in the HumaPen there was no breach of the Code. The Panel considered that the advertisement promoted the use of the HumaPen and thus constituted an advertisement to the public of a prescription only medicine. The advertisement would encourage patients to ask their doctors to prescribe the HumaPen and in effect a Lilly insulin cartridge. The Panel ruled breaches of the Code.

Upon appeal by Lilly, the Appeal Board considered that there were differences between the case now before it and the previous cases. In the previous cases breaches of the Code had been ruled because material aimed at the general public, which had given details of one manufacturer's insulin pen, had been regarded as being promotion of that manufacturer's insulin to the general public.

Turning to the case now at issue, the Appeal Board noted the circumstances which led to the announcement and considered that what the company had done was not unreasonable. The announcement was aimed at existing users and explained that the upgrade for the HumaPen would lead to practical advantages for the user ie 'Easier to see your insulin …', 'Tighter fitting cap'; the Appeal Board considered that without this information some patients might have been concerned about the reasons for the upgrade. If anyone who was not already a HumaPen user telephoned the helpline they were given no information about the device and if they wanted more information about the device they were currently using they were advised to contact their health professional. In the circumstances the Appeal Board did not consider that the announcement about the upgrade for the HumaPen constituted an advertisement to the general public of a prescription only medicine, or that it encouraged patients to ask their doctors to prescribe a HumaPen and in effect a Lilly insulin cartridge. No breach of the Code was ruled.

Novo Nordisk Limited complained about an advertisement (ref HPA4) for HumaPen (a pen style syringe for injecting insulin) which had been placed in Balance, March / April, by Eli Lilly and Company Limited.

The advertisement was headed 'Are you using a HumaPen?', beneath which was stated 'If yes, there is now an upgrade available' followed by illustrations of the pen and the pen opened and a list of changed features. At the bottom was stated 'If you are an existing HumaPen user ask your Healthcare Professional or telephone [number stated] for your FREE UPGRADE PACK'.

COMPLAINT

Novo Nordisk stated that following the Appeal Board's ruling in Case AUTH/1018/4/00 on the advertising of insulin delivery devices to the general public, it wished to complain about this advertisement which, it alleged, was clearly in breach of Clauses 20.1 and 20.2 of the Code.

With regard to both Clause 20.1, which stated that 'medicines must not be advertised to the general public if they are prescription only medicines', and the above ruling, a device should not be promoted to the public if it could only take one manufacturer's insulin. Novo Nordisk believed that the HumaPen could only be used with Lilly insulins and this was backed up in MIMS (February 2001) where it only mentioned 3ml cartridges of Humalog and Humalin to be used in this device. This was confirmed by Lilly itself. Novo Nordisk was certainly unaware of any interchangeability between the use of Lilly and Aventis insulins in either company's pens, especially since the rubber bung thickness on the cartridges was different. Although the advertisement tried to target people already using a HumaPen, it was promoting the HumaPen upgrade in the public domain with product claims and hanging comparisons ('easier to see your insulin as you inject', 'tighter fitting cap' etc). Novo Nordisk stated that if Lilly truly wanted to target HumaPen users, it would have been more appropriate to have used other methods such as a warranty card system which focused on HumaPen users only and not the general public. This advertisement encouraged people to use a HumaPen but in order to do this they would have to be switched to a Lilly insulin. In line with the above mentioned ruling, Novo Nordisk alleged that this was in breach of Clause 20.1 of the Code. Indeed a similar complaint about Aventis Pharma Ltd with regard to its OptiPen Pro advertisement (Case AUTH/1079/9/00) was also upheld.

In line with the rulings in Case AUTH/1018/4/00, Novo Nordisk alleged that in addition to Clause 20.1, the advertisement also breached Clause 20.2 of the Code which stated that 'information about medicines which is made available to the general public either directly or indirectly must be factual and presented in a balanced way' and that 'statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine'. Following this, any discussion of modern pen devices in the public domain that focused on the HumaPen only was not a balanced representation of information. Also, the fact that the device only appeared to take Lilly cartridges meant that a patient attracted by the promotion in this advertisement could request this device from their doctor who would then be pressured into prescribing a Lilly insulin. Novo Nordisk therefore alleged that Clause 20.2 had also been breached.

The basis of this complaint was similar in certain respects to the one lodged by Lilly itself against Novo Nordisk's NovoPen 3 advertisement (Case AUTH/1018/4/00). Although Novo Nordisk considered that its advertising should have been allowed, it respected the rulings on the case. However, it felt that it was only right that other companies also abided by these rulings in order to ensure a fair market place for competition. Therefore, since Lilly had refused to withdraw its advertisement, Novo Nordisk had no option but to refer the matter to the Authority.

RESPONSE

Lilly submitted that there were fundamental differences between this instance and the previous case reports quoted by Novo Nordisk and did not believe that this announcement was in breach of Clauses 20.1 or 20.2 of the Code for the following reasons.

1 In the two case reports quoted by Novo Nordisk a breach was found because the companies were encouraging patients to ask their doctors for a new type of pen which inherently meant the patient was asking for a particular brand of insulin. In both cases the advertisements had described positive features of the devices themselves and were clearly promotional.

The Lilly announcement was not an advertisement/promotional piece for the HumaPen itself and was not encouraging new patients to ask their doctors for it. The announcement referred to the clear cartridge holder upgrade, which was only available and of any advantage to current HumaPen users. This was clearly stated in the announcement and the benefits listed were objective characteristics of the improved cartridge holder rather than medicinal claims made about the device and insulin used with it.

The upgrade was a response by Lilly to feedback given to it by customers about the mechanical improvements they wished to see in the HumaPen. Lilly had designed an improved cartridge holder to allow patients to have the benefits listed, compared to the previous 'opaque cartridge holder'. As the announcement was about the clear cartridge holder, the patient benefits stated were clearly in comparison to the older opaque cartridge holder and did not apply in any way to other insulin delivery devices. In these circumstances it would be inappropriate to discuss other insulin delivery devices.

As insulin pens were designed to have a lifespan of two years, Lilly submitted it was appropriate to inform current patients that the upgrade was available free of charge as part of Lilly's commitment to patient satisfaction. Given the previous rulings of the Panel, when Lilly designed this announcement it was careful to ensure it was not promoting the HumaPen itself and its relative merits. In addition, the announcement was in black and white rather than using Lilly's branded HumaPen colours and Lilly had not included its HumaPen logo. Since patients did not always remember the name of their insulin pen,

Lilly believed it was necessary to include a picture of the HumaPen, both assembled and disassembled, simply to help them to identify the pen and cartridge holder more easily, and to minimise confusion with other devices.

2 In order to discourage patients who were not currently using HumaPen, the announcement was clearly focused on existing HumaPen users with the bold text introducing the material and the question, 'Are you using a HumaPen?'. This was reiterated at the bottom of the page, 'If you are an existing HumaPen user …'. Lilly believed that this was sufficient to make it absolutely clear to non-HumaPen users that this information did not apply to them.

Health professionals were informed prior to the launch of the clear cartridge holder and each diabetes centre had been supplied to allow distribution of upgrades directly to current HumaPen users.

Should any patients not currently using the HumaPen telephone Lilly's upgrade telephone line they were asked if they were currently using a HumaPen? If the answer was no, then they were politely informed that the information did not apply and the call was completed.

Within its complaint Novo Nordisk had tacitly acknowledged that that announcement had targeted HumaPen users. Again, this was fundamentally different to the activities undertaken in the two case reports quoted by Novo Nordisk in which the promotion was not targeted and was aimed at a broad audience.

Lilly introduced its first reusable insulin delivery device, HumaPen, in 1998. It had an ongoing programme of quality assessment and control which included seeking feedback from its customers, both patients and health professionals, to constantly strive to improve its insulin delivery devices. Lilly believed that this information was an important announcement to current HumaPen users of an improvement to their pens, and did not breach either Clause 20.1 or Clause 20.2 of the Code.

PANEL RULING

The Panel noted that in Case AUTH/1018/4/00 it was alleged that a mailing to the general public about Novo Nordisk's NovoPen 3, an insulin injection device, constituted indirect advertising to patients of specific brands of insulin because the device was designed such that it could only be used with Novo Nordisk human insulins. The mailing had been sent by Novo Nordisk. If they wanted more information recipients of the mailing could request a patient video about the NovoPen 3 device. In Case AUTH/1018/4/00 the Panel noted that the Code applied to the promotion of medicines and not the promotion of devices *per se*. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine and the matter would be covered by the Code. The Panel noted that no other manufacturer's insulin cartridge could be used in the NovoPen system. Promotion of the NovoPen 3 system therefore constituted promotion of Novo Nordisk insulin cartridges and was thus within the scope of the Code. The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2, *inter alia*, required that statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel considered that the mailing and the video at issue in Case AUTH/1018/4/00 constituted an advertisement to the public for a prescription only medicine. The mailing would encourage patients to ask their doctors to prescribe the NovoPen 3 and in effect a Novo Nordisk insulin cartridge. Breaches of Clauses 20.1 and 20.2 were ruled which were upheld upon appeal by Novo Nordisk.

Lilly had also complained about materials for patients that had been distributed by Novo Nordisk, Case AUTH/1040/6/00. The allegations concerning Clauses 20.1 and 20.2 had not been proceeded with as they had been covered in Case AUTH/1018/4/00. This was in accordance with Paragraph 5.1 of the Constitution and Procedure.

The Panel noted that Case AUTH/1079/9/00 had concerned an advertisement issued by Aventis for OptiPen Pro which had appeared in a patient magazine. OptiPen Pro was for use with insulin cartridges marketed by Aventis and the Panel's view was that the promotion of OptiPen Pro constituted promotion of the Aventis insulin cartridges and was thus within the scope of the Code. The Panel noted the submission that insulin cartridges from Lilly would fit into the OptiPen Pro but did not consider that this would represent normal practice. In this regard the Panel noted that use of Lilly cartridges required more insulin to prime the OptiPen Pro and that some 20 units of insulin would remain unused. Use of non-Aventis cartridges was therefore not ideal. The Panel noted that the advertisement was headed 'Introducing the New OptiPen Pro'. Eight bullet points listed favourable features of the device such as 'A highly sophisticated injection pen that's simple and easy to use', 'Designed for confident handling' and 'Discreet and elegant'. Readers were told that if they wanted more information on OptiPen Pro they should ask their doctor or diabetes nurse specialist. The Panel considered that the advertisement in a patient magazine promoting the OptiPen Pro constituted promotion of Aventis' insulins to the general public and ruled a breach of Clause 20.1.

The Panel considered that there were similarities between the two previous cases referred to above and the case now before it, Case AUTH/1170/3/01.

The advertisement had appeared in a patient magazine, its purpose being to alert users of HumaPen that the device had been upgraded. The advertisement provided details of the improvements and a telephone number to obtain a free upgrade pack. The insulins that fitted the pen were prescription only medicines.

The Panel considered that readers of the advertisement who were not users of HumaPen might be tempted to find out what was new about the upgraded HumaPen. This would lead to discussions

about the device with healthcare professionals. The Panel did not accept Lilly's submission that because the advertisement did not make any claims for the insulin to be used in the HumaPen there was no breach of Clause 20.1 of the Code.

The Panel considered that the advertisement promoted the use of the HumaPen and thus constituted an advertisement to the public of a prescription only medicine. The advertisement would encourage patients to ask their doctors to prescribe the HumaPen and in effect a Lilly insulin cartridge. The Panel ruled breaches of Clauses 20.1 and 20.2 of the Code.

APPEAL BY LILLY

Lilly stated that it appealed the Panel's rulings for the following reasons:

1 The purpose of the announcement was to achieve the insertion of an improved component in the device of existing HumaPen users.

Lilly stated that it wished to achieve a cartridge holder upgrade to improve patient satisfaction. By definition this only affected existing HumaPen users. Feedback received from health professionals and patients suggested a number of desirable improvements which could be achieved simply by redesigning the cartridge holder. In addition to being transparent, which enabled patients to see the amount of unused insulin, the new component was made of a stronger plastic and permitted a better cap fit than its predecessor. The cartridge holder was a component of the HumaPen which had no value on its own.

2 Any new users of the HumaPen were not affected since all new devices had been fitted with the improved component from October 2000, months before the announcement in the patient magazine.

Lilly stated that its salesforce announcement, to health professionals in diabetes clinics, of the new cartridge holder began in October 2000 well before the advertisement in question. In the event of a non-HumaPen user asking their health professional for advice the clinic would know the upgrade was for existing Lilly device users only. Hence one recommendation in the announcement was for HumaPen users to visit their clinics since they had already been trained on the upgrade. They were not invited to ask about the HumaPen in general but only about upgrading their existing HumaPens.

The upgrade did not affect new patients since HumaPens distributed since October 2000 were fitted with the improved component.

3 Lilly's medical department, being aware of the previous PMCPA ruling against Novo Nordisk, invested considerable effort in trying to design an announcement which would not be perceived as indirect promotion of Lilly insulin.

Lilly stated that it was committed to continuous quality improvement and within the company the primary responsibility to organise the upgrade was with the medical department. The announcement was initiated by the medical department and not by the marketing department. Because of the ruling against Novo Nordisk referred to above the company was aware of the possibility of a reciprocal challenge (Clauses 20.1 and 20.2) and considerable effort was made to avoid the piece being perceived as promoting either the HumaPen or Lilly insulin. Lilly considered that Novo Nordisk's and Aventis' activities and its activities were very different. The other companies' advertising was not targeted and was clearly aimed at encouraging new patients to ask for a new device and hence insulin. The activities supporting the advertisements also reinforced this message of encouragement to ask for a new device. Lilly stated that its information campaign had been targeted specifically to existing HumaPen users about a component of their current device. That the upgrade was not applicable to non-users was reinforced by the clear instructions given to health professionals and to patients via the helpline that if they did not already have a HumaPen the information did not apply to them. The company considered that it had actively discouraged patients who were not already on the HumaPen from asking their doctors for a new device both in the announcement and in its preparatory actions with health professionals and its helpline.

Nevertheless, for the announcement to be effective in eliciting action from HumaPen users it needed to be eye-catching, to target the audience (existing users) and tell that audience what to do.

Because diabetes clinic staff were busy people the company had experienced some apathy in taking time to effect the upgrade. There was a need to induce interest amongst existing users without alarm. Thus the advantage of the upgraded component which was immediately apparent in the picture (better visibility with the new transparent cartridge holder of the insulin cartridge than with the opaque cartridge holder) was mentioned first with 'tighter fitting cap' and 'robust design' second and third. These were not seen as product claims intended to induce interest from non-users since the target audience was already using the device.

4 Lilly tried to ensure that any non-HumaPen users who did respond to the announcement were told that the upgrade did not affect them.

Lilly stated that methods of achieving the upgrade were carefully considered but because of data protection restrictions the company did not know the names/addresses of existing HumaPen users. The warranty card method mentioned by Novo Nordisk was not considered feasible for the same reason.

The material in question was designed as an announcement of the cartridge holder upgrade and not as an advertisement for the HumaPen or indirectly of Lilly insulin. Lilly stated that it took the following steps to maintain a non-promotional focus:- the communication was repeatedly addressed to existing HumaPen users. By implication, if the answer to the question 'Are you using a HumaPen?' was 'no', the information on the component upgrade did not concern the reader. Branding colours/logos were not used.

Lilly submitted that careful consideration was given to graphics and it was felt that including a picture of the device would aid identification and deter non-

HumaPen users from calling the helpline or asking their health professional for advice.

The picture of the HumaPen was not glamorous but highlighted the new component. The pen illustrated was oriented so that the brand name was invisible.

HumaPen users were provided with the simple method of calling the helpline.

The helpline was provided by Lilly with a verbatim which restricted the conversation to existing HumaPen users. In the event of a non-HumaPen user calling the helpline, the helpline identified a non-user immediately when he/she were politely refused further information.

5 Workload in diabetes clinics meant that the helpline was seen as the primary method for a HumaPen user to obtain new cartridge holders. This was simple to control by providing the helpline with an approved verbatim to ensure that non-users were not directed to a potential prescriber.

Lilly stated that many patients visited their clinics only annually or even less frequently and Lilly wished to complete the upgrade over a defined period. The company recognised that additional clinic visits would be inconvenient for both HumaPen users and clinic staff and so it anticipated that the helpline would be the preferred method.

6 The parallel drawn between the announcement and Novo Nordisk's and Aventis' promotional activities was inappropriate.

Lilly noted that in the Panel ruling a direct parallel was drawn between the HumaPen upgrade announcement and the direct to consumer advertising by Novo Nordisk (Case AUTH/1018/4/00) and Aventis (Case AUTH/1079/9/00). A more relevant comparison should be made with a factual public announcement by a manufacturer of a change in the available range of a product. Done appropriately this was not seen as an inducement for members of the public, who were not being treated with the product, to ask their doctors for it but as a way of avoiding confusion and non-compliance amongst patients who were already being treated with that product.

Lilly noted that the Code allowed companies to provide factual information on prescription only medicines to the public as long as it was not promotional. The present ruling seemed to imply that companies could not say anything about the product without this being interpreted as inducing a potential patient to ask their doctor for it which did not seem to be consistent with the Code.

Finally, Lilly stated that the comparisons made were clearly with the old cartridge holder – hence were not hanging. These were not misleading since they referred to the same product not to a competitor's.

In summary, Lilly stated that the announcement was carefully designed as an effective communication to existing HumaPen users offering them a component upgrade. It was intended to be eye-catching and likely to elicit action by existing users whilst avoiding being interpreted as disguised promotion to the public. The action intended was solely for the user to call the helpline or to ask their clinic for the improved device component. Both routes had previously been trained in the upgrade and the helpline, which the company could control, used an approved verbatim preventing non-users from being referred to health professionals. Lilly strongly believed that it had differentiated its activities from those of the Novo Nordisk and Aventis breaches of Clauses 20.1 and 20.2.

At the appeal hearing details of the scripted telephone helpline were given which showed that callers were asked if they were currently using HumaPen to inject their insulin. If the answer was 'No' then callers were told 'Sorry, if you are not currently using HumaPen you don't need an upgrade kit. If you want more information about your existing device, please contact your healthcare professional. Thank you for calling'. The representatives confirmed that only a minority of callers to the helpline were not existing HumaPen users.

APPEAL BOARD RULING

The Appeal Board considered that there were differences between the case now before it and the previous cases referred to by the complainant. In the previous cases breaches of the Code had been ruled because material aimed at the general public, which had given details of one manufacturer's insulin pen, had been regarded as being promotion of that manufacturer's insulin to the general public.

Turning to the case now at issue the Appeal Board noted the circumstances which led to the announcement in a patient magazine and considered that what the company had done was not unreasonable. The announcement was aimed at existing users and explained that the upgrade for the HumaPen would lead to practical advantages for the user ie 'Easier to see your insulin …', 'Tighter fitting cap'; the Appeal Board considered that without this information some patients might have been concerned about the reasons for the upgrade. If anyone who was not already a HumaPen user telephoned the helpline they were given no information about the device and if they wanted more information about the device they were currently using they were advised to contact their health professional.

In the circumstances the Appeal Board did not consider that the announcement about the upgrade for the HumaPen constituted an advertisement to the general public of a prescription only medicine, or that it encouraged patients to ask their doctors to prescribe a HumaPen and in effect a Lilly insulin cartridge. No breach of Clauses 20.1 and 20.2 was ruled. The appeal was successful.

Complaint received **22 March 2001**

Case completed **13 June 2001**

ANONYMOUS v NORTON HEALTHCARE

Alleged failure to pass the ABPI Representatives Examination

An anonymous complainant alleged that a representative of Norton Healthcare had not passed the relevant ABPI examination. It was established practice that anonymous complaints were to be accepted and dealt with in the usual manner.

The Code required representatives to pass the appropriate ABPI representatives examination stating that 'Prior to passing the appropriate examination, they may be engaged in such employment for no more than two years, whether continuous or otherwise'. The Panel noted that the representative in question had commenced employment as a representative in June 1999 and was due to take the examination during May 2001, prior to the expiry of the two year term. No breach of the Code was ruled.

COMPLAINT

An anonymous complainant alleged that a medical representative of Norton Healthcare Limited had not passed the relevant ABPI examination as required by Clause 16.2 of the Code.

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

RESPONSE

Norton Healthcare stated that the representative in question had joined the company from a contract team and would be sitting the ABPI examination for the first time in May 2001, which was well within the two year period permitted by Clause 16.2.

It was the policy of Norton Healthcare always to maintain the highest standards amongst its employees, particularly within its fieldforce. Norton Healthcare gave an assurance that, as a company, it strictly observed and enforced Clause 16.2.

In response to a request for further information Norton Healthcare gave full details of the representative's employment history in the pharmaceutical industry. The representative started work in June 1999 and around a year later joined Norton Healthcare.

It appeared that the representative, due to moving companies, had not been in employment at an appropriate time to sit the examination. However the representative would be sitting the examination in May 2001 which was still within the two year window since joining the industry. This would, however, be the representative's first opportunity of sitting the examination.

PANEL RULING

The Panel noted that Clause 16.2 required representatives to pass the appropriate ABPI representatives examination and stated that 'Prior to passing the appropriate examination, they may be engaged in such employment for no more than two years, whether continuous or otherwise'. The Panel noted that the representative at issue had commenced employment as a representative in June 1999 and was due to take the examination during May 2001; prior to the expiry of the two year term. No breach of Clause 16.2 of the Code was ruled.

Complaint received **26 March 2001**

Case completed **9 May 2001**

CASE AUTH/1172/3/01

SCHWARZ PHARMA v SCHERING-PLOUGH

Promotion of NeoClarityn

Schwarz Pharma complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough, instancing two leavepieces and a detail aid. Schwarz supplied Mizollen (mizolastine).

The claim '40 times more potent than Clarityn at blocking the human H1-receptor' appeared on each of the leavepieces and a similar claim appeared in the detail aid. A similar claim had been considered in Case AUTH/1137/2/01. Schwarz alleged that the claim was misleading. At no point was it stated that this was from an *in vitro* study. Nor did it mention that half of the human H1-receptors studied were cloned and expressed in Chinese hamster ovarian cells. In *in vivo* animal studies the relative potency was an order of magnitude less than this, and there had been no studies in humans comparing the two medicines. Given the disparity between the *in vitro* and *in vivo* results and absence of direct human comparisons, Schwarz did not believe that the *in vitro* study was of significance or relevance clinically. The page of the detail aid headed 'Forty times more potent than Clarityn' included a graph but this did not include mizolastine for comparison, which was the next most potent medicine in the quoted study. This omission exaggerated the potency of desloratadine. Schwarz alleged that the graph was misleading.

The Panel noted that this was similar to a matter considered in Case AUTH/1137/2/01 which concerned a claim that NeoClarityn was 40 times more potent than Clarityn. It had been ruled in breach of the Code. In the present case, the claim referred to the human H1-receptor and was referenced to a poster by Anthes *et al* (2000). The Panel considered that the claim did not make it clear that it was referring to *in vitro* data and queried the relevance to the clinical situation noting that no relevant clinical data had been provided by Schering-Plough. The Panel ruled a breach of the Code. With regard to the detail aid, the Panel noted that the graph in question headed 'Relative potency at the human H1-receptor' compared desloratadine, loratadine, cetirizine and fexofenadine; their relative potencies were 93, 2.2, 1.3 and 1.0 respectively. Only some of the data from Anthes had been included in the graph. Mizolastine had a relative potency of 17, the next highest potency to desloratadine, but this had been omitted from the graph. The basis of selection of the antihistamines had not been made clear. Products which had a relative potency less than loratadine had been shown. The Panel considered that omitting the data for mizolastine was misleading and exaggerated the comparative effects of desloratadine and loratadine. A breach of the Code was ruled.

The claim 'Clarityn with extra clout' appeared on all of the items as a strapline beneath the brand name. A similar claim had been considered in Case AUTH/1137/2/01. Schwarz alleged that the claim was misleading for several reasons. Firstly, whilst desloratadine was a metabolite of loratadine, it was still a different medicine with different side effects, efficacy and clinical experience. The claim implied that NeoClarityn's clinical characteristics were the same, only better, across a wide range of criteria. Areas where this was not so included a narrower therapeutic indication. The claim was all-embracing and was not capable of substantiation. Secondly, there were no studies in patients comparing the two medicines. If this claim was based on the *in vitro* studies then this had not been stated in the material. Since there was no clinical data to show that desloratadine was more effective than loratadine, these *in vitro* studies were of no clinical relevance or significance.

The Panel noted that the materials now at issue were different to those at issue in Case AUTH/1137/2/01. The two leavepieces were headed 'New for hayfever' followed by the brand and generic names and the claim 'Clarityn with extra clout'. The claim also appeared on another page of the leavepiece beneath the brand and generic names. The detail aid was headed 'Introducing NeoClarityn' 'New for hayfever'. The Panel considered that although the new materials stated the indication for NeoClarityn, the claim 'Clarityn with extra clout' would be read as a clinical claim and that NeoClarityn had advantages over Clarityn. There was no direct comparison of the products. The NeoClarityn EPAR stated that 5mg desloratadine was probably not superior to 10mg loratadine. The Panel considered that the claim was misleading, exaggerated and had not been substantiated. A breach of the Code was ruled.

Schwarz noted that the detail aid stated that for a product to treat all of the symptoms of hayfever, it would have to decrease bronchial inflammation. Later on, it was claimed that NeoClarityn was effective across 'all of the main symptoms, including … cough'. Bronchial inflammation and cough were not symptoms of hayfever. Schwarz alleged that this was inconsistent with the marketing authorization. The Panel considered that the impression was given that bronchial inflammation was a symptom of hayfever as it was included with a number of other symptoms beneath the heading 'A product with the following actions would be needed to accommodate all the symptoms of [hayfever]'. Cough was later referred to as a main symptom of hayfever. The Panel noted that Schering-Plough had agreed with Schwarz that bronchial inflammation and cough were not symptoms of hayfever. The Panel considered that the detail aid was inconsistent with NeoClarityn's summary of product characteristics (SPC) and a breach of the Code was ruled.

The claim 'There is <u>still</u> an unfulfilled need for a truly effective therapy' appeared in the detail aid beneath the heading 'Are patients happy with their current hayfever therapy?'. Schwarz considered that the heading and the claim implied that, prior to NeoClarityn, there was no truly effective therapy. Since there were several effective therapies on the

market, some of which also had anti-inflammatory properties, Schwarz alleged that the claim was inaccurate, unbalanced, unsubstantiable, exaggerated, all-embracing and disparaging to its competitors. The Panel noted that a similar allegation had been made in Case AUTH/1141/2/01 when the claim 'Even with 2nd generation antihistamines, there is still an unfulfilled need for a truly effective therapy' had been ruled to be disparaging as it implied that none of the second generation antihistamines were truly effective. In the present case, the Panel considered that its ruling in that case applied. The Panel ruled a breach of the Code as the claim implied that no hayfever therapy was truly effective. There were many treatments available. With regard to the allegations that the claim was inaccurate, unsubstantiable, exaggerated and all-embracing, the Panel considered that the claim implied that one product would be a truly effective therapy. It might be argued that the impression from the detail aid was that NeoClarityn met the unfulfilled need for a truly effective therapy. The claim was exaggerated and therefore not capable of substantiation and breaches of the Code were ruled.

As part of the claim that NeoClarityn had more anti-inflammatory action than Clarityn, a graph was used in the detail aid which was alleged to be misleading. The bar graphs for IL-6 and IL-8 were both drawn using orders of magnitude rather than actual figures. Whilst this in itself was misleading (5×10^7 was 5 times more than 10^7 but on this graph they would be the same), the figures for Clarityn were incorrectly raised an order of magnitude to make the difference more pronounced. In addition, therapeutic levels for loratadine were not marked on the graph. Since the therapeutic dose of loratadine was higher than that of desloratadine, this would further reduce the perceived difference between the two medicines, undermining the claim that NeoClarityn had 'more clout'.

The Panel noted that the claim and graph were referenced to Molet *et al* (1997). The study compared the inhibitory activity of loratadine and desloratadine on histamine-induced activation of endothelial cells. A 50% inhibition of IL-6 secretion was obtained for a dose of desloratadine equal to 2.6×10^{-12} M whereas the same magnitude of effects were only reached for a higher concentration of loratadine 0.3×10^{-6}M. The results for IL-8 given in the study were 0.2×10^{-6}M for loratadine and 10^{-9}M for desloratadine. The Panel considered that by referring only to orders of magnitude the graph was misleading. The difference between the products was exaggerated by the presentation of the data. This was further compounded by the failure to show the therapeutic level of loratadine. A breach of the Code was ruled.

Schwarz alleged that the claims 'Comparable IL-8 inhibition to a steroid' and '… close to dexamethasone's proven strength …' in the detail aid were not capable of substantiation. Desloratadine had less than 75% of dexamethasone's effect in the study mentioned, which was hardly 'close'. The word 'comparable' was admittedly hard to define numerically, but given that there was a statistically significant difference between the effect of these two compounds, Schwarz alleged it was misleading. The Panel noted that the material now at issue was referenced to a study by Lippert *et al* (2000). Loratadine, desloratadine, cetirizine, ranitidine and dexamethasone were studied for their effect on cytokine release. The study referred to the effects of antihistamines on *in vitro* cytokine production being dose dependent with optimal inhibition being observed at antihistamine concentrations reached in the tissue in a therapeutic setting and with at times comparable results to dexamethasone. There did not appear to have been statistical analysis of desloratadine and dexamethasone. The Panel considered that it was misleading to base the claims on the numerical similarity of the results for desloratadine and dexamethasone. Insufficient details had been provided so that the study could be put in context. Schering-Plough had not demonstrated the comparability of the results and the Panel ruled a breach of the Code.

Schwarz stated that the claims beneath the heading 'Re-assurance from a trusted parent molecule' in the detail aid were misleading. They all related to NeoClarityn studies in healthy volunteers, not patients, which was never stated. There was in fact no link whatsoever between the claims on this page and Clarityn. The page implied that clinical experience with Clarityn extrapolated to clinical confidence in NeoClarityn, when in fact they were different medicines with different side effect profiles, efficacy and clinical experience. The Panel considered that the page was attempting to state that NeoClarityn had a similar side effect profile to Clarityn. The Panel considered that the page was misleading. Some of the statements were based on clinical pharmacology data and not data in actual patients. The association of NeoClarityn with the effects of Clarityn was supported in part by the summary of product characteristics (SPC) for NeoClarityn. Nevertheless NeoClarityn was a new medicine. The page was also misleading as it implied that clinical experience with Clarityn could be extrapolated to clinical confidence with NeoClarityn and there was limited evidence in this regard. A breach of the Code was ruled.

The claim 'No sedation or impairment of performance' appeared in the detail aid. Schwarz stated that according to the detail aid NeoClarityn had absolutely no sedation or impairment of performance. This was alleged to be an all-embracing claim. The Panel noted that the NeoClarityn SPC stated that desloratadine was non-sedating. It did not readily penetrate the central nervous system and at the recommended daily dose there was no excess incidence of somnolence as compared to placebo. The SPC also stated that in some patients concentrations of desloratadine might be higher than expected; in some individuals maximum desloratadine concentration was about 3-fold higher. The safety profile of these subjects was not different to that of the general population. The Panel considered that it was not misleading to claim that NeoClarityn caused no sedation and ruled no

breach of the Code in that regard. Turning to impairment of performance however, the Panel noted that the SPC stated 'NeoClarityn has no or negligible influence on the ability to drive or use machines'. The Panel considered, therefore, that the claim that NeoClarityn caused no impairment of performance was misleading and exaggerated and could not be substantiated. Breaches of the Code were ruled.

A cost comparison chart in the detail aid was headed 'Cost per month of commonly used antihistamines'. It contained only three medicines, one of which was NeoClarityn. Schwarz alleged that this was misleading because NeoClarityn was not commonly used. Any newly marketed medicine in such a competitive market would take time to become commonly used. The Panel noted that the chart compared the costs of NeoClarityn, Clarityn and cetirizine. It was headed 'Cost per month of commonly used antihistamines (pack of 30)'. The graph appeared beneath the heading 'Extra performance at no extra cost'. Clarityn and cetirizine were, according to Schering-Plough, the two most prescribed antihistamines in the UK. The Panel considered that readers would not be misled by the comparison although it might have been worded differently. The Panel did not accept the allegation that the graph was an attempt to extrapolate the safety of Clarityn to the use of NeoClarityn as alleged. No breach of the Code was ruled.

Schwarz alleged that, given the seriousness of some of these breaches of the Code, and their sheer number, the materials would reduce confidence in the pharmaceutical industry, in breach of Clause 2. Additionally, these were only the materials Schwarz had seen – there might be others which it did not have access to. Schwarz questioned the effectiveness of the processes in place at Schering-Plough that would allow these claims to be used in the field. The Panel noted that it had ruled a breach of Clause 2 in a previous case, Case AUTH/1137/2/01. The Panel noted that the allegations now before it were different to those in the previous case. Materials had been amended. The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2.

Schwarz wrote subsequently alleging that Schering-Plough was continuing to promote NeoClarityn outside its licence. At a dermatology meeting a Schering-Plough representative distributed NeoClarityn samples. These were signed for by health professionals attending the meeting. NeoClarityn was currently only licensed for hayfever and Schwarz alleged that distributing samples at this meeting was effectively marketing outside of that licence. Dermatologists did not treat hayfever and other physicians did not attend dermatology meetings to learn about hayfever.

The Panel noted that the list of materials used at the meeting included Elcon and Diprobase. NeoClarityn items were also included these being SPCs, leavepieces, pens, jotters and samples. No Clarityn materials were listed as being used. This appeared to be odd as the product was licensed for idiopathic chronic urticaria. The Panel was concerned that NeoClarityn would be thought to have similar indications to Clarityn due to the similarity of the product names. In this regard the Panel noted its rulings above. There was no allegation about the materials available nor about what representatives had said. The Panel did not accept that providing samples of NeoClarityn at the dermatology meeting necessarily constituted promoting outside the licence. It would depend on the circumstances. The attendees would be interested in new products for treating hayfever. There was no evidence that anything untoward had taken place. Given the circumstances the Panel ruled no breach of the Code.

Schwarz Pharma Limited complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough Ltd. Schwarz Pharma stated that the claims and comparisons at issue were present in several promotional items including, but not limited to, two leavepieces (refs NCL/01-055 and NCL/01-056) and a detail aid (ref NCL/01-054). Correspondence between the parties had failed to resolve the matter. Schering-Plough also marketed Clarityn (loratadine). Schwarz supplied Mizollen (mizolastine).

Two complaints had already been made about the promotion of NeoClarityn, Cases AUTH/1137/2/01 and AUTH/1141/2/01. These had been considered by the Panel but had not completed at the time the Panel considered the case now before it. The materials now at issue had different reference numbers to those previously considered, although similar claims were made.

1 Claim '40 times more potent than Clarityn at blocking the human H1-receptor'

A similar claim had been considered in Case AUTH/1137/2/01.

The claim appeared on each of the two leavepieces and a similar claim appeared on page 5 of the detail aid.

COMPLAINT

Schwarz Pharma stated that the claim that NeoClarityn was 40 times more potent than Clarityn was misleading. At no point was it stated that this was from an *in vitro* study only. Nor did it mention that half of the human H1-receptors studied were cloned and expressed in Chinese hamster ovarian cells. Since in *in vivo* animal studies the relative potency was an order of magnitude less than this, and there had been no studies in humans (let alone patients) comparing the potency of these two medicines, the claim was alleged to be in breach of Clause 7.2 of the Code. Additionally, the European public assessment report (EPAR) on NeoClarityn came to the conclusion that '… the clinical efficacy of 5mg desloratadine is probably not superior to 10mg loratadine'. The supplementary information to Clause 7.2 of the Code specifically warned against this type of comparison. Given the disparity between the *in vitro* and *in vivo* results and absence of direct human comparisons, Schwarz did not believe that the *in vitro* study was of significance or relevance clinically.

Schwarz referred to page 5 of the detail aid which was headed 'Forty times more potent than Clarityn', and included a graph. Schering-Plough did not include mizolastine for comparison, which, as stated in a letter to Schwarz, was the next most potent medicine in the quoted study. This type of omission, which exaggerated the potency of desloratadine, had been ruled in breach of the Code in the past. Schwarz therefore alleged that the graph was misleading on two counts under Clauses 7.2 and 7.8.

RESPONSE

Schering-Plough stated that the figure quoted was from the only studies that had looked at the competitive binding of antihistamines at the human H1-receptor. Schering-Plough believed that the material made it clear that this could only refer to *in vitro* work. However, Schering-Plough would continue to refine its message to make it even clearer in future materials.

The conclusions of the experiment were relevant, notwithstanding the difference seen in other, animal studies. As the target of an antihistamine for clinical use was the human H1-receptor, clearly this was the best model to use. Figures of 10 to 20 times more potency were derived from earlier studies that used older and less specific tests for antihistamine potency. The tests were performed in H1-receptors in species other than man (rat, guinea pig, mouse and monkey); using organs that were not the prime target of H1 blockers (brain, lung and ileum); in models which did not necessarily represent the most accurate measurement of the potency of a medicine in man in seasonal allergic rhinitis (histamine-induced lethality in the guinea pig, histamine-induced increases in nasal microvascular permeability in the guinea pig, histamine-induced changes in pulmonary resistance and compliance in the monkey).

The studies referenced in Schering-Plough's materials were the only ones using the cloned H1-receptor and, thus, represented the body of opinion as to the relative potency of desloratadine and loratadine at the human, cloned, H1-receptor.

Schering-Plough submitted that it had not claimed that it had studies in humans comparing potency, nor was any clinical claim made from its potency statement. Schwarz had quoted the EPAR, which stated that the 'clinical efficacy of 5mg desloratadine is probably not superior to 10mg loratadine'. Schering-Plough was unsure of the relevance of this quote here. As stated above, and in correspondence with Schwarz, no clinical claims had been made.

Schwarz was concerned that mizolastine was not included in the graph examining the relative potencies of antihistamines at the cloned human H1-receptor. Clearly Schering-Plough could not reproduce the paper in its entirety. For reasons of brevity, only the most commonly prescribed were included. In this paper the potency of mizolastine was, relative to desloratadine, less than 20% (17/93). Schering-Plough did not consider that omitting mizolastine in any way exaggerated the potency of desloratadine.

The graph was designed to support the claim that desloratadine was the most potent *in vitro* blocker of the cloned human H1-receptor. This claim was fully substantiated by the evidence. Schering-Plough could not see how this graph could be considered misleading.

PANEL RULING

The Panel noted that this was similar to a matter considered in Case AUTH/1137/2/01 which concerned a claim that NeoClarityn was 40 times more potent than Clarityn. It had been ruled in breach of Clauses 7.2 and 7.3 of the Code.

Turning to the case now at issue, Case AUTH/1172/4/01, the Panel noted that the claim now in question referred to the human H1-receptor. The claim was referenced to a poster by Anthes *et al* (2000). The Panel considered that the claim did not make it clear that it was referring to *in vitro* data. The Panel queried the relevance to the clinical situation noting that no relevant clinical data had been provided by Schering-Plough. The Panel noted the supplementary information to Clause 7.2 of the Code that care must be taken with the use of *in vitro* data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel ruled a breach of Clause 7.2 of the Code.

With regard to the detail aid, the Panel noted that the graph in question headed 'Relative potency at the human H1-receptor' compared desloratadine, loratadine, cetirizine and fexofenadine; their relative potencies were 93, 2.2, 1.3 and 1.0 respectively. The Panel noted that only some of the data from Anthes had been included in the graph. Mizolastine had a relative potency of 17, the next highest potency to desloratadine but this had been omitted from the graph. The basis of selection of the antihistamines had not been made clear in the detail aid. The products which had a relative potency less than loratadine had been shown. The Panel considered that omitting the data for mizolastine was misleading and exaggerated the comparative effects of desloratadine and loratadine.. The Panel ruled breaches of Clauses 7.2 and 7.8 of the Code.

2 Claim 'Clarityn with extra clout'

A similar claim had been considered in Case AUTH/1137/2/01.

The claim appeared on all the materials. It was used as a strapline beneath the brand name.

COMPLAINT

Schwarz alleged that the claim was misleading for several reasons.

Firstly, whilst desloratadine was a metabolite of loratadine, it was still a different medicine with different side effects, efficacy and clinical experience. For example, paracetamol's safety profile was completely different to its hepatotoxic metabolites. By stating it in this way (rather than 'More clout than

Clarityn' for example) Schering-Plough was implying that NeoClarityn's clinical characteristics were the same, only better, across a wide range of criteria. Areas where this was not so included a narrower therapeutic indication, NeoClarityn was only licensed for seasonal allergic rhinitis and not licensed for use in children under 12, unlike Clarityn. It was also worth highlighting that NeoClarityn was a prescription only medicine with a black triangle and Clarityn was a pharmacy medicine with years of clinical experience. Schwarz alleged that the claim was all-embracing and was not capable of substantiation in breach of Clause 7.8 of the Code.

Secondly, there were no studies in patients comparing the two medicines. If this claim was based on the *in vitro* studies, as correspondence with Schering-Plough indicated, then this had not been stated in the promotional material. Since there was no clinical data to show that desloratadine was more effective than loratadine (see the EPAR), these *in vitro* studies were of no clinical relevance or significance. Again, the supplementary information to Clause 7.2 warned against this type of comparison.

RESPONSE

Schering-Plough stated that as quoted in the SPC desloratadine was the primary, active metabolite of loratadine. The statement 'Clarityn with extra clout' served to remind the reader of this. The example given by Schwarz was hardly applicable here. Presumably the hepatotoxic metabolite mentioned was the highly reactive intermediate N-acetyl benzoquinoneimine, formed in small quantities. Comparing this toxic, and quantitatively minor metabolite, to a known primary metabolite, a metabolite which had demonstrated that, and again Schering-Plough quoted from the SPC, 'there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine', was not merely exaggerated, but untrue.

The claim was made in the context of a mailing which was solely related to hayfever. No claims were made with respect to other indications. No attempt was made to suggest that desloratadine was licensed for children under 12 years of age, or that it was not a new a medicine and therefore, rightly, subject to the black triangle requirement.

No clinical claims were made. The strapline simply pointed to a fundamental property of the desloratadine molecule, its increased potency over loratadine, as discussed above. That this message was clear would appear to be supported by the fact that Schwarz considered that the claim would be acceptable if it was worded 'More clout than Clarityn' rather than 'Clarityn with extra clout'.

PANEL RULING

The Panel noted that a similar allegation had been considered in Case AUTH/1137/2/01 where the Panel had noted that the NeoClarityn SPC stated that it was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Clarityn was indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis such as sneezing, nasal discharge and itching and ocular itching and burning. Clarityn was also indicated for the relief of symptoms associated with idiopathic chronic urticaria. In the Panel's view the claim would be read as clinical claims and that NeoClarityn had advantages over Clarityn. The Panel had noted the differences in the indications for the products and that there was no direct comparison of the products. The Panel had also noted that the NeoClarityn EPAR stated that 5mg desloratadine was probably not superior to 10mg loratadine. The Panel had considered that the claims were misleading, exaggerated and had not been substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code had been ruled.

The Panel noted that the previous rulings applied to a journal advertisement (NCL/00-005K) and a leavepiece (NCL/00-015). The materials now at issue were different. The two leavepieces (NCL/01/055 and NCL/01-056) were headed 'New for hayfever' followed by the brand and generic names and the claim 'Clarityn with extra clout'. The claim also appeared on another page of the leavepiece beneath the brand and generic names. The detail aid (NCL/01-054) was headed 'Introducing NeoClarityn' 'New for hayfever'. The claim in question appeared on page 3 of the detail aid.

Turning to the case now before it, Case AUTH/1172/3/01, the Panel considered that although the new materials stated the indication for NeoClarityn, the claim 'Clarityn with extra clout' would be read as a clinical claim and that NeoClarityn had advantages over Clarityn. There was no direct comparison of the products. The NeoClarityn EPAR stated that 5mg desloratadine was probably not superior to 10mg loratadine. The Panel considered that the claim was misleading, exaggerated and had not been substantiated. Part of the Panel's rulings previously made would apply here. The Panel ruled breaches of Clauses 7.2 and 7.8.

3 Alleged promotion outside the marketing authorization

This allegation applied to the detail aid.

COMPLAINT

Schwarz pointed out that page 3 of the detail aid stated that for a product to treat all of the symptoms of seasonal allergic rhinitis, it would have to decrease bronchial inflammation. Page 8 of the detail aid claimed that NeoClarityn was effective across 'all of the main symptoms, including … cough'. Bronchial inflammation and cough were not symptoms of seasonal allergic rhinitis. They were therefore symptoms of diseases outside of the product's licence. It was possible that this was an attempt to extend the product's use into other atopic diseases such as asthma. Schwarz alleged that this constituted a breach of Clause 3.2.

In addition, the poster quoted (Salmun *et al* 2000) never mentioned cough as a symptom of seasonal allergic rhinitis, so this was not a simple mistake of copying symptoms across from the study.

RESPONSE

Schering-Plough stated that the page served to reinforce the message that allergic response was a complicated process, with a range of mediators involved.

Schering-Plough agreed that, in spite of the large body of evidence linking rhinitis and asthma, bronchial inflammation and cough were not, *per se*, symptoms of seasonal allergic rhinitis. No claim of efficacy for desloratadine in bronchial inflammation or cough was intended or, Schering-Plough believed, made. Nevertheless, this would be amended to be made clearer in all future materials.

PANEL RULING

The Panel considered that page 3 was laid out such that the impression was given that bronchial inflammation was a symptom of seasonal allergic rhinitis as it was included with a number of other symptoms beneath the heading 'A product with the following actions would be needed to accommodate all the symptoms of seasonal allergic rhinitis'. Page 8 of the detail aid referred to cough as a main symptom of hayfever.

The Panel noted that Schering-Plough agreed with Schwarz that bronchial inflammation and cough were not symptoms of seasonal allergic rhinitis The Panel considered that pages 3 and 8 of the detail aid were inconsistent with NeoClarityn's SPC and a breach of Clause 3.2 of the Code was ruled.

4 Claim 'There is still an unfulfilled need for a truly effective therapy'

A similar claim had been considered in Case AUTH/1141/2/01.

The claim appeared on page 2 of the detail aid beneath the heading 'Are patients happy with their current hayfever therapy?'.

COMPLAINT

Schwarz considered that the heading and the claim implied that, prior to NeoClarityn, there was no truly effective therapy. Since there were several effective therapies on the market, some of which also had anti-inflammatory properties, Schwarz alleged that the claim was inaccurate, unbalanced, unsubstantiable, exaggerated, all-embracing and disparaging to its competitors. Breaches of Clauses 7.2, 7.3 and 8.1 were alleged.

RESPONSE

Schering-Plough submitted that the claim comprised the conclusion of a survey of UK allergy patients to the effect that there was no therapy on the market that was 100% effective in all patients. Schering-Plough believed it was appropriate to inform doctors of the potential dissatisfaction that their patients might have with existing therapies.

Surely Schwarz was not saying that there was an antihistamine which was 100% effective in 100% of cases, that there were no patients who were not completely satisfied with their treatment? If that was the case then Schwarz's view was contradicted by the results of a survey (which Schering-Plough had forwarded to Schwarz) in hayfever patients which demonstrated the lack of complete satisfaction with current hayfever remedies. To claim that this factual statement was inaccurate, unbalanced, unsubstantiable, exaggerated, all-embracing and disparaging, was surely going a little too far.

PANEL RULING

The Panel noted that a similar allegation had been made in Case AUTH/1141/2/01 when the claim 'Even with 2nd generation antihistamines, there is still an unfulfilled need for a truly effective therapy' had been ruled to be disparaging as it implied that none of the second generation antihistamines were truly effective. A breach of Clause 8.1 of the Code had been ruled.

Turning to the case now at issue, Case AUTH/1172/3/01, the Panel considered that its ruling in the previous case applied. The Panel therefore ruled a breach of Clause 8.1 as the claim implied that no hayfever therapy was truly effective. There were many licensed products available.

With regard to the allegations that the claim was inaccurate, unsubstantiable, exaggerated and all-embracing, the Panel considered that the claim implied that one product would be a truly effective therapy. It might be argued that the impression from the detail aid was that NeoClarityn met the unfulfilled need for a truly effective therapy. The claim was exaggerated and a breach of Clause 7.8 of the Code was ruled. It was therefore not capable of substantiation and a breach of Clause 7.3 of the Code was ruled. The Panel considered that these rulings covered the alleged breach of Clause 7.2.

5 Alleged exaggeration of the differences between Clarityn and NeoClarityn in cytokine inhibition

This allegation referred to page 6 of the detail aid.

COMPLAINT

Schwarz stated that as part of the claim that NeoClarityn had more anti-inflammatory action than Clarityn, a graph was used on page 6 of the detail aid that it alleged to be misleading. The bar graphs for IL-6 and IL-8 were both drawn using orders of magnitude rather than actual figures. Whilst this in itself was misleading (5×10^7 was 5 times more than 10^7 but on this graph they would be the same), the figures for Clarityn were incorrectly raised an order of magnitude to make the difference more pronounced. In addition, therapeutic levels for loratadine were not marked on the graph. Since the therapeutic dose of loratadine was higher than that of desloratadine, this would further reduce the perceived difference between the two medicines, undermining the claim that NeoClarityn had 'more clout'. A breach of Clause 7.8 of the Code was alleged.

RESPONSE

Schering-Plough stated that the graph was designed

as a graphical representation of the study which supported the claim '*In vitro*, the NeoClarityn dose-dependent inhibitory effect on pro-inflammatory IL-6 and IL-8 cytokines is more powerful than Clarityn'. The differences in the two compounds in terms of cytokine inhibition were so great (respectively desloratadine was 100,000 and 500 times more potent than loratadine at inhibiting IL-6 and IL-8) that orders of magnitude were accurate enough to give support to the claim above.

Schering-Plough agreed that it might be clearer to quote the full figures and these would be inserted in subsequent editions.

As pointed out above, the differences in potencies between the two medicines were so great, that putting in a line demonstrating the therapeutic concentration of loratadine would make no difference to the claim that '*In vitro*, the NeoClarityn dose-dependent inhibitory effect on pro-inflammatory IL-6 and IL-8 cytokines is more powerful than Clarityn'.

PANEL RULING

The Panel noted that the claim and graph were referenced to Molet *et al* (1997). An abstract was provided. The study compared the inhibitory activity of loratadine and desloratadine on histamine-induced activation of endothelial cells. A 50% inhibition of IL-6 secretion was obtained for a dose of desloratadine equal to 2.6×10^{-12} M whereas the same magnitude of effects were only reached for a higher concentration of loratadine 0.3×10^{-6}M. The results for IL-8 given in the study were 0.2×10^{-6}M for loratadine and 10^{-9}M for desloratadine.

The Panel considered that by referring only to orders of magnitude the graph was misleading. The difference between the products was exaggerated by the presentation of the data. This was further compounded by the failure to show the therapeutic level of loratadine. The Panel ruled a breach of Clause 7.8 of the Code.

6 Claim 'Comparable IL-8 inhibition to a steroid'

This allegation referred to page 7 of the detail aid.

COMPLAINT

Schwarz alleged that the claims 'Comparable IL-8 inhibition to a steroid' and '… close to dexamethasone's proven strength …' on page 7 of the detail aid were not capable of substantiation. Desloratadine had less than 75% of dexamethasone's effect in the study mentioned, which was hardly 'close'. The word 'comparable' was admittedly hard to define numerically, but given that there was a statistically significant difference between the effect of these two compounds, Schwarz believed it was misleading. Breaches of Clauses 7.2 and 7.8 of the Code were alleged.

RESPONSE

Schering-Plough stated that in the study referred to, desloratadine, at a molar concentration one-tenth that of dexamethasone, produced inhibition of IL-8 three-quarters that of dexamethasone. Surely this was, at the very least, comparable.

Schering-Plough was unable to find support in the paper for the statement by Schwarz '… given that there was a statistically significant difference between the effects of these two compounds'.

PANEL RULING

The Panel noted that page 7 of the detail aid was part of a double page spread with page 6 (point 5 above). The material now at issue was referenced to a study by Lippert *et al* (2000). Loratadine, desloratadine, cetirizine, ranitidine and dexamethasone were studied for their effect on cytokine release. The results for desloratadine and for dexamethasone were as shown in the graph in the detail aid. The study referred to the effects of antihistamines on *in vitro* cytokine production being dose dependent with optimal inhibition being observed at antihistamine concentrations reached in the tissue in a therapeutic setting and with at times comparable results to dexamethasone. There did not appear to have been statistical analysis of desloratadine and dexamethasone. The Panel was unsure of Schwarz's reference to a statistical significant difference between the two products.

The Panel considered that it was misleading to base the claims on the numerical similarity of the results for desloratadine and dexamethasone. Insufficient details had been provided so that the study could be put in context. Schering-Plough had not demonstrated the comparability of the results and the Panel therefore ruled breaches of Clauses 7.2 and 7.8 of the Code.

7 Claim 'Re-assurance from a trusted parent molecule'

This claim headed page 10 of the detail aid.

COMPLAINT

Schwarz stated that the claims beneath the heading 'Re-assurance from a trusted parent molecule' were misleading in several ways.

They all related to NeoClarityn studies in healthy volunteers, not patients, which was never stated.

There was in fact no link whatsoever between the claims on this page and Clarityn. For example, the claim 'Lack of clinically relevant cardiovascular effects'. The 'trusted parent molecule' did, however, have cardiovascular side effects as stated in its SPC.

The page implied that clinical experience with Clarityn extrapolated to clinical confidence in NeoClarityn, when in fact they were different medicines with different side effect profiles, efficacy and clinical experience. Since it was known all too well that many side effects were too uncommon to be picked up before marketing, this was a dangerous extrapolation to make, particularly since it was already known that Clarityn had the potential to cause arrhythmias.

RESPONSE

Schering-Plough stated that Clarityn was demonstrably the parent molecule of desloratadine. The SPC stated: 'Preclinical studies conducted with desloratadine and loratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine'.

Examination of the page refuted Schwarz's statement that there was in fact no link between the claims on this page and Clarityn. Clarityn was known to 'Lack clinically relevant interactions with erythromycin and ketoconazole', to be 'truly non-sedating', to 'not impair performance', 'not impair driving performance' and 'not potentiate the effects of alcohol', so did desloratadine.

Schwarz commented on the cardiovascular side effects listed in the Clarityn SPC without referring to the qualifier 'clinically relevant' and the full quote in the SPC, namely 'Tachycardia and syncope have been reported rarely. Causality has not been established'.

PANEL RULING

The Panel noted that the claims on the page were referenced to various poster presentations. The posters had not been provided by Schering-Plough which, when asked for the supporting references, had supplied an annotated copy of the NeoClarityn SPC.

The Panel considered that the page was attempting to state that NeoClarityn had a similar side effect profile to Clarityn. In this regard the Panel noted that the NeoClarityn SPC stated in section 5.3 Preclinical safety data that 'Desloratadine is the primary active metabolite of loratadine. Preclinical studies conducted with desloratadine and loratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine'.

The Panel noted that many of the claims related to statements in the SPC which were based on clinical pharmacology trials. The claim regarding the lack of clinically relevant cardiovascular effects was based on clinical trial data referred to in the SPC in which up to 20mg of desloratadine was administered daily for fourteen days and a clinical pharmacology trial with doses of desloratadine at 45mg daily for ten days.

The Panel considered that the page was misleading. Some of the statements were based on clinical pharmacology data and not data in actual patients. The association of NeoClarityn with the effects of Clarityn was supported in part by the SPC for NeoClarityn nevertheless NeoClarityn was a new medicine. The page was also misleading as it implied that clinical experience with Clarityn could be extrapolated to clinical confidence with NeoClarityn and there was limited evidence in this regard. A breach of Clause 7.2 was ruled.

8 Claim 'No sedation or impairment of performance'

This claim appeared on page 11 of the detail aid.

COMPLAINT

Schwarz stated that according to the detail aid, NeoClarityn had absolutely no sedation or impairment of performance. Firstly, this was only compared to placebo (even placebo would cause some sedation). Secondly, since some 4% of people given NeoClarityn would obtain a C_{max} 3 times (ie 300%) higher than normal, and a lack of sedating effects was only found at doses 50% higher than recommended, there were definitely going to be patients in whom sedation could not be ruled out. This was an all-embracing claim and alleged to be in breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

In relation to Schwarz's first point, Schering-Plough stated that surely most healthcare professionals would take equivalence to placebo to mean 'no intrinsic effect'.

The basis of the logic behind Schwarz's second point appeared to be that there was a dose-response relationship between desloratadine and sedation. Schering-Plough was not aware of such a relationship.

In addition, as mentioned in the SPC: 'Based on a multiple dose clinical trial, in which up to 45mg of desloratadine was administered (9 times the clinical dose) no clinically relevant effects were observed'. It was therefore clear that there was clinical experience at much greater than three times normal concentrations, with no evidence of sedation.

PANEL RULING

The Panel noted that section 5.1 of the NeoClarityn SPC, pharmacodynamic properties, stated that desloratadine was non-sedating. The medicine did not readily penetrate the central nervous system and at the recommended daily dose there was no excess incidence of somnolence as compared to placebo. Section 5.2 of the SPC, pharmocokinetic properties, stated that in some patients concentrations of desloratadine may be higher than expected; in some individuals maximum desloratadine concentration was about 3-fold higher. The safety profile of these subjects was not different to that of the general population. The Panel considered that it was not misleading to claim that NeoClarityn caused no sedation and ruled no breach of Clauses 7.2, 7.3 and 7.8 in that regard.

Turning to impairment of performance however, the Panel noted that section 4.7 of the SPC stated 'NeoClarityn has no or negligible influence on the ability to drive or use machines'. The Panel considered, therefore, that the claim that NeoClarityn caused no impairment of performance was misleading and exaggerated. The claim could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

9 Alleged misleading cost comparison chart

This chart appeared on page 11 of the detail aid.

COMPLAINT

The cost comparison chart was headed 'Cost per month of commonly used antihistamines'. It

contained only three medicines, one of which was NeoClarityn. Schwarz alleged that this was misleading because NeoClarityn was not commonly used. Any newly marketed medicine in such a competitive market would take time to become commonly used. Schwarz believed this was yet another part of Schering-Plough's attempt to extrapolate the safety of Clarityn to the use of NeoClarityn. A breach of Clause 7.2 was alleged.

RESPONSE

Schering-Plough agreed that the chart only contained three medicines. This was for purposes of brevity. It did, however, contain the two most prescribed, by far, antihistamines in Clarityn and cetirizine. As these two taken together represented the bulk of prescriptions, the chart served to inform the majority of prescribers of the relative cost of NeoClarityn.

It would be surprising if a piece on NeoClarityn, with the purpose of educating prescribers on the relative cost of this product, did not contain mention of NeoClarityn. Schering-Plough submitted that no clinical claims were made or implied.

PANEL RULING

The Panel noted that the chart compared the costs of NeoClarityn, Clarityn and cetirizine. It was headed 'Cost per month of commonly used antihistamines (pack of 30)'. The graph appeared beneath the heading 'Extra performance at no extra cost'. Clarityn and cetirizine were, according to Schering-Plough, the two most prescribed antihistamines in the UK. The Panel considered that readers would not be misled by the comparison although it might have been worded differently. The Panel did not accept the allegation that the graph was an attempt to extrapolate the safety of Clarityn to the use of NeoClarityn as alleged. No breach of Clause 7.2 of the Code was ruled.

10 Alleged damage to the image of the pharmaceutical industry

COMPLAINT

Schwarz alleged that, given the seriousness of some of these breaches of the Code, and their sheer number, the materials would reduce confidence in the pharmaceutical industry, in breach of Clause 2. Many of them were specifically mentioned in the Code, or had been held in breach in the past. Additionally, these were only the materials Schwarz had seen – there might be others which it did not have access to. Schwarz questioned the effectiveness of the processes in place at Schering-Plough that would allow these claims to be used in the field.

RESPONSE

Schering-Plough did not respond specifically to this allegation.

PANEL RULING

The Panel noted that it had ruled a breach of Clause 2 in a previous case, Case AUTH/1137/2/01. The Panel had considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. The position was compounded as the indications for the products were not the same. The licensed indications for NeoClarityn were more restricted than for Clarityn. In the Panel's view Schering-Plough had not made sufficient effort to distinguish between the products. The Panel had noted that Clause 2 was used as a sign of particular censure and was reserved for such use. On balance the Panel had considered that the circumstances warranted a ruling of a breach of Clause 2 and a breach of that clause had been ruled.

The Panel noted that the allegations now before it were different to those in the previous case. Materials had been amended. The Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2.

11 Promotion at dermatology meeting

COMPLAINT

Schwarz wrote subsequent to making the above allegations stating that it had been brought to its attention that Schering-Plough was continuing to promote NeoClarityn outside of its licence in breach of Clause 3.2.

At a dermatology meeting a Schering-Plough representative was observed distributing NeoClarityn samples. These were signed for by health professionals attending the meeting. NeoClarityn was currently only licensed for seasonal allergic rhinitis and Schwarz alleged that distributing samples at this meeting was effectively marketing outside of that licence. Dermatologists did not treat seasonal allergic rhinitis and other physicians did not attend dermatology meetings to learn about seasonal allergic rhinitis.

This was further evidence of the company marketing its new product in a manner inconsistent with the Code.

RESPONSE

Schering-Plough stated that the issue related to a regional Dermatology Society Meeting held at a hospital in March.

No attempt had been made by Schwarz to indicate that by providing samples of NeoClarityn the representative in anyway implied that desloratadine was approved for any indication other than hayfever. Schering-Plough was unable to see how fulfilling a request for a sample to a health professional, in accordance with the requirements of the Code, was promoting outside the product licence.

The representative in question promoted a number of Schering-Plough products, including its dermatology and allergy range (which included desloratadine). He had a stand at this meeting where materials concerning dermatology and allergy products were laid out. A list of all the materials on the stand was provided.

Health professionals were interested enough in a new antihistamine for treating to request samples. The samples were distributed in accordance with the provisions of the Code and were given out on request, and signed for. A list of all those who had received samples was provided.

Schering-Plough could not agree with the assertion that dermatologists did not treat seasonal allergic rhinitis. It did not know of any basis for this comment. Dermatologists were qualified medical practitioners, and in the course of their practice would see, and were able to treat, a number of pathologies outside the skin. Treating hayfever was not necessarily a specialist skill. In addition there was a well-known link between the allergic diseases. A significant percentage of a dermatologist's work revolved around the treatment of various dermatological manifestations of allergy, such as chronic idiopathic urticaria and atopic eczema. Patients with these conditions had a higher incidence of seasonal allergic rhinitis than the general population. With around two-fifths of the population suffering from hayfever it would be difficult for a dermatologist to avoid contact with patients suffering with this condition. Also, at this meeting were a number of general practitioners who held appointments as clinical assistants in dermatology. These individuals would also see, and treat, seasonal allergic rhinitis.

In relation to Schwarz's statement that other physicians did not attend dermatology meetings to learn about seasonal allergic rhinitis, Schering-Plough stated that physicians attended meetings to learn. Surely learning at meetings was not limited to the agenda items, as was evidenced by the value of social and other interactions at these events, where health professionals had the opportunity to learn from each other. The number who requested samples of this product was evidence that physicians were interested in learning about hayfever.

In summary, Schering-Plough could find no evidence that its representative promoted desloratadine for any indication other than for hayfever, or that he distributed samples in any way that was in breach of the Code.

PANEL RULING

The Panel noted that the list of materials used at the meeting included Elcon and Diprobase. NeoClarityn items were also included. These being SPCs, fishleave cards, pens, jotters and samples. No Clarityn materials were listed as being used. This appeared to be odd as the product was licensed for idiopathic chronic urticaria.

The Panel was concerned that NeoClarityn would be thought to have similar indications to Clarityn due to the similarity of the product names. In this regard the Panel noted its rulings above. It was important that the materials and the representatives were very clear about the licensed indications for NeoClarityn. There was no allegation about the materials available nor about what representatives had said.

The Panel did not accept that providing samples of NeoClarityn at the dermatology meeting necessarily constituted promoting outside the licence. It would depend on the circumstances. The attendees would be interested in new products for treating hayfever. There was no evidence that anything untoward had taken place. Given the circumstances the Panel ruled no breach of Clause 3.2 of the Code.

Complaint received **28 March 2001**

Case completed **1 June 2001**

CASE AUTH/1174/4/01

AVENTIS PHARMA v SCHERING-PLOUGH

Promotion of NeoClarityn

Aventis Pharma complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough, the items at issue being a journal advertisement and a dosage card.

The claim 'New NeoClarityn gives you the same confidence as Clarityn...' appeared in the journal advertisement. A similar claim had previously been considered in Case AUTH/1137/2/01. Aventis stated that the claim for confidence, which was not further specified, implied confidence in the efficacy and safety of NeoClarityn, amongst other aspects of the product's qualities. Clarityn was licensed for the treatment of both seasonal and perennial allergic rhinitis, whilst NeoClarityn was licensed for the treatment of seasonal allergic rhinitis alone. NeoClarityn, therefore, could not give the same confidence in terms of efficacy as Clarityn. This comparison was misleading. Moreover, confidence in the safety profile of NeoClarityn, a new product, could not be substantiated by extensive post-marketing data.

In Case AUTH/1137/2/01, the Panel's view had been that the claims that NeoClarityn gave the same confidence as Clarityn would be read as being more than a reference to the products' safety profiles. It might be read as a reference to the products' indications. The journal advertisement mentioned increased potency of NeoClarityn as a difference. The Panel had considered that claims relating to NeoClarityn giving the same confidence as Clarityn were not sufficiently qualified. The products had different indications and there was no comparative data. The claims were misleading and not capable of substantiation and a breach of the Code had been ruled. The ruling in Case AUTH/1137/2/01 applied to the present case and a breach of the Code was ruled.

The claim in the journal advertisement '...with 40 times more potency' had been considered in Case AUTH/1137/2/01. Aventis stated that the claim was based on a single study outlining *in vitro* data which showed increased potency at a cloned H1-receptor. There was no clinical basis for the claim and it had no clinical relevance. The data misled as to its significance. In Case AUTH/1137/2/01, the Panel had noted that the claim for potency was based on *in vitro* data. The claim was referenced to Anthes *et al* which was the only study using the cloned human H1-receptor. The claim at issue did not make it clear that it was referring to *in vitro* data. Further, the Panel had queried the relevance to the clinical situation, noting that no relevant clinical data had been supplied by Schering-Plough. A breach of the Code had been ruled. The Panel considered that the ruling applied to the present case and a breach of the Code was ruled.

The claim 'Clarityn with extra clout', which appeared on the dosage card, had been considered in Case AUTH/1137/2/01. Aventis stated that Clarityn was licensed for the treatment of both seasonal and perennial allergic rhinitis, while NeoClarityn was licensed only for the treatment of seasonal allergic rhinitis. In view of the decreased range of treatment indications for NeoClarityn, compared with Clarityn, and the lack of clinical superiority of NeoClarityn over the parent compound Aventis was at a loss as to understand how Schering-Plough could justify this claim. Schering-Plough stated that the claim was partly based on *in vitro* data outlined in the summary of product characteristics (SPC) that showed that NeoClarityn had the property of inhibiting release of proinflammatory cytokines. However, the SPC clearly stated 'the clinical relevance of the observations remain to be confirmed' and therefore the claim had no established clinical relevance. Aventis alleged that the claim was misleading. In Case AUTH/1137/2/01, the Panel's view was that the claims at issue would be read as clinical claims and that NeoClarityn had advantages over Clarityn. The Panel had noted the differences in the indications for the products and that there was no direct comparison of the products. The Panel had also noted that the NeoClarityn EPAR stated that 5mg desloratadine was not superior to 10mg loratadine. The Panel had considered that the claims were misleading, exaggerated and had not been substantiated. A breach of the Code had been ruled. In the case now before it, the Panel considered that the claim 'Clarityn with extra clout' in the dosage card was covered by its previous ruling and ruled a breach of the Code.

In relation to the claim 'Quick and effective relief' in the dosage card, Aventis alleged that the claim 'Quick' with no further qualifying statement was an opinion of Schering-Plough and constituted a hanging comparison. Quick was a relative term and needed a reference against which meaningful comparisons could be made. The Panel considered that the description of NeoClarityn as 'quick' was not a hanging comparison as alleged. The Panel considered that a claim for quick and effective relief had to be read in the light of other products. The claim was not for the quickest effect nor that NeoClarityn was quicker than other products. The Panel noted that some of the other antihistamines referred to onset of action within one hour or that peak plasma levels were reached between 30 and 60 minutes. On balance the Panel did not consider that the claim was misleading as alleged and ruled no breach of the Code.

Aventis Pharma Ltd complained about the promotion of NeoClarityn (desloratadine) by Schering-Plough Ltd. The complaint concerned an advertisement (ref NCL/00-005D) in GP, 2 February 2001, and a dosage card (ref NC/COO-414).

Three previous complaints had already been made about the promotion of NeoClarityn, Cases AUTH/1137/2/01, AUTH/1141/2/01 and AUTH/1172/3/01. These had been considered by the Panel but had not been completed at the time the Panel considered the case now before it. The journal advertisement had previously been the subject of complaint in Case AUTH/1137/2/01. The dosage card referred to by Aventis had not been the subject of previous complaints.

A Journal advertisement

1 Claim 'New NeoClarityn gives you the same confidence as Clarityn ...'

A similar claim had been considered in Case AUTH/1137/2/01.

COMPLAINT

Aventis Pharma stated that the claim for confidence, which was not further specified, implied confidence in the efficacy and safety of NeoClarityn, amongst other aspects of the product's qualities.

Clarityn was licensed for the treatment of both seasonal and perennial allergic rhinitis, whilst NeoClarityn was licensed for the treatment of seasonal allergic rhinitis alone. NeoClarityn, therefore, could not give the same confidence in terms of efficacy as Clarityn. This comparison was misleading in breach of Clause 7.2 of the Code.

Moreover, confidence in the safety profile of NeoClarityn, a new product on the market, could not be substantiated by extensive post-marketing data.

RESPONSE

Schering-Plough stated that the advertisement was designed to promote NeoClarityn for seasonal allergic rhinitis only. Within this context NeoClarityn did have at least comparable efficacy to Clarityn, a result that was not surprising, as desloratadine was the active metabolite of loratadine. No claims were made of efficacy outside the hayfever indication.

Clinical studies in volunteers and patients had demonstrated the similarity in the side effect profile of the two products, in particular the lack of cardiotoxic and sedative properties that had caused concern with antihistamines in the past.

Schering-Plough stated that in its current materials it more clearly specified the similarities between the two products, and listed that, like Clarityn, NeoClarityn was known to 'lack clinically relevant interactions with erythromycin and ketoconazole', be 'truly non-sedating', 'not impair performance', 'not impair driving performance' and 'not potentiate the effects of alcohol'.

This similarity was reflected in the preclinical studies conducted with desloratadine and loratadine which demonstrated that there were no qualitative or quantitative differences in the toxicity profiles of desloratadine and loratadine at comparable levels of exposure to desloratadine.

PANEL RULING

The Panel noted the relevant part of its ruling in Case AUTH/1137/2/01. The Panel's view had been that the claims that NeoClarityn gave the same confidence as Clarityn would be read as being more than a reference to the products' safety profiles. It might be read as a reference to the products' indications. The journal advertisement mentioned increased potency of NeoClarityn as a difference. The Panel had considered that claims relating to NeoClarityn giving the same confidence as Clarityn were not sufficiently qualified. The products had different indications and there was no comparative data. The claims were misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 had been ruled.

The Panel noted Schering-Plough's submission that the advertisement was designed to promote NeoClarityn for seasonal allergic rhinitis only. Seasonal allergic rhinitis, or hayfever, was not mentioned in the main body of the advertisement. The Panel considered that the allegation of a breach of Clause 7.2 was covered by its ruling in the previous case. A breach of Clause 7.2 was ruled.

A2 Claim '... with 40 times more potency'

This claim had been considered in Case AUTH/1137/2/01 and a similar claim had been considered in Case AUTH/1172/4/01.

COMPLAINT

Aventis stated that the claim was based on a single study outlining *in vitro* data, which showed increased potency at a cloned H1-receptor. There was no clinical basis for the claim and it had no clinical relevance. The data misled as to its significance and therefore was alleged to be in breach of Clause 7.2 of the Code.

RESPONSE

Schering-Plough stated that the claim was based on two studies, which demonstrated that at the cloned human H1-receptor, NeoClarityn was at least 40 times as potent as its parent molecule. All current materials made it clear that this derived from *in vitro* data with cloned H1-receptors. No clinical claim was made.

The relative potency of NeoClarityn compared to Clarityn was a fundamental property of the desloratadine molecule and as such it was surely appropriate to inform physicians of this fact.

PANEL RULING

The Panel noted the relevant part of one of its rulings in Case AUTH/1137/2/01. The Panel had noted that the claim for potency was based on *in vitro* data. The claim was referenced to Anthes *et al* which was the only study using the cloned human H1-receptor. The supplementary information to Clause 7.2 of the Code stated that care must be taken with the use of *in vitro* data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel had noted that the claim at issue did not make it clear that it was referring to *in vitro* data. Further, the Panel had queried the relevance to the clinical situation, noting that no relevant clinical data had been supplied by Schering-Plough. The Panel had ruled breaches of Clauses 7.2 and 7.3 of the Code. The Panel had considered that the alleged breach of Clause 7.8 was covered by its ruling of a breach of Clause 7.2.

The Panel considered that the allegation of a breach of Clause 7.2 of the Code was covered by its ruling in

the previous case. A breach of Clause 7.2 was ruled.

B Dosage card

1 Claim 'Clarityn with extra clout'

This claim had been considered in Case AUTH/1137/2/01.

COMPLAINT

Aventis stated that Clarityn was licensed for the treatment of both seasonal and perennial allergic rhinitis, while NeoClarityn was licensed only for the treatment of seasonal allergic rhinitis. In view of the decreased range of treatment indications for NeoClarityn, compared with Clarityn, and the lack of clinical superiority of NeoClarityn over the parent compound, Aventis was at a loss as to understand how Schering-Plough could justify this claim. Furthermore, in the written response received from Schering-Plough, it was stated that the claim was partly based on *in vitro* data outlined in the summary of product characteristics (SPC) that showed that NeoClarityn had the properties of inhibiting release of proinflammatory cytokines. However, the SPC clearly stated 'the clinical relevance of the observations remain to be confirmed' and therefore the claim had no established clinical relevance.

Aventis alleged that the claim was misleading and constituted a breach of Clause 7.2 of the Code.

RESPONSE

Schering-Plough stated that desloratadine was the active metabolite of loratadine. The claim was designed to succinctly inform the prescriber of the characteristics of a product that was *in vitro* a more active metabolite of a well-known parent compound. No claim regarding clinical efficacy was made.

Nevertheless, it was correct that desloratadine had activity in areas which loratadine did not. It had been shown *in vitro* as stated in the SPC that desloratadine had the properties of 'inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8 and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells'. While the SPC stated 'The clinical relevance of these observations remains to be confirmed', Schering-Plough knew that previous work on loratadine did not show the same antiallergic effect.

In addition, with respect to clinical data, while many of the current desloratadine publications were against placebo, in all trials examined, desloratadine had at least a numerical advantage over placebo (and in several a statistically significant advantage) in terms of treating the symptom of nasal congestion. A review of the loratadine literature showed a lack of efficacy of loratadine on nasal congestion. This consistent result, over a number of trials, demonstrated that, for at least this significant symptom, desloratadine had more 'clout' than loratadine.

While Schering-Plough believed it relevant to bring this data to the Authority's attention now, it reiterated that it did not intend to and believed that it had not made a claim of clinical superiority for desloratadine compared to loratadine. In fact, in all material where the pre-clinical data related to desloratadine was discussed it was clearly stated this was *in vitro* data.

PANEL RULING

The Panel noted the relevant part of its ruling in Case AUTH/1137/2/01. The Panel had noted that the NeoClarityn SPC stated that it was indicated for the relief of symptoms associated with seasonal allergic rhinitis. Clarityn was indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitic such as sneezing, nasal discharge and itching and ocular itching and burning. Clarityn was also indicated for the relief of symptoms associated with idiopathic chronic urticaria. In the Panel's view the claims at issue would be read as clinical claims and that NeoClarityn had advantages over Clarityn. The Panel had noted the differences in the indications for the products and that there was no direct comparison of the products. The Panel had also noted that the NeoClarityn EPAR stated that 5mg desloratadine was not superior to 10mg loratadine. The Panel had considered that the claims were misleading, exaggerated and had not been substantiated. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code had been ruled.

Turning to the case now before it, Case AUTH/1174/4/01, the Panel considered that the claim 'Clarityn with extra clout' in the dosage card was covered by its previous ruling. The Panel ruled a breach of Clause 7.2 of the Code.

B2 Claim 'Quick and effective relief'

COMPLAINT

Aventis alleged that the claim 'Quick' with no further qualifying statement was an opinion of Schering-Plough and constituted a hanging comparison. Quick was a relative term and needed a reference against which meaningful comparisons could be made. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Schering-Plough submitted that in the context of treating hayfever, it was fair to say that a product with an onset of action in 28 minutes was quick.

This was supported by two papers, Finn *et al* and Horak *et al*, that examined the speed of onset of this product. The respective authors of these papers concluded '… indicating a rapid onset of action' and 'Thus, desloratadine has a rapid onset of action, within 28 minutes'.

PANEL RULING

The Panel considered that the description of NeoClarityn as 'quick' was not a hanging comparison as alleged. The claim 'Quick and effective relief' did not, in the Panel's view, need a reference against which meaningful comparisons could be made.

The Panel noted that Horak *et al* reported that the

median time to onset of action was 48.5 minutes. The 28 minutes referred to by Schering-Plough related to 50% of all subjects who experienced at least a two point reduction in total symptom severity score. The study by Finn was carried out on patients with seasonal allergic rhinitis and asthma. The data on the onset of action was limited. Patients had a significant improvement in am instantaneous total symptom score (TSS) 24 hours after the first dose of desloratadine indicating a rapid onset of action and full 24 hour efficacy. A statistically significant reduction in TSS was also observed at the first assessment approximately 12 hours after the first dose of desloratadine. The study concluded that the results indicated that desloratadine had a rapid onset of action. Section 5.2 of the SPC, Pharmacokinetic properties, stated that plasma concentrations could be detected within thirty minutes of administration.

The Panel considered that a claim for quick and effective relief had to be read in the light of other products. The claim was not for the quickest effect nor that NeoClarityn was quicker than other products. The Panel noted that some of the other antihistamines referred to onset of action within one hour or that peak plasma levels were reached between 30 and 60 minutes. On balance the Panel did not consider that the claim was misleading as alleged and ruled no breach of Clause 7.2 of the Code.

Complaint received **5 April 2001**

Case completed **1 June 2001**

CASE AUTH/1175/4/01 ***NO BREACH OF THE CODE***

PHARMACIST v PFIZER

Viagra journal advertisements

A pharmacist complained about two journal advertisements for Viagra (sildenafil) issued by Pfizer. One advertisement bore a photograph of a couple sitting together with the headlines 'They used to do everything together', 'they still do'. A claim beneath stated 'it's been shown to be effective up to eighty percent of the time …'. The complainant alleged that the advertisement misled with regard to the 80% efficacy rate cited. 'Up to' implied that such a rate was to be expected on all occasions. Clearly this was not so and there were data which would suggest that 80% was not representative of the body of evidence for Viagra. The complainant believed that the Authority had previously ruled that the unqualified use of 'up to' was unacceptable.

The Panel considered that the efficacy data for Viagra 50mg or 100mg was of most clinical relevance to prescribers given that the majority of patients would receive these doses. In the Panel's view the clinical data presented supported the claim that Viagra had been shown to be effective up to eighty percent of the time. Although some studies had reported success in slightly less than 80% of patients using 50mg of Viagra, all of the studies reported success in excess of 80% of patients with the 100mg dose. Overall the Panel considered that the claim represented the balance of the data and ruled no breach of the Code. Use of the wording 'up to' when describing an expected response had been considered misleading in two past cases where the Panel had considered that the stated response would be expected in an entire patient population and that was not so. In the case now before it the Panel considered that the circumstances were different. The stated response, 'up to eighty percent', was not a sub-group analysis representing the best possible outcome. The Panel did not consider that in this instance the wording 'up to' was misleading. No breach of the Code was ruled.

The other advertisement was headed 'We're proud that Viagra has been awarded the prestigious Prix Galien' and bore an illustration of the award beneath which was the claim 'We're even prouder of the impact it's had on the lives of over 10 million men'. The complainant alleged that the claim was misleading as it could not be substantiated by the IMS dated cited. The wording implied that Viagra had benefited more than 10 million men in only a positive manner. Unless the use of the word 'impact' was also referring to some of the negative aspects of treatment, such as death, then this claim was clearly an exaggeration. The complainant presumed that Pfizer's pride was based on a cohort study data of more than 10 million patients who were interviewed to assess the impact, positive or otherwise, of this treatment. If not, then the use of prescribing statistics such as the number of patients receiving Viagra simply did not equate to being able to make such a claim.

The Panel noted that the number of patients who had been treated with Viagra (over 10 million) had been calculated from IMS data of June 2000. By calculating the cost per patient and applying that to total world sales the number of patients treated was determined. As of June 2000 the data showed that 10.1 million men had been treated; data to December 2000 showed that that figure had risen to 12.3 million. The Panel noted the efficacy data discussed above and that 12.3 million men had been treated with Viagra. The fact that erectile dysfunction was more openly discussed was in part due to the impact of Viagra. The claim would be read as Viagra having had a positive impact. In the circumstances the Panel considered that it was not misleading or exaggerated to state that Viagra had had an impact on the lives of over 10 million men. No breach of the Code was ruled.

A pharmacist complained about two journal advertisements (refs 10504 and 13017) for Viagra (sildenafil) issued by Pfizer Limited.

When writing to Pfizer the Authority drew attention to Clauses 7.2, 7.3 and 7.8 of the Code.

1 Advertisement 10504 March 2001

This advertisement bore a photograph of a couple sitting together with the headlines 'They used to do everything together', 'they still do'. A claim beneath stated 'it's been shown to be effective up to eighty percent of the time …'.

COMPLAINT

The complainant alleged that the advertisement misled with regard to the efficacy rate cited ie '… effective up to eighty percent of the time …'. 'Up to' implied that this efficacy rate was to be expected on all occasions. Clearly this was not so and there were data which would suggest that 80% was not representative of the body of evidence for this treatment. The complainant was led to believe that the Authority had previously ruled that the unqualified use of this particular wording was unacceptable.

RESPONSE

Dealing firstly with the efficacy of Viagra, Pfizer stated that the following data pertained to studies examining the efficacy and safety of Viagra in men with a broad spectrum of causes of erectile dysfunction:

Data on file (STUDY 148-102) published as Goldstein *et al* (1998): 532 men with erectile dysfunction of a variety of aetiologies were randomised to receive placebo (n=199), 25mg (n=96), 50mg (n=105) or 100mg (n=101) of sildenafil. The heterogeneity of the aetiology of the men's erectile dysfunction reflected the range seen in clinical practice. Event log data showed the following proportion of men achieving erections hard enough for sexual intercourse during the last 4 weeks of treatment: placebo 50%; 25mg 72%; 50mg 80%; 100mg 85%. After 24 weeks of treatment improved erections were reported by patients in the following proportions: placebo 25%; 25mg 56%; 50mg 77%;100mg 84%.

Data on file (STUDY 148-103) published as Goldstein *et al* (1998): 329 men with erectile dysfunction were randomly assigned to take placebo or 50mg of sildenafil. These men had a broad range of baseline characteristics, and again were representative of those patients seen in clinical practice. The dose of sildenafil was then titrated up to 100mg or down to 25mg dependent on efficacy and tolerability. After 24 weeks of treatment, the proportions of men reporting improvements in erections were: placebo (n=118) 19%; sildenafil all doses (n=136) 74%. Ninety eight percent of men were taking 50 or 100mg of sildenafil in the treatment group at the end of the study.

Montorsi *et al* (1999): 514 men with erectile dysfunction of varying aetiologies were randomly assigned placebo (n=114), 25mg (n=119), 50mg (n=122) or 100mg (n=118) sildenafil. The distribution of aetiologies was representative of the distribution of erectile dysfunction aetiologies. At 12 weeks, the proportions of men answering 'yes' to the Global Efficacy Question 'did the treatment you received during the last 4 weeks improve your erections?' were: placebo 24%; 25mg 67%; 50mg 78%; 100mg 86%.

Dinsmore *et al* (1998): 111 men suffering from broad spectrum erectile dysfunction were randomised to receive flexible dose sildenafil, with reference to age-matched healthy control subjects. After 12 weeks of treatment, the proportion of men answering 'yes' to the Global Efficacy Question was: sildenafil (n=57) 81%; placebo (n=54) 18%. Seventy nine percent of patients were taking either 50mg or 100mg sildenafil at completion of the double blind phase. For those patients receiving sildenafil who had at least one successful attempt at intercourse, the proportions ranged from 73-86%.

Guay *et al* 2001 (currently unpublished): 521 men with erectile dysfunction with a broad spectrum of concomitant diseases and erectile dysfunction aetiologies were studied. Their associated risk factors (including medications, lifestyles factors and medical conditions) were appropriately controlled prior to institution of sildenafil treatment. Overall, there was an 82% successful intercourse rate with sildenafil treatment.

Pfizer submitted that with the majority of patients receiving sildenafil prescribed 50 or 100mg, the efficacy data for these two doses were of more clinical relevance to prescribers than the data for 25mg.

The above body of efficacy data available for men with a broad range of erectile dysfunction causes taking the standard treatment dose of 50 or 100mg of sildenafil, demonstrated an overall efficacy rate based on their responses to the Global Efficacy Question 'did the treatment you have been receiving in the last 4 weeks improve your erections?' of near or above 80%.

In relation to the use of the phrase 'up to', Pfizer stated that it agreed with the complainant that some sub-populations of erectile dysfunction patients had a lower response rate to sildenafil treatment than 80% (Feldman and Waterbury 1998; Blonde *et al* 2000). However, many other groups of patients could expect an efficacy rate far in excess of 80% (Rosen *et al* 1999; Shabsigh *et al* 1999). The efficacy claim of 'up to eighty percent' gave prescribers a well substantiated, evidence-based expectation of overall efficacy in patients suffering from erectile dysfunction who might have a wide range of concomitant medical conditions, pharmacotherapy and psychological factors. These data reflected the 'real-life' erectile dysfunction patient as they included patients with a wide variety of co-morbidities and aetiologies.

Pfizer noted that Cases AUTH/970/1/00 and AUTH/972/1/00 were cited by the complainant as an example of the use of the phrase 'up to' which had been previously ruled in breach of the Code. However, those cases were not comparable with the current complaint. The claim in the previous cases referred only to a limited study sub-population, representing the best possible results and not the body of clinical study evidence.

A company had claimed '… lowers LDL-cholesterol in up to 44%' and then qualified this figure in a footnote, explaining that this figure referred only to female

study participants. The study in question was designed to compare the efficacy of two dosages in the per-protocol population. The efficacy of the higher dose by gender was not specified as a primary end point and females represented only 34% of the study population. Other studies failed to show a similarly large decrease in LDL-cholesterol. The complaint regarding the use of the term 'up to' had been upheld because 'it provided no reasonable guide to the physician'.

By contrast, in the advertisement now at issue, use of the term 'up to eighty percent' reflected: fair and balanced representation of the body of data available; results of pre-determined end points for determination of efficacy of Viagra treatment; the efficacy for patients with a broad range of causes of erectile dysfunction reflecting those seen in UK clinical practice; neither the best nor the worst efficacy data for Viagra, rather the most frequent and representative and a reasonable and realistic expectation of efficacy for physicians prescribing Viagra.

Pfizer did not consider that there had been a breach of the Code.

PANEL RULING

The Panel noted that the licensed dose of Viagra was 50mg which, according to efficacy and tolerability could be increased to a maximum of 100mg. In the elderly a first dose of 25mg should be used.

The Panel noted that a placebo-controlled, flexible dose-escalation study, where a starting dose of Viagra 50mg could be doubled or halved according to therapeutic response and adverse events, showed that 98% of men took either 50 or 100mg (Goldstein *et al*). Another flexible dose study showed that 79% of patients were taking either 50mg or 100mg of sildenafil at completion of the double blind phase (Dinsmore *et al*). The Panel considered that the efficacy data for Viagra 50mg or 100mg was of most clinical relevance to prescribers given that the majority of patients would receive these doses. In the Panel's view the clinical data presented supported the claim that Viagra [50 or 100mg] had been shown to be effective up to eighty percent of the time. Although some studies had reported success in slightly less than 80% of patients using 50mg of Viagra, all of the studies reported success in excess of 80% of patients with the 100mg dose. Overall the Panel considered that the claim represented the balance of the data and ruled no breach of Clauses 7.2 and 7.3 of the Code.

The Panel noted that use of the wording 'up to' when describing an expected response had been considered misleading in Cases AUTH/970/1/00 and AUTH/972/1/00. In those cases the Panel considered that the stated response would be expected in an entire patient population which was not so. The stated response only applied to a sub-group of patients. A breach of the Code was ruled which was upheld on appeal. Turning to the case now before it, Case AUTH/1175/4/01, the Panel considered that the circumstances were different. The stated response, 'up to eighty percent' was not a sub-group analysis representing the best possible outcome. The Panel noted its ruling above. It did not consider that in this instance the wording 'up to' was misleading. No breach of Clause 7.2 was ruled.

2 Advertisement 13017 March 2001

This advertisement was headed 'We're proud that Viagra has been awarded the prestigious Prix Galien' and bore an illustration of the Prix Galien award beneath which was the claim 'We're even prouder of the impact it's had on the lives of over 10 million men'.

COMPLAINT

The complainant alleged that the claim was misleading as it could not be substantiated by the IMS dated cited. The wording implied that Viagra had benefited more than 10 million men in only a positive manner. Unless the use of the word 'impact' was also referring to some of the negative aspects of treatment with Viagra, such as death, then this claim was clearly an exaggeration.

The complainant presumed that the Pfizer pride was based on a cohort study data of more than 10 million patients who were interviewed to assess the impact, positive or otherwise, of this treatment. If not, then the use of prescribing statistics such as the number of patients receiving Viagra simply did not equate to being able to make such a claim and implied that all patients were impacted positively by treatment with Viagra.

RESPONSE

Pfizer stated that it was aware from prescribing statistics (IMS data) that as of June 2000, more than 10 million men worldwide had been prescribed Viagra. Pfizer did not claim in its materials that Viagra had been effective in all those men for whom it was prescribed, although it believed it had demonstrated that an efficacy rate of up to 80% in broad spectrum erectile dysfunction continued to be supported.

At the time of this advertisement actually appearing (from March 2001 onwards) later IMS data in fact considerably exceeded the figure of 10 million and considering the efficacy rate of Viagra, Pfizer's claim appeared to be quite conservative.

Pfizer's claim related, though, not simply to clinical efficacy in those for whom Viagra was prescribed. The benefit in patients in whom Viagra was effective was not in dispute; however Pfizer argued that a prescription for Viagra was an indication of medical confirmation of a diagnosis of erectile dysfunction and its implications, which in itself had an impact on the sufferer's life.

Erectile dysfunction was a distressing condition to both the sufferer and his family and the impact of seeking a physician's input into the management of erectile dysfunction extended well beyond the supply of a prescription for an effective treatment. The availability of an effective oral treatment for erectile dysfunction, Viagra, had impacted broadly on both the general public awareness of the condition and the ability of men suffering with the condition to seek

help with the problem from their own general practitioner, irrespective of whether or not they were prescribed any treatment. Presentation rates for erectile dysfunction in the UK had increased substantially since Viagra first became available in September 1998, reflecting this increased awareness.

Pfizer drew attention to the published text of the speech of the professor who presented the Prix Galien award that was the subject of this advertisement: 'The drug has become a household name. The fact that it has launched a thousand jokes and even more column inches should not distract us from its significant benefits: quite apart from being an effective treatment, it [Viagra] has brought men's health in general, and impotence in particular, out of the closet'. While Pfizer did not quote this text in its advertisement it believed that the statement would be widely accepted in the medical community and strongly supported Pfizer's claim. Erectile dysfunction was no longer the source of embarrassment and shame for men that it once was. This enormous step forward was due in significant measure to the availability of Viagra.

As a prescription-only medicine, patients prescribed Viagra would have sought medical advice and been diagnosed as suffering with erectile dysfunction, and as a consequence might also have had other medical conditions, such as diabetes or cardiovascular disease, diagnosed, prior to receiving their prescription. Pfizer therefore believed that the claim that the prescription for Viagra had had an 'impact' on the lives of those ten million men for whom it had been prescribed could be justified and supported, and that the claim did not breach Clauses 7.2 nor 7.8 nor represent an exaggeration. Indeed it could be argued that in reality many more than the ten million men actually prescribed Viagra had benefited from the increased public awareness of erectile dysfunction which had resulted from the availability of an effective oral treatment.

PANEL RULING

The Panel noted that the number of patients who had been treated with Viagra (over 10 million) had been calculated from IMS data of June 2000. By calculating the cost per patient and applying that to total world sales the number of patients treated was determined. As of June 2000 the data showed that 10.1 million men had been treated with Viagra. IMS data to December 2000 showed that that figure had risen to 12.3 million.

The Panel noted the efficacy data discussed in point 1 above and that 12.3 million men had been treated with Viagra. The fact that erectile dysfunction was more openly discussed was in part due to the impact of Viagra. The claim would be read as Viagra having had a positive impact. In the circumstances the Panel considered that it was not misleading or exaggerated to state that Viagra had had an impact on the lives of over 10 million men. No breach of Clauses 7.2, 7.3 and 7.8 were ruled.

Complaint received **10 April 2001**

Case completed **4 June 2001**

CASE AUTH/1177/4/01

UCB PHARMA v AVENTIS PHARMA

Telfast journal advertisement

UCB Pharma complained about a Telfast (fexofenadine) journal advertisement issued by Aventis Pharma. The prominent claim 'Clearly superior in hayfever*' appeared in the upper right-hand quarter of the advertisement. The asterisk referred the reader to a statement in the lower right-hand quarter of the advertisement which read 'With clearly superior efficacy compared to loratadine, a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile, it's easy to see why Telfast works so well in hayfever'. UCB supplied Zirtek (cetirizine).

UCB alleged that the claim 'Clearly superior in hayfever' was intended to suggest a superlative position for Telfast in the treatment of hayfever and was an all-embracing claim that was designed to mislead. Even though the references to comparator products might prevent the comparison from hanging, they did not support this general superiority claim. The claim was therefore unsubstantiated. In order to make a general superiority claim for the treatment of hayfever, there had to be a clearly demonstrated superiority in all aspects of treatment in comparison to all currently available treatments. It was not sufficient to compare efficacy against one product and side effects against another.

UCB alleged that the claim: '...clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile...' was all-embracing. The supportive references mainly considered subjective reports of somnolence of fexofenadine compared with cetirizine and did not support the general claim of a better side effect profile or better safety. The studies did not support the implication that a lower incidence of subjectively reported somnolence led to reduced risk of harm. Mann *et al*, which was cited, concluded that 'sedation might result in an increase in accident and injury, but we found no such difference between the antihistamines'. This supported the view that there was no 'clearly favourable safety profile', even when only sedation was considered.

In relation to the claim '… a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile …', the Panel noted that the Telfast summary of product characteristics (SPC) stated that 'In controlled clinical trials the most commonly reported adverse events were headache (7.3%), drowsiness (2.3%), nausea (1.5%), dizziness (1.5%) and fatigue (0.9%). The incidence of these events was similar to placebo. According to the cetirizine SPC 'In objective tests of psychomotor function, the incidence of sedation with cetirizine was similar to that of placebo. There have been occasional reports of mild and transient side effects such as headache, dizziness, drowsiness, agitation, dry mouth and gastrointestinal discomfort'.

Mann *et al* concluded that the frequency with which sedation was reported in post-marketing surveillance studies of loratadine, cetirizine, fexofenadine and acrivastine, by prescription event monitoring studies, was low with all four medicines; fexofenadine and loratadine might be more appropriate for people working in safety critical jobs. The authors reported that it was already known that 'second generation 'non-sedating' antihistamines are usually considered to be equivalent in efficacy but their sedating properties are less clear'. Howarth *et al* compared the efficacy and safety of fexofenadine and cetirizine in the treatment of seasonal allergic rhinitis; there were no differences in efficacy between the two. The study concluded, *inter alia*, that the combined incidence of drowsiness or fatigue was greater with cetirizine (9%) than with placebo (4%) (p=0.07) or fexofenadine (4%) (p=0.02). The study indicated that headache was the most frequent treatment related adverse event for both medicines. The incidence of drowsiness (6%) and fatigue (2%) when considered as separate adverse events were greater for cetirizine than fexofenadine or placebo but this difference was not statistically significant. Mason *et al* concluded that the safety data 'suggested that the risks associated with the use of fexofenadine were extremely low compared with the benefits likely to be achieved on treatment. The lack of increase in the incidence of sedation at increasing doses of the drug, in addition to the apparent lack of cardiovascular side-effects may distinguish fexofenadine in terms of safety when compared with other currently available H1 receptor antagonists'.

The Panel noted that neither the claim at issue nor the advertisement mentioned sedation. The Panel considered that the claim would be read as a general claim for a superior side effect profile of Telfast compared to cetirizine and a general claim for a favourable safety profile; it was not restricted to sedation. The Panel considered that the evidence before it did not indicate that Telfast had a clearly superior side effect profile compared with cetirizine and a clearly favourable safety profile. The claim overstated the data. It was misleading, not capable of substantiation and exaggerated and breaches of the Code were ruled.

The Panel considered that the headline claim 'Clearly superior in hayfever*' would be read as a general claim for the superiority of Telfast in comparison to all currently available treatments. The Panel noted the submission from Aventis that the statement was qualified by reference to the comparators in the qualification 'With clearly superior efficacy compared to loratadine, a clearly superior side effect profile compared to cetirizine and a clearly favourable side effect profile …' but it was an accepted principle under the Code that a claim could not be qualified by reference to a footnote or to claims elsewhere. Any qualification should be part of or appear in the same immediate visual field as the claim itself. The Panel queried whether the design and layout of the advertisement at issue was such that the qualification appeared in the same visual field. The Panel also noted its ruling above. The Panel considered the bold claim 'Clearly superior in hayfever' would not be read as

an efficacy comparison with loratadine and a side effect profile compared to cetirizine. It would be read as an overall claim of superiority and no data had been supplied to support such a claim. The Panel considered that the claim was exaggerated, all-embracing and misleading as alleged and breaches of the Code were ruled.

UCB Pharma Limited complained about a Telfast (fexofenadine) advertisement (ref TEL0630201) issued by Aventis Pharma Ltd which had appeared in Pulse on 17 March. The prominent claim 'Clearly superior in hayfever*' appeared in the upper right-hand quarter of the advertisement. The asterisk referred the reader to a statement in the lower right-hand quarter of the advertisement which read 'With clearly superior efficacy compared to loratadine, a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile, it's easy to see why Telfast works so well in hayfever'. UCB supplied Zirtek (cetirizine).

COMPLAINT

UCB Pharma alleged that the claims in the advertisement were misleading, all-embracing and unsubstantiated in breach of Clauses 7.2, 7.3 and 7.8 of the Code.

In the advertisement the statement 'Clearly superior in hayfever' was intended to suggest a superlative position for Telfast in the treatment of hayfever. This was an all-embracing claim that was designed to mislead. Even though the references to comparator drugs might prevent the comparison from hanging, they did not support this general superiority claim. The claim therefore was unsubstantiated.

UCB stated that in order to make a general superiority claim for the treatment of hayfever, there had to be a clearly demonstrated superiority in all aspects of treatment in comparison to all currently available treatments. It was not sufficient to compare efficacy against one product and side effects against another.

UCB alleged that the claim: '...a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile...' was all-embracing. The supportive references mainly considered subjective reports of somnolence of fexofenadine compared with cetirizine and did not support the general claim of a better side effect profile or better safety.

The meaning of safety as defined by the Oxford Dictionary was 'freedom from danger or risks'.

The studies did not support the implication that a lower incidence of subjectively reported somnolence led to reduced risk of harm. In fact the Mann report, which was cited, investigated this very hypothesis and concluded that: 'sedation might result in an increase in accident and injury, but we found no such difference between the antihistamines'. This direct quotation from a major post marketing surveillance study supported the view that there was no 'clearly favourable safety profile', even when only sedation was considered.

RESPONSE

With regard to the claim 'Clearly superior in hayfever', Aventis Pharma stated that Clause 7.8 of the Code defined 'superlatives' as 'grammatical expressions which denoted the highest quality or degree, such as best, strongest, widest, etc'. Furthermore, the Oxford Dictionary defined the word 'superlative' as 'of the highest quality or degree'. The statement 'Clearly superior in hayfever' therefore by definition did not constitute a superlative. The superlative of superior was 'the most superior'.

Aventis submitted that the claim was qualified by reference to comparators in which it clearly stated the comparisons that it made. UCB stated that in order to make a general superiority claim for the treatment of hayfever, there had to be a clearly demonstrated superiority in all aspects of treatment in comparison to all currently available treatments.

With regard to the claim '...a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile...', Aventis noted that UCB had suggested that sedation received undue prominence in consideration of the side effect profile of these antihistamines. Historically, sedation had been a major concern associated with the use of the older antihistamines. Therefore, the non-sedating nature of an antihistamine such as Telfast that did not cross the blood-brain barrier constituted an important feature of the safety profile of this class of medicines. This was well supported by the cited references Mann *et al* (2000) found in their Prescription Event Monitoring study that '… and fexofenadine are associated with a lower incidence of sedation than … cetirizine'. This difference was statistically significant.

Howarth *et al* (1999) directly compared fexofenadine with cetirizine, and found a statistically significantly greater combined incidence of drowsiness or fatigue with cetirizine than fexofenadine.

Mason *et al* (1999) was a review article which stated that 'Unlike some other antihistamines, such as … cetirizine, fexofenadine is truly non-sedating …'.

In conclusion, Aventis believed that the advertisement did not constitute a breach of Clauses 7.2, 7.3 or 7.8 of the Code.

PANEL RULING

The Panel firstly considered the claim '… a clearly superior side effect profile compared to cetirizine and a clearly favourable safety profile …'. The Panel noted that section 4.8 of the Telfast summary of product characteristics (SPC) headed 'Undesirable Effects' stated 'In controlled clinical trials the most commonly reported adverse events were headache (7.3%), drowsiness (2.3%), nausea (1.5%), dizziness (1.5%) and fatigue (0.9%)'. The incidence of these events was similar to placebo. The Panel noted that according to the cetirizine SPC 'In objective tests of psychomotor function, the incidence of sedation with cetirizine was similar to that of placebo. There have been occasional reports of mild and transient side effects such as headache, dizziness, drowsiness, agitation, dry mouth and gastrointestinal discomfort'. The Panel noted that the claim at issue with regard to the side effect profile compared to cetirizine was referenced to Mann *et al* and Howarth *et al* and with regard to the 'clearly favourable safety profile' was referenced to Mason *et al*, Nicholson *et al* (2000),

Nicholson *et al* (1999), Pratt C M *et al* (1999) and IMS data (2000). The Panel noted the allegation that the supportive references mainly considered subjective reports of somnolence of Telfast compared with cetirizine and did not support the general claim of a better side effect profile or better safety. The Panel also noted Aventis' submission that the non-sedating nature of Telfast which did not cross the blood brain barrier constituted an important feature of the safety profile of this class of medicines and cited Mann *et al*, Howarth *et al* and Mason *et al* in this regard.

The Panel noted that Mann *et al* investigated the frequency with which sedation was reported in post-marketing surveillance studies of loratadine, cetirizine, fexofenadine and acrivastine. The design was prescription event monitoring studies. The report listed the most frequently reported events for loratadine in the first month of treatment and provided corresponding values for the other antihistamines. The study authors concluded that the risk of sedation was low with all four medicines, fexofenadine and loratadine might be more appropriate for people working in safety critical jobs. The authors noted that prescription event monitoring data had various strengths and weaknesses. The authors noted that the data collection period for fexofenadine was later than for any of the other medicines but were not aware of any publicity which might have affected the reporting of sedation. The authors reported that it was already known that 'second generation 'non-sedating' antihistamines are usually considered to be equivalent in efficacy but their sedating properties are less clear'.

Howarth *et al* was a double blind placebo controlled study comparing the efficacy and safety of fexofenadine and cetirizine in the treatment of seasonal allergic rhinitis. There were no differences in efficacy between fexofenadine and cetirizine. The study concluded, *inter alia*, that the combined incidence of drowsiness or fatigue was greater with cetirizine (9%) than with placebo (4%) (p=0.07) or fexofenadine (4%) (p=0.02). The study indicated that headache was the most frequent treatment related adverse event for both fexofenadine and cetirizine. The Panel noted however that the incidence of drowsiness (6%) and fatigue (2%) when considered as separate adverse events were greater for cetirizine than fexofenadine or placebo but this difference was not statistically significant.

The Panel noted that Mason *et al* which reviewed the systemic safety of fexofenadine concluded that the safety data reported in the study 'suggested that the risks associated with the use of fexofenadine were extremely low compared with the benefits likely to be achieved on treatment. The lack of increase in the incidence of sedation at increasing doses of the drug, in addition to the apparent lack of cardiovascular side-effects may distinguish fexofenadine in terms of safety when compared with other currently available H1 receptor antagonists'.

The Panel noted that neither the claim at issue nor the advertisement mentioned sedation. The Panel considered that the claim would be read as a general claim for a superior side effect profile of Telfast compared to cetirizine and a general claim for a favourable safety profile; it was not restricted to sedation. The Panel considered that the evidence before it did not indicate that Telfast had a clearly superior side effect profile compared with cetirizine and a clearly favourable safety profile. The claim overstated the data. It was misleading, not capable of substantiation and exaggerated. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

The Panel considered that the headline claim 'Clearly superior in hayfever*' would be read as a general claim for the superiority of Telfast in respect of all aspects in comparison to all currently available treatments for hayfever. The Panel noted the submission from Aventis that the statement was qualified by reference to the comparators in the qualification 'With clearly superior efficacy compared to loratadine, a clearly superior side effect profile compared to cetirizine and a clearly favourable side effect profile …'. The Panel noted that it was an accepted principle under the Code that a claim could not be qualified by reference to a footnote or to claims elsewhere in the advertising. Any qualification should be part of or appear in the same immediate visual field as the claim itself. The Panel queried whether the design and layout of the advertisement at issue was such that the qualification appeared in the same visual field. The Panel also noted its ruling on the qualification above. The Panel considered the bold claim 'Clearly superior in hayfever' would not be read as an efficacy comparison with loratadine and a side effect profile compared to cetirizine. It would be read as an overall claim of superiority and no data had been supplied to support such a claim. The Panel considered that the claim was exaggerated, all-embracing and misleading as alleged and breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

Complaint received **17 April 2001**

Case completed **18 June 2001**

CASE AUTH/1178/4/01

AVENTIS PHARMA and PROCTER & GAMBLE v MERCK SHARP & DOHME

Fosamax journal advertisement

Aventis Pharma and Procter & Gamble complained jointly about a journal advertisement for Fosamax 70mg (alendronate) issued by Merck Sharp & Dohme. The heading 'The first once-weekly treatment for post-menopausal osteoporosis to prevent fracture' was followed by three bullet points. The first claimed 'Proven efficacy' and stated that 'Fosamax once weekly 70mg is therapeutically equivalent to Fosamax 10mg daily at increasing BMD'. The second referred to convenience and the third read 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' and was referenced to Schnitzer *et al*. 'Once weekly Fosamax 70mg' appeared in logo format in the bottom right-hand corner.

The complainants alleged that both parts of the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' were misleading. Firstly, it was alleged that the claim misled as to the overall safety profile of alendronate 70mg in a general osteoporotic population; the referenced study, Schnitzer *et al*, did not provide support for the claim of 'well tolerated' in a broad population. In order to extrapolate a 'well tolerated' claim to a general patient population, tolerability data must be compared with that of a control group. The Schnitzer study had no placebo control group, just a comparator, alendronate 10mg. The authors found the tolerability to be similar across treatment groups. An osteoporotic population in whom a bisphosphonate was likely to be prescribed had been described by van Staa *et al*; 37% of subjects used H2 antagonists or antacids in the year before inclusion in the analysis and NSAID and aspirin use was also increased in this population compared with a non-osteoporotic control cohort. An osteoporotic population could be considered at higher risk of gastrointestinal (GI) adverse events. Across the alendronate studies, higher risk patients with active GI disease and/or regular users of NSAIDs, aspirin, H2 antagonists or proton pump inhibitor therapy were excluded. The result was that relatively few patients in the alendronate clinical trials were in these high risk populations and hence it was inappropriate to claim 'well tolerated' in a general osteoporotic population. Because studies of alendronate 10mg had substantial exclusion criteria relating to GI risk, and because 70mg was being compared with 10mg, it was inappropriate to make a claim about tolerability for 70mg in a broad patient population. Furthermore, Schnitzer *et al* excluded patients with active GI disease. It was difficult to understand how an unqualified 'well tolerated' claim for Fosamax 70mg could be made based on data from a population known to be at lower risk for GI adverse events. Bauer *et al* theorized that the relatively healthy patient population created by the exclusion criteria might help explain the increase in upper GI adverse events seen in post-marketing experience with alendronate 10mg. Aventis and Procter & Gamble pointed out that for the 10mg dose, post-marketing experience was different from observations in clinical trials, and resulted in serious post-approval labelling modifications. Published post-marketing data demonstrated that alendronate 10mg daily was associated with significant oesophageal and gastric adverse events, despite the fact that controlled clinical trials did not identify this important issue.

Aventis and Procter & Gamble stated that serious adverse events, such as oesophageal ulceration, might occur at a lower incidence in a selected clinical study population than in clinical practice (Dowd *et al*). The Schnitzer study included 519 patients taking Fosamax 70mg once-weekly, but excluded those with major upper GI disease. So even though the authors stated that alendronate 70mg was 'generally well tolerated', the paper provided insufficient substantiation for extrapolation of such a claim to overall tolerability in a general osteoporotic population. The Fosamax 70mg summary of product characteristics (SPC) included the special warning that alendronate could cause local irritation of the upper GI mucosa, and potentially worsen underlying disease. It was stated that caution should be used in patients with active upper GI problems, and that oesophageal reactions might be severe and might require hospitalisation. Oesophageal ulceration was listed as a common adverse event.

Secondly, Aventis and Procter & Gamble alleged that the claim was misleading in terms of the safety of alendronate 70mg in patients at high risk of GI adverse events. The claim that the product was tolerated 'Even in patients on concurrent NSAID/aspirin regimens' was not justified and was not supported by Schnitzer *et al*, which stated 'Approximately 50% of patients used NSAIDs and/or aspirin at some point during the study. There were no between-group differences in the incidence of upper GI adverse events in these patients during the periods of exposure to NSAIDs/aspirin'. In 1996 the MCA/CSM noted that 'The frequency of upper gastro-intestinal adverse reactions appears to be greater when alendronate sodium is used in conjunction with non-steroidal anti-inflammatory drugs and aspirin'. In 1998 a reminder was issued, stating that 'Caution is required if the patient is also taking NSAIDs'. Graham and Malaty examined the potential for a synergistic effect of alendronate and naproxen on gastric ulcers. As well as demonstrating a statistically significant gastric ulcer risk for alendronate therapy, the authors documented quadrupled risk with concomitant (COX-nonspecific) NSAID ingestion. The authors commented that 'until epidemiologic studies clearly show that alendronate use is not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving alendronate (and vice versa)'. The complainants

also referred to a study by Rothschild *et al*, wherein the authors concluded that there appeared to be a clinically important risk of gastric disease when alendronate was used in combination with a COX-nonspecific NSAID, and advised caution in prescription of alendronate with NSAIDs.

The Panel noted that Fosamax 70mg was indicated for the treatment of postmenopausal osteoporosis to prevent fractures. It should only be swallowed upon arising with a full glass of plain water, and taken at least 30 minutes before the first food, beverage or medication of the day. The SPC stated that Fosamax could cause local irritation of the upper GI mucosa. Because of a potential for worsening of the underlying disease, caution should be used when Fosamax was given to patients with active upper GI problems. 'Oesophageal reactions (sometimes severe and requiring hospitalisation) … have been reported in patients receiving Fosamax'. It was also stated that 'The risk of severe oesophageal adverse experiences appeared to be greater in patients who failed to take Fosamax properly and/or who continued to take Fosamax after developing symptoms suggestive of oesophageal irritation'. The SPC stated that 'although specific interaction studies were not performed, in clinical studies Fosamax was used concomitantly with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions'.

The Panel noted that Schnitzer *et al* evaluated the efficacy and safety of oral Fosamax 10mg od, 35mg twice weekly and 70mg once weekly in postmenopausal women with osteoporosis. Women were not excluded because of previous or active GI disease but were excluded if there was a history of major upper GI mucosal erosive disease. Patients were not excluded if, *inter alia*, there was concomitant use of aspirin or NSAIDs. The authors stated that the assessment of the safety profiles for the three treatment regimens focussed primarily on the analysis of upper GI adverse experiences. In general the three dosing regimens were well tolerated, the study did not have a placebo comparison group, the incidences of adverse experiences were low and similar to those observed in the placebo arms of previous alendronate studies after one year. There were no serious upper GI adverse experiences reported in the once or twice weekly treatment groups; the incidence of serious upper GI adverse experiences was significantly lower in the 70mg once weekly compared to the 10mg daily group. The authors noted that approximately 50% of patients used NSAIDs and/or aspirin at some point during the study. There were no between-group differences in the incidence of upper GI adverse events in these patients during the periods of exposure to NSAIDs/aspirin.

The Panel noted the placebo controlled studies with 70mg once weekly referred to by Merck Sharp & Dohme; Van Dyke *et al* and Lanza *et al*. Van Dyke *et al* assessed the safety of Fosamax 70mg once weekly in periodontal disease in men and women. The abstract stated that one year data showed that the overall and upper GI safety and tolerability profile of Fosamax was very favourable compared to placebo. Lanza *et al* concluded that Fosamax 70mg once weekly was not associated with endoscopic upper GI mucosal lesions compared to placebo in men and women. The mean gastric erosion scores in both treatment groups (Fosamax and placebo) were significantly lower than in those given aspirin.

The Panel noted the submission that the level of NSAID/aspirin use and rate of peptic ulcers in Schnitzer *et al* was consistent with the osteoporotic control group in van Staa. De Groen analysed adverse oesophageal effects reported to Merck Sharp & Dohme through post-marketing surveillance and stated that as of 5 March 1996 an estimated 470,000 patients worldwide had received prescriptions for alendronate for the treatment of osteoporosis. Merck Sharp & Dohme had received a total of 1213 reports of adverse events of which 199 were related to the oesophagus. A total of 51 patients (26%) had oesophageal adverse events classified as serious or severe. The Panel noted that the figure of 26% related to the percentage of patients in the study with serious or severe oesophageal adverse events compared to the number of patients with any oesophageal event. Of the 199 patients experiencing any oesophageal adverse event 17 of 28 patients (61%) for whom information was available on both water intake and posture had taken alendronate incorrectly. The SPC stated that taking the medicine with insufficient water or failing to remain upright for 30 minutes after taking the dose were known to increase the risk of oesophageal retention of swallowed tablets. Merck Sharp & Dohme had submitted that there were pre-clinical data to suggest that once weekly dosing would be better tolerated, it could not be assumed that rates of oesophageal adverse events were the same with 70mg once weekly as with 10mg once daily.

The Panel did not consider that the claim that Fosamax 70mg once weekly was 'well tolerated' in relation to a general osteoporotic population when administered in accordance with the SPC was misleading as alleged. No breach of the Code was ruled in this regard.

The Panel noted that interaction with NSAIDs/aspirin was not mentioned in the Fosamax SPC. Graham and Malaty recommended that until epidemiological studies clearly showed that Fosamax use was not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving Fosamax, and vice versa. In FIT, which examined the upper GI tract safety profile of Fosamax 5 and 10mg, approximately 88% of all FIT participants reported at least one day of NSAID or aspirin use during the study. Event rates were higher during NSAID use compared with non use in both placebo and Fosamax treatment groups. In each case sensitivity analysis showed that there was no evidence that concurrent use of Fosamax and NSAIDs resulted in an excess of gastroduodenal or oesophageal events compared with concurrent use of NSAIDs and placebo.

The claim at issue referred to an NSAID regimen.

The relevant patient population in Schnitzer had taken NSAIDs or aspirin at some point in the study. In the Panel's view not all of these patients would have been on a regimen; some would have used NSAIDs once or occasionally. There was little data in the Schnitzer study in this regard. The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The claim was misleading and a breach of the Code was ruled.

Aventis Pharma Ltd and Procter & Gamble Pharmaceuticals, UK Ltd submitted a joint complaint about a Fosamax (alendronate sodium) journal advertisement (ref 12-01 FSM.00.GB.60500.J) issued by Merck Sharp & Dohme Limited.

The advertisement was headed 'The first once-weekly treatment for post-menopausal osteoporosis to prevent fracture'. This was followed by three bullet points. The first bullet point claimed 'Proven efficacy' and stated that 'Fosamax once weekly 70mg is therapeutically equivalent to Fosamax 10mg daily at increasing BMD'; the second bullet point referred to convenience; the third read 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' and was referenced to Schnitzer *et al* (2000). 'Once weekly Fosamax 70mg' appeared in logo format in the bottom right hand corner.

COMPLAINT

Aventis Pharma and Procter & Gamble alleged that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' was misleading. The complainants were concerned about both the general and the specific parts of the claim. The complainants divided the complaint into two parts: firstly, safety in a general osteoporotic population and secondly, safety in patients taking NSAIDs/aspirin.

A Safety in a general osteoporotic population

It was alleged that the claim misled as to the overall safety profile of alendronate 70mg in a general osteoporotic population. The referenced study by Schnitzer *et al* did not provide support for the claim of 'well tolerated' in a broad population, for the following reasons:

1 *The 70mg weekly dose had only been compared to the 10mg daily dose in this study*

Aventis and Procter & Gamble stated that in order to extrapolate a 'well tolerated' claim to a general patient population, tolerability data must surely be compared with that of a control group. The Schnitzer study had no placebo control group, just a comparator: the alendronate 10mg tablet. The authors found the tolerability to be similar across treatment groups.

2 *Most clinical trials for alendronate 10mg, as well as for 70mg, excluded patients at risk of gastrointestinal adverse events*

Aventis and Procter & Gamble stated that an osteoporotic population in whom a bisphosphonate was likely to be prescribed had been described by van Staa *et al* (1997). In this population, 37% of subjects used H_2 antagonists or antacids in the year before inclusion in the analysis. NSAID and aspirin use was also increased in this population compared with a non-osteoporotic control cohort. An osteoporotic population could be considered at higher risk of gastrointestinal adverse events.

Across the alendronate studies, higher risk patients with active gastrointestinal disease and/or regular users of NSAIDs, aspirin, H2 antagonists or proton pump inhibitor therapy were excluded by protocol at study enrolment. The complainants provided a table which showed the exclusion criteria in alendronate clinical trials by Watts *et al* (1999), Bauer *et al* (2000) and Schnitzer *et al*. The result was that relatively few patients in the alendronate clinical trials were in these high risk populations (eg in the FIT study, less than 2% were on gastroprotective drugs such as H_2 antagonists) and hence it was inappropriate to claim 'well tolerated' in a general osteoporotic population when the clinical data did not reflect this. Because studies of alendronate 10mg had substantial exclusion criteria relating to gastrointestinal risk, and because 70mg was being compared with 10mg, it was alleged to be inappropriate to make a claim about tolerability for 70mg in a broad patient population.

Furthermore, Schnitzer *et al* excluded patients with active gastrointestinal disease. It was difficult to understand how an unqualified 'well tolerated' claim for Fosamax 70mg could be made based on data from a population known to be at lower risk for gastrointestinal adverse events.

Bauer *et al* (2000), summarizing the gastrointestinal tolerability profile of alendronate, theorized that the relatively healthy patient population created by Merck's exclusion criteria might help explain the increase in upper gastrointestinal adverse events seen in post-marketing experience with alendronate 10mg.

3 *Post-marketing experience of serious adverse events with alendronate 10mg resulted in a labelling change and 'Dear Doctor' letter*

Aventis and Procter & Gamble pointed out that for the 10mg dose, post-marketing experience was different from observations in clinical trials, and resulted in serious post-approval labelling modifications, which should not have been lightly dismissed by Merck Sharp & Dohme in response to inter-company correspondence.

Published post-marketing data demonstrated that alendronate 10mg daily was associated with significant oesophageal and gastric adverse events, despite the fact that controlled clinical trials did not identify this important issue. De Groen *et al* (1996) summarised this post-marketing experience, reporting that about 25% of patients had serious or severe effects, and 16% were hospitalised. In March 1996 Merck Sharp & Dohme sent out a 'Dear Doctor' letter in the UK, which warned doctors of increased oesophageal reactions and explained the importance of following the dosing instructions strictly in order to minimise gastrointestinal adverse events. The labelling for alendronate was amended worldwide at this time. In the UK, the summary of product characteristics (SPC) was amended to include revised dosage instructions, stricture and achalasia as a

contraindication, and a cautionary statement for patients with upper gastrointestinal problems such as dysphagia, oesophageal disease, gastritis, duodenitis and peptic ulceration. As a result of such adverse events, alendronate 10mg still carried a black triangle (requiring all adverse events to be reported) five years after launch, even though this was typically only required for the first two years after registration.

Merck Sharp & Dohme had maintained that oesophageal reactions were related to incorrect dosing of alendronate. However, since the 'Dear Doctor' letter such reactions continued to be reported (eg De Groen; Pizzani *et al* (1997); Medicines Control Agency / Committee on Safety of Medicines (MCA / CSM), 1998; Adverse Drug Reactions Advisory Committee, 1999). In August 1998, the MCA / CSM issued a reminder about 'severe oesophageal reactions with alendronate' in its bulletin, Current Problems in Pharmacovigilance, which stated 'Around 1-2% of patients taking alendronate sodium may experience oesophageal reactions, even when following the dosing instructions'.

4 *The Schnitzer study did not allow an evaluation of serious adverse events of lower incidence*

Aventis and Procter & Gamble stated that serious adverse events, such as oesophageal ulceration, might occur at a lower incidence in a selected clinical study population than in clinical practice (Dowd *et al* 2000). The Schnitzer study included 519 patients taking Fosamax 70mg once-weekly, but excluded those with major upper gastrointestinal disease. So even though the authors stated that alendronate 70mg was 'generally well tolerated', the paper provided insufficient substantiation for extrapolation of such a claim to overall tolerability in a general osteoporotic population.

Section 4.4 of the SPC Fosamax Once-Weekly 70mg included the special warning that alendronate could cause local irritation of the upper gastrointestinal mucosa, and potentially worsen underlying disease. It was stated that caution should be used in patients with active upper gastrointestinal problems, and that oesophageal reactions might be severe and might require hospitalisation. Oesophageal ulceration was listed as a common adverse event (occurring in 1-10% of patients during clinical studies and / or post-marketing use) in the Fosamax 70mg SPC.

In summary, the 70mg weekly dose had only been compared to the 10mg daily dose, which had been associated with significant gastrointestinal safety issues. Alendronate studies, including the Schnitzer study, had excluded patients at risk of gastrointestinal adverse events. As the size of the Schnitzer study did not allow an evaluation of serious adverse events of lower incidence, a claim of 'well tolerated' in a general osteoporotic population based on experience in a single study of only 519 patients taking the 70mg dose, could not be considered fair, balanced or responsible.

Aventis and Procter & Gamble stated that even if this claim of 'well-tolerated' was acceptable for a general osteoporotic population, expansion of the claim to the vulnerable population of NSAID / aspirin users was not justified.

B Safety in patients taking NSAIDs/aspirin

The claim that alendronate 70mg was tolerated 'Even in patients on concurrent NSAID / aspirin regimens' was not supported by the cited reference Schnitzer *et al*, which stated:

'Approximately 50% of patients used NSAIDs and / or aspirin at some point during the study. There were no between-group differences in the incidence of upper GI adverse events in these patients during the periods of exposure to NSAIDs / aspirin'.

The companies alleged that this claim misled as to the overall safety profile of alendronate 70mg in this population, for the following reasons:

1 *Conflicting data in combination with limited clinical trial data were available on the safety of concurrent use of NSAIDs and/or aspirin with Fosamax.*

Aventis and Procter & Gamble stated that Merck Sharp & Dohme referred to a 'weight of clinical endpoint data showing that there is no increase in peptic ulceration when NSAIDs / aspirin are used in conjunction with FOSAMAX'. Firstly, absence of ulceration was only one aspect of tolerability and did not support an all-encompassing tolerability claim. Secondly, the complainants were surprised by this statement, given the data to the contrary.

In the UK, in 1996 the MCA / CSM noted in Current Problems in Pharmacovigilance that 'The frequency of upper gastro-intestinal adverse reactions appears to be greater when alendronate sodium is used in conjunction with non-steroidal anti-inflammatory drugs and aspirin'. In 1998 a reminder was issued in the same bulletin, stating that 'Caution is required if the patient is also taking NSAIDs'.

The existence of conflicting study data was confirmed by Merck Sharp & Dohme in inter-company correspondence where it referred to a recent article in the BMJ 'questioning the GI tolerability of alendronate used in conjunction with NSAIDs'. This article referred to recently published data from Graham and Malaty (2001) that contradicted the statement that alendronate was well tolerated 'even in patients on concurrent NSAID / aspirin regiments'. This randomised, crossover study examined the potential for a synergistic effect of alendronate and naproxen on gastric ulcers. Although this was a small study, it was well designed and published in a peer-reviewed journal. As well as demonstrating a statistically significant gastric ulcer risk for alendronate therapy, the authors documented quadrupled risk with concomitant (COX-nonspecific) NSAID ingestion. After 10 days' administration, gastric ulcers were found in 8% of subjects receiving alendronate, 12% receiving naproxen, and 38% receiving both alendronate and naproxen ($p<0.05$ for the combination versus either medicine alone). The authors commented that: 'until epidemiologic studies clearly show that alendronate use is not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving alendronate (and vice versa)'.

Aventis and Procter & Gamble referred additionally to a study by Rothschild *et al* (2000), presented at the

American College of Rheumatology meeting which demonstrated that clinically important interactions with NSAIDs might occur, even if symptoms were not apparent. The records of 350 consecutive patients were examined, noting haemoglobin levels prior to initiation of alendronate and after three months of use, as well as concomitant NSAID ingestion. Gastrointestinal toxicity was assessed by measuring blood loss. Thirteen percent of individuals on both alendronate and a COX-nonspecific NSAID had significant blood loss (in excess of 2 grams). The authors concluded that there appeared to be a clinically important risk of gastric disease when alendronate was used in combination with a COX-nonspecific NSAID, and advised caution in prescription of alendronate with NSAIDs.

2 *Overall tolerability data were not provided for this group of patients*

Aventis and Procter & Gamble noted that these data were not provided in the Schnitzer paper and had not been provided by Merck Sharp & Dohme in inter-company correspondence. Only upper gastrointestinal adverse events were mentioned for this population of NSAID and/or aspirin users. It was alleged that an unqualified 'well-tolerated' claim could not be made based on this support.

3 *The data that were provided for this group were inadequate to support the claim*

Aventis and Procter & Gamble alleged that there were two aspects of the claim that were inadequately supported, concerning the definition of an NSAID/aspirin regimen, and the definition of concurrent in relation to adverse event reporting.

The complainants stated that Merck Sharp & Dohme had explained that 'patients on concurrent NSAID/aspirin regimens' in this study referred to 'regular use, intermittent use, occasional use and conceivably single use of an NSAID or aspirin'. According to this definition, a patient who took one aspirin on a single occasion would be included as being on an NSAID/aspirin regimen. Such a patient would be at significantly lower risk of gastrointestinal adverse events than a patient regularly taking such medications, and might be less likely to report an adverse event if it occurred once. NSAID/aspirin use in this study was limited, and there were no data on continuous use, dose of NSAID or aspirin used, or type of NSAID (eg whether cyclooxygenase-2 (COX-2) medicines, which were generally associated with lower gastrointestinal toxicity than COX-nonspecific medicines, were included in the analysis). Patient-year NSAID exposure data would also help the physician interpret the data.

In the complainants' pre-complaint letter to Merck Sharp & Dohme, they requested clarification of the definition of 'concurrent' in relation to adverse event reporting in this study. Merck Sharp & Dohme's response letter stated that, "During the periods of exposure to NSAIDs/aspirin' means what it says upper GI adverse events that occurred when the patient was taking NSAIDs or aspirin'. It was still unclear what criteria were used for adverse events to be included in the analysis for this group of patients. Because of the potential for a synergistic effect of NSAIDs/aspirin and alendronate described above, the question was whether combined intake (intake on the same day) would lead to gastrointestinal adverse events on that and subsequent days. The number of patients that took NSAIDs/aspirin on a regular basis and took Fosamax 70mg tablet on the same day must be limited in this study.

Given the published data discussed above, Aventis and Procter & Gamble stated that it was inappropriate to use such limited data to support such a broad safety claim.

In addition, during the mutual recognition filing of the complainants' postmenopausal osteoporosis medicine, Actonel, the companies were requested to include NSAID/aspirin users, defined as regular users (3 or more days per week), in the special populations section of the SPC (Section 5.2), due to the importance of this high risk population in osteoporosis treatment. This special population was absent from the alendronate SPC, due to the exclusion criteria of Merck's registration trials.

In summary, the assessment of the safety of the concurrent use of alendronate and NSAIDs/aspirin had not been evaluated to sufficient scientific standards in the Schnitzer study to negate the contradictory data from other studies.

Aventis Pharma and Procter & Gamble therefore alleged that the journal advertisement was misleading to physicians in terms of the safety of alendronate both in a general osteoporotic population and in groups at high risk of gastrointestinal adverse events, and was therefore in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the claim 'Well tolerated. Even in patients on concurrent NSAID/aspirin regimens' was supported by the data available, and therefore in accordance with the Code.

Schnitzer *et al* studied alendronate once weekly 70mg, twice weekly 35mg and once daily 10mg in the treatment of osteoporosis in postmenopausal women. The conclusions regarding the regimens used in the study, published in a peer reviewed journal, were 'All treatment regimens were well tolerated with a small incidence of upper gastrointestinal (GI) adverse experiences', 'In general, the three dosing regimens were well tolerated', '… daily alendronate is generally well tolerated, with an incidence of adverse experiences in alendronate-treated patients similar to that in patients treated with placebo in controlled clinical studies'. The patient population recruited for Schnitzer's study was broadly in line with the recommendations (contraindications and precautions) of the SPC and the prescribing information included in the advertisement. It was certainly not a population at low risk for gastrointestinal adverse events as about 23% suffered them over the course of the 12 months of the study. Trends for oesophageal and gastric or duodenal irritation favoured the once weekly regimen, and for serious upper gastrointestinal adverse events this was statistically different. Placebo controlled studies with once weekly 70mg were consistent with the claim: Van Dyke *et al* (2000) and Lanza *et al* (2000).

With regard to NSAIDs and aspirin, there was one small study with an endoscopic endpoint (of dubious significance) that had been quoted to question the use of alendronate in conjunction with NSAIDs (Graham and Malaty). Therefore the overwhelming balance of clinical data showed that there was no adverse interaction either for the daily or weekly dosing regimens. The most frequent adverse events for both NSAIDs and alendronate were those related to the gastrointestinal tract and this data was referred to in Schnitzer's paper. The SPC for alendronate contained no statement with regard to NSAID interaction.

The term well tolerated was widely used in relation to alendronate once weekly 70mg by the authors of the Schnitzer study. It was entirely reasonable that it was used in the context of promotion.

A Safety in a general osteoporotic population

1 *The 70mg weekly dose had only been compared to the 10mg daily dose in this study*

Merck Sharp & Dohme stated that the relevant definitions of control were: verb – to verify (a scientific experiment) by conducting a parallel experiment in which the variable being investigated was held constant or was compared with a standard, or as a noun – a standard of comparison used in a statistical analysis.

Merck Sharp & Dohme submitted that alendronate 10mg daily was certainly a control group under these definitions. It would have been unethical to conduct two year long studies with a placebo arm, as there were now a number of available treatments for postmenopausal osteoporosis (indeed the most recent revision of the Declaration of Helsinki expected only an active control in this situation). Alendronate daily had been very extensively studied, and it was perfectly reasonable to use it as a 'standard' active control for comparison in this study as its therapeutic profile was well established. Schnitzer's study addressed the issue of the absence of a placebo group; 'In general, all three treatment groups were well tolerated. Although this study did not have a placebo comparison group, the incidence of adverse experiences was low, and similar to those observed in the placebo arms of previous alendronate studies after one year'. In addition, Merck Sharp & Dohme submitted that there were placebo controlled studies with alendronate once weekly 70mg (Van Dyke and Lanza *et al*) which supported the conclusions regarding adverse event rates for once weekly versus placebo.

2 *Most clinical trials for alendronate 10mg, as well as for 70mg, excluded patients at risk of gastrointestinal adverse events*

Merck Sharp & Dohme stated that the study on which the claim was based, and therefore the one at issue, was that published by Schnitzer *et al*. In general, the precautions and contraindications within the SPC reflected the exclusion criteria for this clinical trial, as it was this information that regulatory authorities reviewed in granting the licence. So when alendronate once weekly 70mg was used in accordance with the prescribing information, as in the study, it was well tolerated. There were many references to 10mg once daily tolerability in the complaint. However, the advertisement related to once weekly 70mg.

The study populations studied in alendronate studies had not been low risk for gastrointestinal events and data from Schnitzer's study were consistent with osteoporotic control population in van Staa's study. Approaching 50% of patients had an upper gastrointestinal adverse event over the 4.5 years of the Fracture Intervention Trial (FIT) and more than 80% took NSAIDs or aspirin. Patients were not excluded from Schnitzer's study if they were taking NSAIDs, aspirin, medication for dyspepsia. 35% of patients reported use of NSAIDs and/or aspirin in the 14 days before being randomised into Schnitzer's study, and approximately 50% during the duration of the study. This level of use was entirely consistent with the van Staa study quoted in the complaint (in the osteoporotic control group reported NSAID use in 31.4% and aspirin use in 10.8% mean follow up was 1.17). The rate of peptic ulcers in Schnitzer's study was consistent with the osteoporotic control group in van Staa (1.1% for 10mg od, 0.2% for 70mg ow and 0.7% in the van Staa study).

Bauer *et al* discussed a number of possibilities for the discordance between clinical trial results and impression in clinical practice, and concluded that 'the most likely contributing factor for the perception that alendronate frequently causes gastrointestinal tract intolerance is that upper gastrointestinal tract complaints are common among older women'.

3 *Post-marketing experience of serious adverse events with alendronate 10mg resulted in a labelling change and 'Dear Doctor' letter*

Merck Sharp & Dohme reiterated that the claim at issue related to the tolerability of alendronate once weekly 70mg.

De Groen *et al* examined post-marketing adverse event reports of osteoporosis in patients taking alendronate 10mg daily. The complaint grossly misled when quoting de Groen as to the tolerability of alendronate. It was not about 25% of patients taking alendronate where serious or severe effects were reported but just over 0.0001% (51/475,000). 26% of 199 oesophageal adverse events were serious or severe, a very different statement. When information was available just over 60% of patients with an oesophageal adverse event had not followed the recommended dosing instructions. Merck Sharp & Dohme stated that it would like the issuing of a letter to prescribers to be clear. The term 'Dear Doctor' letter was usually interpreted as a regulatory enforced action. This letter was discussed with the regulators, but was a voluntary action on the part of Merck Sharp & Dohme. It, and subsequent information from MCA/CSM, reminded prescribers and pharmacists of the importance of the dosing recommendations. Merck Sharp & Dohme did certainly not take the issue lightly. Following the letter and other actions to reinforce dosing instruction with prescribers, pharmacists and patients, the numbers of oesophageal adverse events fell markedly even with increasing numbers of patients being treated.

In contrast to the complaint's implication re gastric adverse events, the alendronate SPC stated quite clearly that 'a causal relationship has not been established'.

The requirement for a black triangle had recently been removed by the MCA / CSM for the daily formulation of alendronate (alendronate still appeared on the web listing as this did not reflect different formulations or indications). A black triangle was actually required for a minimum of two years. There were a number of factors that might have influenced the CSM apart from adverse events eg the size of the population being treated post-marketing and during the time that the daily formulation had been available new indications were added such as steroid induced osteoporosis and prevention.

As stated above, 61% of post-marketing oesophageal adverse events were associated with non-adherence to dosing instructions. Van Staa *et al* observed 1.2% of untreated osteoporosis patients suffered oesophagitis or ulcers. In Schnitzer's study the rates of oesophageal adverse events did show a trend in favour of the once-weekly formulation, and there were preclinical data to suggest that once weekly dosing would be better tolerated so it could not be assumed that that rates of oesophageal adverse events were the same with 70mg once weekly as with 10mg once daily.

4 *The Schnitzer study did not allow an evaluation of serious adverse events of lower incidence*

As stated in point 3 of the complaint, oesophageal ulcer was listed as common in the SPC. Dowd *et al* suggested patient selection as only one possible reason for perceived differences in rates of oesophagitis in clinical trials compared with post-marketing experience. Others were discussed including instruction of patients on how to take medication and co-morbidity.

There were multiple statements to the effect that alendronate once weekly 70mg was well tolerated in the study by Schnitzer *et al*. The claim accurately reflected the authors' opinions and was also consistent with data from placebo controlled studies. Merck Sharp & Dohme believed it was fully compliant with the Code.

B Safety in patients taking NSAIDs/aspirin

Merck Sharp & Dohme stated that no interactions had been identified with alendronate and NSAIDs / aspirin. Apart from issues relating to absorption of alendronate the SPC stated 'No other drug interactions of clinical significance are anticipated … in clinical trials Fosamax was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions'.

1 *Conflicting data in combination with limited clinical trial data were available on the safety of concurrent use of NSAIDs and/or aspirin with Fosamax*

Merck Sharp & Dohme stated that ulceration was certainly only one aspect of gastrointestinal tolerability, so upper gastrointestinal events were considered. In Schnitzer's study there were no between group differences in the incidence of upper gastrointestinal events in patients during the periods of exposure to NSAIDs / aspirin. This was also true for the Fracture Intervention Trial (FIT) which included almost 6,500 patients, in which more than 80% of patients took NSAIDs / aspirin.

There had been a number of label changes to the Fosamax SPC in the UK since the launch of the product in 1995, only some of which were detailed in the complaint. Merck Sharp & Dohme particularly drew attention to the removal of the warning / precaution regarding NSAIDs that appeared in the original SPC resulting from the original marketing application. This warning was removed in May 1999 with the submission of the data from FIT mentioned in the paragraph above. Warnings regarding NSAIDs did not appear in the current SPC for Fosamax or Fosamax 70mg Once Weekly. The advice regarding NSAIDs from CSM quoted in the complaint predated the data and licence amendment, and was no longer relevant.

Merck Sharp & Dohme stated that there were many issues with the endoscopy study of Graham *et al*. It included only 26 volunteers; 18 men and 8 women aged 30-50 years, hardly representative of the postmenopausal population. The treatment period was short, only 10 days for each regimen. The endpoint was an endoscopic one. The relevance of short term endoscopic ulcers was considered extremely uncertain in the field of NSAID induced ulceration, and this was even more true for bisphosphonates. The daily alendronate formulation was used.

It was a cross-over design with a washout as short as a week between treatment periods. Epidemiological studies indicated that NSAID ulcerogenic potential could last for at least a month. It was for this reason that such studies were almost always parallel group studies. It contained no placebo group to establish the background rate of ulcers in the population studied. Many of these issues were discussed in an editorial regarding a different study (an editorial in Gastroenterology, 2000), but were common to this one. In summary this study had many design issues, and the weight of clinical data for much larger studies with clinical endpoints and placebo controls showed no increase in the rate of ulcers for the combination of alendronate with NSAID over either alone.

The complainants then referred to a study by Rothschild *et al* with an endpoint of even more uncertain value. Unfortunately, this was only presented as an abstract, and in the absence of any detail it was impossible to assess its credibility. FIT was a large prospective study that considered the issue of NSAID-alendronate interaction and found none. Decreases in haemoglobin were not included in the SPC, as this issue had not been identified in any clinical trials or post-marketing.

2 *Overall tolerability data were not provided for this group of patients*

Merck Sharp & Dohme believed the main concern regarding tolerability of NSAIDs and alendronate for prescribers related to the gastrointestinal tract (and indeed the complaint mentioned no others), and therefore Schnitzer was used as the reference. Overall tolerability data for the NSAID / aspirin group could

be provided on request and was included with the response. There was no significant difference in overall tolerability, and no meaningful differences in any body system.

3 *The data provided for this group was inadequate to support the claim*

Merck Sharp & Dohme stated that upper gastrointestinal experiences included all those adverse experiences that related to the upper gastrointestinal tract. This was an extensive list but included for example dyspepsia, acid regurgitation, nausea, abdominal pain, abdominal distension, vomiting, as well as those detailed in figure 4 of Schnitzer's study. The analysis for upper gastrointestinal adverse events in those on NSAIDs / aspirin considered those adverse events that occurred on days that NSAIDs / aspirin were taken. Patients might get side effects such as dyspepsia from NSAIDs, aspirin or alendronate with a single dose. NSAIDs also varied in their propensity to cause nuisance symptoms or ulcers. The object of a randomised trial was to balance these in the comparator arms. Any cut off based on duration of use NSAID could be criticised on this basis. Damage to the gastrointestinal mucosa had been reported by 24 hours with aspirin. The one quoted by the complainants of three or more days would seem to be pretty arbitrary. As discussed above, extensive trial data showed there was no 'synergistic effect' of alendronate and NSAIDs. The Schnitzer study stated 'Further analysis revealed that there was no temporal relationship between the onset of upper GI adverse experiences and dosing of the once weekly tablet'.

Merck Sharp & Dohme stated that it was not sure why the complaints raised the issue of regulatory questions with regard to Actonel (risedronate) and NSAIDs. There would appear to be no regulatory requirement to include this as a special population. The question did not arise for alendronate, so one could only assume that the regulators were satisfied with the data previously provided for alendronate daily and that from Schnitzer's study.

PANEL RULING

The Panel noted that the Fosamax once weekly 70mg tablet SPC stated that it was indicated for the treatment of osteoporosis in postmenopausal women to prevent fractures. The SPC included detailed information about how to take Fosamax. The product should only be swallowed upon arising with a full glass of plain water. It had to be taken at least 30 minutes before the first food, beverage or medication of the day. Section 4.4 of the SPC headed 'Special warnings and special precautions for use' stated that Fosamax could cause local irritation of the upper gastrointestinal mucosa. Because of a potential for worsening of the underlying disease, caution should be used when Fosamax was given to patients with active upper gastrointestinal problems. 'Oesophageal reactions (sometimes severe and requiring hospitalisation) … have been reported in patients receiving Fosamax'. It was also stated that 'The risk of severe oesophageal adverse experiences appeared to be greater in patients who failed to take Fosamax properly and / or who continued to take Fosamax after developing symptoms suggestive of oesophageal irritation'. Section 4.5 of the SPC headed 'Interaction with other medicaments and other forms of interaction' stated, *inter alia*, that 'although specific interaction studies were not performed, in clinical studies Fosamax was used concomitantly with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions'. Section 4.8 headed 'Undesirable effects' listed a range of gastro-intestinal (3.7 to 0%), musculoskeletal (2.9 and 0.2%) and neurological (0.4%) adverse events which occurred in ≥1% in patients receiving 70mg Fosamax in a one year study. Corresponding data for Fosamax 10mg / day over a three year study was included in the SPC. A list of common (≥1 / 100, <1 / 10) gastrointestinal adverse experiences reported during clinical studies and / or post-marketing use were abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, melaena, dysphagia, abdominal distension and acid regurgitation. Uncommon (≥1 / 1000, <1 / 100) gastrointestinal adverse experiences were listed as nausea, vomiting, gastritis, oesophagitis and oesophageal erosions. Rare (≥1 / 10000, <1 / 1000) gastrointestinal adverse experiences were listed as oesophageal stricture, oropharyngeal ulceration, gastric or duodenal ulcers, some severe and with complications, although a causal relationship had not been established.

The Panel noted that the claim at issue was referenced to Schnitzer *et al* (2000) which was a one year, randomized, double blind, multicentre study designed to evaluate the efficacy and safety of oral Fosamax 10mg od, 35mg twice weekly and 70mg once weekly in postmenopausal women with osteoporosis. Women were not excluded because of previous or active gastrointestinal disease but were excluded if there was a history of major upper gastrointestinal mucosal erosive disease defined as a) significant upper gastrointestinal bleeding within the last year requiring hospitalisation or transfusion, b) recurrent peptic ulcer disease documented by radiographic or endoscopic means, c) dyspepsia that was uncontrolled by medication and d) oesophageal stricture or dysmotility. Patients were not excluded if, *inter alia*, there was concomitant use of aspirin or non-steroidal anti-inflammatory medications. The study authors stated that the assessment of the safety profiles for the three treatment regimens focussed primarily on the analysis of upper gastrointestinal adverse experiences. In general the three dosing regimens were well tolerated, the study did not have a placebo comparison group, the incidences of adverse experiences were low and similar to those observed in the placebo arms of previous alendronate studies after one year. There were no significant differences among the three treatments groups in the proportion of patients with upper gastrointestinal adverse experiences or in those discontinuing due to upper gastrointestinal experiences. Further analysis showed that there was no temporal relationship between the onset of upper gastrointestinal adverse experiences and dosing with the once weekly tablet. Serious upper gastrointestinal experiences were also analysed; there were no serious upper gastrointestinal adverse experiences reported in the once or twice weekly treatment groups; the incidence of serious upper gastrointestinal adverse experiences was significantly lower in the 70mg once

weekly compared to the 10mg daily group. The study authors noted that approximately 50% of patients used NSAIDs and/or aspirin at some point during the study. There were no between-group differences in the incidence of upper gastrointestinal adverse events in these patients during the periods of exposure to NSAIDs/aspirin.

The Panel noted the placebo controlled studies with 70mg once weekly referred to by Merck Sharp & Dohme; Van Dyke *et al* (2000) and Lanza *et al* (2000). Van Dyke *et al*, an abstract, was a placebo controlled multicentre 2 year study which assessed the safety of Fosamax 70mg once weekly in periodontal disease in men and women. The abstract stated that one year data showed that the overall and upper gastrointestinal safety and tolerability profile of Fosamax was very favourable compared to placebo. P values were not provided. Lanza *et al* (2000) concluded that Fosamax 70mg once weekly was not associated with endoscopic upper gastrointestinal mucosal lesions compared to placebo in men and women. The mean gastric erosion scores in both treatment groups (Fosamax and placebo) were significantly lower than in those given aspirin.

The Panel noted Merck Sharp & Dohme's submission that in general the precautions and contraindications in the SPC reflected the exclusion criteria for Schnitzer *et al*. The Panel noted the exclusion criteria in Watts 1999, Bauer 2000 and Schnitzer 2000 and the allegation that relatively few patients in alendronate clinical trials (10mg and 70mg) were those in high risk population. The Panel noted the submission that the level of NSAID/aspirin use and rate of peptic ulcers in Schnitzer *et al* was consistent with the osteoporotic control group in van Staa (1997).

The Panel noted the parties' submissions regarding the post-marketing reports associated with Fosamax 10mg. De Groen (1996) analysed adverse esophageal effects reported to Merck Sharp & Dohme through post-marketing surveillance. De Groen stated that as of 5 March 1996 an estimated 470,000 patients worldwide had received prescriptions for alendronate for the treatment of osteoporosis. Merck Sharp & Dohme had received a total of 1213 reports of adverse events of which 199 were related to the oesophagus. A total of 51 patients (26%) had oesophageal adverse events classified as serious or severe.

The Panel noted that the figure of 26% related to the percentage of patients in the study with serious or severe oesophageal adverse events compared to the number of patients with any oesophageal event. The study also provided information on how patients had taken their medicine. Of the 199 patients experiencing any oesophageal adverse event 17 of 28 patients (61%) for whom information was available on both water intake and posture had taken alendronate incorrectly. The Panel noted the detailed information in the SPC regarding taking Fosamax. The effects of taking the medicine with insufficient water or failing to remain upright for 30 minutes after taking the dose were known to increase the risk of oesophageal retention of swallowed tablets. The Panel also noted Merck Sharp & Dohme's submission that there were pre-clinical data to suggest that once weekly dosing would be better tolerated, it could not be assumed that rates of oesophageal adverse events were the same with 70mg once weekly as with 10mg once daily.

The Panel did not consider that the claim that Fosamax 70mg once weekly was 'well tolerated' in relation to a general osteoporotic population when administered in accordance with the SPC was misleading as alleged. No breach of Clause 7.2 was ruled in this regard.

The Panel noted that interaction with NSAIDs/aspirin was not mentioned in the Fosamax SPC.

The Panel noted that Graham and Malaty (2001) was an endoscopic blind crossover randomised single centre endoscopic study in healthy volunteers designed to assess whether Fosamax and naproxen were synergistic as causes of gastric ulcers. The study authors concluded that the combination regimen resulted in a significantly higher degree of gastric damage than either drug alone ($P<0.05$). In addition, treatment with naproxen alone was significantly more injurious than alendronate alone ($P<0.05$). No oesophageal injury was seen in any group. Duodenal injury was mild but was significantly more common in the alendronate-naproxen group than with the alendronate-alone group ($P<0.05$). The authors recommended that until epidemiological studies clearly showed that Fosamax use was not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving Fosamax, and vice versa.

The Panel noted that in FIT which examined the upper gastrointestinal tract safety profile of Fosamax 5 and 10mg, approximately 88% of all FIT participants reported at least one day of NSAID or aspirin use during the study. Event rates were higher during NSAID use compared with non use in both placebo and Fosamax treatment groups. In each case sensitivity analysis showed that there was no evidence that concurrent use of Fosamax and NSAIDs resulted in an excess of gastroduodenal or oesophageal events compared with concurrent use of NSAIDs and placebo. The 70mg dose was not examined. The Panel noted its comments above on the relevant data in Schnitzer *et al* and Merck Sharp & Dohme's submission regarding the potential difference in the incidence of adverse events between the 10 and 70mg dose.

The Panel noted that the claim at issue referred to an NSAID regimen. The relevant patient population in Schnitzer had taken NSAIDs or aspirin at some point in the study. In the Panel's view not all of these patients would have been on a regimen; some would have used NSAIDs once or occasionally. There was little data in the Schnitzer study in this regard. The Panel considered on balance that it had been provided with insufficient evidence to support the claim in relation to a patient population on an NSAID/aspirin regimen. The claim was misleading and a breach of Clause 7.2 was ruled.

Complaint received **19 April 2001**

Case completed **8 June 2001**

PRIMARY CARE GROUP v MERCK SHARP & DOHME

Conduct of representative

A primary care group (PCG) pharmacist complained on its behalf about the way in which a representative from Merck Sharp & Dohme had promoted Cozaar (losartan) which was licensed for the treatment of hypertension. The complainant stated that on two occasions GPs in different local areas had brought to her attention that GPs had been informed that Cozaar had a licence for heart failure. Merck Sharp & Dohme's medical information department had confirmed that Cozaar was only so licensed in Ireland and that the licence for use in heart failure at present did not cover England. The complainant was concerned that local GPs were being encouraged to prescribe Cozaar out of licence and were being misinformed.

The Panel noted that Cozaar was indicated only for the treatment of hypertension. A series of representatives briefing documents on the Evaluation of Losartan in the Elderly (ELITE II) Study referred in emboldened print to the UK licensed indication, the Code of Practice and the need to focus on promoting Cozaar for use in hypertension only. A background document explained that the original ELITE study (1997), evaluated the effects of long-term treatment with Cozaar in elderly patients with symptomatic heart failure. The secondary outcome measures were positive for Cozaar and formed the basis of 23 successful applications worldwide for a licence for the use of the product in heart failure. ELITE II was a larger study designed to explore the primary hypothesis that in symptomatic heart failure treatment with Cozaar, compared to captopril, would reduce all-cause mortality. Representatives were instructed to refer all questions from their customers to the medical information department and reminded of the medical and legal implications if they were to discuss heart failure with customers.

Whilst the Panel noted that the briefing documents reminded representatives to promote Cozaar for hypertension only, it was concerned about the amount of detailed information provided on the ELITE II study, given that representatives were instructed to forward enquiries on heart failure to the medical information department. In the present Cozaar detail aid a bullet point on the final page 'Leader in comprehensive A-II antagonist end-point trials', listed, *inter alia*, 'ELITE II – Heart failure survival study'. The Panel was concerned that such a reference appeared in promotional material. In the Panel's view this would encourage representatives to raise the matter with GPs.

Merck Sharp & Dohme had stated that it could not investigate further unless the representative could be identified. The complainant had received two reports about the representative's conduct from general practitioners within the PCG. The Panel considered that without the identity of the representative it was not possible to ascertain precisely what had occurred. Although it was concerned about the reference to the ELITE II – Heart failure survival study in the detail aid, the Panel considered that in the circumstances it was obliged to rule no breach of the Code.

A primary care group (PCG) pharmacist complained on its behalf about the way in which a representative from Merck Sharp & Dohme Limited had promoted Cozaar (losartan). Cozaar was licensed for the treatment of hypertension.

COMPLAINT

The complainant stated that on two occasions GPs in different local areas had brought to her attention that a medical representative from Merck Sharp & Dohme had been informing the GPs that Cozaar had a licence for heart failure. Merck Sharp & Dohme's medical information department had confirmed that Cozaar was only so licensed in Ireland and that the licence for use in heart failure at present did not cover England.

The complainant was concerned that local GPs were being encouraged to prescribe Cozaar out of licence and were being misinformed.

When writing to Merck Sharp & Dohme the Authority drew attention to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it had not briefed representatives to promote Cozaar in heart failure as Cozaar did not have a heart failure licence. The company was, however, unable to identify the representative concerned and could not investigate whether the individual had acted 'off-brief'.

Merck Sharp & Dohme submitted that its salesforce was last briefed on the company's ELITE II study (Evaluation of Losartan In the Elderly) in November 1999. The briefing document was very explicit that Merck Sharp & Dohme did not have a heart failure licence and representatives should only promote Cozaar for licensed indications. Merck Sharp & Dohme, however, was aware from the representatives that some of the local cardiologists and physicians recommended GPs to start Cozaar for heart failure in certain patient groups, and this might have led local GPs to believe that it was an approved indication.

Merck Sharp & Dohme submitted that it had made no misleading statements about heart failure other than clarification of the above mentioned ELITE II study. These statements had been provided to representatives on a reactive basis to questions about ELITE II. There were no promotional items referring to the use of Cozaar in heart failure.

Merck Sharp & Dohme stated that it briefed all representatives on an initial and regular basis on its approved promotional campaigns. Representatives had not been briefed on any Cozaar heart failure licence and campaign. Representatives were last briefed at a national meeting in September 2000 at which the focus was entirely on hypertension in various sub-groups.

Merck Sharp & Dohme noted that the complainant had copied her letter to its customer services department; the company had therefore been in direct contact with her to try to establish the identity of the individual representative and/or GPs involved, but without success. The local managers had discussed the issue with representatives who worked in the area and the representatives concerned had no recollection of ignoring company advice and promoting Cozaar in heart failure. Therefore, unless the representative could be identified, Merck Sharp & Dohme stated that it could not investigate the matter further.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for further information the PCG prescribing advisor stated that she was satisfied with the response by Merck Sharp & Dohme. It was unfortunate that the PCG did not have the name of the representative involved, as it would not be ethical for it to reveal the names of the GPs who passed this information to it without their consent.

She hoped that the discussion within the company would be sufficient to deter the representative involved from misleading GPs in the future.

PANEL RULING

The Panel noted that according to its SPC Cozaar was indicated only for the treatment of hypertension. The Panel noted that a series of representatives briefing documents on the Evaluation of Losartan in the Elderly (ELITE II) Study referred in emboldened print to the UK licensed indication, the Code of Practice and the need to focus on promoting Cozaar for use in hypertension only. A background document accompanying a memorandum dated 01/11/99 explained that the original ELITE study, published in 1997, evaluated the effects of long-term treatment with Cozaar in elderly patients with symptomatic heart failure. The secondary outcome measure, the combined end-point of death and/or hospitalisation, showed a 32% risk reduction in favour of Cozaar (p=0.075) compared with captopril. These results formed the basis of 23 successful applications worldwide for a licence for the use of Cozaar in heart failure. ELITE II was a larger study designed to explore the primary hypothesis that in symptomatic heart failure treatment with Cozaar, compared to captopril, would reduce all-cause mortality. Representatives were instructed to refer all questions from their customers to the medical information department and reminded of the medical and legal implications if they were to discuss heart failure with customers.

Whilst the Panel noted that the briefing documents reminded representatives to promote Cozaar for hypertension only, it was concerned about the amount of detailed information, including a question and answer document and a copy of some slides, provided on the ELITE II study, given that representatives were instructed to forward enquiries on heart failure to the medical information department. The Panel noted that in the present Cozaar detail aid (ref 04-02 CZR.00.GB.10340.DA.5c. CW.0401) a bullet point on the final page 'Leader in comprehensive A-II antagonist end-point trials', listed, i*nter alia*, 'ELITE II – Heart failure survival study'. The Panel was concerned that such a reference appeared in promotional material. In the Panel's view this would encourage representatives to raise the matter with GPs.

Merck Sharp & Dohme had stated that it could not investigate further unless the representative could be identified. The complainant had received two reports about the representative's conduct from general practitioners within the PCG. The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. However the Panel considered that without the identity of the representative it was not possible to ascertain precisely what had occurred. Although the Panel was concerned about the reference to the ELITE II – Heart failure survival study in the detail aid the Panel considered that in the circumstances it was obliged to rule no breach of Clauses 3.2, 7.2 and 15.2 of the Code.

Complaint received **1 May 2001**

Case completed **18 July 2001**

CASE AUTH/1182/5/01

ACCIDENT & EMERGENCY CONSULTANT v ELAN PHARMA

Highlighter pen in the form of a syringe

A consultant in accident & emergency complained about a promotional aid which had been used by Elan Pharma.

The complainant stated that a member of the public had been very worried by finding what appeared to be a half-full syringe in the hospital car park. On further investigation this was found to be a highlighter pen made in the form of a half-filled syringe with botulinum toxin NeuroBloc written on it. At first glance this pen certainly appeared like a syringe. It was only once the complainant had removed the cap that she realised that it was not a syringe. It had caused significant concern to a member of the public who made a special journey from the far end of the hospital car park to the accident and emergency department to hand it in, believing that it was a piece of medical equipment. It had presumably undermined that individual's confidence in the hospital if he/she thought staff would leave half-filled syringes lying about. In an age where drug misuse was rife, the complainant felt that it was wrong to produce a 'toy' resembling a syringe.

The Panel noted that one side of the pen read 'NeuroBloc' above 'botulinum toxin type B solution for injection'. A graduated scale 0-5ml appeared on the reverse above the phrase 'measurement not to scale'. The syringe was transparent and appeared to be full. The tip of the marker pen was covered by a partially opaque elongated cap. The Panel noted that the pen was to highlight the fact that NeuroBloc was the only botulinum toxin available as a ready to use solution. The Panel did not accept Elan's submission that only a cursory glance confirmed that this was a marker pen and not a real syringe. The Panel considered that, unless advised to the contrary, the appearance of the item, the phrase 'solution for injection', the scale and the opaque cap might lead a recipient to form the initial view that the item was a syringe. Further investigation would reveal otherwise. The item had caused significant concern to a member of the public and the complainant had realised that it was not a syringe only upon removal of the cap. The Panel considered that the company had failed to recognise the special nature of medicines and to maintain high standards and a breach of the Code was ruled.

It was an established principle under the Code that a pen, albeit an item of general utility, was an acceptable promotional aid. The Panel noted that the pen cost 53 pence, excluding VAT, and was therefore inexpensive as required by the Code. The Panel noted the supplementary information to the Code which stated that 'Names of medicines should not be used on promotional aids when it would be inappropriate to do so, for example, when it might mislead as to the nature of the item'. The Panel considered that the name did not in itself mislead as to the nature of the item, but was one of a series of factors which were relevant. This aspect had been covered by its ruling of a breach above.

A consultant in accident & emergency complained about a promotional aid produced by Elan Pharma Limited.

COMPLAINT

The complainant stated that the previous week a member of the public had attended the accident & emergency department very worried after having found what appeared to be a half-full syringe in the hospital car park. On further investigation this was found to be a promotional item, in fact a highlighter pen, made in the form of a half-filled syringe with botulinum toxin NeuroBloc written on it.

The complainant stated that at first glance this promotional pen certainly appeared like a syringe. It was only once the complainant had removed the cap that she realised that it was not a syringe. It caused significant concern to a member of the public who made a special journey from the far end of the hospital car park to the accident & emergency department to hand it in, believing that it was a piece of medical equipment, and it presumably undermined that individual's confidence in the hospital if he/she thought staff would leave half filled syringes lying about.

In an age where drug misuse was rife, the complainant felt that it was wrong to produce a 'toy' resembling a syringe.

When writing to Elan Pharma the Authority drew attention to Clauses 9.1, 18.1 and 18.2 of the Code.

RESPONSE

Elan Pharma stated that the promotional item in question was a blue marker pen in the shape of a syringe that carried the name NeuroBloc, a type B botulinum toxin indicated for the treatment of cervical dystonia. These pens had been given to the neurological hospital sales teams for distribution to health professionals and their administrative staff.

The reason for providing an item in the form of a syringe was to highlight the fact that NeuroBloc was the only botulinum toxin available as a ready to use solution making it immediately available for injection. The item was obtained from a reputable company that provided a wide variety of promotional aids to the industry. Elan pointed out that a number of different pens in the form of a syringe were available from the catalogue.

Elan stated that it was surprised to receive this complaint because only a cursory glance confirmed that this was a marker pen and not a real syringe. The item was quite safe and presented no danger to

anyone who might come across it. The pen was inexpensive (£0.53 excluding VAT per item) and relevant to the practice of medicine and so complied fully with Clauses 18.1, 18.2 and 18.3. Elan believed that this promotional aid was an appropriate and legitimate part of its commercial activities and was consistent with Clause 9.1.

PANEL RULING

The Panel noted that one side of the pen read 'NeuroBloc', above 'botulinum toxin type B solution for injection'. A graduated scale 0-5ml appeared on the reverse above the phrase 'measurement not to scale'. The syringe was transparent and appeared to be full. The tip of the marker pen was covered by a partially opaque elongated cap. The Panel noted that the pen was to highlight the fact that NeuroBloc was the only botulinum toxin available as a ready to use solution.

The Panel did not accept Elan's submission that only a cursory glance confirmed that this was a marker pen and not a real syringe. The Panel considered that, unless advised to the contrary, the appearance of the item, the phrase 'solution for injection', the scale and the opaque cap might lead a recipient to form the initial view that the item was a syringe. Further investigation would reveal otherwise. The Panel noted the complainant's submission that the item had caused significant concern to a member of the public. The complainant had realised that it was not a syringe only upon removal of the cap. The Panel noted that the item had been distributed by Elan's neurological hospital sales teams to health professionals and administrative staff. The Panel considered that on balance it might not be immediately apparent to healthcare professionals that the item was not a syringe; the company had failed to recognise the special nature of medicines and to maintain high standards as required by Clause 9.1 of the Code. A breach of that clause was ruled.

Clause 18.1 covered gifts and inducements with Clause 18.2 setting out the parameters for acceptable promotional aids. The Panel noted that it was an established principle under the Code that a pen, albeit an item of general utility, was an acceptable promotional aid. The Panel noted that the pen cost 53 pence, excluding VAT, and was therefore inexpensive as required by Clause 18.2 and its supplementary information. The Panel also noted the supplementary information to Clause 18.2 which stated that 'Names of medicines should not be used on promotional aids when it would be inappropriate to do so, for example, when it might mislead as to the nature of the item'. The Panel considered that the name did not in itself mislead as to the nature of the item, but was one of a series of factors which were relevant. This aspect had been covered by its ruling of a breach of Clause 9.1 above. The Panel ruled no breach of Clause 18.1 of the Code.

Complaint received **3 May 2001**

Case completed **11 June 2001**

CODE OF PRACTICE REVIEW – AUGUST 2001

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1101/11/00	**Clement Clarke v AstraZeneca**	**Promotion of the Turbohaler and information about the In-Check device**	**Breaches Clauses 4.1, 7.2 and 15.9**	**Appeal by respondent**	**Page 3**
1107/11/00	**General Practitioner v Novartis**	**Arrangements for audit**	**Breaches Clauses 2, 9.1 and 15.2**	**Appeal by complainant**	**Page 16**
1121/1/01	**SmithKline Beecham v Takeda**	**Promotion of Actos**	**Two breaches Clause 7.2**	**Appeal by complainant**	**Page 24**
1123/1/01	**Takeda v SmithKline Beecham**	**Promotion of Avandia**	**Breach Clause 4.2 Sixteen breaches Clause 7.2 Four breaches Clause 7.3 Four breaches Clause 7.8 Breach Clause 8.1**	**Appeals by complainant and respondent**	**Page 31**
1130/1/01	**Consultant Psychiatrist v Lilly**	**Zyprexa 'Dear Healthcare Professional' letter**	**Breaches Clauses 9.1 and 10.1**	**Appeal by complainant**	**Page 55**
1131/1/01	**Boehringer Ingleheim v Novartis**	**Promotion of Aredia**	**Four breaches Clause 7.2 Breaches Clauses 7.3 and 7.8**	**No appeal**	**Page 59**
1132/1/01& 1133/1/01	Merck Sharp & Dohme v Yamanouchi Pharma and GlaxoSmithKline	Flomax MR journal advertisement	No breach	Appeal by respondents	Page 66
1134/2/01	**Chugai Pharma v Amgen**	**Neupogen mailing**	**Two breaches Clause 7.2**	**Appeal by respondent**	**Page 75**
1135/2/00	Patient v AstraZeneca	Sponsored asthma nurse	No breach	No appeal	Page 79
1137/2/01	**UCB Pharma v Schering-Plough**	**Promotion of NeoClarityn**	**Breach Clause 2 Five breaches Clause 7.2 Four breaches Clause 7.3 Two breaches Clause 7.8**	**No appeal**	**Page 83**
1139/2/01 & 1140/2/01	**Chairman of Trust Pharmacy & Therapeutics Committee v Pharmacia and Pfizer**	**Promotion of Celebrex outside its licence**	**Pharmacia – breaches Clauses 3.2, 7.2 and 15.2 Pfizer – no *prima facie case***	**No appeal**	**Page 90**
1141/2/01	**UCB Pharma v Schering-Plough**	**Promotion of NeoClarityn**	**Three breaches Clause 7.2 Three breaches Clause 7.3 Three breaches Clause 7.8 Breach Clause 8.1**	**No appeal**	**Page 94**
1142/2/01	**Consultant Physician v Takeda**	**Meetings about Actos**	**Breach Clause 18.1**	**Appeal by respondent**	**Page 98**
1147/2/01	**Wyeth v Organon Laboratories**	**Promotion of Zispin**	**Two breaches Clause 7.2 Breach Clause 7.8**	**Appeal by respondent**	**Page 106**
1149/2/01	**Paragraph 16/Director v GlaxoSmithKline**	**Engerix B poster**	**Breach Clause 4.7**	**Appeal by respondent**	**Page 110**
1150/3/01	Continence Adviser v Norgine	Promotion of Nocutil	No breach	No appeal	Page 112

1152/3/01	**Lundbeck v GlaxoSmithKline**	**Promotion of Seroxat**	**Breach Clause 2 Five breaches Clause 7.2 Breaches Clauses 7.6 and 7.8 Three breaches Clauses 8.1 Breach Clause 21**	**No appeal**	**Page 113**
1157/3/01	General Practitioner v Sanofi-Synthélabo	Conduct of representatives	No breach	No appeal	Page 124
1160/3/01 & 1161/3/01	**Merck Sharp & Dohme v Pharmacia and Pfizer**	**Celebrex leavepiece**	**Breach Clause 3.2 Three breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.8**	**No appeal**	**Page 126**
1162/3/01	**GlaxoSmithKline v AstraZeneca**	**Promotion of Oxis12 Turbohaler and Bricanyl Turbohaler**	**Nine breaches Clause 7.2 Breach Clause 7.6**	**No appeal**	**Page 133**
1163/3/01	Medical Secretary to Local Medical Committee v Aventis Pasteur MSD	Local purchasing group	No breach	No appeal	Page 142
1165/3/01	**University Clinical Lecturer v Janssen-Cilag**	**Conduct of representative**	**Breach Clause 15.2**	**No appeal**	**Page 144**
1168/3/01	**Novo Nordisk v Pharmacia**	**Polaroid camera for child patients**	**Breach Clause 18.1**	**No appeal**	**Page 148**
1170/3/01	Novo Nordisk v Lilly	Promotion of HumaPen	No breach	Appeal by respondent	Page 150
1171/3/01	Anonymous v Norton Healthcare	Alleged failure to pass ABPI representatives examination	No breach	No appeal	Page 155
1172/3/01	**Schwarz Pharma v Schering-Plough**	**Promotion of NeoClarityn**	**Breach Clause 3.2 Six breaches Clause 7.2 Two breaches Clause 7.3 Six breaches Clause 7.8 Breach Clause 8.1**	**No appeal**	**Page 156**
1174/4/01	**Aventis Pharma v Schering-Plough**	**Promotion of NeoClarityn**	**Three breaches Clause 7.2**	**No appeal**	**Page 166**
1175/4/01	Pharmacist v Pfizer	Viagra journal advertisements	No breach	No appeal	Page 169
1177/4/01	**UCB Pharma v Aventis Pharma**	**Telfast journal advertisement**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.8**	**No appeal**	**Page 173**
1178/4/01	**Aventis Pharma and Procter & Gamble v Merck Sharp & Dohme**	**Fosamax journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 176**
1181/5/01	Primary Care Group v Merck Sharp & Dohme	Conduct of representative	No breach	No appeal	Page 185
1182/5/01	**Accident & Emergency Consultant v Elan Pharma**	**Highlighter pen in the form of a syringe**	**Breach Clause 9.1**	**No appeal**	**Page 187**

PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).