PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 47 FEBRUARY 2005

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

Complaints in 2004 down on 2003

In 2004 the Authority received 119 complaints under the Code of Practice as compared with 131 in 2003. There were 127 complaints in 2002 and 138 in 2001.

The average number of complaints received each year since the Authority was established at the beginning of 1993 is 125, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997 without any perceptible reason for the variations seen.

There were 119 cases to be considered in 2004, as compared with 122 in 2003. Though not so in 2004, the number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

The number of complaints from health professionals has slightly exceeded the number from pharmaceutical companies, there having been forty-eight from health professionals and forty-six from pharmaceutical companies (both members and non-members of the ABPI). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

One complaint was made by the Medicines and Healthcare products Regulatory Agency, one by the Royal College of General Practitioners, one by a member of the public and one by a pharmaceutical company employee. Two were anonymous.

The remaining nineteen complaints were nominally made by the Director and arose from media criticism, other complaints, voluntary admissions, alleged breaches of undertaking and scrutiny of advertisements.

New independent member of the Appeal Board

Professor Richard Hobbs has been appointed to the Code of Practice Appeal Board as an independent medical member and is welcomed by the Authority. Professor Hobbs is Head of Primary Care and General Practice at the University of Birmingham as well as being a part-time GP.

Publication error

Please note that the last page of the index was missing from the printed copy of the November 2004 review. The missing page can be downloaded from the website.

Review on the Internet

The Code of Practice Review is now available at www.pmcpa.org.uk by following the Code of Practice Review link.

Welcome back

Lisa Matthews, who left the Authority at the end of last year to take up a job in her home town in Kent, has returned as PA to Etta Logan and Jane Landles. Lisa has responsibility within the Authority for the development of IT. The Authority welcomes Lisa's return and looks forward to her contribution to its work in her new role.

Examinations for representatives

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

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

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

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

The ABPI 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.

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar date on which places remain available is:

Friday, 6 May

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 4).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

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 5).

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/1557/2/04

PIERRE FABRE/DIRECTOR v AVENTIS PHARMA

Breach of undertaking

Pierre Fabre complained that Aventis Pharma was continuing to use a clinical paper contrary to the Appeal Board's ruling in Case AUTH/1525/10/03. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

In Case AUTH/1525/10/03 Pierre Fabre had complained about the unsolicited provision of Fossella *et al* (2003) by Aventis. The paper, which reported the outcome of the TAX 326 study, had been distributed as part of the promotion of Taxotere and although it contained the pivotal data supporting the licensed use of Taxotere plus cisplatin the study had also included another treatment arm, Taxotere plus carboplatin, which was unlicensed. Copies of the published paper had been provided in a promotional folder. The Panel had considered that such provision constituted promotion of the unlicensed combination of Taxotere and carboplatin. A breach of the Code was ruled which was upheld on appeal. The form of undertaking and assurance was signed on 30 January 2004 and indicated that the promotional use of Fossella *et al* would cease forthwith and that the folder had last been used on 14 January 2004.

Pierre Fabre noted that the folder was used on 25 February 2004 at the Scottish Intercollegiate Guidelines Network's Lung Cancer Guidelines open meeting. The clinical paper had been temporarily separated from the folder; a placard placed immediately adjacent to the folder read 'If you would like a copy of the Fossella *et al* publication of the TAX 326 study, please ask the sales representative at this stand'. Pierre Fabre noted that the folder and the reprint were thus reunited and the promotion of Taxotere continued to be in breach of the Code.

Pierre Fabre stated that despite any undertaking and assurance in relation to the Appeal Board's ruling in Case AUTH/1525/10/03, it was clear that this activity was contrary to the spirit and purpose of the Code. It was inappropriate for sales representatives to openly solicit direct requests for material in conjunction with the folder. Such action seriously undermined the Authority and brought the pharmaceutical industry into disrepute.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that on acceptance of the ruling of a breach of the Code in Case AUTH/1525/10/03, Aventis informed its representatives that copies of Fossella *et al* could not be provided without a signed medical information request form from the customer. The relevant briefing document went on to state that the folder could still be used to start the discussion with the customer and that once a signed request had been received then Fossella *et al* could be put into the folder. The document referred to pre-printed/completed medical information request forms, although copies of these were not provided. Representatives were further informed that they could still use the empty folders on their exhibition stands but that they should use a place holder (assumed to be the placard) to draw attention to the fact that a signed request form was needed should the customer require a copy of Fossella *et al*. The briefing document stated 'Use the empty gatefolder [folder] to engage customer in a dialogue of TAX 326. Secure a signature for a copy of the paper on the pre-printed form … Provide a copy of the paper and place in the gatefolder'. The Panel noted that the folder had now been overstickered with 'Please note the reprint is not included'.

The Code stated that the term promotion did not include replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, but only if they related solely to the subject matter of the enquiry, were accurate, did not mislead and were not promotional in nature. In order to benefit from this exemption such enquiries had to be unsolicited.

The Panel noted that Aventis had instructed its representatives to secure a request for Fossella *et al;* pre-printed/completed request forms had been provided. Attention had been drawn to the fact that the Fossella reprint was available through use of the placard and also the sticker on the promotional folder. The Panel considered that Aventis was soliciting requests for Fossella *et al* and in effect promoting the unlicensed use of Taxotere in combination with carboplatin. A breach of the Code was ruled.

The Panel considered that Aventis had failed to comply with its undertaking and so ruled a breach of the Code. The Panel considered that by continuing with an activity previously found to be in breach of the Code, Aventis had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel considered that high standards had not been maintained and a further breach was ruled.

The Panel noted that the Constitution and Procedure required it to report a company to the Code of Practice Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board in relation to additional sanctions. Failure to comply with an undertaking was a serious matter. It appeared that Aventis' arrangements were inadequate and in the Panel's view its attempts to comply with the undertaking in Case AUTH/1525/10/03 were disingenuous. The Panel decided that the circumstances warranted reporting Aventis to the Appeal Board.

The Appeal Board noted that in Case AUTH/1525/10/03, the Panel had ruled Aventis in

breach of the Code for distributing copies of Fossella *et al*, unsolicited, in a promotional folder. This ruling had been upheld on appeal by Aventis. In the case now before it, Case AUTH/1557/2/04, the Appeal Board noted that Aventis had modified the folder by way of a sticker which stated that the reprint was not included. Aventis had also produced a placard for use on a meeting stand which referred to Fossella *et al* and invited readers to request a reprint of the study. The Appeal Board considered that both actions were naive; Aventis had in effect solicited requests for Fossella *et al* in breach of its previous undertaking.

The Appeal Board noted that the Aventis representatives had confirmed that the folder was still in use and the placard was no longer in use.

The Appeal Board understood the importance of the study; nevertheless Aventis' use of it had to comply with the Code. The Appeal Board was concerned that the folder was still in use albeit amended. The sticker 'Please note: Reprint not included' would encourage requests for the Fossella paper.

The Appeal Board considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. The Appeal Board considered, however, that by taking the steps that it had to comply with its previous undertaking Aventis had in effect ignored the previous rulings of the Appeal Board. The Appeal Board noted that Aventis had undergone audits in October 2002 and June 2003. The Appeal Board considered that the circumstances were such that it decided to report Aventis to the ABPI Board of Management.

When the report was considered by the ABPI Board, Aventis acknowledged that it had made a serious mistake and apologised unreservedly. The company had withdrawn Fossella *et al* from its representatives who had been formally briefed on the requirements of the Code. Unsolicited distribution of the paper had stopped. Aventis had reviewed its standard operating procedures and was determined to maintain high standards. Since May 2004 (when the case was considered by the Appeal Board) there had not been any further complaints about the distribution of Fossella *et al*.

Aventis stated that the case raised an important issue. Fossella *et al* was a registration study and such studies were often not entirely in accordance with the marketing authorization. Omission of results not covered by the marketing authorization could be seen as misrepresentation of the data. Health professionals, particularly those in oncology, needed to assess all the data to reach a decision about the use of products.

The Board noted the explanation given by Aventis as to the recurrence following the provision of the undertaking. In the circumstances the Board decided that no further action was required. The Board considered that the apology from Aventis had been contrite with a full admission of guilt.

Pierre Fabre Ltd complained that Aventis Pharma Ltd was continuing to use a clinical paper contrary to the Appeal Board's ruling in Case AUTH/1525/10/03. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Code of Practice Appeal Board.

In Case AUTH/1525/10/03 Pierre Fabre had complained about the unsolicited provision of Fossella *et al* (2003) by Aventis Pharma. The paper, which reported the outcome of the TAX 326 study, had been distributed as part of the promotion of Taxotere and although it contained the pivotal data supporting the licensed use of Taxotere plus cisplatin the study had also included another treatment arm, Taxotere plus carboplatin, which was unlicensed. Copies of the published paper had been provided in a promotional folder. The Panel had considered that such provision constituted promotion of the unlicensed combination of Taxotere and carboplatin as alleged. A breach of the Code was ruled which was upheld on appeal. The form of undertaking and assurance was signed on 30 January 2004 and indicated that the promotional use of Fossella *et al* would cease forthwith and that the folder had last been used on 14 January 2004.

COMPLAINT

Pierre Fabre noted that the folder was used on 25 February 2004 at the Scottish Intercollegiate Guidelines Network's Lung Cancer Guidelines open meeting. The clinical paper had been temporarily separated from the folder; a placard placed immediately adjacent to the folder read 'If you would like a copy of the Fossella *et al* publication of the TAX 326 study, please ask the sales representative at this stand'. Pierre Fabre noted that the folder and the reprint were thus reunited and the promotion of Taxotere continued to be in breach of Clause 3.2 of the Code.

Pierre Fabre stated that despite any undertaking and assurance in relation to the Appeal Board's ruling in Case AUTH/1525/10/03, it was clear that this activity was contrary to the spirit and purpose of the Code. It was inappropriate for sales representatives to openly solicit direct requests for material in conjunction with the folder. Such action seriously undermined the Authority and brought the pharmaceutical industry into disrepute.

When writing to Aventis, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22 of the Code in addition to Clause 3.2 cited by Pierre Fabre.

RESPONSE

Aventis stated that following the outcome of Case AUTH/1525/10/03 copies of Fossella *et al* had not been provided without prior receipt of a signed customer request form. The promotional folder and clinical paper had been separated and unsolicited copies of Fossella *et al* were no longer provided. The statement on the promotional folder which indicated the inclusion of the paper within had been removed.

Aventis submitted that given that Fossella *et al* was the only reference for the licensed combination of Taxotere and cisplatin it had used a placard on its promotional stands to alert interested parties that copies could be requested. The placard made no promotional claims but the company now appreciated that it might be viewed as a promotional request in its own right; use of the placard had ceased.

In response to a request for further information Aventis stated that on the day that it was notified in writing of the Appeal Board's ruling in Case AUTH/1525/10/03 it held a teleconference with its sales force explaining the outcome. A briefing document explaining the position along with clear instructions on adherence to the ruling was sent to the sales force three days later; a copy was provided.

Aventis stated that the briefing document informed its representatives that, with immediate effect copies of Fossella *et al* could not be provided unsolicited and a signed medical information request form would be needed for every copy provided. The empty gatefold could be used to discuss the study in question and could continue to be used on the stands but given that the gatefolds were empty, the placard was provided to draw attention to the fact that if customers required a copy of the paper they would need to ask the sales representative.

Aventis did not consider that provision of reprints of clinical papers upon request was inappropriate. However, on reflection, the company acknowledged the complaint and had stopped using the placard. Furthermore, a sticker had been placed on the gatefold indicating that the paper was not included. A copy of the amended folder was provided.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that on acceptance of the ruling of a breach of the Code in Case AUTH/1525/10/03, Aventis informed its representatives that copies of Fossella *et al* could not be provided without a signed medical information request form from the customer. The relevant briefing document went on to state that the folder could still be used to start the discussion with the customer and that once a signed request had been received then Fossella *et al* could be put into the folder. The document referred to pre-printed/completed medical information request forms although copies of these were not provided. Representatives were further informed that they could still use the empty folders on their exhibition stands but that they should use a place holder (assumed to be the placard) to draw attention to the fact that a signed request form was needed should the customer require a copy of Fossella *et al*. The summary to the briefing document read 'Use the empty gatefolder [folder] to engage customer in a dialogue of TAX 326. Secure a signature for a copy of the paper on the pre-printed form … Provide a copy of the paper and place in the gatefolder'. The Panel noted that the folder had now been overstickered with 'Please note the reprint is not included'.

The Panel noted that Clause 1.2 of the Code stated that the term promotion did not include replies made in response to individual enquiries from members of the health professions or appropriate administrative staff or in response to specific communications from them whether of enquiry or comment, but only if they related solely to the subject matter of the enquiry, were accurate, did not mislead and were not promotional in nature. In order to benefit from this exemption such enquiries had to be unsolicited.

The Panel noted that Aventis had instructed its representatives to secure a request for Fossella *et al*; pre-printed/completed request forms had been provided. Attention had been drawn to the fact that the Fossella reprint was available through use of the placard and also the sticker on the promotional folder. The Panel considered that Aventis was soliciting requests for Fossella *et al* and in effect promoting the unlicensed use of Taxotere in combination with carboplatin. A breach of Clause 3.2 was ruled.

The Panel considered that Aventis had failed to comply with its undertaking and so ruled a breach of Clause 22 of the Code. The Panel considered that by continuing with an activity previously found to be in breach of the Code, Aventis had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that the Constitution and Procedure required it to report a company to the Code of Practice Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2) in relation to additional sanctions as set out in Paragraphs 10.3, 10.4 and 12.1 of the Constitution and Procedure. Failure to comply with an undertaking was a serious matter. It appeared that Aventis' arrangements were inadequate and in the Panel's view its attempts to comply with the undertaking in Case AUTH/1525/10/03 were disingenuous. The Panel decided that the circumstances warranted reporting Aventis to the Appeal Board.

COMMENTS FROM AVENTIS

When returning the undertaking and assurance Aventis provided an explanation of the case to assure the Authority of Aventis' commitment to uphold decisions taken by the Authority.

Aventis noted that the history of this case dated back to October 2003. Aventis submitted that the nub of Case AUTH/1525/10/03 was the unsolicited provision of Fossella *et al*. Aventis had designed a folder to facilitate distribution of the publication. Fossella *et al* was a seminal study because it was the largest randomised phase III study ever undertaken in advanced non-small-cell lung cancer and it was also the registrational study for the first-line combination licence with cisplatin, granted by the European

Agency for the Evaluation of Medicinal Products (EMEA) in January 2003.

Aventis noted that the complaint from Pierre-Fabre that led to Case AUTH/1525/10/03 had related to the unsolicited provision of the reprint of Fossella *et al*. The folder itself was not a cause for concern and was not subject to discussion at the appeal hearing. As such, following the Appeal Board's ruling on use of the reprint, Aventis had not considered that its continued use of the empty folder was a violation of the ruling. Indeed the folder was clearly labelled to state that the reprint was not included. The sticker therefore did not alert the customer that a copy of the reprint was available on request as was suggested by the Panel.

Aventis submitted that the briefing document stated that the folder could be used to engage the customer in a discussion of the study. The folder only described the licensed regimen of Taxotere/cisplatin and discussion would therefore only focus on this area. Following the discussion, should the customer request a copy of the publication they would sign a medical information request form.

Aventis submitted that its dilemma, which was raised at the appeal in Case AUTH/1525/10/03, was that the data for its licensed regimen as well as the unlicensed regimen of Taxotere/carboplatin, was presented within the same publication. Aventis could not extract this information from the paper. Promotional use of Fossella *et al* therefore represented licensed as well as unlicensed use of Taxotere. Due to this situation, the Appeal Board had ruled that Aventis would need to secure the medical information request prior to provision of the paper. Since the ruling Aventis had not provided copies of the paper without the signature from the requestor.

Aventis submitted that given the nature of stand meetings, numerous customers circulating seeking information, it made the decision to use a placard to alert those customers interested in the study that they could request copies from the representative. Aventis submitted that it was careful to ensure that the placard stated no claims or other information relating to the outcomes of the study, however it failed to appreciate at the time of approval that the placard might still be seen to promote the use of the unlicensed combination in Fossella *et al*. Aventis had envisaged using the placard merely as a way to ensure customers were able to request the data for the licensed combination. Aventis submitted that the promotion of Taxotere/carboplatin had never been a strategy and thus in retrospect it accepted that use of the placard in such a way might have been inappropriate.

Aventis submitted that this had been an unfortunate oversight but assured that at no time did it knowingly act outside of the ruling. Aventis took its interactions with the Authority extremely seriously and had mechanisms in place to ensure strict compliance with any rulings. Aventis had reviewed its process with respect to this particular incident and taken steps to ensure such breaches were not repeated.

REPORT TO APPEAL BOARD

The Appeal Board noted that in Case AUTH/1525/10/03, the Panel had ruled Aventis in breach of Clause 3.2 of the Code for distributing copies of Fossella *et al*, unsolicited, in a promotional folder. This ruling had been upheld on appeal by Aventis. In the case now before it, Case AUTH/1557/2/04, the Appeal Board noted that Aventis had modified the folder by way of a sticker which stated that the reprint was not included. Aventis had also produced a placard for use on a meeting stand which referred to Fossella *et al* and invited readers to request a reprint of the study. The Appeal Board considered that both actions were naive; Aventis had in effect solicited requests for Fossella *et al* in breach of its previous undertaking.

The Appeal Board noted that Aventis had confirmed that the folder was still in use and the placard was no longer in use.

The Appeal Board understood the importance of the study; nevertheless Aventis' use of it had to comply with the Code. The Appeal Board was concerned that the folder was still in use albeit amended. The sticker 'Please note: Reprint not included' would encourage requests for the Fossella paper.

The Appeal Board considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings. The Appeal Board considered, however, that by taking the steps that it had to comply with its previous undertaking Aventis had in effect ignored the previous rulings of the Appeal Board. The Appeal Board noted that Aventis had undergone audits in October 2002 and June 2003. The Appeal Board considered that the circumstances were such that it decided to report Aventis to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

REPORT TO ABPI BOARD

Aventis acknowledged that it had made a serious mistake and apologised unreservedly. The company had withdrawn Fossella *et al* from its representatives who had been formally briefed on the requirements of the Code. Unsolicited distribution of the paper had stopped. Aventis had reviewed its standard operating procedures and was determined to maintain high standards. Since May 2004 (when the case was considered by the Appeal Board) there had not been any further complaints about the distribution of Fossella *et al*.

Aventis stated that the case raised an important issue. Fossella *et al* was a registration study and such studies were often not entirely in accordance with the marketing authorization. Omission of results not covered by the marketing authorization could be seen as misrepresentation of the data. Health professionals, particularly those in oncology, needed to assess all the data to reach a decision about the use of products.

The ABPI Board noted the explanation given by Aventis as to the recurrence following the provision of the undertaking. In the circumstances the Board

decided that no further action was required. The ABPI Board considered that the apology from Aventis had been contrite with a full admission of guilt. It was, however, agreed that following Aventis' merger with Sanofi-Synthelabo the Board's views should be brought to the attention of the new management.

Complaint received	**27 February 2004**
PMCPA proceedings completed	**13 May 2004**
ABPI Board consideration	**4 November 2004**

CASE AUTH/1593/6/04

NOVO NORDISK v AVENTIS PHARMA

Lantus leavepieces

Novo Nordisk complained about five leavepieces for Lantus (insulin glargine) issued by Aventis Pharma. Lantus was a basal insulin manufactured by recombinant DNA technology. Novo Nordisk supplied a range of insulins.

A leavepiece 'Lantus in type 2 diabetes' included a heading 'Lantus – optimising control for type 2 insulin-naïve patients on oral agents'. There then followed the claim 'Effective control with good tolerability and low risk of weight gain' and a bar chart depicting the mean A_{1c} improvement with: evening administration of basal insulin plus oral hypoglycaemics, twice-daily mixed insulin or multiple injection insulin. The improvements in A_{1c} were 1.9, 1.8 and 1.6 respectively. Beneath the bar chart was the claim 'In insulin-naïve patients, one daily injection of insulin, combined with oral therapy, provides the same glycaemic control as insulin monotherapy but requires fewer injections'. Another bar chart on the same page showed the mean weight gain: 1.2kg with evening administration of basal insulin plus oral hypoglycaemics ($p<0.05$), 1.8kg with twice-daily mixed insulin and 2.9kg with multiple injection insulin.

Novo Nordisk alleged that the bar charts were misleading in that they were not from a study involving Lantus. The referenced study (Yki-Järvinen *et al* 1992) compared five different therapy regimens involving isophane insulin, oral hypoglycaemic agents and human insulin. To compound the misleading impression the data on A1c and weight had been selected to portray the most favourable by showing basal insulin administered in the evening producing an A_{1c} improvement of 1.9% and weight gain of 1.2kg. Had the data for oral hypoglycaemics plus basal insulin administered in the morning been included, the improvement in A_{1c} would have been 1.7% and the weight gain 2.2kg ie less favourable values than those quoted for twice-daily mixed insulin (1.8% and 1.8kg respectively).

Novo Nordisk did not consider that the cited study supported the claims made adjacent to the graphs; the data was presented selectively and inappropriately. The company alleged that the page, taken in its entirety, was misleading.

The Panel noted that the bar charts at issue appeared on a page headed 'Lantus – optimising control for type 2 insulin-naïve patients on oral agents'. The bar charts showed that basal insulin plus oral hypoglycaemic agents improved A_{1c} more than twice daily mixed insulin or multiple insulin injections and that it caused less weight gain than the other two regimens. Given the context in which it appeared, readers would assume that the data depicted for basal insulin and oral hypoglycaemic agents related to Lantus which was not so. Moreover, the results shown for basal insulin plus oral hypoglycaemic agents related to evening administration of the insulin. If the results for morning administration had been shown then twice daily mixed insulin would have appeared to have been the more favourable regimen in terms of A_{1c} improvements and weight gain. The Panel considered that the leavepiece was misleading as alleged and not capable of substantiation and ruled breaches of the Code.

A leavepiece 'Lantus and weight control' bore the claim 'Choosing a regimen with predictable and physiological blood glucose control' on a page featuring two graphs, one of which showed that blood insulin levels of Lantus were almost constant throughout the day.

Novo Nordisk noted that no references were given for the claim 'Choosing a regimen with predictable and physiological blood glucose control'. It was not aware of any published studies involving Lantus which supported the claims of predictability and physiological control, and Aventis had not provided any. Despite Aventis' assertion that no claim was intended, there was a clear implication that Lantus produced predictable and physiological blood glucose control. Furthermore, the Lantus summary of product characteristics (SPC) stated that 'the time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual'.

Novo Nordisk added that the flat line on the graph which was intended to be the profile for Lantus was unreferenced and misleading. Novo Nordisk was unaware of any evidence to support such a profile and Aventis had failed to provide any.

The Panel noted that the Lantus SPC stated that after injection small amounts of insulin glargine were continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action. It was also stated that as with all insulin, the time course of action of insulin glargine might be affected by physical activity and other variables and that the time course of action of insulin and insulin analogues such as

insulin glargine might vary considerably in different individuals or within the same individual.

The Panel noted that the page at issue was headed 'Choosing a regimen with predictable and physiological blood glucose control'. Contrary to Aventis' submission the Panel considered that, in the context of a Lantus leavepiece, this would be taken as a claim for Lantus ie that Lantus produced a predictable and physiological blood glucose control. This impression was enhanced by the graph below which showed that blood insulin levels of Lantus were almost constant throughout the day. The Panel considered that although there was data to show that injections of Lantus resulted in smooth blood insulin levels, the SPC nonetheless noted that variability might occur between and within individuals. The Panel considered that the headline and the graph were too dogmatic as to the predictability of the action of Lantus. The Panel considered that the page was misleading in this regard and not capable of substantiation and ruled breaches of the Code.

Upon appeal by Aventis, the Appeal Board noted the wording of the Lantus SPC regarding the predictable concentration/time profile and the variable time course of action. Nonetheless, in the Appeal Board's view predictability of response to insulin would be well understood by health professionals. The Appeal Board did not consider that the target audience would assume that the claim was for absolute predictability. There was data to show that Lantus produced a more predictable response than other insulins such as NPH. The Appeal Board thus considered that within the wide context of treating diabetes with insulin the claim 'Choosing a regimen with predictable and physiological blood glucose control' was not misleading as alleged and could be substantiated. The Appeal Board ruled no breach of the Code.

A bar chart entitled 'Mean weight change in type 1 and type 2 diabetes Observational Studies' appeared in the same leavepiece. Data presented showed that treatment of either type 1 (Russman *et al* 2003) or type 2 (Schreiber *et al* 2003) diabetics with Lantus resulted in a slight decrease in weight. Figures above the bars related to A_{1c} control.

Novo Nordisk noted that there was a non-significant difference in weight change from baseline for type 2 diabetes (marked with a double asterisk). However, this was presented alongside data from a study which showed a statistically significant change in weight for type 1 diabetes in a similar style with a p value (<0.02) placed in small text at the bottom. The p value above the type 2 diabetes bar referred to A_{1c} reduction and not weight change. Novo Nordisk alleged that such artwork was misleading. Furthermore, using a single-arm uncontrolled observational study to make a claim of weight control without a comparator was not scientifically valid. It was also not a balanced overview of the available data on Lantus as many published studies had shown weight gain.

The Panel noted that the main message of the leavepiece was that Lantus caused little or no weight gain. In that regard the Panel noted that results showing no significant difference in weight from baseline therapy were clinically important. The bar chart at issue showed weight change from baseline treatment in type 1 and type 2 diabetics who were changed onto Lantus therapy instead of their former basal insulin. The type 1 diabetics lost weight (83.2kg vs 78.1kg; p<0.02) as did the type 2 diabetics (94.9kg vs 86.7kg; p=ns). The Lantus bars were marked with one or two asterisks; these referred the reader to the p values which appeared to one side of the chart, one of which was statistically significant the other of which was not. Without reference to these p values, which effectively appeared as footnotes, the visual impression was that there was a statistically significant difference between baseline treatment and Lantus therapy in both groups which was not so. P values directly above both pairs of bars noted statistical significance (p<0.05 and p=0.0003) but these referred to A_{1c} reduction and not to the weight data. The Panel considered that the bar chart was misleading with regard to the statistical significance of the data therein and was not capable of substantiation on this point. Breaches of the Code were ruled which were upheld on appeal by Aventis.

The Panel noted that Novo Nordisk had also alleged that the bar chart was not a balanced overview of the available data on Lantus as many published studies had shown weight gain. No such studies had been cited by Novo Nordisk. The bar chart did not depict weight loss *per se*, but the fact that Lantus did not cause weight gain. The heading above the bar chart was 'Lantus and weight control' while the claim below the chart was 'Significant reduction in A_{1c} without weight gain when switching from existing therapies'. No breach of the Code was ruled.

A leavepiece 'Where next for patients with poor glycaemic control on pre-mixed insulins?' bore the claim 'Compared to NPH [neutral protamine Hagedom], Lantus in a basal bolus regimen can offer: … improved glycaemic control in type 1 patients' referenced to Ashwell and Amiel (2003).

Novo Nordisk noted that Ashwell and Amiel compared two basal bolus insulin regimens; Lantus (basal) plus lispro (bolus), and NPH (basal) plus human insulin (bolus). It was not valid to state that Lantus alone offered improved control, as it was impossible to assess what contribution insulin lispro made to the improvement in control seen in these patients. In Novo Nordisk's view the claim could only be attributed to the regimen of Lantus plus lispro and not to Lantus in isolation. Novo Nordisk alleged that the claim was not substantiated by the evidence given.

The Panel noted that the claim 'Compared to NPH, Lantus in a basal bolus regimen can offer… improved glycaemic control in type 1 patients' was referenced to Ashwell and Amiel. The poster provided by Aventis was Ashwell *et al* which the Panel assumed related to the same study. The poster reported a comparison of Lantus plus insulin lispro and NPH insulin plus unmodified human insulin. Although the results showed improved glycaemic control in the Lantus group such an advantage could

not be wholly attributed to Lantus given that the two regimens differed in their use of bolus insulin. The Panel considered that to cite such a study as a reference to the claim at issue was misleading as alleged. A breach of the Code was ruled. Ashwell *et al* did not substantiate the claim. The Panel noted, however, that the claim could be substantiated by Rosetti *et al* (2003).

A leavepiece 'Use of Lantus in childhood diabetes' included the claim 'Lantus helps poorly controlled children towards A_{1c} targets'.

Novo Nordisk noted that the claim was supported by Jackson *et al* (2003) which was a single-arm, non-randomised study with no control (or comparator) group in a small sample of 37 patients. The authors postulated that the observed benefits of Lantus might have been primarily related to improved compliance with therapy rather than to a change in insulin, as 63% of the children received supervised injections at school after being switched to Lantus. Novo Nordisk considered that if the children had been changed to any therapy and been supervised to improve compliance, a benefit would almost certainly have been seen. The company alleged that Jackson *et al* did not support the claim of superior glycaemic control to NPH in children.

The Panel noted that the authors of Jackson *et al* had postulated that the significantly better glycaemic control observed in the Lantus group was because patients with poor glycaemic control had been selected, therefore allowing greater opportunity for major improvement and, most importantly, the timing of Lantus at noon offered a stable and supervised mealtime for children and adolescents at school whose supper and bedtime hours at home were often irregular and unsupervised. The authors concluded that the benefits of therapy with Lantus might have been primarily related to improved compliance.

The Panel considered that the claim at issue 'Lantus helps poorly controlled children towards A_{1c} targets' implied an advantage for Lantus *per se*. It appeared, however, from the cited reference, that the advantage was due to improved compliance rather than the medicine itself. No other data had been provided to substantiate the claim. The Panel considered that the claim was misleading and could not be substantiated as alleged. Breaches of the Code were ruled.

Upon appeal by Aventis, the Appeal Board noted that the claim in question was based solely on the results of Jackson *et al*, a single arm, uncontrolled, retrospective study. In the Appeal Board's view the design of the study was such that it would not produce conclusive results. The Appeal Board noted the authors' own comments on the study design and interpretation of the results. The Appeal Board further noted that in Jackson *et al* Lantus had been administered each day at lunchtime. The Lantus SPC, however, stated 'In children efficacy and safety of Lantus have only been demonstrated when given in the evening'.

The Appeal Board considered that the claim 'Lantus helps poorly controlled children towards A_{1c} targets' implied an advantage for Lantus *per se*. It appeared, however, from Jackson *et al* that the advantage might have been due to improved compliance rather than the medicine itself. In addition the Appeal Board noted its concerns regarding the robustness of the study design. No other data had been provided to substantiate the claim. The Appeal Board considered that the claim was misleading and could not be substantiated as alleged. The Appeal Board upheld the Panel's ruling of breaches of the Code.

The claims 'Superior glycaemic control from a simple once-daily injection' and 'Insulin glargine substantially improved glycaemic control in children and adolescents with poorly controlled type 1 diabetes' appeared in the same leavepiece. Novo Nordisk alleged that these claims were hanging comparisons.

The Panel considered that neither claim made it clear with what Lantus was being compared. The claims appeared in emboldened print such that the reader's eye was drawn to them at the outset. Although reference to switching from NPH appeared on a bar chart, two bullet points beneath the bar chart and in the small-print describing the study design, it was not immediately obvious to the reader at the outset with what Lantus was being compared. The Panel considered that both claims were hanging comparisons and ruled breaches of the Code.

A page in a leavepiece 'Optimising control for your type 1 diabetes patients' was headed 'Superior glycaemic control versus NPH' and featured a graph showing 8-point 24 hour self-monitored blood glucose levels. The graph was referenced to Ashwell *et al*. Beneath the graph was, *inter alia*, the claim '44% reduction in nocturnal hypoglycaemia'.

Novo Nordisk noted that the graph compared the 8-point glucose profiles of Lantus plus lispro with NPH plus human insulin; however the suppressed zero exaggerated the difference between these two regimens in breach of the Code.

Novo Nordisk noted the claim for a 44% reduction in nocturnal hypoglycaemia also came from Ashwell *et al*. It was not clear from where and how 44% was derived. This was also selective use of the data, as Ashwell *et al* stated that the frequency of nocturnal hypoglycaemia was lower with the Lantus plus lispro regimen during months 2 to 4 and month 1 only, and this was a 32 weeks (8 months) study.

Novo Nordisk alleged that the title of the page 'Superior glycaemic control versus NPH' was misleading, as it implied that Lantus offered superior glycaemic control versus NPH, as above. This study compared a regimen of Lantus plus lispro with NPH plus human insulin, and it was therefore not possible to draw any conclusions about Lantus compared to NPH as any observed difference could just as well be due to a difference between human insulin and insulin lispro. In fact, at the bottom of the same piece under the subtitle 'Study conclusions', it was stated that 'Compared to NPH + human insulin, the combination of Lantus + lispro offers … clinically significant improvement in glycaemic control', which was a correct claim for the Lantus plus lispro regimen.

The Panel noted that, contrary to Aventis' submission, the graph at issue was not exactly as it had appeared in the poster from Ashwell *et al*. In the leavepiece the y axis ran from 9 to 15 and not from 6mmol/l to 15mmol/l as in the poster. In the leavepiece the line for NPH plus human insulin was continuous whereas on the poster it was not joined between the time points of post-breakfast and pre-lunch. Furthermore a p value of <0.018 in the leavepiece was given as p=0.018 in the original. The Panel accepted that blood glucose should never reach zero but nonetheless considered that shortening the y axis such that it ran only from 9mmol/l to 15mmol/l exaggerated the difference between the two insulin regimens as alleged. A breach of the Code was ruled.

With regard to the claim that compared to NPH plus human insulin, the combination of Lantus plus lispro offered a '44% reduction in nocturnal hypoglycaemia' the Panel noted that the referenced poster referred to a 44% reduction in the *rate* (emphasis added) of nocturnal hypoglycaemia episodes per month. The poster also stated that there was no difference in experience of total severe or nocturnal severe hypoglycaemia. The results of Ashwell *et al* had thus been incorrectly cited in the leavepiece. The Panel considered that the claim was misleading in this regard and breaches of the Code were ruled.

With regard to the title of the page 'Superior glycaemic control versus NPH' the Panel considered that its comments above about the design of Ashwell *et al* applied here. A breach of the Code was ruled. The claim could be substantiated by Rosetti *et al*.

Novo Nordisk Limited complained about the promotion of Lantus (insulin glargine) by Aventis Pharma Ltd. Lantus was a basal insulin manufactured by recombinant DNA technology. Intercompany dialogue had failed to resolve the issues. Novo Nordisk supplied a range of insulins.

A Leavepiece (ref LAN2750403) 'Lantus in type 2 diabetes'

Page 2 of this four page leavepiece included the heading 'Lantus – optimising control for type 2 insulin-naïve patients on oral agents'. There then followed the claim 'Effective control with good tolerability and low risk of weight gain' and a bar chart depicting the mean A_{1c} improvement with: evening administration of basal insulin plus oral hypoglycaemics, twice-daily mixed insulin or multiple injection insulin. The improvements in A_{1c} were 1.9, 1.8 and 1.6 respectively. Beneath the bar chart was the claim 'In insulin-naïve patients, one daily injection of insulin, combined with oral therapy, provides the same glycaemic control as insulin monotherapy but requires fewer injections'. At the bottom of page 2 was another bar chart which showed the mean weight gain with various insulin regimens. These were: 1.2kg with evening administration of basal insulin plus oral hypoglycaemics ($p<0.05$), 1.8kg with twice-daily mixed insulin and 2.9kg with multiple injection insulin.

COMPLAINT

Novo Nordisk alleged that the bar charts were misleading in that they were not from a study involving Lantus. The referenced study (Yki-Järvinen *et al* 1992) compared five different therapy regimens involving isophane insulin, oral hypoglycaemic agents and human insulin. To compound the misleading impression the data on A_{1c} and weight had been selected to portray the most favourable by showing basal insulin administered in the evening producing an A_{1c} improvement of 1.9% and weight gain of 1.2kg. Had the data for oral hypoglycaemics plus basal insulin administered in the morning been included, the improvement in A_{1c} would have been 1.7% and the weight gain 2.2kg; the A_{1c} improvement would have been smaller and magnitude of weight gain larger. These would have been less favourable than values quoted for twice-daily mixed insulin, which were 1.8% and 1.8kg respectively.

Novo Nordisk did not consider that the cited study supported the claims made adjacent to the graphs; the data was presented selectively and inappropriately. The company alleged that the page, taken in its entirety, was misleading in breach of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code.

RESPONSE

Aventis stated that, as indicated to Novo Nordisk in May, the leavepiece had been withdrawn; the company therefore did not see the value of commenting upon an item that was no longer in use.

In response to a request for further information Aventis stated that following an earlier complaint from Novo Nordisk regarding the use of a suppressed zero on the y axis of graphs showing changes in A_{1c}, it withdrew the leavepiece now at issue (LAN2750403). The company then reviewed the leavepiece in its entirety and noted that the depiction of the results from Yki-Järvinen *et al* had the potential to mislead. The company accepted that the leavepiece was in breach of Clause 7.8 of the Code.

PANEL RULING

The Panel noted that the bar charts at issue appeared on a page headed 'Lantus – optimising control for type 2 insulin-naïve patients on oral agents'. The bar charts showed that basal insulin plus oral hypoglycaemic agents improved A_{1c} more than twice daily mixed insulin or multiple insulin injections and that it caused less weight gain than the other two regimens. Given the context in which it appeared, readers would assume that the data depicted for basal insulin and oral hypoglycaemic agents related to Lantus which was not so. Moreover, the results shown for basal insulin plus oral hypoglycaemic agents related to evening administration of the insulin. If the results for morning administration had been shown then twice daily mixed insulin would have appeared to have been the more favourable regimen in terms of A_{1c} improvements and weight gain. The Panel considered that page 2 of the leavepiece was misleading as alleged and not capable of substantiation and ruled breaches of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code.

B Leavepiece (ref LAN4091103) 'Lantus and weight control'

1 Claim 'Choosing a regimen with predictable and physiological blood glucose control'

This claim appeared on page 2 of this six page, gate folded leavepiece. The page featured two graphs one of which showed that blood insulin levels of Lantus were almost constant throughout the day.

COMPLAINT

Novo Nordisk noted that no references were given for the claim 'Choosing a regimen with predictable and physiological blood glucose control'. The company was not aware of any published studies involving Lantus which supported the claims of predictability and physiological control, and Aventis had not provided any. Despite Aventis' assertion that no claim was intended, there was a clear implication that Lantus produced predictable and physiological blood glucose control. Furthermore, the Lantus summary of product characteristics (SPC) stated that 'the time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual'.

Novo Nordisk added that the flat line on the graph which was intended to be the profile for Lantus was unreferenced and misleading. Novo Nordisk was unaware of any evidence to support such a profile and Aventis had failed to provide any. Breaches of Clauses 7.2 and 7.4 of the Code were alleged.

RESPONSE

Aventis stated that pages 1 and 2 of the leavepiece referred to the problem of possible association between hypoglycaemia and weight gain and the fact that a clinician would look to choose a regimen with predictable and physiological blood glucose control to avoid hypoglycaemia. The claim at issue was only the title to page 2 and was not associated with Lantus or any claims. As such, there was no requirement to provide references for the title.

Aventis noted that predictability referred to the likelihood that a given individual would experience the same glucose lowering effect following injections of the same doses of insulin on different occasions. As with all complex metabolic systems, there was an inherent degree of variability but there was a published consensus amongst eminent diabetologists that Lantus was predictable in its effect. (Lepore *et al* 2000; Riddle and Rosenstock 2003; Bolli and Owens 2000; Lantus SPC).

Aventis stated that the graph, a graphical representation of the Lantus profile, was supported by the references associated with the statement beneath it (Lepore *et al*; Bolli and Owens; the Lantus SPC). Aventis noted that Section 5.1 of the Lantus SPC stated 'from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action'. Novo Nordisk was wrong to suggest that references had not been provided.

Aventis noted that Fanelli *et al*, although not cited in the leavepiece, also demonstrated a duration of action of Lantus at steady state of 24 hours, with a profile showing no pronounced peaks.

Therefore the graph on page 2 was a balanced and fair likeness of the pharmacokinetic profile of Lantus. This type of representation was recognised practice; Aventis noted that similar graphs appeared on Novo Nordisk's website.

PANEL RULING

The Panel noted that section 5.1, Pharmacodynamic properties, of the Lantus SPC stated that after injection small amounts of insulin glargine were continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action. The same section of the SPC also stated that as with all insulin, the time course of action of insulin glargine might be affected by physical activity and other variables and that the time course of action of insulin and insulin analogues such as insulin glargine might vary considerably in different individuals or within the same individual.

The Panel noted that the page at issue was headed 'Choosing a regimen with predictable and physiological blood glucose control'. Contrary to Aventis' submission the Panel considered that, in the context of a Lantus leavepiece, this would be taken as a claim for Lantus ie that Lantus produced a predictable and physiological blood glucose control. This impression was enhanced by the graph below which showed that blood insulin levels of Lantus were almost constant throughout the day. The Panel considered that although there was data to show that injections of Lantus resulted in smooth blood insulin levels, the SPC nonetheless noted that variability might occur between and within individuals. The Panel considered that the headline and the graph were too dogmatic as to the predictability of the action of Lantus. The Panel considered that the page was misleading in this regard and not capable of substantiation and ruled breaches of Clauses 7.2 and 7.4 of the Code.

APPEAL BY AVENTIS

Aventis considered that the Panel had accepted in its ruling that Lantus had been conclusively shown to produce smooth 'physiological' insulin levels. It appeared therefore that the Panel had ruled against the claim that Lantus produced 'predictable' blood glucose control. Aventis however considered that this claim was both accurate and capable of substantiation.

Aventis stated that it was important to appreciate that clinical trials of insulins commonly utilised two separate measures of 'predictability':

- Inter-patient variability – the variability in metabolic action of the same dose of the same insulin, when administered to different individuals
- Intra-patient variability – the variability in metabolic action of the same dose of the same insulin, when administered to the same individual on different occasions

Aventis stated that intra-patient variability was often considered to be the most clinically relevant measure of the 'predictability' of an insulin, as it was important for people to experience the same metabolic effect from their prescribed dose of insulin on different days, in order to allow them to achieve stable blood glucose control. Inter-patient variability might be a less important measure, as in practice, insulin doses were titrated on an individual basis relative to the specific metabolic requirement of that individual. However as both were measures of 'predictability', in order to make a robust claim in this domain, a product should have data to support the claim for both measures of predictability.

Inter-patient variability

Aventis noted that Gerich *et al* (2003) had reported analysis of three phase 1 studies to establish the degree of fluctuation from mean serum insulin levels following the administration of Lantus. Fluctuation was measured by the percentage deviation around average serum insulin concentration over 24 hours (PF24). The first two studies were relevant as regards inter-patient variability. In study 1, healthy volunteers (n=36) were randomised to receive 0.3IU/kg of Lantus, NPH or ultralente. Subjects who received Lantus had lower mean PF24 (20%) than those receiving NPH (32%) or ultralente (47%) ($p<0.0001$). This equated to 50% less variability with Lantus. In study 2, subjects with type 1 diabetes (n=20) received Lantus or NPH. Subjects receiving Lantus had lower mean PF24 (14%) than those receiving NPH (26%) ($p<0.0001$). This equated to 50% less variability with Lantus. Aventis submitted that both studies therefore showed less intra-patient variability for Lantus versus the comparator insulins.

With regard to intra-patient variability Aventis noted that Gerich *et al* also reported a third study in which subjects with type 1 diabetes (n=15) received their first dose of Lantus on day 1 and subsequent doses on each of the next 11 days. Insulin lispro was used at mealtimes. In this study mean PF24 results were not significantly different on days 2, 5 or 12 showing that Lantus maintained minimal fluctuation with repeated dosing over consecutive days.

Aventis noted that in Raskin *et al* (2000) type 1 diabetics receiving basal-bolus treatment with NPH insulin and insulin lispro were randomised to receive Lantus once daily (n=310) or NPH once or twice daily depending on each subject's pre-study NPH regimen (n=309). All patients continued with insulin lispro at mealtimes over the course of the 16-week study. The measure of intra-patient variability in this study utilised measures of fasting blood glucose (FBG) taken on seven consecutive occasions before the clinic visit. The ranked change from baseline in variability of fasting blood glucose was analysed by ANCOVA. At baseline, both treatment groups showed comparable variability in FBG. By week 16 however, the median decrease in variability between patients receiving Lantus and those receiving NPH achieved statistical significance ($p=0.0427$). The significance was maintained at study end point, with a median decrease in variability of 3.44mmol/l in patients treated with Lantus and 0.79mmol/l in those receiving NPH ($p=0.0124$). The authors concluded that there was less day-to-day variability in FBG levels in those treated with Lantus compared to those continuing to receive NPH.

Riddle *et al* (2003) randomised poorly controlled patients with type 2 diabetes, ($HbA_{1c} > 7.5\%$) despite using one or two oral hypoglycaemic agents, to either Lantus (n=367) or NPH (n=389) at bedtime whilst continuing their pre-study oral agents. The measure of intra-patient variability in this study was similar to that used by Raskin *et al* ie variability between seven sequential FBG measures. At 24 weeks the mean deviation from the median of fasting values for individual subjects was greater with NPH (1.13mmol/l) than with Lantus (1.02mmol/l) ($p=0.013$). The authors concluded that with Lantus there was less within-subject variability between the seven sequential fasting measurements over the course of the treatment.

Aventis noted that Gerich *et al* had shown that people receiving Lantus experienced similar minimal fluctuations when they received this insulin over consecutive days. Whilst Raskin *et al* and Riddle *et al* both showed that the use of Lantus produced less variability in FBG compared to NPH and hence greater predictability for those people being treated with it.

In summary, Aventis submitted that the data demonstrated that Lantus was associated with both improved intra- and inter-patient variability versus the respective comparator insulins used. It was that data which led to the statement in the Lantus SPC, accepted by the EMEA: 'After injection into the subcutaneous tissue, the acidic solution is neutralised leading to the formation of microprecipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action'. In Aventis' view, the subsequent statement in the SPC: 'The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual', was a generic statement applicable to all insulins, reflecting that the metabolic response to a given dose of an insulin varied not only due to the pharmacokinetics of that insulin but also due to activities undertaken by the individual who had received the insulin eg exercise, food intake etc. Aventis submitted that the data above showed that in terms of its inherent pharmacokinetics, Lantus provided predictable time/action profile (Gerich *et al* and Lantus SPC). In addition, in terms of day-to-day use in subjects undertaking their normal activities (Raskin *et al* and Riddle *et al*), Lantus produced greater stability in FBG than NPH. Aventis therefore submitted that the claim that Lantus produced predictable blood glucose control was both accurate and substantiable.

Aventis therefore did not consider that the headline and the graph were too dogmatic as to the predictability of Lantus and therefore that the page was not in breach of Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM NOVO NORDISK

Novo Nordisk considered that the title to page 5 of

the leavepiece 'Choosing a regimen with predictable and physiological blood glucose control' was an unreferenced claim supplemented by a statement that followed the two graphs: 'Lantus provides steady, predictable, 24-hour basal insulin supply which closely mimics the body's own basal insulin secretion'.

Novo Nordisk stated that Heise *et al* (2004) showed that there was more within-subject variability than with insulin detemir. In the euglycaemic glucose clamp study reported by Heise *et al*, coefficient of variations (CVs) for pharmacodynamic endpoints GIR-AUC $_{0\text{-}12\,h}$ (Glucose Infusion Rate, Area Under the Curve, 0-12 hours) were 46% for insulin glargine and 27% for insulin detemir; and CVs for GIR-AUC $_{0\text{-}24\,h}$ were 48% for insulin glargine and 27% for insulin detemir; CVs for GIR $_{max}$ (maximum GlR) were 36% for insulin glargine and 23% for insulin detemir ($p< 0.001$ for all comparisons). These results clearly showed that Lantus had higher intra-subject variation, and was therefore less predictable, compared with insulin detemir.

Novo Nordisk noted that the Lantus SPC provided similar advice that corroborated well with data reported by Heise *et al*. The Lantus SPC stated that 'the time course of action of insulin and insulin analogues such as insulin glargine *may vary considerably* in different individuals or within the same individual' (emphasis added). Novo Nordisk alleged that the claim of 'predictable, 24-hour basal insulin supply…' for Lantus contradicted the SPC.

APPEAL BOARD RULING

The Appeal Board noted that Heise *et al* (2004) was not available at the time of the complaint; as such it could form no part of its consideration.

The Appeal Board noted that Section 5.1, Pharmacodynamic properties, of the Lantus SPC stated that after injection small amounts of insulin glargine were continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action. The same section of the SPC also stated that as with all insulins, the time course of action of insulin glargine might be affected by physical activity and other variables and that the time course of action of insulin and insulin analogues such as insulin glargine might vary considerably in different individuals or within the same individual.

In the Appeal Board's view predictability of response to insulin would be well understood by health professionals. The Appeal Board did not consider that the target audience would assume that the claim was for absolute predictability. There was data to show that Lantus produced a more predictable response than other insulins such as NPH. The Appeal Board thus considered that within the wide context of treating diabetes with insulin the claim 'Choosing a regimen with predictable and physiological blood glucose control' was not misleading as alleged and could be substantiated. The Appeal Board ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

2 Bar chart entitled 'Mean weight change in type 1 and type 2 diabetes Observational Studies'

This bar chart appeared on page 4 of the leavepiece. Data was shown which showed that treatment of either type 1 (Russman *et al* 2003) or type 2 (Schreiber *et al* 2003) diabetics with Lantus resulted in a slight decrease in weight. Figures above the bars related to A_{1c} control.

COMPLAINT

Novo Nordisk noted that there was a non-significant difference in weight change from baseline for type 2 diabetes (marked with a double asterisk). However, this was presented alongside data from a study which showed a statistically significant change in weight for type 1 diabetes in a similar style with a p value (<0.02) placed in small text at the bottom. The p value above the type 2 diabetes bar referred to A_{1c} reduction, and not weight change. Novo Nordisk alleged that such artwork was misleading in breach of Clauses 7.2 and 7.4 of the Code. Furthermore, using a single-arm uncontrolled observational study to make claim of weight control without a comparator was not scientifically valid. It was also not a balanced overview of the available data on Lantus as many published studies had shown weight gain.

RESPONSE

Aventis submitted that the bar chart accurately represented the data in the references cited (Russman *et al* and Shreiber *et al*). The title to the chart clearly stated that the data was taken from 'Observational Studies'. The y axis of the graph represented weight in kg and the x axis indicated the two populations, namely type 1 and type 2 diabetes. The data was portrayed in accordance with the Code; the p values both significant and non-significant were treated in a similar manner, namely the use of asterisks above the bars with the values to the right of the chart (to reduce clutter within the chart area). In addition, comprehensive explanatory information was given to the right of the chart, allowing the reader to make an informed decision on the data.

The use of observational data in this context was extremely powerful as it represented real world data and was relevant to clinicians and diabetics alike.

Based on the above, Aventis submitted there was no breach of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that the main message of the leavepiece was that Lantus caused little or no weight gain. In that regard the Panel noted that results showing no significant difference in weight from baseline therapy were clinically important. The bar chart at issue showed weight change from baseline treatment in type 1 and type 2 diabetics who were changed onto Lantus therapy instead of their former basal insulin. The type 1 diabetics lost weight (83.2kg vs 78.1kg; $p<0.02$) as did the type 2 diabetics (94.9kg vs 86.7kg; p=ns). The Lantus bars were marked with one or two asterisks; these referred the reader to the p values which appeared to one side of the chart, one of

which was statistically significant the other of which was not. Without reference to these p values, which effectively appeared as footnotes, the visual impression was that there was a statistically significant difference between baseline treatment and Lantus therapy in both groups which was not so. P values directly above both pairs of bars noted statistical significance ($p<0.05$ and $p=0.0003$) but these referred to A_{1c} reduction and not to the weight data. The Panel considered that the bar chart was misleading with regard to the statistical significance of the data therein and was not capable of substantiation on this point. Breaches of Clauses 7.2 and 7.4 were ruled. These rulings were appealed by Aventis.

The Panel noted that Novo Nordisk had also alleged that the bar chart was not a balanced overview of the available data on Lantus as many published studies had shown weight gain. No such studies had been cited by Novo Nordisk. The bar chart did not depict weight loss *per se*, but the fact that Lantus did not cause weight gain. The heading above the bar chart was 'Lantus and weight control' while the claim below the chart was 'Significant reduction in A_{1c} without weight gain when switching from existing therapies'. No breach of Clause 7.4 was ruled. This ruling was not appealed by Novo Nordisk.

APPEAL BY AVENTIS

Aventis stated that any weight change during the course of insulin treatment must be interpreted in the light of concurrent HbA_{1c} changes. The use of insulin often resulted in the deposition of adipose tissue due in part to the anabolic effect of insulin itself together with the inevitable reduction in glycosuria as blood glucose levels were better controlled (the additional glucose became available to the body and, if in excess to its metabolic needs, was stored as glycogen and fat). The goal of treatment with insulin was to achieve the best possible glycaemic control whilst minimising weight gain. This was especially important in the management of type 2 diabetes as resistance to the effects of insulin increased as adiposity increased. Therefore Aventis submitted that in showing the HbA_{1c} changes that occurred during these two studies it had provided important data that, far from being misleading, allowed interpretation of the changes in weight to be represented appropriately.

In addition Aventis noted that the title of page 4 was 'Lantus and weight control'. The aim of the bar chart and indeed the whole leavepiece was to show that Lantus caused little or no weight gain and not to suggest that Lantus was associated with weight loss. Aventis noted that the Panel recognised this. Aventis had not intended to imply a statistically significant weight loss in both studies; the title of the page made its actual aim clear.

Aventis submitted that a health professional experienced in the management of diabetes would look at this bar chart and its legend to seek evidence of weight neutrality in the face of the clear improvements in glycaemic control evidenced by the HbA_{1c} changes. Aventis submitted that the data was presented in a clear and holistic fashion that was not misleading and that it substantiated the claim of 'Lantus and weight control' and was therefore not in breach of Clauses 7.2 or 7.4 of the Code.

Aventis added that the leavepiece was not intended for 'a casual observer', hence the level of detail included on each bar chart that ensured the reader could fully interpret the data being presented.

COMMENTS FROM NOVO NORDISK

Novo Nordisk agreed that whilst weight changes during the course of insulin treatment needed to be considered in the light of concurrent HbA_{1c} changes, it wished to emphasise the importance of the accuracy of data representation in promotional materials.

Novo Nordisk noted that the page of the leavepiece in question showed a chart with bars from two studies, one in type 1 diabetes (Russman *et al*), the other in type 2 diabetes (Schreiber *et al*). The Lantus bars showed changes in weight: statistically significant in type 1 diabetics but not statistically significant in the study in type 2 diabetics. The weight readings of the bars were denoted with asterisks. The p values for weight changes were outside the box, in small print at the bottom right-hand corner. Importantly, the p values for changes in A_{1c}, which were significant for both studies, were printed immediately above the weight bars. Such visual representation was likely to lead readers to falsely think that the significant p values referred to weight change whereas they referred to the changes in A_{1c}. A more accurate way of representing these data would be to print the p values for weight change directly above the weight bars, clearly indicating that weight change was not statistically significant for the study in type 2 diabetes.

APPEAL BOARD RULING

The Appeal Board considered that the presentation of data was confusing. Results for weight change and A_{1c} reduction had been positioned such that the p values for the A_{1c} reduction appeared to be related to the weight change data. The p values for the weight change data were printed outside the box that contained all of the rest of the data and thus appeared as a footnote. The Appeal Board considered that the bar chart was misleading with regard to the statistical significance of the data therein and not capable of substantiation on this point. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4 of the Code. The appeal on this point was unsuccessful.

C Leavepiece (ref LAN4320703) 'Where next for patients with poor glycaemic control on pre-mixed insulins?'

Claim 'Compared to NPH [neutral protamine Hagedom], Lantus in a basal bolus regimen can offer: … improved glycaemic control in type 1 patients'

This claim on page 4 was referenced to Ashwell and Amiel (2003).

COMPLAINT

Novo Nordisk noted that Ashwell and Amiel

compared two basal bolus insulin regimens; Lantus (basal) plus lispro (bolus) and NPH (basal) plus human insulin (bolus). It was not valid to state that Lantus alone offered improved control, as it was impossible to assess what contribution insulin lispro made to the improvement in control seen in these patients. Novo Nordisk stated that in its view the claim could only be attributed to the regimen of Lantus plus lispro and not to Lantus in isolation. Novo Nordisk alleged that the claim was not substantiated by the evidence given, in breach of Clauses 7.2 and 7.4 of the Code.

Novo Nordisk was concerned with the conclusions drawn from the comparison of the two regimens, not the study itself, which was a valid study comparing regimens. Although Aventis stated that the piece concerned the use of Lantus in a basal bolus regimen, it did not clearly state that the bolus therapy in the two regimens was different.

Novo Nordisk did not consider that the addition of another reference at this stage was relevant, as this was not referenced in the leavepiece at issue. The Code stated that references should be provided if requested, and that references should be given to substantiate any claim; Novo Nordisk did not consider that Aventis' interpretation of the Code (that substantiation should be provided if requested) was correct. Novo Nordisk alleged breaches of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Aventis noted that the claim clearly referred to Lantus being used as part of a basal bolus regimen. Also the page in question summarised the entire piece. It had been clearly stated that the A_{1c} reductions seen in Ashwell and Amiel were when Lantus was used 'in conjunction with rapid acting insulin analogues'. Aventis denied a breach of the Code.

As further substantiation Aventis had provided Novo Nordisk with Rosetti *et al* (2003). In this study patients were randomized either to stay on their current treatment of intensive NPH plus lispro insulin or to switch to one of two Lantus plus lispro insulin regimens. The study showed a statistically significant reduction in A_{1c} of 0.4% at 3 months in both Lantus groups compared to baseline, whereas no reduction was seen in the NPH arm, thus improved glycaemic control was achieved with Lantus.

Aventis noted that Clause 7.4 stated that any claim must be capable of substantiation; Clause 7.8 stated that substantiation must be provided without delay at the request of the health professions or appropriate administrative staff. Aventis believed that it had acted in the spirit of the Code as in its view, the information presented on the page was clear and therefore the references provided were adequate. Moreover, as this was not to the satisfaction of Novo Nordisk, further substantiation was provided.

Aventis denied breaches of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel disagreed with Novo Nordisk's view that Aventis could not use a study other than the one cited in the leavepiece to substantiate the claim at issue. Clause 7.6 of the Code required references to be given when material referred to published studies. Companies were not obliged to reference other claims and could provide material not cited in the advertising in response to a request for substantiation.

The Panel noted that the claim 'Compared to NPH, Lantus in a basal bolus regimen can offer… improved glycaemic control in type 1 patients' was referenced to Ashwell and Amiel. The poster provided by Aventis was Ashwell *et al* which the Panel assumed related to the same study. The poster reported a comparison of Lantus plus insulin lispro and NPH insulin plus unmodified human insulin. Although the results showed improved glycaemic control in the Lantus group such an advantage could not be wholly attributed to Lantus given that the two regimens differed in their use of bolus insulin. The Panel considered that to cite such a study as a reference to the claim at issue was misleading as alleged. A breach of Clause 7.2 was ruled. Ashwell *et al* did not substantiate the claim. The Panel noted, however, that the claim could be substantiated by Rosetti *et al*. On that basis the Panel ruled no breach of Clause 7.4 of the Code.

D Leavepiece (ref LAN4161203) 'Use of Lantus in childhood diabetes'

1 Claim 'Lantus helps poorly controlled children towards A_{1c} targets'

COMPLAINT

Novo Nordisk noted that the claim was supported by Jackson *et al* (2003) which was a single-arm, non-randomised study with no control (or comparator) group in a small sample of 37 patients. The authors postulated that the observed benefits of Lantus might have been primarily related to improved compliance with therapy rather than to a change in insulin, as 63% of the children received supervised injections at school after being switched to Lantus. Novo Nordisk considered that if the children had been changed to any therapy and been supervised to improve compliance, a benefit would almost certainly have been seen. The company alleged that Jackson *et al* did not support the claim of superior glycaemic control to NPH in children in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Aventis noted that Jackson *et al* was a retrospective analysis of children and adolescents who had been switched to Lantus following failure of an intensive NPH-based regimen to maintain A_{1c} below 8%. Prior to switching, all patients received NPH insulin 2-3 times daily in addition to their rapid-acting insulin at mealtimes. The results showed that the regimen was well accepted; many patients commented that they appreciated its flexibility. Apart from two patients

who went on to an insulin pump, the remainder elected to stay on Lantus; no patient chose to return to NPH insulin. In addition, the provision of the basal component of treatment was once a day – this could therefore be given entirely under supervision by the school if the child/family could not be relied on to administer treatment. As a result of this children were likely to receive a greater proportion of their prescribed insulin dose. The authors concluded that the analysis described the effectiveness of Lantus in lowering A_{1c} in poorly controlled children and adolescents with type 1 diabetes.

Aventis considered that Novo Nordisk's submission that if the children had been changed to any therapy and been supervised to improve compliance, a benefit would almost certainly have been seen, was pure hypothesis generation, and although possible, the facts were: Lantus was a once daily insulin which increased compliance and/or facilitated the use of supervised administration. Jackson *et al* showed that using Lantus contributed to better control.

It was therefore clear that features related to Lantus 'helped' contribute to improved glycaemic control achieved in the children studied.

PANEL RULING

The Panel noted that in the discussion section of Jackson *et al*, the authors had postulated that the significantly better glycaemic control observed in the Lantus group was due to two reasons. Firstly, that patients with poor glycaemic control had been selected, therefore allowing greater opportunity for major improvement. Secondly, and perhaps, according to the authors, most importantly, the timing of Lantus at noon offered a stable and supervised mealtime for children and adolescents at school whose supper and bedtime hours at home were often irregular and unsupervised. The authors concluded that the benefits of therapy with Lantus might have been primarily related to improved compliance.

The Panel considered that the claim at issue 'Lantus helps poorly controlled children towards A_{1c} targets' implied an advantage for Lantus *per se*. It appeared, however, from the cited reference, that the advantage was due to improved compliance rather than the medicine itself. No other data had been provided to substantiate the claim. The Panel considered that the claim was misleading and could not be substantiated as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

APPEAL BY AVENTIS

Aventis submitted that with regard to Jackson *et al* it was important to note that in attempting to routinely achieve optimal glycaemic control, the investigators utilised both an intensive regimen of insulin injections together with frequent follow up by a multidisciplinary team (every two or three months depending on HbA_{1c}). The patients included in the study had poor metabolic control ($HbA_{1c} > 8\%$) and had been receiving the basal portion of their intensive regimen as NPH insulin two or three times per day. The requirement to give NPH with such frequency was because it had a relatively short duration of action (12-16 hours) so multiple injections were required to provide adequate basal insulin replacement over a 24-hour period.

Aventis noted that Jackson *et al* acknowledged that in their inner-city population, missed insulin injections might contribute to the difficulty of achieving good glycaemic control. This problem of poor concordance was highly likely to be exacerbated by the use of a regimen requiring multiple injections. However the clinical reality of using NPH insulin was that multiple injections were required and that these repeated injections could not all be conveniently supervised by agencies outside the family home. The time action profile of Lantus, however, was such that a single daily injection provided adequate basal insulin replacement over a 24-hour period. It was this characteristic of Lantus that allowed 62% of the subjects in this study to receive their single daily dose of Lantus prior to lunch, under the supervision of the school nurse (presumably excluding weekends and school holidays over the six month study).

Aventis argued that even if the overall improvement in HbA_{1c} observed over the course of the study were postulated to be entirely due to 62% of the cohort receiving Lantus under supervision whilst at school, this improvement would be as a direct result of Lantus being used rather than NPH. The pharmacokinetics of Lantus allowed the single daily dosing regimen that in turn allowed school supervision. Aventis contended that the observed improvement (which extended beyond the 62% of the cohort) was therefore very much due to the specific characteristics of Lantus *per se*.

Aventis did not know of any basal insulins other than Lantus that were both licensed and commonly used by paediatricians to provide adequate daily basal insulin substitution following a single injection. Aventis submitted, therefore, that the claim 'Lantus helps poorly controlled children towards A_{1c} targets' was substantiated by this study and was not in breach of Clauses 7.2 and 7.4.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted that Aventis had selected a single-arm, uncontrolled, retrospective study based on chart analysis of 37 patients as the principal basis of the claim. It was well recognised that retrospective studies suffered from potential investigator biases. Without a prospective parallel comparator, interpretation of data could be tainted. In this study, patients with poorly controlled diabetes were switched from NPH insulin to insulin glargine based on 'clinical decisions'. Historical data were then used as the basis of analysis. There was no randomisation or alternatives in the study; all poorly controlled patients with $HbA_{1c} > 8\%$ who were not on insulin pump therapy were offered insulin glargine.

Novo Nordisk noted that Jackson *et al* had stated in their discussion section that the significant reduction in HbA_{1c} could be due to the fact that patients were in poor glycaemic control in the first place. The authors further cautioned that the benefits of this therapy might have been primarily related to improved

compliance with insulin administration. Novo Nordisk noted that the Panel had agreed with these points. In a non-randomised, single-arm, retrospective study with no comparator, these potential confounding factors could potentially bias the results of the study. The authors quite appropriately interpreted the findings with caution. Novo Nordisk therefore alleged that the claim 'insulin glargine substantially improved glycaemic control in children and adolescents with poorly controlled type 1 diabetes' was too dogmatic and not capable of being substantiated by Jackson *et al*.

Novo Nordisk also noted that other studies in children and adolescents did not support Aventis' claims. Murphy *et al* (2003) reported a prospective, randomised, cross-over study in 28 adolescent type 1 diabetics which showed no significant difference in HbA_{1c} levels between insulin glargine/lispro and NPH insulin/regular human insulin. With a more robust study design in the form of a prospective, randomised, cross-over study, the authors concluded that combination therapy with insulin glargine plus lispro was at least as effective as regular human insulin plus NPH insulin. Novo Nordisk alleged that this was quite different from 'substantially improved' as claimed by Aventis. Schober *et al* (2001) reported in a letter a prospective, randomised study of type 1 diabetics aged 5-16 (n=349). There was no difference between insulin glargine and NPH insulin in GHb (glycosylated haemoglobin). The authors concluded that insulin glargine provided glycaemic control that was at least as effective as NPH insulin in children and adolescents with type 1 diabetes. Novo Nordisk alleged that again this was a study with a more robust design which showed equivalence ('at least as effective') rather than 'substantially improved'.

In summary, Novo Nordisk noted that Aventis had taken a single-arm, uncontrolled, retrospective study to support its claim of 'Insulin glargine substantially improved glycaemic control in children and adolescents with poorly controlled type 1 diabetes' despite two randomised studies showing insulin glargine providing glycaemic control at least as good as NPH insulin. The claim at issue had not taken into account confounding factors, and had exaggerated the benefits of insulin glargine. Novo Nordisk supported the Panel's ruling that this was in breach of Clauses 7.2 and 7.4 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the claim in question 'Lantus helps poorly controlled children towards A_{1c} targets' was based solely on the results of Jackson *et al*, a single arm, uncontrolled, retrospective study. In the Appeal Board's view the design of the study was such that it would not produce conclusive results. The Appeal Board noted the authors' own comments on the study design and interpretation of the results. The Appeal Board further noted that in Jackson *et al* Lantus had been administered each day at lunchtime. The Lantus SPC, however, stated 'In children efficacy and safety of Lantus have only been demonstrated when given in the evening'.

The Appeal Board considered that the claim 'Lantus helps poorly controlled children towards AIC targets' implied an advantage for Lantus *per se*. It appeared, however, from Jackson *et al*, that the advantage might have been due to improved compliance rather than the medicine itself. In addition the Appeal Board noted its concerns regarding the robustness of the study design. No other data had been provided to substantiate the claim. The Appeal Board considered that the claim was misleading and could not be substantiated as alleged. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

2 Claims 'Superior glycaemic control from a simple once-daily injection' and 'Insulin glargine substantially improved glycaemic control in children and adolescents with poorly controlled type 1 diabetes'

COMPLAINT

Novo Nordisk alleged that these claims were hanging comparisons in breach of Clause 7.2 of the Code.

RESPONSE

Aventis agreed that, in isolation, the claims would be hanging comparisons, however both appeared on the page of the leavepiece detailing Jackson *et al*. Read in the context of the whole page it was clear on four separate occasions that this superior glycaemic control was seen in responders switching from NPH. There was also a concise explanation of the study design to the right of the bar chart which appeared on the same page. Aventis denied breaches of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel considered that neither claim made it clear with what Lantus was being compared. The claims appeared in emboldened print such that the reader's eye was drawn to them at the outset. Although reference to switching from NPH appeared on a bar chart, two bullet points beneath the bar chart and in the small-print describing the study design it was not immediately obvious to the reader at the outset with what Lantus was being compared. The Panel considered that both claims were hanging comparisons as alleged. Breaches of Clause 7.2 were ruled.

E Leavepiece (ref LAN3610803) 'Optimising control for your type 1 diabetes patients'

Page 4 of the leavepiece was headed 'Superior glycaemic control versus NPH' and featured a graph showing 8-point 24 hour self-monitored blood glucose levels. The graph was referenced to Ashwell *et al*. Beneath the graph was, *inter alia*, the claim '44% reduction in nocturnal hypoglycaemia'.

COMPLAINT

Novo Nordisk noted that the graph compared the 8-point glucose profiles of Lantus plus lispro with NPH

plus human insulin, however the suppressed zero exaggerated the difference between these two regimens. Novo Nordisk was disappointed that Aventis suggested that a graph comparing two products which used an axis with a suppressed zero could be agreed between companies to be scientifically acceptable. Novo Nordisk alleged a breach of Clause 7.8 of the Code. When such graphs were used in published data comparing, for example, intensive and conventional therapies using non-product specific regimens there might be an argument for using such a scale for clarity. However graphs like this, to compare specific marketed products and support product-related claims were in breach of the Code.

Novo Nordisk noted the claim for a 44% reduction in nocturnal hypoglycaemia also came from Ashwell *et al*. It was not clear from where and how 44% was derived. This was also selective use of the data, as Ashwell *et al* stated that the frequency of nocturnal hypoglycaemia was lower with the Lantus plus lispro regimen during months 2 to 4 and month 1 only, and this was a 32 weeks (8 months) study.

Novo Nordisk alleged that the title of the page 'Superior glycaemic control versus NPH' was misleading, as it implied that Lantus offered superior glycaemic control versus NPH, as in point C above. This study compared a regimen of Lantus plus lispro with NPH plus human insulin, and it was therefore not possible to draw any conclusions about Lantus compared to NPH as any observed difference could just as well be due to a difference between human insulin and insulin lispro. In fact, at the bottom of the same piece under the subtitle 'Study conclusions', it was stated that 'Compared to NPH + human insulin, the combination of Lantus + lispro offers … clinically significant improvement in glycaemic control', which was a correct claim for the Lantus plus lispro regimen.

Novo Nordisk alleged that the leavepiece was in breach of Clauses 7.2, 7.3, 7.4 and 7.8 of the Code.

RESPONSE

Aventis stated that the graph was reproduced in its entirety from the published abstract and had not been altered in anyway. The y axis was unlinked to the x axis, indicating that it did not start from zero.

The range of values for blood glucose in the field of diabetes research was well known and many graphs in peer-reviewed published studies were not depicted from a value of 0, either for mmol/l or mg/dl. Based on this, Aventis had invited Novo Nordisk to discuss and agree on what would be considered acceptable given that many instances would arise when papers would be quoted in each company's respective materials. It was Aventis who should be disappointed that Novo Nordisk had not taken up the offer to discuss such issues in the wider context.

Aventis noted that Novo Nordisk had included numerous graphs with suppressed zeros on its website which was accessible to health professionals. In fact, the y axes on these graphs were linked to the x axes and were therefore undoubtedly misleading.

With regard to the claim of a 44% reduction in the rate of nocturnal hypoglycaemia and the attribution of effectiveness, Aventis explained that firstly the comparative rate of nocturnal hypoglycaemia was made between each 16-week arm of study whilst the patient was on either one of the regimens before cross over. The abstract stated that over the 16 weeks during which the patient received Lantus plus lispro insulin compared to during which they received NPH plus human insulin, there was a 44% reduction in the rate of nocturnal hypoglycaemia. Aventis' use of the data was not selective but represented the way that the study was conducted and reported.

Aventis noted that the item was a bound leavepiece. It was clearly stated on page 2, both in the diagrammatic representation of the study and the text below, that the comparison was between Lantus plus lispro insulin and NPH plus human insulin. On page 3, both graphs clearly stated the two regimens and in addition, the heading to the bullet point referring to a 44% reduction in nocturnal hypoglycaemia also clearly stated the comparative arms.

Aventis disagreed that the title of the page 'Superior glycaemic control versus NPH' was misleading. In all of its promotional pieces, the company had endeavoured to make it clear if the study referred to a combination regimen and to provide a balanced view of the data. On this page the regimens compared were mentioned three times and the claim at the bottom of the page was clearly made in relation to the combination, not a claim for Lantus alone.

Aventis considered that it was clear to the educated reader that the claim at issue referred to the combination and did not represent a claim for Lantus alone, and that the items did not breach Clauses 7.2, 7.4 and 7.8 of the Code.

PANEL RULING

The Panel noted that, contrary to Aventis' submission, the graph at issue was not exactly as it had appeared in the poster from Ashwell *et al*. In the leavepiece the y axis ran from 9 to 15 and not from 6mmol/l to 15mmol/l as in the poster. In the leavepiece the line for NPH plus human insulin was continuous whereas on the poster it was not joined between the time points of post-breakfast and pre-lunch. Furthermore a p value of <0.018 in the leavepiece was given as p=0.018 in the original.

The Panel accepted that blood glucose should never reach zero but nonetheless considered that shortening the y axis such that it ran only from 9mmol/l to 15mmol/l exaggerated the difference between the two insulin regimens as alleged. A breach of Clause 7.8 was ruled.

With regard to the claim that compared to NPH plus human insulin, the combination of Lantus plus lispro offered a '44% reduction in nocturnal hypoglycaemia', the Panel noted that the referenced poster referred to a 44% reduction in the *rate* (emphasis added) of nocturnal hypoglycaemia episodes per month. The poster also stated that there was no difference in experience of total severe or nocturnal severe hypoglycaemia. The results of Ashwell *et al* had thus been incorrectly cited in the leavepiece. The Panel

considered that the claim was misleading in this regard. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

With regard to the title of the page 'Superior glycaemic control versus NPH', the Panel considered that its comments about the design of Ashwell *et al* at point C above applied here. A breach of Clause 7.2 was ruled. The claim could be substantiated by Rosetti *et al*. No breach of Clause 7.4 was ruled.

Complaint received **4 June 2004**

Case completed **12 November 2004**

CASE AUTH/1597/6/04

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Patient review services

A general practitioner complained about the promotion of Seretide (salmeterol/fluticasone), Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) by GlaxoSmithKline.

The complainant had recently received two letters from GlaxoSmithKline, each headed 'The New GP Contract'. One letter stated that demonstrating effective management of asthma could be worth £5,400 to a practice in 2004 and £8,640 in 2005 and that GlaxoSmithKline could help the reader to achieve the 72 points in the Quality Outcomes Framework allocated to asthma. The other letter dealt similarly with the management of Type 2 diabetes. At the foot of both letters was a proforma for the GP to complete to indicate the best time to call.

The complainant had telephoned the support line and was told that GlaxoSmithKline offered a service where an 'independent group' came into a practice and changed patients on Serevent (salmeterol) and Flixotide (fluticasone) to Seretide. The complainant stated that both Serevent and Flixotide would come off patent in the next few years and therefore GlaxoSmithKline had a commercial interest in switching patients to Seretide. The complainant believed that the service was a marketing exercise to maintain market share for GlaxoSmithKline. The complainant believed that GlaxoSmithKline was also involved in similar switches with Avandia and Avandamet.

GlaxoSmithKline's response indicated that it offered GP practices a number of services; the Panel decided to consider each separately.

The Panel noted that the Airways Integrated Management Service (AIMS) was introduced to health professionals by the AIMS representative. The AIMS detail aid bore prescribing information for, *inter alia*, Seretide and some pages bore the Seretide product logo. The detail aid referred to the Gaining Optimal Asthma Control (GOAL) study in which '44% of Seretide patients achieved total control'. One page, headed 'Say no to separate inhalers', featured a photograph which showed that a Serevent inhaler plus a Becotide 100 inhaler were equal to a Seretide inhaler. The Panel considered that the service was part of the promotion of Seretide and other GlaxoSmithKline products; it was not described as anything else in the material.

The detail aid explained how AIMS worked. Under a heading of 'What Next?' step 1 was given as 'Decide which of your patients or groups you want to convert to Seretide …'. Doctors were told that the transfer of patients could be done, free of charge, by a third party or by the practice staff sponsored at £15/hour for up to 15 hours. Page 6 of the detail aid stated that in a practice of 3 GPs and 4500 patients, the typical cost savings would be £9,789.

The service would thus benefit a practice in two ways, by saving it the expense of carrying out the switch itself and by saving it prescribing costs. The arrangements as described in the detail aid amounted to a pecuniary advantage given as an inducement to prescribe Seretide. The Panel thus ruled a breach of the Code. High standards had not been maintained and a breach of the Code was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions; this had been carried out by a third party on behalf of GlaxoSmithKline or by the practice. The Panel thus ruled no breach of the Code in that regard. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

With regard to the asthma patient review service (APRS), the Panel noted that respiratory care associates (RCAs) introduced the service to health professionals although introductory letters could be sent by the Seretide representative. The APRS detail aid did not refer to any medicines by brand or generic name; only medicine classes were mentioned ie corticosteroids or bronchodilators. The first few pages of the APRS detail aid were very similar to the first few pages of the AIMS detail aid. One page, headed 'You can achieve total control in almost half your patients', discussed the results of the GOAL study. A bar chart depicted 44% of patients on combination achieving total control in GOAL. The combination product was Seretide although this was not stated. The APRS leavepiece stated that the landmark GOAL study had redefined the aims of asthma management and established a new composite outcome measure of 'Total Control'. Total control was defined and it was stated that aiming for it should benefit all patients. At the foot of the leavepiece it was stated that Allen & Hanburys might be able to help practices review their asthma patients.

The Asthma Patient Review Programme Folder appeared to be for GP practices. It set out the patient review protocol including identification of inadequately controlled asthma patients. The therapy recommendation form stated that unless there was a clear therapeutic reason for change the following principles would apply: the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of the treatment regime where possible.

The asthma training manual for the agency nurses involved in delivering the APRS stated that the aims and objectives of the service were 'To provide an independent Nurse service to Primary and Secondary care in order to enhance and improve the quality of life and severity of disease for Patients with Asthma through improved Patient management, following the guidance of the BTS/SIGN Guidelines 2003'. There was general information on the anatomy, physiology and epidemiology of asthma together with information about asthma and daily life and a detailed discussion of all of the devices available for treatment. It was stated that the GP had prescribing responsibility and that GPs must authorize all recommendations. The agency nurses were told that at no time could they change prescription information on the computer or print any prescriptions off in support of their clinical recommendations. The need to have all documentation complete and signed was stressed.

Overall, the Panel considered that the APRS was not unacceptable; it would benefit the NHS and enhance patient care. Provision of the service was not linked to the prescription of any specific medicine. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breaches of the Code were ruled.

The Panel noted GlaxoSmithKline's submission that there were currently no switch programmes in operation for Avandia and Avandamet and that the diabetic patient review service (DPRS) was based on the same principles as the APRS. Provision of the service was not linked to the prescription of any medicine. The service would help to assess, evaluate and improve the care of Type 2 diabetics in a systematic way to enhance health and quality of life. Overall the Panel considered that the DPRS was not unacceptable; it would benefit the NHS and enhance patient care. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breaches of the Code were ruled.

A general practitioner complained about the promotion of Seretide (salmeterol/fluticasone), Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant had recently received two letters from GlaxoSmithKline, each headed 'The New GP Contract'. In the asthma letter it was stated that demonstrating effective management of asthma could be worth £5,400 to a practice in 2004 and £8,640 in 2005. It was further stated that GlaxoSmithKline could help the reader to achieve the 72 points in the Quality Outcomes Framework allocated to asthma. At the foot of the letter was a proforma for the GP to complete to indicate the best time to call. The letter, on GlaxoSmithKline paper, was from a named individual.

The diabetes letter was similar. It stated that effective management of Type 2 diabetes could be worth £7,425 in 2004 and £11,880 in 2005. It was further stated that GlaxoSmithKline could help the reader to achieve the 99 points in the Quality Outcomes Framework allocated to Type 2 diabetes. At the foot of the letter was a proforma for the GP to complete to indicate the best time to call. This letter was not from an individual; it was on GlaxoSmithKline headed paper.

The complainant had telephoned the support line for more information and was told that GlaxoSmithKline offered a service where an 'independent group' came into a practice and changed patients on Serevent (salmeterol) and Flixotide (fluticasone) to Seretide (a combination product).

The complainant stated that as both Serevent and Flixotide would come off patent in the next few years GlaxoSmithKline had a commercial interest in switching patients to Seretide. The complainant believed that the service was a marketing exercise to maintain market share for GlaxoSmithKline.

The complainant alleged that the activity was in breach of the Code and noted that in Case AUTH/1561/3/04 the Panel's ruling stated 'The difficulty [with switching] was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine ….. in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the [switch service] would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe [the medicine]. The Panel thus ruled a breach of Clause 18.1 of the Code'.

The complainant believed that GlaxoSmithKline was also involved in similar switches with Avandia and Avandamet.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 18.1 of the Code.

RESPONSE

GlaxoSmithKline stated that the mailings referred to the Asthma Patient Review Service (APRS) and the Diabetes Patient Review Service (DPRS), which were non-promotional patient audits delivered through an independent agency. The APRS was the subject of

Case AUTH/1515/9/03; the processes in this programme were reviewed by the Panel as part of that complaint. Although the conduct of the nurse concerned was in breach of the Code, the Panel made no ruling on the audit itself. GlaxoSmithKline stated that the DPRS service was based upon the same robust principles and processes as the APRS. The letters at issue invited the doctor to complete and return the tear-off portion, indicating a convenient time for the sender to call, should the doctor be interested in receiving more information on the audit initiatives.

The letters originated centrally from within GlaxoSmithKline, and were sent on behalf of the respiratory care associate (RCA). There was an important difference in the role of the RCA compared to that of a Seretide representative, in that the RCA role was non-promotional. The RCA provided educational, audit and structured care initiatives and did not provide any product information, nor any branded materials.

The support line number called by the complainant, and the only telephone number provided in the letter, was that of the Customer Contact Centre. The Customer Contact Centre would not have been aware of the details of these audit initiatives since they were non-promotional activities and therefore the call would have been transferred to the medical information department.

The medical information team was trained to understand fully the nature of any enquiry received. The medical information officer attempted to clarify the exact nature of the enquiry and was in the process of explaining this when the caller abruptly hung up. The medical information officer could not contact the caller with further information because the caller had not provided his details. As a result, GlaxoSmithKline considered that the caller might have misinterpreted the information provided and mistaken the non-promotional audit initiative for a promotional switch programme.

GlaxoSmithKline had one initiative that might be described as a switch programme; the Airways Integrated Management Service (AIMS). AIMS was designed to assist doctors transfer patients currently receiving both an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist bronchodilator (LABA) to a therapeutically equivalent combination formulation.

1 AIMS

AIMS in its present form grew out of a CFC Transition Service initiated in 2001 designed to support practices wishing to transfer controlled asthma patients to CFC-free inhalers in accordance with the Montreal Protocol of 1990. This was because patients receiving CFC-containing beclometasone dipropionate inhalers would ultimately have to be switched to a CFC-free formulation. The service was offered unconditionally, with no obligation for the practice to prescribe GlaxoSmithKline's products or see its representatives. Copies of the representatives' briefing document and questions and answers document relating to the CFC Transition Service were provided.

The current service was designed to assist doctors in the transfer of patients receiving both an ICS and a LABA to a therapeutically equivalent combination formulation: the example given in the AIMS literature was Seretide (salmeterol/fluticasone propionate). A number of potential benefits for both the patients and the practice were described in the AIMS literature these being:

- Simplified treatment using a single inhaler
- Improved control and compliance
- Cost savings: based on national GP database information, an average GP practice could save an estimated £9,789 per year. Patients paid one prescription charge and the NHS paid one dispensing fee
- CFC-free transition

The AIMS programme was promoted, but not delivered, by a team of 60 dedicated AIMS representatives. This was a promotional sales force.

Process

GlaxoSmithKline stated that the AIMS representative either called in person to make an appointment to see a GP or wrote a letter of introduction outlining AIMS with the offer to meet the doctor to more fully explain the programme.

The AIMS detail aid and summary leavepiece outlined the potential clinical and economic benefits of Seretide over a LABA and an ICS in separate inhalers.

Overview

1 The practice decided which patient types it wished to review, and authorized this decision.

2 Either a specialist independent IT company or practice staff (nurse, doctor, pharmacist or manager) searched for patients fulfilling selection criteria on the practice computer to produce a list. This process was authorized by the doctor(s).

3 The list was reviewed by the doctor(s), who then decided an appropriate course of action which might include a therapy change or an invitation to attend for an asthma review. This activity was solely agreed and authorized by the doctor(s). Patient information remained confidential and was retained within the practice.

4 The prescribing database was updated either by the IT company or practice staff.

5 For patients for whom a therapy change was made without asthma review, a letter of notification, customised by the doctor(s) was sent, together with a patient feedback card.

If the IT company was not required, remuneration of £15/hour, up to 15 hours was available to support the practice in the review process.

The AIMS documentation pack comprised the AIMS Authorization Form, the AIMS Application for Financial Support, AIMS Patient Sample Letters, information on the IT company and patient feedback cards. The pack was supplied to the practice by the AIMS representative, who took no further part in the review.

Implementation via Magister

1 Using the AIMS Authorization Form the GP authorized the file search to identify patients who might be suitable for a therapy transfer. The doctors chose the range of patients to be searched for. This required two GP signatories. A written undertaking to ensure transparency of communication within the practice was required. The facilitator from the IT company had to give a written undertaking of confidentiality. A medication list for the file search was determined, which also required written authorization by a GP.

2 The GP reviewed the list of patients generated by the search, and identified those whom he wished to review in person. The GP authorized the facilitator from the IT company to make the repeat medication changes on the prescribing database. The review and authorization were confirmed in writing by the GP.

3 Patients were informed of the planned change or invited to make an appointment for an asthma review via a letter from the practice. Sample letters were provided in the Patient Sample Letter pack, which might be customised by the practice, as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.

4 Final sign-off for completion of the AIMS programme was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures.

5 Once completed, the authorization form was returned to the IT company by the facilitator.

Implementation via practice staff

1 The AIMS Application for Financial Support was completed at the time of agreement to initiate the review.

2 The GP reviewed the list of patients generated by the search, identified those patients whom he wished to review in person, and nominated a member of the practice staff to complete repeat medication changes on the prescription database, according to written instructions.

3 Patients were informed of the planned change or invited to make an appointment for an asthma review via a letter from the practice. Sample letters were provided in the Patient Sample Letter pack, which might be customised by the practice, as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.

4 Final sign-off for completion of the AIMS programme was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures. Once the application for funding was completed, the application form was sent to or collected by the AIMS representative and the application for funding was processed by GlaxoSmithKline.

GlaxoSmithKline stated that the overarching theme to the AIMS programme was about potential benefit – to the patient in terms of treatment simplification by using a single inhaler allied to the likelihood of increased compliance; to the practice and NHS in terms of potential cost savings and to the environment by reducing CFC emissions. GPs were not obliged to transfer their patients onto a specific combination inhaler. Confidential data on file indicated that not all patients reviewed by the AIMS service had been transferred to Seretide.

GlaxoSmithKline refuted the allegation that either of the services discussed above offered a pecuniary advantage and an inducement to prescribe. All services required authorization by the GP at every stage who made the final decision of any therapy change. Financial support at £15/hour, up to a maximum of 15 hours ie £225, was provided to the practice as reimbursement of time spent in implementing the process. GlaxoSmithKline did not believe that this payment could be misconstrued as an inducement to prescribe. Furthermore, the services had the potential to significantly impact on patients' lives and as such were in the public interest.

GlaxoSmithKline believed that this complaint stemmed from a fundamental misunderstanding of the service that was being offered. The complainant had been offered an audit service, but having called GlaxoSmithKline for more information spoke to a member of staff who was not involved in the service delivery. Unfortunately the complainant did not allow the ensuing conversation to complete and GlaxoSmithKline did not have the complainant's details to provide clarification.

GlaxoSmithKline was confident that the services referred to above complied with the Code and all allegations of any breaches were refuted.

In response to a request for further information GlaxoSmithKline provided the following details.

2 Details of the Asthma Patient Review Service ('APRS') provided in relation to Case AUTH/1515/9/03

GlaxoSmithKline stated that the APRS was a non-promotional patient audit initiative delivered through either an independent agency or carried out by the practice. The review service was sponsored by GlaxoSmithKline as a service to medicine. It was arranged with participating practices through non-promotional GlaxoSmithKline personnel, namely the respiratory care associate (RCA) and subsequently delivered through either an independent agency or the practice.

GlaxoSmithKline commissioned the agency to provide qualified nurses to administer the patient review and required it to ensure that such nurses followed the operations manual throughout. Nurses were trained by the agency independently of GlaxoSmithKline. Both the RCAs and the nurses received appropriate training regarding the non-promotional nature of their role and the policies and procedures to be followed. Copies of the training materials were provided. Additional materials were provided to assist in clarification.

3 APRS vs AIMS

GlaxoSmithKline stated that the two services were not the same, specifically

- AIMS was outlined to the practice by representatives, whereas APRS was outlined by non-promotional RCAs
- Only in the APRS were anonymised data sent to the Asthma Research Unit and a quarterly report generated
- AIMS was not associated with achieving Quality Outcomes Framework targets for general practice, whereas the APRS could be.

APRS

GlaxoSmithKline stated that the APRS was a non-promotional patient audit initiative. It was introduced and arranged with participating practices via the RCA but delivered through either an independent agency or the practice. The service aimed to assist practices review their poorly controlled patients, as defined by the practice itself. The patients were reviewed by either the agency nurse or the practice nurse who, with the permission of the practice, checked various aspects of patient treatment and recommended changes to patient management as clinically appropriate. Signed consent from the practice was obtained at every step.

The intention of the audit was to improve patient care, and the service was offered to practices without any conditions regarding treatment choice, or product bias. Only the nurse had access to patient records, with the consent of the practice, and patient confidentiality was maintained. The nurses' remuneration was not linked to any sales figures or treatment changes. Neither the agency nurses nor the RCAs were involved with promotion or promotional materials.

Practices were introduced to the APRS either by an RCA calling in person to make an appointment, or by receiving a letter of introduction from either the RCA or the Seretide representative (an example was provided). The letter outlined how the APRS could help practices achieve Quality Outcomes Framework targets through review of their asthma patients. The letter invited the doctor to complete the tear-off portion, indicating a convenient time for the RCA to call (only the RCA; no other GlaxoSmithKline staff would call), if the practice was interested in receiving more information on the initiative. It was unfortunate that in this case the complainant did not follow up with the RCA, who would have been able to confirm the process for APRS, rather than calling someone else in GlaxoSmithKline to ask for details of a switch programme, which this was not.

The APRS process was as follows:

- The RCA and practice agreed criteria for the APRS to identify poorly controlled patients (as defined by the practice).
- A specialist independent IT company searched for patients fulfilling selection criteria on the practice computer to produce a list. If the practice elected to use the IT company this must be authorized by the practice. However, this process could be carried out by the practice itself should it so wish.
- Letters were sent to the patients, inviting them for review (example letters were provided).
- A pilot project was ongoing in selected practices whereby the list of patients with their contact numbers was given to a local ambulance service NHS Trust, which conducted telephone triage and booked appropriate patients into clinic for review (details were provided). In the remaining practices, this process was carried out by practice staff.
- Should the practice desire, data were forwarded to an independent academic research unit for analysis. At review by either the agency nurse or the practice nurse, patients were told that anonymised data relating to their asthma would be passed to an independent academic research unit and their consent was obtained.
- Data collected at review might be recorded electronically in readiness for forwarding to the Asthma Research Unit, should this be the practices' preferred option. The software was installed only with the practices' written consent. Otherwise, data were recorded in paper format in the Asthma Record Book.
- At the end of each month, data collected during the month were sent to the Asthma Research Unit.
- At the end of each quarter, the Asthma Research Unit generated a report for the practice.

4 Diabetes services

GlaxoSmithKline stated that there were currently no switch programmes in operation for Avandia and Avandamet.

The diabetes patient review service (DPRS) was a non-promotional audit initiative based upon the same robust principles and processes as the APRS (copies of the DPRS materials were provided).

PANEL RULING

The Panel decided to consider each service separately. The Panel did not dispute that changes in medication might significantly impact on patients' lives for many reasons. However all arrangements had to comply with the Code.

1 AIMS

The Panel noted that AIMS representative introduced the service to health professionals. AIMS was clearly linked to the promotion of Seretide. The AIMS detail aid (ref 20528422 SFL/DAP/04/11347/1 – FP/March 2004) used to describe the service to health professionals bore prescribing information for Seretide, Flixotide, Serevent, Becotide (beclometasone) and Becloforte (high dose beclometasone) on the back page. Pages 4, 5 and 6 each bore the Seretide product logo. The detail aid referred to the GOAL study in which '44% of Seretide patients achieved total control'. Page 5 of the detail aid was headed 'Say no

to separate inhalers' and featured a photograph which showed that a Serevent inhaler plus a Becotide 100 inhaler were equal to a Seretide inhaler. The detail aid explained how AIMS worked. Under a heading of 'What Next?' step 1 was given as 'Decide which of your patients or groups you want to convert to Seretide …'. Doctors were told that the transfer of patients could be done, free of charge, by Magister or by the practice staff sponsored at £15/hour for up to 15 hours. Page 6 of the detail aid stated that in a practice of 3 GPs and 4500 patients, the typical cost savings would be £9,789.

The Panel considered that the service was part of the promotion of Seretide and other GlaxoSmithKline products; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services.

The application for financial support (ref SFL/ATF/04/11967/120549613 – FP/March 2004) referred to rationalisation of long-acting ß$_2$ agonist and inhaled corticosteroid therapy. The suggested search included patients on salmeterol or formoterol (AstraZeneca or Novartis) plus inhaled corticosteroids marketed by Baker Norton, 3M, AstraZeneca, Trinity and Celltech as well as GlaxoSmithKline products.

Switching patients to Seretide might be a less expensive way of prescribing Serevent and Becotide. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard the Panel noted that the AIMS detail aid recommended using AIMS to switch patients to Seretide. The service was promoted by representatives. Although other materials were more general and did not refer to switching patients to Seretide the Panel nonetheless noted that Clause 18.1 of the Code stated that 'No gift, benefit in kind of pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. AIMS was introduced to GPs via the detail aid as a service to help them switch patients to Seretide and in doing so save on prescribing costs. The service would thus benefit a practice in two ways, by saving it the expense of carrying out the switch itself and by saving it prescribing costs. The arrangements as described in the detail aid amounted to a pecuniary advantage given as an inducement to prescribe Seretide. The Panel thus ruled a breach of Clause 18.1 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions; this had been carried out by a third party on behalf of GlaxoSmithKline or by the practice. The Panel thus ruled no breach of Clause 15.2. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a mark of particular censure.

During its consideration of this aspect the Panel noted that there did not appear to be up-to-date instructions to representatives. Copies of briefing documents for the CFC service were provided but these were dated 2001. No briefing material on AIMS had been provided.

2 APRS

The Panel noted that RCAs introduced the service to health professionals although introductory letters could be sent by the Seretide representative. The APRS detail aid (ref SFL/DAP/04/11902/1-FP/March 2004) did not refer to any medicines by brand or generic name; only medicine classes were mentioned ie corticosteroids or bronchodilators. The first few pages of the APRS detail aid were very similar to the first few pages of the AIMS detail aid. Page 5 was headed 'You can achieve total control in almost half your patients' and discussed the results of the GOAL study. A bar chart depicted 44% of patients on combination achieving total control in GOAL. The combination product was Seretide although this was not stated. The APRS leavepiece (ref SFL/LVP/04/11440/1) stated that a landmark study, the Gaining Optimal Asthma Control (GOAL) study had redefined the aims of asthma management and established a new composite outcome measure of 'Total Control'. Total control was defined and it was stated that aiming for it should benefit all patients. At the foot of the leavepiece it was stated that Allen & Hanburys might be able to help practices review their asthma patients.

The Asthma Patient Review Programme Folder appeared to be a folder for GP practices. It set out the patient review protocol including identification of a target group of asthma patients whose asthma was not well controlled. The therapy recommendation form stated that unless there was a clear therapeutic reason for change the following principles would apply: the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of the treatment regime where possible.

The asthma training manual for the agency nurses delivering the APRS described the aims and objectives of the service as 'To provide an independent Nurse service to Primary and Secondary care in order to enhance and improve the quality of life and severity of disease for Patients with Asthma through improved Patient management, following the guidance of the BTS/SIGN Guidelines 2003'. There was general information on the anatomy, physiology and epidemiology of asthma together with information about asthma and daily life and a detailed discussion of all of the devices available for treatment. In a section detailing the aims and objectives of the service it was stated that the GP had prescribing responsibility and that GPs must authorize all recommendations. The agency nurses were told that at no time could they change prescription information on the computer or print any

prescriptions off in support of their clinical recommendations. The need to have all documentation complete and signed was stressed.

Overall, the Panel considered that the APRS was not unacceptable in relation to the requirements of Clause 18.1; it would benefit the NHS and enhance patient care. Provision of the service was not linked to the prescription of any specific medicine. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clause 18.1 of the Code was ruled. The Panel also ruled no breach of Clauses 15.2, 9.1 and 2 of the Code.

3 DPRS

The Panel noted GlaxoSmithKline's submission that there were currently no switch programmes in operation for Avandia and Avandamet and that the DPRS was based on the same principles as the APRS. The only medicines to be mentioned by name in the DPRS Diabetes First key cards were ascarbose and metformin. Any other medicines were only referred to by class ie sulphonylureas and glitazones. The key cards did not link provision of the service to the prescription of any medicine. Key card 1 explained that the audit would help to assess, evaluate and improve the care of Type 2 diabetics in a systematic way to enhance health and quality of life. Overall the Panel considered that the DPRS was not unacceptable in relation to the requirements of Clause 18.1; it would benefit the NHS and enhance patient care. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clause 18.1 was ruled. The Panel also ruled no breach of Clauses 15.2, 9.1 and 2 of the Code.

Complaint received **17 June 2004**

Case completed **11 October 2004**

CASE AUTH/1604/7/04

VOLUNTARY ADMISSION BY TAKEDA

Hospitality for health professionals

Takeda advised the Authority and sought guidance about three corporate events at which it had provided hospitality to health professionals and others. The Director decided that the matters were sufficiently serious for them to be taken up as a formal complaint. This accorded with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

Takeda submitted that it had paid for health professionals to attend the Association of the British Pharmaceutical Industry (ABPI) annual dinner; hotel bills and travel costs had also been paid by Takeda. The company submitted that the dinner was a legitimate meeting for health professionals to attend and considered that it was in the interests of industry as a whole for some of them of be there. It was the forum for serious speeches on matters of major relevance to the pharmaceutical industry and to UK healthcare practice. The hospitality was secondary to the meeting and the costs were appropriate and not disproportionate to the occasion.

A second event involved health professionals and partners being given tickets to a London Symphony Orchestra (LSO) concert sponsored by Takeda, where there was also a short presentation on Takeda's corporate financial investment into a hospital. It was a corporate occasion sponsored by the Japanese parent company, to which many diverse guests were invited. It was not specifically aimed at health professionals. This meeting was hosted by global directors of Takeda; Takeda UK viewed it as an international event attended by senior managers.

Finally, the managing director of Takeda UK had invited a small number of guests including health professionals to two international rugby matches. The gathering did not constitute a meeting organised for health professionals and was not considered to be a promotional meeting. The person responsible understood that this was a corporate event and hence outwith the Code. The attendees were European and global opinion leaders; no sales personnel attended.

The Panel noted Takeda's submission that all three meetings were corporate events. The Code did not refer to corporate events *per se*. The Panel considered that corporate events were a legitimate activity for a pharmaceutical company to undertake. Whether a corporate event was covered by the Code would depend on the arrangements. In the Panel's view, in order to be exempt from the Code corporate events must not otherwise be meetings organised for health professionals or appropriate administrative staff, bearing in mind that meetings organised for such groups which were wholly or mainly of a social or sporting nature were unacceptable. Corporate events could include health professionals or administrative staff but must also include a significant proportion of other guests from a different background. Further, health professionals should be invited to attend such events as senior representatives of professional organisations, hospital trusts, primary care trusts (PCTs) etc, not as prescribers or persons who recommended medicines.

The Panel noted that 27 health professionals who were considered opinion leaders in their respective

fields, and invited in this capacity, attended the ABPI annual dinner as guests of Takeda. The Panel noted Takeda's submission that it was unable to disclose the identity of the guests.

The Panel noted that the ABPI annual dinner was not a meeting organised for health professionals *per se*. However each company that attended could invite guests of their choosing and in that sense the Panel considered that each company's involvement had to be judged on its own merits. The Panel noted that Takeda's involvement in the ABPI annual dinner was such that it had organised a meeting for health professionals. Almost all of the company's guests were health professionals. Further, given the information before it, the Panel was not satisfied that all of the health professionals had been invited in capacities other than prescribers or persons who recommended medicines.

The Panel noted that the event was a formal occasion. Details of the costs were provided, including accommodation costs for 21 of the guests.

The Panel noted that matters of importance to the pharmaceutical industry and providers of healthcare were discussed at the ABPI annual dinner. Much discussion took place before and after dinner. Predinner drinks were served. After dinner hospitality was provided by some pharmaceutical companies. The venue was a prestigious hotel and the level of hospitality was significant. There was a social element to the occasion.

The Panel considered that although the ABPI annual dinner was an important event and an opportunity for networking etc, it could not be described as having a clear educational content with hospitality secondary to the main purpose as required by the Code. The Panel considered that by inviting almost only health professionals, Takeda UK had in effect organised a meeting for health professionals. High standards had not been maintained. Breaches of the Code were ruled. The Panel noted there would be some professional benefit in attending the ABPI annual dinner. Taking all the circumstances into account the Panel decided that on balance there was no breach of Clause 2.

With regard to the LSO, the Panel noted that Takeda was one of its major sponsors and guests were invited to one of its concerts by different Takeda group companies; Takeda described it as a corporate event. Guests were invited to a private Takeda reception before the concert, again at the interval and to dinner afterwards. Neither the invitation nor a subsequent letter confirming the arrangements mentioned a short presentation on Takeda's corporate investment into a hospital which Takeda had referred to in its response. The approximate cost per head for the drinks/buffet was provided. Takeda UK had used its tickets to invite only health professionals and their partners. Eight professors and two consultant physicians attended, eight of whom came with their partners. No travel expenses were reimbursed. Takeda UK had effectively organised a meeting for doctors; the evening was purely a social event to which partners had been invited. High standards had not been maintained. Breaches of the Code were ruled. On balance the Panel decided that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry; a breach of Clause 2 of the Code was ruled.

In relation to the two international rugby matches, the Panel noted that seven health professionals had attended one and nine health professionals had attended the other. Takeda had thus organised meetings for health professionals which were wholly social and sporting events; the cost per head was £750 which the Panel considered was more than those attending would have paid for themselves. High standards had not been maintained. Breaches of the Code were ruled. The arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry; a breach of Clause 2 was ruled.

The Panel was concerned about the invitations and arrangements for the LSO concert and the rugby matches. Takeda had arranged meetings for health professionals which thus brought the arrangements within the scope of the Code. The meetings were of a wholly social and/or sporting nature with no professional benefit. Partners had been invited to the LSO concert and the level of hospitality provided at the rugby matches was excessive. These were serious matters. In accordance with Paragraph 8.2 of the Constitution and Procedure the Panel considered that the arrangements for the LSO concert and rugby matches were such that they warranted reporting Takeda to the Code of Practice Appeal Board.

The Appeal Board was extremely concerned about the arrangements for the events. There appeared to be a serious lack of understanding of the requirements of the Code; the impression created by taking doctors to rugby matches was totally unacceptable. The Appeal Board decided that, as set out in Paragraph 10.4 of the Constitution and Procedure, Takeda should be required to undergo an audit of its procedures relating to the Code with particular reference to its policies on meetings and hospitality. This would be carried out as soon as possible. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

Upon receipt of the audit report the Appeal Board noted that Takeda wished to continue to improve its systems on an ongoing basis. The Appeal Board noted that progress had been made. It was concerned about the arrangements at Takeda for sponsoring individuals to attend international meetings. It decided that the company should be re-audited in six months' time (July 2005) which would enable those undertaking the audit to look at the arrangements for such meetings. A report on the second audit would be sent to the Appeal Board in due course for it to decide whether to take any further action.

Takeda UK Limited advised the Authority and sought its guidance about three corporate events at which it had provided hospitality to health professionals and others. The Director decided that the matters were sufficiently serious for them to be taken up as a

formal complaint. This accorded with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The events at issue were the annual dinner of the Association of the British Pharmaceutical Industry (ABPI), a classical concert and two international rugby matches.

COMPLAINT

Firstly, Takeda submitted that the ABPI annual dinner was a legitimate meeting for health professionals to attend and considered that it was in the interests of industry as a whole for some health professionals to attend this event. It was the forum for serious speeches on matters of major relevance to the pharmaceutical industry and to UK healthcare practice. The hospitality was secondary to the meeting and the costs were appropriate and not disproportionate to the occasion.

Secondly, Takeda explained that some health professionals and partners were given tickets to a London Symphony Orchestra (LSO) concert sponsored by Takeda, where there was also a short general presentation on Takeda's corporate financial investment into a hospital. Takeda Chemical Industries, Japan, had been for a number of years, and still was one of the major sponsors of the LSO. As such Takeda UK was provided with a number of tickets for the event. It was a corporate occasion sponsored by the Japanese parent company, to which many diverse guests were invited. It was not in any way specifically aimed at health professionals. This meeting was hosted by global directors of Takeda and Takeda UK viewed it as an international event attended by senior managers of Takeda UK.

Finally, Takeda referred to the entertainment of a small number of guests including health professionals at international rugby matches on two occasions at the invitation of the managing director of Takeda UK. The gathering did not constitute a meeting organised for health professionals and was not considered to be a promotional meeting. It was the understanding of the person responsible that this was a corporate event and hence fell outside of the Code. The attendees were European and global opinion leaders; no sales personnel attended.

Takeda emphasized that it treated its responsibilities under the Code very seriously and had tried to seek guidance on the application of the Code in relation to these corporate events. However, Takeda considered that, for the reasons outlined above, the events might not amount to a breach of the Code and it was willing to make a voluntary admission only concerning the occurrence of the events.

When writing to Takeda to inform it that the matter was to be treated as a formal complaint and that a detailed response was thus required, the Director asked Takeda to respond in relation to the requirements of Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

In relation to hospitality provided at the ABPI annual dinner, Takeda explained that it took 27 health professionals and paid for the tickets, pre-dinner drinks and accommodation where required. In addition travel expenses were offered and 12 guests were reimbursed their travel costs.

The event was a legitimate meeting for health professionals to attend and Takeda considered that it was in the interests of the industry as a whole for some health professionals to attend this annual event, particularly since it was the forum for serious speeches on matters of major relevance to the pharmaceutical industry and to UK healthcare practice. Takeda considered that the hospitality was secondary to the meeting and the costs were appropriate and not disproportionate to the occasion. Takeda provided details of the costs incurred per head for tickets, travel and accommodation together with details of attending Takeda personnel and the professional status of the guests, who were described as opinion leaders in their field.

Takeda did not consider that Clause 2 applied to this event as it was not promotional in nature and there were no activities or materials associated with promotion. The guests were invited to attend a dinner where matters of interest to the industry and to healthcare providers generally were discussed. Takeda did not consider that this activity brought discredit to or reduced confidence in the pharmaceutical industry and suggested that attendance at the dinner would demonstrate the serious and committed nature of the industry to the health professions and providers.

Similarly Takeda considered that the activity recognised the professional nature of its guests and could not have caused offence. The event maintained the high standards of the industry. There were no promotional materials associated with this event.

In relation to Clause 19.1, Takeda considered that it was a legitimate meeting for health professionals to attend as it was of general interest to leading members of the profession for the reasons set out above. The hospitality was at an appropriate level commensurate with the nature of the occasion.

Takeda denied breaches of Clauses 2, 9.1 or 19.1 of the Code.

In relation to the LSO concert Takeda explained that its parent company was, and had been for a number of years, one of the major sponsors of the LSO. Many diverse guests were invited to attend the concert by different Takeda group companies. Takeda UK was provided with a number of tickets for the event and invited some health professionals and their partners to attend. There was a short general presentation on Takeda's corporate financial investment into a hospital. Takeda viewed this as a corporate event attended by senior managers of the company. Takeda provided details of the costs per person incurred in relation to drinks/buffet and the professional status of 10 guests, 8 of whom attended with their partners.

In respect of Clause 2, Takeda did not consider that this concert was a promotional meeting. The event did not refer to Takeda products and was international in nature, attended by guests from

diverse backgrounds. The event did not reduce confidence in or bring discredit to the industry. Takeda considered that the short general presentation on corporate financial investment into a hospital had enhanced the industry's reputation. Takeda therefore considered that this meeting was not in breach of Clause 2.

In respect of Clause 9.1 Takeda submitted that the meeting was not promotional, was of the highest standard and could not have caused any offence. There were no promotional materials associated with the event. Takeda did not consider this meeting to be in breach of Clause 9.1.

Because the meeting arose out of corporate sponsorship and because the event was attended by guests of various professional backgrounds and from different countries, Takeda had considered that the Code did not apply. After the event, clarification and guidance on this point in relation to Clause 19.1 had been sought from the Authority. If, however, it was considered by the Authority that the Code applied in this case, Takeda accepted that the health professionals and their wives should not have been invited as the event was mainly of a social nature and hospitality should not extend beyond members of the health professions.

In relation to health professionals entertained at international rugby matches Takeda explained that on two occasions its managing director paid for a small number of guests to attend a rugby match arranged by an external PR company. The gathering did not constitute a meeting organised for health professionals and was not considered to be a promotional meeting. It was the understanding of the person responsible that this was considered a corporate event and hence fell outside of the Code. European and global opinion leaders attended; no sales personnel were present.

In relation to Clause 2 of the Code, Takeda did not consider that the rugby matches were promotional or that the events brought discredit upon or reduced confidence in the pharmaceutical industry. Takeda therefore did not consider this to be a breach of Clause 2 of the Code.

Similarly, in respect of Clause 9.1 Takeda considered that the events were not promotional in nature and that high standards were maintained and that the activities were not likely to have caused offence. No promotional materials were used at the events. Takeda therefore believed these activities were not in breach of Clause 9.1 of the Code. With respect to Clause 19.1, Takeda accepted that this meeting was wholly of a sporting or social nature and accepted that it should not have taken place.

Takeda stated that the cost per head could not be confirmed at present as it had been bought as part of a package – ticket and luncheon only, no accommodation. Two Takeda personnel had attended on each occasion. At the first match there had been seven health professionals (three consultant physicians, one specialist register, one senior lecturer and two general practitioners). At the second match there had been nine health professionals (five professors of medicine, three consultant physicians and one research fellow).

Takeda explained that it had a procedure in place for approval of meetings arranged for health professionals in accordance with the Code. However, as the meetings referred to above were considered by the staff arranging them to be corporate events, which were not promotional in nature and not attended by sales representatives, the procedure was not followed on these occasions.

As a result of these events coming to light, a full review of all relevant internal procedures had been undertaken. Procedures had been revised and strengthened and in particular measures had been put in place to ensure that all meetings planned by any employee underwent an appropriate medico-legal review in order to ensure compliance with the Code. Takeda had also immediately put into place in-house refresher training on the Code for all health professional-facing staff, both in the field and in head office.

In response to a request for further information Takeda explained that it was unable to disclose the names of the guests invited to any of the events for data protection reasons in view of the restrictions upon such disclosures under the Data Protection Act.

In relation to the ABPI dinner, Takeda explained that most guests were speakers and members of advisory panels for many pharmaceutical companies due to their experience and knowledge. The cost per head was: ticket (£100) plus drinks (£20.50). Accommodation was paid for 21 out of the 27 guests and the cost was £210 per room. Hence the total cost for accommodation for all guests was £4,410. The guests were 27 health professionals all considered opinion leaders in their respective fields and invited in this capacity: 16 professors (diabetes, cardiology, vascular surgery, elderly care, clinical pharmacology), 7 consultant physicians (diabetes, elderly care, clinical pharmacology), 3 senior GPs and 1 research fellow.

In relation to the LSO concert Takeda explained that the invited guests were all based in the London area and were considered to be key opinion leaders in their respective fields. Ten health professionals attended and of these 8 attended with partners, some of whom were health professionals in their own right; 8 professors (cardiology, elderly care, cardiovascular disease, clinical pharmacology) and 2 consultant physicians (clinical pharmacology and cardiology). The extension of the invitation to partners who were not health professionals was a regrettable oversight. The dinner was served in the Barbican conservatory. No travel expenses were reimbursed.

In relation to the international rugby matches, the guests were all leading key opinion leaders in their respective areas. Again, many were well-respected as speakers and members of advisory panels for many pharmaceutical companies due to their experience and knowledge. Takeda's public relations company had developed a relationship with these and other experts so that they could seek their advice on a number of issues. They were selected as guests on the basis of their expertise within different therapy areas: five were professors and the remainder were experts within different areas. The cost per head was £750 and this included all drinks and food. Takeda did not

pay for any travel expenses or accommodation. A total of 16 health professionals attended the two events; at the first: 3 consultant physicians, 1 specialist registrar, 1 senior lecturer and 2 GPs; at the second: 5 professors of medicine, 3 consultant physicians and 1 research fellow.

PANEL RULING

The Panel noted that the provisions of Clause 19 of the Code applied to meetings organised for health professionals regardless of whether the meetings were promotional or not. 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. 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 costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind. Meetings organised for groups of doctors, other health professionals and/or administrative staff which were wholly or mainly of a social or sporting nature were unacceptable. The supplementary information also stated that the requirements of the Code did not apply to the provision of hospitality other than to those referred to in Clause 19.1. For example, a company could provide hospitality at a meeting of organic chemists. They were neither health professionals nor administrative staff.

The Panel noted Takeda's submission that all three meetings were corporate events. The Code did not refer to corporate events *per se*. The Panel considered that corporate events were a legitimate activity for a pharmaceutical company to undertake. They were part of normal business practice. Whether a corporate event was covered by the Code would depend on the arrangements. This was a difficult matter. In the Panel's view, in order to be exempt from the Code corporate events must not otherwise be meetings organised for health professionals or appropriate administrative staff, bearing in mind that meetings organised for such groups which were wholly or mainly of a social or sporting nature were unacceptable. Corporate events could include health professionals or administrative staff but must also include a significant proportion of other guests from a different background. Further, the capacity in which health professionals were invited to attend such events was an important factor. In the Panel's view inviting health professionals in their capacity as prescribers or persons who recommended medicines to a corporate event with no educational or scientific input would be in breach of the Code. Such health professionals might be invited to attend in relation to their roles such as senior representatives of professional organisations, hospital trusts, primary care trusts (PCTs), etc.

The Panel noted Takeda's submission that the ABPI annual dinner was a legitimate meeting for health professionals to attend: it was the forum for serious speeches on matters of major relevance to the pharmaceutical industry and to UK healthcare practice. The Panel noted that in their capacity as members of the Authority the Director, Secretary and Deputy Secretary of the Authority had attended the ABPI annual dinner. The Authority's guests included the independent members of the Code of Practice Appeal Board and others who acted as consultants. The Authority paid for its staff and guests to attend the ABPI annual dinner. The Panel noted that this was the first time a complaint had been received about the ABPI annual dinner.

The Panel noted that 27 health professionals attended as guests of Takeda; 16 professors, 7 consultant physicians, 3 senior GPs and 1 research fellow. Takeda had submitted that the guests were considered opinion leaders in their respective fields and were invited in this capacity. The Panel noted Takeda's submission that it was unable to disclose the identity of the guests. However, having attended the dinner as members of the Authority the Panel had before it the booklet for the ABPI annual dinner 2004 which, *inter alia*, listed the expected guests of each company, including Takeda and provided details of their names and professional affiliation. The booklet did not state the capacity in which the individuals had been invited. The Panel noted that although these details might not accurately reflect those who attended on the night, it nonetheless assumed that invitations to attend had been extended to each person listed. The booklet for the dinner listed 35 named health professionals as being the guests of Takeda. Two other named guests of Takeda were from a named organisation.

The Panel noted that the ABPI annual dinner was not a meeting organised for health professionals *per se*. However each company that attended could invite guests of their choosing and in that sense the Panel considered that each company's involvement had to be judged on its own merits. The Panel noted that Takeda's involvement in the ABPI annual dinner was such that it had organised a meeting for health professionals. Almost all of the company's guests were health professionals. Further, given the information before it, the Panel was not satisfied that all of the health professionals had been invited in capacities other than prescribers or persons who recommended medicines. Takeda had declined to provide detailed information on this point. The Panel considered that Takeda's arrangements came within the scope of the Code.

The Panel noted that the event was a formal occasion; the cost of each ticket was £100 plus drinks at £20.50. Accommodation was paid for 21 out of 27 guests at £210 per room; the total cost for each of these 21 guests was thus £330.50.

The Panel noted that matters of importance to the pharmaceutical industry and providers of healthcare were discussed at the ABPI annual dinner. The event was attended by senior figures in the pharmaceutical industry, the department of health, politicians and providers of healthcare. Speeches were given on relevant topics. Much discussion took place before and after dinner. Predinner drinks were served. After

dinner hospitality was provided by some pharmaceutical companies. The venue was a prestigious hotel and the level of hospitality was significant. There was a social element to the occasion.

The Panel considered that although the ABPI annual dinner was an important event and an opportunity for networking etc, it could not be described as having a clear educational content with hospitality secondary to the main purpose as required by Clause 19 of the Code. The Panel considered that by inviting almost only health professionals Takeda UK had in effect organised a meeting for health professionals. A breach of Clause 19.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted there would be some professional benefit in attending the ABPI annual dinner. Taking all the circumstances into account the Panel decided that on balance there was no breach of Clause 2.

The Panel noted that Takeda was one of the major sponsors of the LSO and guests were invited to one of its concerts by different Takeda group companies; Takeda described it as a corporate event. The Panel noted that the invitation dated 10 November 2003 was signed by the managing director. The concert began at 7.30pm. Guests were invited to a private Takeda reception before the concert and again at the interval; dinner afterwards was in the Barbican conservatory. Neither the invitation nor a subsequent letter confirming the arrangements mentioned a short presentation on Takeda's corporate investment into a hospital which Takeda had referred to in its response. The approximate cost per head for the drinks/buffet was £65. Takeda UK had used its tickets to invite only health professionals and their partners. Eight professors and two consultant physicians attended, eight of whom came with their partners. No travel expenses were reimbursed. Takeda UK had effectively organised a meeting for doctors; the evening was purely a social event to which partners had been invited. A breach of Clause 19.1 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled. On balance the Panel decided that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry; a breach of Clause 2 of the Code was ruled.

In relation to the international rugby matches, Takeda had considered these to be corporate events. The Panel noted that 3 consultant physicians, 1 specialist registrar, 1 senior lecturer and two GPs had attended the first match and 5 professors of medicine, 3 consultant physicians and 1 research fellow had attended the second. Takeda had thus organised meetings for health professionals which were wholly social and sporting events; the cost per head was £750 which the Panel considered was more than those attending would have paid for themselves. A breach of Clause 19.1 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled. The arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry; a breach of Clause 2 was ruled.

The Panel was concerned about the invitations and arrangements for the LSO concert and the rugby matches. Takeda had arranged meetings for health professionals which thus brought the arrangements within the scope of the Code. The meetings were of a wholly social and/or sporting nature with no professional benefit. Partners had been invited to the LSO concert and the level of hospitality provided at the rugby matches was excessive. These were serious matters. In accordance with Paragraph 8.2 of the Constitution and Procedure the Panel considered that the arrangements for the LSO concert and rugby matches were such that they warranted reporting Takeda to the Code of Practice Appeal Board for it to consider the matter in relation to the requirements of Paragraphs 10.3, 10.4 and 12.1 of the Constitution and Procedure.

After consideration by the Code of Practice Panel but before Takeda was informed of the outcome, Takeda stated that some of the information provided in its voluntary admission about the rugby matches was incorrect. Takeda had previously stated that the cost per head was £750 which included all drinks and food and that the company did not pay for any travel expenses or accommodation. Despite having confirmed with the PR agency which organised these events that this statement was accurate, it had come to Takeda's attention that it had made payments for travel and accommodation for a small number of guests who attended these events. The total cost not previously notified was around £3,400. Full details were provided and included payments for flights and a chauffeur service for some guests.

Takeda apologised for inadvertently providing inaccurate information and gave its assurance that this was an oversight; it had not intended to mislead or misrepresent the facts. The additional information now accurately reflected the hospitality provided at these events.

COMMENTS FROM TAKEDA

When returning the requisite undertaking and assurance, Takeda submitted that it regretted the activities that led to the Panel rulings but considered that the interpretation of the Code's guidance on these matters was not clear in certain instances. Takeda was committed to ensuring that such infringements did not recur.

At the consideration of the report to the Appeal Board, the Takeda representatives stated that the company deeply regretted the breaches. Takeda believed at the time that the events were outside the Code. The company had reviewed all relevant procedures and had re-educated its staff. It would be taking a fresh look at all its activities.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about the arrangements for the LSO concert and the rugby matches. There appeared to be a serious lack of understanding of the requirements of the Code; the impression created by taking doctors to rugby matches was totally unacceptable. The Appeal Board decided that, as set out in Paragraph 10.4 of the Constitution and Procedure, Takeda should be

required to undergo an audit of its procedures relating to the Code with particular reference to its policies on meetings and hospitality. This would be carried out as soon as possible. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Upon receipt of the audit report the Appeal Board noted that Takeda wished to continue to improve its systems on an ongoing basis. The Appeal Board noted that progress had been made. It was concerned about the arrangements at Takeda for sponsoring individuals to attend international meetings. It decided that the company should be re-audited in six months' time (July 2005) which would enable those undertaking the audit to look at the arrangements for such meetings. A report on the second audit would be sent to the Appeal Board in due course for it to decide whether to take any further action.

Proceedings commenced 6 July 2004

Undertaking received 15 October 2004

Proceedings completed 10 January 2005

CASE AUTH/1606/7/04 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER/DIRECTOR v WYETH

Alleged breach of undertaking

A general practitioner complained about a switch programme run by Wyeth. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The complainant stated that as a follow-up to a previous visit when he had expressed an interest in switching from Zoton capsules to Zoton FasTab, a Wyeth representative gave him literature which spelt out the cost savings which could be made. The representative then suggested that she could arrange for an independent company to do the switch. The complainant signed up for this and it was due to be done in July. Since then the complainant had noted a BMJ article which had discussed Case AUTH/1561/3/04 wherein breaches of the Code had been ruled in relation to a switch programme run by Wyeth. The complainant was concerned that to proceed with the switch might be a breach of the Code.

The Panel noted that Case AUTH/1561/3/04 had concerned arrangements for a switch service known as the Formulary Based Implementation (FBI) Service, whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab. The Panel had noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements had amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of the Code had been ruled.

The Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the present service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral proton pump inhibitor (PPI) of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel noted that representatives were instructed that all practices signed up under the withdrawn FBI service must be re-signed under the new service. The regional business managers had been told why the previous service was withdrawn and instructed the representatives in relation to the revised service. Representatives had to confirm that documentation in relation to the original service was returned to head office or destroyed locally.

The Panel noted Wyeth's submission that the complainant had requested a review of his PPI prescribing from Zoton to Zoton FasTab and had informed the representative at the outset that this prescribing decision had been agreed with the relevant PCT. The Panel also noted Wyeth's submission that the medication review spreadsheet was completed and signed before any service offerings were discussed.

The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel therefore ruled no breach of the Code.

A general practitioner complained about a switch programme run by Wyeth Pharmaceuticals. As the complaint involved an alleged breach of undertaking

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

The complaint referred to an article published in the BMJ, 26 June, which had discussed Case AUTH/1561/3/04 wherein breaches of the Code had been ruled in relation to a switch programme run by Wyeth.

COMPLAINT

The complainant stated that he was approached by a Wyeth representative on 2 July. This was a follow-up to an earlier visit when he had expressed an interest in the cost savings from switching from Zoton capsules to Zoton FasTab. He was given literature which spelt out the cost savings which could be made. The representative then suggested that she could arrange for an independent company to come in to do the switch. The complainant signed up for this and it was due to be done in July.

Since then the complainant's attention had been drawn to the article in the BMJ and he was concerned that to proceed with the switch might be a breach of the Code.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Wyeth submitted that it had fully complied with the undertaking given in the previous case, Case AUTH/1561/3/04. The Formulary Based Implementation Service (FBI) and all associated materials in respect of which the undertaking dated 7 June 2004 was given were withdrawn with immediate effect from the sales force by memorandum dated 2 June 2004. The service had not been offered nor materials used since that date. Wyeth provided a copy of a memorandum and associated forms of undertaking, all of which were completed in accordance with the procedure stated therein. The service offering to which this complaint related was part of the new service offering, as described below, which Wyeth subsequently designed and developed in order to avoid any such further breaches of the Code following Case AUTH/1561/3/04. Wyeth considered that this service offering and associated material was fully Code compliant and confirmed that the activity carried out by the named Wyeth representative was fully in accordance with Code, compliant with company procedures with respect to this service offering and associated material.

Wyeth's service range in the gastrointestinal therapy area had been redesigned and developed, and the new range launched, so that all such services offered were non-brand specific and therefore could be offered and performed in respect of any relevant brand of medication (ie proprietary or generic) of the GP's choice. Further, the new material and the material use sequence now made it clear that the GP's prescribing decision had been made in writing in advance of any offer of a service to assist in implementing that decision being made by Wyeth. The Wyeth service offering now clearly fell under the provisions of Clause 18.1 of the Code and its supplementary information which allowed the provision of medical and education services which would enhance patient care or benefit the NHS if they were provided in such a way as to not be an inducement to prescribe any medicine.

Wyeth confirmed that the representatives visit and all subsequent actions were carried out in accordance with the company's procedures, and with all material provided to the sales force by the company in respect of this service offering. The procedure was as follows:

1 The GP expressed an interest in a review of their or their practice's proton pump inhibitor (PPI) prescribing.

2 In a visit separate to any product-related visit, or in a clearly separated part of the same visit, and following confirmation from the GP that they had an interest in a review of their or their practice's PPI prescribing, the representative followed the procedure as set out in the representatives' briefing document 'Action Plan: GastroCare Service Offerings' (ref: ZZOT3580), the relevant pages of which were provided. Briefly, the GP completed and signed the medication review spreadsheet to illustrate the prescribing decision s/he had made or was making and wanted to implement. If the only medication change the GP wished to make, as shown by the completed medication review spreadsheet, was that of changing prescribing from one formulation of the same PPI to another in a dose for dose switch, then in order to assist the GP in implementing that prescribing decision the representative offered the service most appropriate to that type of change, in this case the GP Systems Specialist Implementation (GPSSI) Service, using the GPSSI pack (ref ZZOT3588) to show the GP how the service would be carried out. If the GP decided to accept the service offering, the practice booking and consent form was completed by the GP and arrangements then made by the Wyeth representative with an external supplier to carry out the service at the practice.

Wyeth noted that the complainant had stated that he had previously expressed an interest in a review of his PPI prescribing specifically from Zoton to Zoton FasTab. On making a follow-up visit the named representative was informed by the GP from the start that he wished to carry out such a review and that this prescribing decision had already been agreed with the relevant primary care trust. Discussions about cost savings were held prior to any discussions about completion of the medication review spreadsheet and therefore prior to any discussions about available service offerings.

Notwithstanding that the GP had made his previously agreed prescribing decision known to the named representative at the start of the visit, the representative continued to follow the procedure and asked the GP to complete the Medication Review Spreadsheet thereby giving the GP the opportunity to

instead request a review of his or his practice's PPI prescribing from and to any PPI. On this occasion the GP chose a Zoton to Zoton FasTab dose for dose switch as illustrated by the medication review spreadsheet that he completed and signed before any service offerings were discussed or any particular service offering made. The service appropriate to that review choice (and indeed for any change of prescribing from one formulation of the same PPI to another in a dose for dose switch) was then offered by the named representative and accepted by the GP, as illustrated by the booking and consent form for the GPSSI service completed and signed by the complainant.

Based on the above, Wyeth did not consider that any activity or materials associated with promotion had brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore there was no breach of Clause 2 of the Code. High standards were maintained at all times both by the representative and by the content and use of all material associated with the relevant service offering and therefore there had been no breach of Clause 9.1. Wyeth had ensured that it had complied with all aspects of the undertaking given in respect of Case AUTH/1561/3/04 and hence there had been no breach of Clause 22 of the Code.

In response to a request for further information Wyeth explained that the regional business managers (RBMs) were given a presentation as part of a workshop at their quarterly management meeting held on 9 June 2004. The presentation included a section on the outcome of Case AUTH/1561/3/04 and a description of the new revised service offering, plus a clear reminder regarding the product and service separation aspect; a copy of the relevant part of this presentation (ref ZZOT3589) and a GastroCare Process Flowchart (ref ZZOT3601) were provided. The RBMs then cascaded the information presented to them and provided the flowcharts to the representatives as part of their regional meetings. The representatives were also provided with the Action Plan (ref ZZOT3580) as previously submitted. Wyeth explained that the fieldforce was advised that all services signed up under the withdrawn FBI Service documentation must be re-signed using the new GPSSI Service documentation and procedure. As the withdrawn FBI Service would take no more than a day to complete depending on patient list size, the situation where a service had been started but not completed would not arise.

Wyeth drew attention to the relevant page from the RBM presentation relating to product and service separation and noted that the Flowchart began with an instruction for the sales representative to close the product call before commencing any discussion relating to service. Although the importance of product and service separation was known and understood by the field force, these points were verbally reinforced by the RBMs when cascading this information to the representatives.

In relation to the product-related part of the visit, the detail aid (ref ZZOT3462a) used by the representative in question during the first visit to the complainant had been withdrawn from use due to price changes and therefore no original materials were available, however, colour pdfs of the original detail aids were provided. The only product-related material used by the sales representative was during the product part of the second visit to the complainant and this related to cost (ref ZZOT3543).

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the FBI service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard, the Panel noted that the switch programme at issue involved two products marketed by the same company; prescriptions for Zoton FasTab were not being generated at the expense of another company's product. Nonetheless, Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. Thus in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements had amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of Clauses 9.1 and 18.1 had been ruled.

The Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the present service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral PPI of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet (ref ZZOT3587) explained that the Gastrocare service was available to review any oral PPI dose at the

request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel noted that representatives were instructed that all practices signed up under the withdrawn FBI service must be re-signed under the new service. The regional business managers had been told why the previous service was withdrawn and instructed the representatives in relation to the revised service. Representatives had to confirm that documentation in relation to the original service was returned to head office or destroyed locally.

The Panel noted Wyeth's submission that the complainant had requested a review of his PPI prescribing from Zoton to Zoton FasTab and had informed the representative at the outset that this prescribing decision had been agreed with the relevant PCT. The Panel also noted Wyeth's submission that the medication review spreadsheet was completed and signed before any service offerings were discussed.

The booklet GP Systems Specialist Implementation Pack (ref ZZOT3585) explained the role of the GP Systems Specialist in relation to the implementation of the GP prescribing requests as set out in the medication review spreadsheet. Wyeth submitted that this was the procedure to be implemented in the complainant's practice. No details were provided about the alternative service, the Gastrocare audit review. The Panel noted, however, that it was not the subject of complaint.

The Panel considered the arrangements only in relation to the alleged breach of undertaking. It did not consider the arrangements in relation to the requirements of Clause 18.1; it had no complaint in that regard. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel therefore ruled no breach of Clause 22. It thus followed there was no breach of Clauses 9.1 or 2.

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During its consideration of this case the Panel was concerned about the arrangements for the implementation of the revised service in relation to the requirements of Clause 18.1. The Panel noted that it had no complaint before it in this regard. The Panel was particularly concerned about the role of the representative and the representative's briefing instructions.

The Panel noted the supplementary information to Clause 18.1 Provision of Medical and Educational Goods and Services, Section 1(ii), stated that 'If medical/generic representatives provide, deliver or demonstrate medical and educational goods and services then this must not be linked in any way to the promotion of products'. The Panel noted that the presentation to regional business managers advised representatives to promote Gastrocare in full in the same call as Zoton FasTab provided … 'Zoton FasTab has been fully & effectively sold with the approved closing statements for product use and change' and 'No product promotion takes place during GastroCare Service promotion/discussion'.

The Gastrocare Process Flow Chart instructed representatives during the Zoton FasTab part of the call to ask '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton'? Representatives were then to explain that Wyeth provided a single Gastrocare service to achieve such medication review objectives. The representative would then introduce the service referring to the medication review table which showed the various PPI options. Health professionals were to indicate which ones they wanted to implement. The representative could then talk about the appropriate methods since the method of implementation differed depending on the PPI prescribing decision. Following this the doctor was to complete and sign the medication review.

The Panel noted that in its submission Wyeth stated that the prescribing decision of the GP was made in writing in advance of the offer of the service to assist in implementing the decision. It was unclear how this would work in practice; GPs would surely not complete the company's medication review form other than in relation to the provision of a service. Wyeth's submission on this point was also inconsistent with the Gastrocare Process Flow chart. The Panel queried whether the role of the representative in the provision of the service met the requirements of the supplementary information to Clause 18.1. The representative promoted Zoton FasTab and the service was introduced, according to the Flow chart, after the representative had promoted a switch from lansoprazole capsules to Zoton FasTab. The Panel was concerned that the role of the representative in relation to the service was linked to the promotion of Zoton FasTab and this would be the impression given to GPs. The Panel decided to take up its concerns as a separate complaint with Wyeth. This was in accordance with Paragraph 17.1 of the Constitution and Procedure (Case AUTH/1652/11/04).

Complaint received **7 July 2004**

Case completed **1 November 2004**

CASE AUTH/1607/7/04

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Airways Integrated Management Service

A general practitioner complained about the Airways Integrated Management Service (AIMS) sponsored by Allen & Hanburys, which was part of GlaxoSmithKline. The complainant had been approached by an Allen & Hanburys representative about switching patients from inhaled steroid and salmeterol to Seretide [salmeterol/fluticasone]. The practice would have the staff time funded by Allen & Hanburys to do this work. The complainant had not agreed to this but wondered if it was a breach of the Code. A copy of a letter from the representative to the complainant was provided.

The Panel noted that the AIMS programme had already been considered in Case AUTH/1597/6/04. The arrangements as described in a detail aid had been considered to amount to a pecuniary advantage given as an inducement to prescribe Seretide and a breach of the Code had been ruled. A further breach had been ruled because high standards had not been maintained. A ruling of a breach of Clause 2 had not been considered to be warranted.

The Panel considered that the ruling in Case AUTH/1597/6/04 regarding a pecuniary advantage given as an inducement to prescribe Seretide applied also in the present case and a breach of the Code was ruled. A breach was also ruled because the arrangements failed to recognise the special nature of medicines. A ruling of a breach of Clause 2 was not considered to be warranted.

A general practitioner complained about the Airways Integrated Management Service (AIMS) sponsored by Allen & Hanburys, which was part of GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant had been approached by an Allen & Hanburys representative about switching patients from inhaled steroid and salmeterol to Seretide [salmeterol/fluticasone]. The practice would have the staff time funded by Allen & Hanburys to do this work. The complainant had not agreed to this but wondered if it was a breach of the Code. A copy of a letter from the representative to the complainant was provided.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 9.2 and 18.1 of the Code.

RESPONSE

GlaxoSmithKline stated that it was unclear whether the complainant was concerned about the AIMS itself, the financial support available, or both. It was also unclear as to whether the complainant had not agreed to proceed with the AIMS programme, or had not agreed to financial support in implementing the programme, or both.

The AIMS was designed to assist doctors transfer patients receiving both inhaled corticosteroid (ICS) and inhaled long acting beta$_2$-agonist bronchodilator (LABA) to a therapeutically equivalent combination: the example given in the AIMS literature was Seretide. The AIMS programme was promoted, but not delivered, by a team of dedicated AIMS representatives. This was a promotional sales force.

The AIMS programme proceeded as follows:

- The practice decided which patient types it wished to review, and authorized this decision.
- Either a specialist independent IT company or practice staff (nurse, doctor, pharmacist or manager) searched for patients fulfilling selection criteria on the practice computer to produce a list. This process was authorized by two doctors in the practice.
- This list was reviewed by the doctors, who then decided an appropriate course of action. This might include a therapy change or an invitation to attend for an asthma review. This activity was solely agreed and authorized by the doctors, and it was the doctors' decision as to whether a therapy change was warranted, and if so, to what. Patient information remained confidential and was retained within the practice.
- The prescribing database was updated either by the IT company or practice staff.
- For those patients for whom a therapy change was made without asthma review, a letter of notification, customised by the doctors, was sent, along with a patient feedback card.
- If the IT company was not required, remuneration of £15/hour, up to 15 hours was available to support the practice in this review process.

If the practice decided to proceed with the AIMS programme a pack comprising the AIMS Authorisation Form, the AIMS Application for Financial Support Form, the AIMS Patient Sample Letters, information on the IT company and Patient Feedback cards, was supplied by the AIMS representative, who took no further part in the review.

GlaxoSmithKline stated that the overarching theme to the AIMS programme was about potential benefit – to the patient in terms of treatment simplification by using a single inhaler allied to the likelihood of increased compliance, to the practice and NHS in terms of potential cost savings and to the environment by reducing CFC emissions in accordance with the Montreal Protocol of 1990. Doctors were not obliged to transfer patients onto a specific combination inhaler. Confidential data on file indicated that not all patients reviewed by the AIMS had been transferred to Seretide.

The complainant was concerned that the AIMS programme offered a pecuniary advantage and was

therefore an inducement to prescribe, in breach of the Code. GlaxoSmithKline refuted the suggestion that any of the services at issue were in breach of the Code. All services required full authorization by the GP, at every stage, and it was the GP who finally decided any therapy change. Financial support of £15/hour, up to a maximum of 15 hours ie £225, was given to the practice as reimbursement of time spent in implementing the process. GlaxoSmithKline did not consider that this payment could be misconstrued as an inducement to prescribe; its provision was in keeping with the requirements of the Code and in accordance with the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. Furthermore, the AIMS programme and similar review services potentially had a significant impact on patients' lives and as such GlaxoSmithKline considered that they were in the public's interest. In GlaxoSmithKline's opinion all materials and activities relating to this case recognised the special nature of medicines and the professional nature of the audience to which they were directed, and were not likely to cause offence. GlaxoSmithKline firmly considered that neither the AIMS programme, nor the provision of financial support contained therein, were in breach of Clauses 2, 9.2 and 18.1 of the Code.

GlaxoSmithKline noted that the complainant stated that he had been approached by an Allen & Hanburys' representative about switching patients from inhaled steroid and salmeterol to Seretide and that the practice would have staff time funded by Allen & Hanburys to do this work. The complainant had further stated that he had not agreed to this. However the opening paragraph of the letter from the representative to the complainant stated 'Thank you for meeting with me and agreeing to proceed with the Allen & Hanburys Airways Integrated Management Service – AIMS'. 'Agreeing to proceed' was at odds with the complaint. It was difficult to identify when this particular letter might have been sent since the copy provided by the Authority had been anonymised, and was not dated. However, investigation of the GlaxoSmithKline databases for customer mailings and representative contacts in the preceding three months indicated that two post-call letters confirming agreement to proceed with a practice-led AIMS programme had been sent. In both cases a copy of the AIMS Application for Financial Support form had been supplied.

GlaxoSmithKline stated that if a practice did not agree to proceed with an AIMS event then the representative would not send an 'Agreed to Proceed' letter. If a practice was interested in the service but needed additional information or further time to consider the AIMS service then the representative would send an alternative 'AIMS Process' letter (copy provided).

GlaxoSmithKline submitted that the representative in question was appropriately trained, experienced and registered in accordance with GlaxoSmithKline and Code requirements and that his interactions with customers were in accordance with GlaxoSmithKline and Code approved processes and procedures.

GlaxoSmithKline stated that, in conclusion, it was confident that all the services referred to complied with the Code and refuted all allegations of any breaches of Clauses 2, 9.2 and 18.1. It firmly believed that both the theme and content of the AIMS programme, and the conduct of the representative fully complied with the letter and spirit of the Code. GlaxoSmithKline did not know how any misunderstanding might have occurred, but hoped that the information provided herein would serve to inform any future discussions the Authority had with the complainant on this matter.

PANEL RULING

The Panel noted that the AIMS programme had been considered in Case AUTH/1597/6/04 as follows:

Case AUTH/1597/6/04

The Panel had noted that the AIMS representative introduced the service to health professionals. AIMS was clearly linked to the promotion of Seretide. The AIMS detail aid (ref 20528422 SFL/DAP/04/11347/1 – FP/March 2004) used to describe the service to health professionals bore prescribing information for Seretide, Flixotide, Serevent, Becotide (beclometasone) and Becloforte (high dose beclometasone) on the back page. Pages 4, 5 and 6 each bore the Seretide product logo. The detail aid referred to the GOAL study in which '44% of Seretide patients achieved total control'. Page 5 of the detail aid was headed 'Say no to separate inhalers' and featured a photograph which showed that a Serevent inhaler plus a Becotide 100 inhaler were equal to a Seretide inhaler. The detail aid explained how AIMS worked. Under a heading of 'What Next?' step 1 was given as 'Decide which of your patients or groups you want to convert to Seretide …'. Doctors were told that the transfer of patients could be done, free of charge, by Magister or by the practice staff sponsored at £15/hour for up to 15 hours. Page 6 of the detail aid stated that in a practice of 3 GPs and 4500 patients, the typical cost savings would be £9,789.

The Panel had considered that the service was part of the promotion of Seretide and other GlaxoSmithKline products; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services.

The application for financial support (ref SFL/ATF/04/11967/120549613 – FP/March 2004) referred to rationalisation of long-acting beta$_2$-agonist and inhaled corticosteroid therapy. The suggested search included patients on salmeterol or formoterol (AstraZeneca or Novartis) plus inhaled corticosteroids marketed by Baker Norton, 3M, AstraZeneca, Trinity and Celltech as well as GlaxoSmithKline products.

Switching patients to Seretide might be a less expensive way of prescribing Serevent and Becotide. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a

specific medicine. In this regard the Panel noted that the AIMS detail aid recommended using AIMS to switch patients to Seretide. The service was promoted by representatives. Although other materials were more general and did not refer to switching patients to Seretide the Panel nonetheless noted that Clause 18.1 of the Code stated that 'No gift, benefit in kind of pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. AIMS was introduced to GPs via the detail aid as a service to help them switch patients to Seretide and in doing so save on prescribing costs. The service would thus benefit a practice in two ways, by saving it the expense of carrying out the switch itself and by saving it prescribing costs. The arrangements as described in the detail aid amounted to a pecuniary advantage given as an inducement to prescribe Seretide. The Panel had thus ruled a breach of Clause 18.1 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions; this had been carried out by a third party on behalf of GlaxoSmithKline or by the practice. The Panel had thus ruled no breach of Clause 15.2. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a mark of particular censure.

During its consideration of this aspect the Panel noted that there did not appear to be up-to-date instructions to representatives. No briefing material on AIMS had been provided.

The Panel noted that GlaxoSmithKline had provided the requisite undertaking and assurance with regard to the implementation of the service. The complainant had not appealed the Panel's rulings of no breach of Clauses 15.2 and 2 of the Code.

Case AUTH/1607/7/04

The Panel noted its rulings in Case AUTH/1597/6/04 of breaches of Clauses 18.1 and 9.1 of the Code. The Panel noted that in the present case, Case AUTH/1607/7/04, the AIMS programme had been considered in relation to the requirements of Clause 9.2 rather than Clause 9.1 of the Code. Clause 9.1 related to high standards and Clause 9.2 required, *inter alia*, all material and activities to recognize the special nature of medicines and the professional nature of the audience. The Panel considered that its ruling of a breach of Clause 18.1 in Case AUTH/1597/6/04 applied to the present case; a breach of Clause 18.1 was ruled. The Panel considered that the arrangements failed to recognize the special nature of medicines; a breach of Clause 9.2 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a mark of particular censure.

The Panel noted GlaxoSmithKline's submission that it had identified two post-call letters confirming agreement to proceed with a practice-led AIMS programme. No specific documentation to support its submission was provided. The Panel noted that it could contact the complainant and ask for comments on the discrepancy. The Panel considered that in the circumstances ie that GlaxoSmithKline had already accepted rulings of breaches of Clauses 18.1 and 9.1 of the Code in Case AUTH/1597/6/04, there was little merit in establishing whether the complainant had agreed to proceed with a practice-led AIMS.

Complaint received **12 July 2004**

Case completed **15 November 2004**

CASE AUTH/1608/7/04

ROCHE v NOVARTIS

Promotion of Zometa

Roche complained about the promotion of Zometa (zoledronic acid) by Novartis. Zometa was presented as a concentrate for solution for infusion and licensed for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. It could also be used to treat tumour-induced hypercalcaemia. Roche supplied Bondronat (ibandronic acid) tablets for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. Bondronat was also available as a concentrate for intravenous administration. Bondronat IV had the same indications as Bondronat tablets and in addition was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. Both Zometa and Bondronat belonged to a class of medicines known as bisphosphonates.

There were four items at issue: a detail aid, a prostate cancer leavepiece, a breast cancer leavepiece and a multiple myeloma leavepiece.

Roche noted that page 3 of the detail aid included a table of data in which ibandronic acid was incorrectly cited as ibandronate. This was both inaccurate and misleading. A further allegation was that the correct generic name was not mentioned.

The Panel noted that although ibandronic acid was the term used in the Bondronat summary of product characteristics (SPC), the product was also referred to as ibandronate both in published papers and by Roche itself. The Panel did not consider that reference to ibandronate was either misleading or inaccurate as alleged. No breach of the Code was ruled.

The Panel considered that although the chart referred to ibandronate, regardless of what was stated in the Bondronat SPC Novartis could not be accused of promoting it. No breach of the Code was ruled in this regard.

Roche noted the claim 'The potential for poor compliance (and associated treatment failure) is high, with up to 30% of patients failing to follow the schedule correctly' appeared below the table of data referred to above. The table compared the relative potency, infusion time, availability and administration of Zometa, pamidronate, oral clodronate and oral ibandronate. The cited references failed to include any data for ibandronate. It was alleged that there was a breach of the Code in relation to the requirement to provide substantiation upon request.

The Panel noted that Roche had only quoted the second half of the claim. When read in context with the first half it was clear that the strict dosing schedule of oral bisphosphonates was not followed correctly by up to 30% of patients. The Panel considered that the claim 'the potential for poor compliance (and associated treatment failure) is high' would be applicable to any bisphosphonate with a strict dosing schedule.

The Panel noted that Bondronat tablets had to be taken after an overnight fast of at least 6 hours and at least 30 minutes before the first food of the morning. The Panel considered that the dosing schedule was such that some patients might fail to follow it. Although the cited reference did not mention ibandronate *per se* it was nonetheless a bisphosphonate with a strict dosing regimen. The Panel did not consider that the claim was misleading as alleged or that it disparaged Bondronat. No breach of the Code was ruled.

The Panel noted that there was no indication that data to substantiate the claim at issue had been requested or that such a request had not been complied with. No breach of the Code was ruled.

Roche noted that the claim 'Zometa – now even faster and easier to prepare …' appeared as the heading on page 13 of the detail aid and on the first inside flap of each leavepiece. Below the heading practical details were given as to the administration of Zometa.

Roche alleged that the claim was a hanging comparison. There was insufficient explanation, unlike the front page.

The Panel noted that the front covers of all of the materials in question featured the headline 'A New Solution'. Each cover also featured a photograph of a vial of Zometa together with the statement 'Zometa … is now in solution making it even faster and easier to prepare as no reconstitution is needed'. The Panel considered that it was clear that the detail aid and leavepieces were, *inter alia*, introducing the reader to the new formulation of Zometa.

The Panel noted that Roche had not quoted the whole of the claim at issue. In full, it read, 'Zometa – now even faster and easier to prepare, no reconstitution needed'. The inclusion of the word 'now' implied a comparison with the new formulation's predecessor. The Panel did not consider, given the context in which it appeared, that the claim was a hanging comparison. It was clear that the comparison was with the old formulation of Zometa. No breach of the Code was ruled.

Roche noted the claim 'a distinct advantage of zoledronic acid [Zometa] is the shorter infusion time of 15 minutes' appeared at the bottom of each of the pages at issue above. The claim was referenced to Joshua *et al* (2002). Roche alleged that the claim was a hanging comparison.

The Panel noted that Joshua *et al* was an assessment of patient preferences for IV Zometa or IV pamidronate. The authors had stated, as quoted in the detail aid and leavepieces, that 'A distinct advantage of zoledronic acid [Zometa] is the shorter infusion time of 15 minutes'. In the context in which it appeared in Joshua *et al* it was thus obvious that the statement was a comparison of

Zometa with pamidronate. The Panel considered, however, that, in the context of the material at issue, the statement as a claim for Zometa was a hanging comparison. There was an implied comparison with another medicine although which one was not stated. A breach of the Code was ruled.

Roche alleged that the claim 'The only bisphosphonate which can be given as a 15 minute infusion …', which appeared on the front covers of each piece of promotional material, was incorrect. Bondronat had been used as a 15 minute infusion in trials and trialists would find this claim confusing. Published data for the Bondronat 15 minute infusion was now available. Roche suggested that the claim was reworded to state 'The only bisphosphonate licensed as a 15 minute infusion'. Roche alleged that in the light of this information about Bondronat, this claim was in breach of the Code.

The Panel noted that the licensed dose for Bondronat IV was 6mg over 1 hour. Although the product had been infused over shorter times in clinical trials, it was to healthy volunteers or to patients other than those covered by the licensed indication at an unlicensed dose. In the circumstances the Panel considered it unreasonable to expect a claim about the licensed use of Zometa to take into account the unlicensed uses of a competitor. Given the context in which it appeared the Panel considered that readers would correctly assume that the claim related to the licensed use of bisphosphonates. No breach of the Code was ruled.

Roche noted that the claim 'Zometa provides significant benefits in relief from bone pain' appeared in the prostate cancer leavepiece and was referenced to Saad *et al* (2003) and Saad *et al* (2002). Roche alleged that the claim was misleading as it implied significant benefits throughout the cited trials. Roche noted that bone pain was not significantly reduced in half of the time points.

The Panel noted that the bar chart referred to by Novartis was the same as that considered in Case AUTH/1594/6/04. In its consideration of that case the Panel had considered that the visual impression of the bar chart was that at every time point Zometa-treated patients had lower pain scores than those treated with placebo and that such differences were meaningful. This was not so. At months 6, 12, 15 and 18, although there was a trend to a lower pain score with Zometa, there was no statistically significant difference between it and placebo. The Panel considered that the chart was misleading and ruled a breach of the Code. Novartis had appealed the ruling. The appeal had yet to be heard.

The Panel considered that the same principle applied in the claim now at issue in Case AUTH/1608/7/04. The claim implied that Zometa always provided statistically significantly better bone pain relief than placebo which was not so. The claim was misleading in that regard and the Panel ruled a breach of the Code.

Roche noted the claim 'Zometa decreases the risk of a skeletal complication in multiple myeloma compared to pamidronate' appeared in the multiple myeloma leavepiece and was referenced to Rosen *et al* (2003) and alleged that it was inconsistent with the Zometa SPC which stated '… Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs'.

The Panel noted that the statement in Section 5.1 of the Zometa SPC referred to by Roche related to a group of patients with multiple myeloma or breast cancer with at least one bone lesion. The claim in question referred only to patients with multiple myeloma. The two patient groups were different. The Panel thus did not consider that the claim was inconsistent with the Zometa SPC as alleged. No breach of the Code was ruled.

Roche noted that the claim 'Zometa – effective bone protection in multiple myeloma' appeared in the multiple myeloma leavepiece at the foot of two pages which formed a double page spread headed 'Zometa – proven efficacy in bone lesions and metastases from multiple myeloma'.

Roche considered that the claim suggested that Zometa had a protective effect against the progression of myeloma and alleged that this was not in accordance with the SPC.

The Panel noted that the claim appeared at the foot of the two pages which referred to the efficacy of Zometa in bone lesions and metastases from multiple myeloma. It was stated on the two pages that Zometa decreased the risk of a skeletal complication and was effective and well tolerated in the treatment of osteolytic and mixed bone metastases in multiple myeloma. There was no inference that Zometa had a protective effect against the progression of myeloma *per se* as alleged. No breach of the Code was ruled.

Roche Products Limited complained about the promotion of Zometa (zoledronic acid) by Novartis Pharmaceuticals UK Ltd.

Zometa was presented as a concentrate for solution for infusion and licensed for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. It could also be used to treat tumour-induced hypercalcaemia. Roche supplied Bondronat (ibandronic acid) tablets for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. Bondronat was also available as a concentrate for intravenous administration. Bondronat IV had the same indications as Bondronat tablets and in addition was also indicated for the treatment of tumour-induced hypercalcaemia with or without metastases. Both Zometa and Bondronat belonged to a class of medicines known as bisphosphonates.

There were four items at issue: a detail aid (ref ZOM03001623); a prostate cancer leavepiece (ref ZOM03001627); a breast cancer leavepiece (ref ZOM03001625) and a multiple myeloma leavepiece (ref ZOM03001626). Many of the allegations made by Roche were closely similar to those made by it in a previous case, Case AUTH/1594/6/04. On the day

that the present complaint, Case AUTH/1608/7/04, was received the parties were informed of the Panel's rulings in Case AUTH/1594/6/04. On the day that Novartis responded to Case AUTH/1608/7/04 both it and Roche submitted appeals in Case AUTH/1594/6/04. When the Panel made its rulings detailed below the appeals in Case AUTH/1594/6/04 had yet to be heard. Only the allegations which were different to those in Case AUTH/1594/6/04 were considered in the present case, Case AUTH/1608/7/04.

1 Use of the term ibandronate

Page 3 of the detail aid included a table of data comparing four bisphosphonates of which 'oral ibandronate' was one.

COMPLAINT

Roche noted that ibandronic acid was cited as ibandronate. There was no explanation as to why this terminology was used and, hence, this was both inaccurate and misleading in breach of Clause 7.2 of the Code. The correct generic name was not mentioned and a breach of Clause 3.2 was alleged.

RESPONSE

Novartis was not sure if Roche meant that ibandronic acid was correctly or *incorrectly* cited as ibandronate, but in any event Bondronat detail aids (ref P116052 and P116043/0104), both dated January 2004, also used the term 'ibandronate' (copies of the relevant pages were provided). Many publications, including a recent one in the British Journal of Cancer, March 2004, entitled 'Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomized, placebo-controlled phase III studies' also used this term, so it was clearly well-recognised and in common use. Novartis did not consider that it was inaccurate to refer to ibandronate and thus denied a breach of Clause 7.2. The company noted, however, that 'ibandronic acid' was the term used in the Bondronat summary of product characteristics (SPC).

With respect to the allegation of a breach of Clause 3.2, Novartis referred to the Panel's ruling in Case AUTH/1594/6/04, wherein the Panel noted that Clause 1.2 of the Code defined 'promotion' as any activity undertaken by a pharmaceutical company, or with its authority which promoted the prescription, supply, sale or administration of its medicines. Since Bondronat was not Novartis' product, the company did not consider that it was in breach of Clause 3.2.

PANEL RULING

The Panel noted that although ibandronic acid was the term used in the Bondronat SPC, the product was also referred to as ibandronate both in published papers and by Roche itself. The Panel did not consider that reference to ibandronate was either misleading or inaccurate as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that Clause 1.2 of the Code defined 'promotion' as any activity undertaken by a pharmaceutical company, or with its authority which promoted the prescription, supply, sale or administration of *its* medicines (emphasis added). It was thus an established principle under the Code that one company could not be accused of promoting a competitor company's products. The Panel noted that, nonetheless, references to competitor products had to comply, *inter alia*, with Clause 7.2. The Panel considered, therefore, that although the chart referred to ibandronate, regardless of what was stated in the Bondronat SPC Novartis could not be accused of promoting it. No breach of Clause 3.2 was ruled.

2 Claim 'The potential for poor compliance (and associated treatment failure) is high, with up to 30% of patients failing to follow the schedule correctly'

This claim appeared below the table of data in question at point 1 above. The table compared the relative potency, infusion time, availability and administration of Zometa, pamidronate, oral clodronate and oral ibandronate. The claim was referenced to Ashcroft *et al* (2003) and Atula *et al* (2003).

COMPLAINT

Roche noted that the claim appeared immediately below the comparator table and clearly referred to medicines in that table. However, the cited references failed to include any data for ibandronate. Unless the statement could be supported it was in breach of Clauses 7.3, 7.5 and 8.1.

RESPONSE

Novartis noted that the claim appeared in a table of data relating to bioavailability. The claim in full read: 'With oral bisphosphonates, patients must follow a strict dosing schedule. The potential for poor compliance (and associated treatment failure) is high, with up to 30% of patients failing to follow the schedule correctly'. Without the first sentence, 'the schedule' in the second sentence would have no context.

Novartis stated that all oral bisphosphonates currently available had strict dosing schedules, with a variable period of fasting required before and, in the case of oral Bondronat but not the other oral bisphosphonates, after dosing. This was the subject of part of Case AUTH/1572/4/04, in which the Panel ruled that oral Bondronat was less flexible in terms of timing of dosage than other oral bisphosphonates.

The references cited to substantiate the claim discussed oral bisphosphonates in general, stating their low bioavailability (generally around 1% or less) and the fact that this was reduced further by concurrent intake of food or drink.

Although the references did not specifically mention ibandronic acid, it seemed reasonable – given the stricter dosing schedule of ibandronic acid compared with clodronate, the other oral bisphosphonate listed in the table – to use a generic reference to oral bisphosphonates, since it was specifically *the scheduling* which made compliance a problem.

Novartis did not consider that the claim was misleading, or in breach of Clause 7.3.

The company was not aware that Roche had requested copies of the references cited, or that they were not supplied in a timely fashion; Novartis denied a breach of Clause 7.5.

Further, the company did not consider, given its comments above about the stricter dosing scheduling of oral ibandronic acid compared to oral clodronate, that the claim disparaged oral ibandronic acid. It was not, therefore, in breach of Clause 8.1.

PANEL RULING

The Panel noted that Roche had only quoted the second half of the claim. When read in context with the first half it was clear that the strict dosing schedule of oral bisphosphonates was not followed correctly by up to 30% of patients. The Panel considered that the claim 'the potential for poor compliance (and associated treatment failure) is high' would be applicable to any bisphosphonate with a strict dosing schedule.

The Panel noted that Bondronat tablets had to be taken after an overnight fast of at least 6 hours and at least 30 minutes before the first food of the morning. The Panel considered that the dosing schedule was such that some patients might fail to follow it. Although the cited reference did not mention ibandronate *per se* it was, nonetheless, a bisphosphonate with a strict dosing regimen. The Panel did not consider that the claim was misleading as alleged or that it disparaged Bondronat. No breach of Clauses 7.3 and 8.1 was ruled.

The Panel noted that Roche had alleged a breach of Clause 7.5 which required substantiation for any claim etc to be provided without delay at the request of members of the health professions or appropriate administrative staff. There was no indication that data to substantiate the claim at issue had been requested or that such a request had not been complied with. No breach of Clause 7.5 was ruled.

3 Claim: 'Zometa – now even faster and easier to prepare …'

This claim appeared as the heading on page 13 of the detail aid and on the first inside flap of each leavepiece. Below the heading practical details were given about the administration of Zometa.

COMPLAINT

Roche alleged that the claim was a hanging comparison in breach of Clause 7.2 of the Code. There was insufficient explanation, unlike the front page. The word faster was similar to fast as considered in Case AUTH/1594/6/04.

RESPONSE

Novartis noted that the claim in full read: 'Zometa – now even faster and easier to prepare, no reconstitution needed'. The company did not consider that this was a hanging comparison in breach of Clause 7.2. It was clear that no reconstitution was now needed. The previous formulation of Zometa needed reconstitution.

PANEL RULING

The Panel noted that the front covers of all of the materials in question featured the headline 'A New Solution'. Each cover also featured a photograph of a vial of Zometa together with the statement 'Zometa … is now in solution making it even faster and easier to prepare as no reconstitution is needed'. The Panel considered that it was clear that the detail aid and leavepieces were, *inter alia*, introducing the reader to the new formulation of Zometa.

The Panel noted that Roche had not quoted the whole of the claim at issue. In full, it read, 'Zometa – now even faster and easier to prepare, no reconstitution needed'. The inclusion of the word 'now' implied a comparison with the new formulation's predecessor. The Panel did not consider, given the context in which it appeared, that the claim was a hanging comparative. It was clear that the comparison was with the old formulation of Zometa. No breach of Clause 7.2 was ruled.

The Panel did not accept Roche's view that the use of the word 'faster' was similar to 'fast' as considered in Case AUTH/1594/6/04 (points 15 and 13). The Panel had ruled no breach of Clauses 7.2 and 7.5 of the Code with regard to 'fast' and no breach of Clause 7.2 of the Code with regard to 'quick'. Roche had not appealed the Panel's rulings. These claims appeared on pages comparing Zometa with other bisphosphonates. The Panel noted that in the case now before it, Case AUTH/1608/7/04, the comparison was between the old and new formulations of Zometa.

4 Claim 'a distinct advantage of zoledronic acid [Zometa] is the shorter infusion time of 15 minutes'

This claim appeared at the bottom of each of the pages at issue in point 3 above. The claim was referenced to Joshua *et al* (2002).

COMPLAINT

Roche alleged that the claim was a hanging comparison in breach of Clause 7.2 of the Code.

RESPONSE

Novartis stated that this was a direct quotation, hence it appeared in quotation marks and referred to the infusion time of Zometa being short. Fifteen minutes was generally considered 'short', and certainly shorter than many other infusions. Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that Joshua *et al* was an assessment of patient preferences for IV Zometa or IV pamidronate.

The authors had stated, as quoted in the detail aid and leavepieces, that 'A distinct advantage of zoledronic acid [Zometa] is the shorter infusion time of 15 minutes'. In the context in which it appeared in Joshua *et al* it was thus obvious that the statement was a comparison of Zometa with pamidronate. The Panel considered however, that in the context of the material at issue, the statement as a claim for Zometa was a hanging comparison. There was an implied comparison with another medicine although which one was not stated. A breach of Clause 7.2 was ruled.

5 Claim 'The only bisphosphonate which can be given as a 15 minute infusion …'

This claim appeared on the front covers of each piece of promotional material alongside a photograph of a vial of Zometa.

COMPLAINT

Roche stated that the claim was incorrect. Bondronat had been used as a 15 minute infusion in trials and trialists would find this claim confusing. Published data for the Bondronat 15 minute infusion was now available; Pecherstorfer *et al* (2003) and Neugebauer *et al* (2001). Roche suggested that the claim was reworded to state 'The only bisphosphonate licensed as a 15 minute infusion'. Roche alleged that, as it stood, in the light of this information about Bondronat, this claim was in breach of Clause 7.2.

RESPONSE

Novartis agreed that Zometa was the only bisphosphonate licensed to be given as a 15 minute infusion.

Novartis pointed out that the Neugebauer poster referred to healthy volunteers given a 15 minute infusion of 6mg ibandronic acid (6mg was the licensed dose for patients with bone metastases). The Pecherstorfer poster referred to patients with bone metastases (from breast cancer, prostate cancer and multiple myeloma) given an unlicensed dose – described in the poster as 'non-standard' – of 4mg ibandronic acid as a 30 minute infusion. Bondronat was licensed currently only for breast cancer. Pecherstorfer *et al* also repeated the Neugebauer data.

Thus there did not appear to be data at present in the public domain of patients with bone metastases receiving the standard 6mg (licensed) dose of Bondronat as a 15 minute infusion. Novartis denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the licensed dose for Bondronat IV was 6mg over 1 hour. Although the product had been infused over shorter times in clinical trials it was to healthy volunteers or to patients other than those covered by the licensed indication at an unlicensed dose. The Panel noted that, as it had stated in point 1 above, references to competitor products had to comply, *inter alia*, with Clause 7.2. Reference to the unlicensed use of competitor products might be regarded as misleading. The Panel considered that each case should be considered on its own merits. In the circumstances the Panel considered it unreasonable to expect a claim about the licensed use of Zometa to take into account the unlicensed uses of a competitor. Given the context in which it appeared the Panel considered that readers would correctly assume that the claim related to the licensed use of bisphosphonates. No breach of Clause 7.2 was ruled.

6 Claim 'Zometa provides significant benefits in relief from bone pain'

This claim appeared in the prostate cancer leavepiece and was referenced to Saad *et al* (2003) and Saad *et al* (2002).

COMPLAINT

Roche alleged that the claim was misleading, in breach of Clause 7.2 of the Code, as it implied significant benefits throughout the cited trials. Roche noted that bone pain was not significantly reduced in half of the time points.

RESPONSE

Novartis noted that the claim appeared under a sub-heading 'Zometa significantly lowers pain scores at 2 years compared to placebo', and immediately below a bar chart depicting the mean change in pain scores from baseline over the course of a two year study in patients with metastatic prostate cancer receiving either Zometa or placebo. At the end of the study, and at various time points during the study, there was a significant difference between the pain scores in the two groups, and at all time points where statistical significance was not reached, there was a strong trend in favour of Zometa. Novartis did not consider that the claim was misleading and denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the bar chart referred to by Novartis was the same as that considered in Case AUTH/1594/6/04. In its consideration of that case the Panel had considered that the visual impression of the bar chart was that at every time point Zometa-treated patients had lower pain scores than those treated with placebo and that such differences were meaningful. This was not so. At months 6, 12, 15 and 18, although there was a trend to a lower pain score with Zometa, there was no statistically significant difference between it and placebo. The Panel considered that the chart was misleading and ruled a breach of Clause 7.2 of the Code. Novartis had appealed the ruling. The appeal had yet to be heard when the Panel considered Case AUTH/1608/7/04. [The Appeal Board ruled that the bar chart was not in breach of the Code on appeal by Novartis.]

The Panel considered that the same principle applied in the claim now at issue in Case AUTH/1608/7/04. The claim implied that Zometa always provided statistically significantly better bone pain relief than placebo which was not so. The claim was misleading in that regard and the Panel ruled a breach of Clause 7.2 of the Code.

7 Claim 'Zometa decreases the risk of a skeletal complication in multiple myeloma compared to pamidronate'

This claim appeared in the multiple myeloma leavepiece and was referenced to Rosen *et al* (2003).

COMPLAINT

Roche alleged that the claim was inconsistent with the Zometa SPC which stated '… Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs' and thus in breach of Clause 3.2.

RESPONSE

Novartis noted that Roche had quoted from Section 5.1 of the Zometa SPC that Zometa and pamidronate were comparable in efficacy in the *prevention of SREs*. This was true, but was not the subject of the claim, which was the *reduction in risk of a skeletal complication*.

Novartis noted that Section 5.1 of the SPC stated 'In a third phase III randomised, double-blind trial, 4mg Zometa or 90mg pamidronate every 3 to 4 weeks were compared in patients with multiple myeloma or breast cancer with at least one bone lesion. The results demonstrated that Zometa 4mg showed comparable efficacy to 90mg pamidronate in the prevention of SREs. The multiple event analysis revealed a significant risk reduction of 16% in patients treated with Zometa 4mg in comparison with patients receiving pamidronate.'

Thus, in this phase III trial including multiple myeloma patients, the overall results ie the multiple event analysis – regarded as the most statistically robust and clinically meaningful – demonstrated a significant risk reduction [of a skeletal complication] of 16% for Zometa compared with pamidronate.

Novartis submitted that the claim was consistent with the terms of the marketing authorization and not in breach of Clause 3.2.

PANEL RULING

The Panel noted that the statement in Section 5.1 of the Zometa SPC referred to by Roche related to a group of patients with multiple myeloma or breast cancer with at least one bone lesion. The claim in question referred only to patients with multiple myeloma. The two patient groups were different. The Panel thus did not consider that the claim was inconsistent with the Zometa SPC as alleged. No breach of Clause 3.2 was ruled.

8 Claim 'Zometa – effective bone protection in multiple myeloma'

This claim appeared in the multiple myeloma leavepiece at the foot of two pages which formed a double page spread headed 'Zometa – proven efficacy in bone lesions and metastases from multiple myeloma'.

COMPLAINT

Roche considered that the claim suggested that Zometa had a protective effect against the progression of myeloma. The company alleged that this was not in accordance with the SPC, in breach of Clause 3.2 of the Code.

RESPONSE

Novartis noted that Zometa was licensed for 'Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone'. The company explained that multiple myeloma was a haematopoietic malignancy involving the bone marrow leading to diffuse osteoporosis or discrete osteolytic lesions – in effect, a disease of bone. Zometa had been shown to be effective specifically in multiple myeloma, among other malignancies, in protecting patients against bone complications.

Therefore, given that the SPC stated 'Prevention of skeletal related events', and that treatment with Zometa protected against these events in multiple myeloma, Novartis did not consider that this claim was in breach of Clause 3.2.

PANEL RULING

The Panel noted that the claim appeared at the foot of the two pages which referred to the efficacy of Zometa in bone lesions and metastases from multiple myeloma. It was stated on the two pages that Zometa decreased the risk of a skeletal complication and was effective and well tolerated in the treatment of osteolytic and mixed bone metastases in multiple myeloma. There was no inference that Zometa had a protective effect against the progression of myeloma *per se* as alleged. No breach of Clause 3.2 was ruled.

Complaint received **23 July 2004**

Case completed **14 October 2004**

CASE AUTH/1610/7/04

PRIMARY CARE TRUST ADVISOR v ROCHE

Letter about Xenical sent to patients

A new drugs and technology advisor to a primary care trust alleged that a letter sent by Roche would lead patients to ask their GP for Xenical (orlistat) to help them lose weight. The complainant stated that the letter appeared to be aimed at patients no longer receiving Xenical as it stated 'So, if your weight's crept back on and you're feeling the need to lose a few pounds again you may want to discuss this with your GP. He or she has helped you before, they could help you again!' The implications of this statement did not concur with the licensed indications for Xenical. The summary of product characteristics stated that before starting therapy patients had to have lost at least 2.5kg over a period of four consecutive weeks with diet alone and that treatment should only be continued for more than 12 weeks if patients had lost at least 5% of their body weight as measured at the start of treatment.

The complainant noted that although the letter did not actually direct patients to request Xenical, recipients in one local practice had interpreted it in that way and had asked the GP to prescribe Xenical on a subsequent occasion.

The Panel noted that although the letter was sent to patients who at one time had been prescribed Xenical, some of them might no longer be taking the medicine. There could be a variety of reasons as to why treatment had stopped; eg insufficient weight loss over 12 weeks. There could thus be some patients for whom continued therapy was inappropriate.

The letter mentioned Xenical five times. The Panel considered that the letter would remind those patients who no longer took Xenical that they had received the medicine in the past and would encourage those that still needed help to lose weight to go back to the doctor and ask for Xenical. The Panel considered that in respect of those patients who no longer took Xenical the letter constituted an advertisement for the product. The Panel further considered that high standards had not been maintained. Breaches of the Code were ruled.

With the benefit of all the papers before it the Panel regretted that the Authority had not asked Roche to consider the requirements of Clause 2 in its response to the complaint. The Panel had serious concerns about the number of letters which Roche had sent – 14,609. The Panel was also very concerned that Roche had sent the letters, which referred to Xenical, knowing that some recipients would no longer be taking the medicine. In the Panel's view it was irrelevant that those patients who were not currently taking Xenical had been prescribed it in the past. In the circumstances the Panel considered that, had it had the opportunity, it would have ruled Roche in breach of Clause 2 of the Code for bringing discredit upon the industry.

The Panel considered that directly contacting members of the public/patients to advertise a prescription only medicine was a serious matter and that the circumstances warranted reporting Roche to the Appeal Board.

The Appeal Board noted that the letter in question was sent in June/July 2004 to patients who had registered on XenicalMAP (motivation, advice, pro-active support) between June 2003 and March 2004. Nonetheless, the Appeal Board considered that Roche had been extremely careless in sending out the letter without being certain that every recipient was currently still taking Xenical. The Appeal Board noted the rulings of the Code of Practice Panel and although it had concerns about Roche's actions it nonetheless decided that, in the circumstances, no further action was required.

A new drugs and technology advisor to a primary care trust complained about a letter (ref P9791136) sent by Roche Products Limited to patients who had previously registered with the Xenical (orlistat) patient helpline MAP (motivation, advice and pro-active support) whilst receiving treatment with Xenical. Xenical was indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients (body mass index (BMI) ≥ 30kg/m2) or overweight patients (BMI ≥ 25kg/m2) with associated risk factors.

Roche explained that the letter was sent to 14,609 patients who had previously registered on the support programme having been prescribed Xenical; the majority of them (12,746) registered between 1 June 2003 and 31 March 2004. The letters were sent between 4 June and 15 July 2004 because the summer months could be a particularly difficult time, even for the most highly motivated patients, to continue to adhere to a weight management programme.

COMPLAINT

The complainant stated that the letter appeared to be aimed at patients no longer receiving Xenical and suggested: 'So, if your weight's crept back on and you're feeling the need to lose a few pounds again you may want to discuss this with your GP. He or she has helped you before, they could help you again'. The complainant alleged that this directly led patients to ask their GP for Xenical on a subsequent occasion in breach of Clause 20.2 of the Code.

The complainant added that the implications of the statement did not concur with the licensed indications for Xenical as patients might not have lost the desired weight, or have achieved sufficient response to treatment in order to continue. The complainant noted that the Xenical summary of product characteristics (SPC) stated 'Treatment with orlistat should only be started if diet alone has previously produced a weight loss of at least 2.5kg over a period of 4 consecutive weeks. Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5% of the body weight as measured at the start of drug therapy'.

The complainant noted that although the letter did not actually direct patients to request Xenical,

recipients in one local practice had interpreted it in that way and had asked the GP to prescribe Xenical on a subsequent occasion.

When writing to Roche, the Authority asked it to respond in relation to Clauses 9.1 and 20.1 in addition to Clause 20.2 as cited by the complainant.

RESPONSE

Roche explained that MAP was an adherence programme, accepted as a Medicines Partnership Project, to help encourage and motivate overweight and obese patients to lose weight in order to reduce their health risks. The programme provided dietary and exercise advice and information to patients in the pre-prescription phase (patients must lose 2.5kg prior to being prescribed Xenical) and, for those already prescribed Xenical, the support line could respond to enquiries about medication, as well as providing supportive information and literature. A detailed description of the service was provided.

Roche stated that the letter was intended to encourage successful weight management including maintenance of the weight loss achieved, as it was well known that moderate weight loss over a prolonged period was the most successful way to reduce health risks resulting from carrying excess weight. Encouraging patients either to recontact MAP or their GP was suggested in order to improve concordance with their weight management programme which should continue (with or without Xenical) for months or years in order to be effective for the long term. Roche did not consider that the letter was different from a patient awareness campaign. The suggestion to discuss weight management with the GP was not intended to stimulate a request for Xenical but to remind patients that overweight and obesity put their health at risk and that health professionals were the best people to help. The GP could recommend any method of weight management including pharmacotherapy of which there were non-Xenical options. The offer of a Food and Activity Diary from MAP was not related to Xenical but was provided to all patients contacting the support line, as it provided them with basic weight management advice.

Data confirmed that MAP was a valuable support programme, which improved concordance and compliance and resulted in weight loss equivalent to that achieved in clinical trials. Additional data suggested that the combination of Xenical and MAP resulted in clinically significant benefits across all disease specific quality of life domains. It therefore seemed sensible to encourage patients already receiving Xenical, but who had not been contactable by MAP after their registration, to recontact the support line to increase the likelihood of ongoing success with their weight management. However, knowing that some of the patients might no longer be receiving the medicine, it was important that the letter was appropriate for all patients whether still on Xenical or not.

Roche stated that the complainant was incorrect in stating that the implications of the statement did not concur with the licensed indications for the product, as patients might not necessarily have lost the desired weight, or have achieved sufficient response to treatment in order to continue. As explained above, patients had been prescribed Xenical previously and whether the medicine was to continue being supplied was entirely in the hands of the prescriber.

PANEL RULING

The Panel noted that although the letter was sent to patients who at one time had been prescribed Xenical, some of them might no longer be taking the medicine. There could be a variety of reasons as to why treatment had stopped; the Panel noted that the Xenical SPC stated that treatment should be discontinued after 12 weeks if patients had been unable to lose at least 5% of the body weight as measured at the start of therapy. There could thus be some patients for whom continued therapy was inappropriate.

The letter mentioned Xenical five times and in that regard the Panel disagreed with Roche's submission that the letter was not different from a patient awareness campaign, from which the Panel assumed that Roche meant a disease awareness campaign. The Panel considered that the letter would remind those patients who no longer took Xenical that they had received the medicine in the past and would encourage those that still needed help to lose weight to go back to the doctor and ask for Xenical.

The Panel considered that in respect of those patients who no longer took Xenical the letter constituted an advertisement for the product. A breach of Clause 20.1 was ruled. The letter would encourage patients to ask their doctor to prescribe Xenical. A breach of Clause 20.2 was ruled. The Panel further considered that high standards had not been maintained and ruled a breach of Clause 9.1 of the Code.

With the benefit of all the papers before it the Panel regretted that the Authority had not asked Roche to consider the requirements of Clause 2 in its response to the complaint. The Panel had serious concerns about the number of letters which Roche had sent – 14,609. The Panel was also very concerned that Roche had sent the letters, which referred to Xenical, knowing that some recipients would no longer be taking the medicine. In the Panel's view it was irrelevant that those patients who were not currently taking Xenical had been prescribed it in the past. In the circumstances the Panel considered that, had it had the opportunity, it would have ruled Roche in breach of Clause 2 of the Code for bringing discredit upon the industry.

The Panel noted that the Constitution and Procedure was such that it could report a company to the Code of Practice Appeal Board if that company failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2) in relation to additional sanctions as set out in Paragraphs 10.3, 10.4 and 12.1. Directly contacting members of the public/patients to advertise a prescription only medicine was a serious matter. The Panel decided that the circumstances warranted reporting Roche to the Appeal Board.

COMMENTS FROM ROCHE

Roche accepted the Panel's rulings of breaches and provided the requisite undertaking and assurance, Roche stated that the aim of the XenicalMAP was to enhance care and provide support for patients to complement that which they received from their health professionals. It had been developed and evolved over the past 7 years with the aim of providing the type of partnership between the pharmaceutical industry and the NHS that the government had encouraged. For that reason, the programme was a Medicines Partnership Project, which had been cited by the Department of Health as a good example of collaboration between the industry and the health service. The programme was ongoing.

Roche stated that it accepted the Panel's findings of breaches reluctantly as it had never intended to advertise Xenical to the public. Roche submitted that the XenicalMAP programme was an example of positive patient support from the industry, which should enhance the reputation of the pharmaceutical industry as a whole.

Roche noted that obesity was a chronic, relapsing, life-threatening disease which was a major public health problem in the UK. It was also a known risk factor for cardiovascular disease, diabetes, and many other serious chronic illnesses, some of which were key priorities for the NHS. Obesity remained, however, a challenging disease to treat and ongoing motivation of the patient was key to successful long-term management. This was the premise for the development of the XenicalMAP programme, which was designed with the following key objectives in mind: to provide effective dietary advice and information for patients either prior to or while taking Xenical; to help patients set realistic, achievable treatment goals; to help patients lose weight with Xenical and optimise their treatment outcomes.

Roche submitted that patients were never pro-actively contacted without their prior consent. Data presented at the European Congress of Obesity this year demonstrated that patients' adherence improved with ongoing support from the programme compared to patients who did not have this support. The evidence collected from XenicalMAP suggested that the weight loss achieved by patients was comparable with that achieved in clinical studies.

Roche submitted that the letter was sent to patients who had agreed to pro-active contact from XenicalMAP. It was not sent to anyone known to have stopped Xenical. At the time of the support line's last contact with these patients they were all still taking Xenical. However, the management of obesity must take account of its relapsing remitting nature. Patients who lost weight using various methods often relapsed and were lost to follow-up. Evidence showed that if such patients were motivated, once again benefit could be obtained. It was clear that those patients on weight management programmes who were supported regularly by health professionals were more likely to lose weight at an appropriate rate and thereby increase the chances of successful long-term weight management. XenicalMAP provided support from independent health professionals which helped to alleviate some of the time demands within the surgery, while providing much needed support for the patient.

Roche considered it wise to encourage patients who were no longer receiving Xenical but who still wanted to lose weight to return to their doctor for weight management advice. Some of these patients might have been prescribed Xenical again but others might have been tried on other medicines including sibutramine or a non-pharmacological alternative.

Roche submitted that the XenicalMAP programme had been recognised as a success by health professionals and patients who had found the programme to be a welcome support.

At the consideration of the report the Roche representatives outlined the history of MAP and submitted that MAP was recognised as providing excellent patient support. The representatives explained that there were two forms of MAP, one for patients attempting to lose weight and the second for patients prescribed Xenical which was known as XenicalMAP. The patients sent the letter in question had previously registered on XenicalMAP and had given permission for future contact. Roche accepted the Panel's rulings and the representatives acknowledged that in hindsight it had been a mistake to send the letter out on XenicalMAP notepaper as this referred to Xenical in both the header and the footer.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that the letter in question was sent in June/July 2004 to patients who had registered on XenicalMAP between June 2003 and March 2004. Nonetheless, the Appeal Board considered that Roche had been extremely careless in sending out the letter without being certain that every recipient was currently still taking Xenical. In this regard it noted that Xenical was mentioned three times in the body of the letter in addition to the two mentions in the header and footer. The Appeal Board noted the rulings of the Code of Practice Panel and although it had concerns about Roche's actions it nonetheless decided that, in the circumstances, no further action was required.

Complaint received	**30 July 2004**
Undertaking received	**23 September 2004**
Proceedings completed	**13 October 2004**

CASE AUTH/1616/8/04

ROCHE/DIRECTOR v SCHERING-PLOUGH

ViraferonPeg and Rebetol leavepieces

Roche complained about four leavepieces for ViraferonPeg (pegylated interferon (peginterferon) alfa-2b) and Rebetol (ribavirin) issued by Schering-Plough. Roche supplied Pegasys (peginterferon alfa-2a). The complaint involved, *inter alia*, an alleged a breach of undertaking and that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

Roche explained that Pegasys and ViraferonPeg were both pegylated interferons licensed for the treatment of chronic hepatitis C (HCV) and given as once weekly injections, usually in combination with ribavirin. The two products differed in the size and structure of their molecules and so they had different pharmacological properties and hence posologies. Pegasys was dosed at 180mcg for all patients, irrespective of weight. This flat dosing was one of the major competitive advantages of Pegasys. ViraferonPeg was given on a dose/bodyweight basis.

Roche noted that in general, heavier patients were less likely to obtain an SVR (sustained viral response) through interferon therapy. Manus *et al* (2001), the registration study on which the ViraferonPeg posology was based, stated that '… logistic regression analysis showed that baseline weight was an important factor of SVR'. The authors went on to state that '… weight was no longer significant after controlling for ribavirin dose'. There was no mention of controlling for ViraferonPeg dosing and Roche did not consider that this was a sufficiently robust analysis upon which to base the claim 'When ViraferonPeg and Rebetol are dosed according to bodyweight, in line with their licence, weight ceases to be a prognostic factor for SVR'. Roche noted that a 2001 publication by a committee of the Food and Drug Administration stated that peginterferon alfa-2b [ViraferonPeg] clearly showed higher SVR rates in patients who weighed less than 65kg than those who weighed more. Therefore the claim that bodyweight ceased to be a prognostic factor for SVR was not accurate, objective or based on an up-to-date evaluation of all the evidence and was exaggerated.

The Panel noted that the licensed dose of ViraferonPeg was 1.5mcg/kg/week when administered in combination with ribavirin capsules. The licensed dose of ViraferonPeg for patients weighing > 85kg was 150mcg. There was no provision to give higher doses in heavier patients. The Panel thus noted that patients weighing more than 100kg would in effect receive a dose of less than 1.5mcg/kg.

Rebetol was only licensed to be used in combination with ViraferonPeg or interferon alpha-2b. The dose, based on bodyweight, was divided into three bands; 800mg for patients weighing < 65kg; 1000mg for patients weighing 65-85kg and 1,200mg for patients weighing >85kg. Section 5.1 of the Rebetol summary of product characteristics (SPC) referred, *inter alia*, to Rebetol clinical trials and noted that one trial showed that response rates depended on the dose of Rebetol. In patients who received >10.6mg/kg, response rates were significantly higher than in those patients that received ≤ 10.6mg/kg, while response rates in patients who received >13.2mg/kg Rebetol were even higher. This data appeared to be the same as that published by Manns *et al*. Two bar charts in different leavepieces both referred to 'ViraferonPeg 1.5mcg/kg + Rebetol >10.6mg/kg'. The Panel noted that the Rebetol SPC did not refer to a larger dose than 1,200mg which was for patients of 85kg or more. Once a patient weighed more than 113.2kg, however, a dose of 1,200mg Rebetol would equate to less than 10.6mg/kg. The Panel considered that at that point weight would become a prognostic factor for SVR.

In the Panel's view the claim 'When ViraferonPeg and Rebetol are dosed according to bodyweight, in line with their licence, weight ceases to be a prognostic factor for SVR' ignored the fact that, given the dosage instructions in the SPC, in heavy patients (>100kg) the dose of ViraferonPeg would fall below 1.5mg/kg and in others (>113.2kg) the dose of Rebetol would be <10.6mg/kg. In these patients weight would be a prognostic factor. The Panel considered that the claim was misleading in that regard. A breach of the Code was ruled. The Panel also considered that the claim was exaggerated in that it implied that in all patients, whatever their weight, weight was not a prognostic factor. A breach of the Code was ruled.

Roche alleged that the claim 'ViraferonPeg and Rebetol, when dosed according to body weight in line with their licence, is the only pegylated interferon/ribavirin combination for which weight is no longer a prognostic factor for SVR' was inaccurate and did not reflect all available evidence. Indeed a peer-reviewed critique of weight-based dosing of pegylated interferons reinforced Roche's position that it was inaccurate to state that weight was no longer a prognostic factor with this combination (Ferenci 2003).

The Panel noted its comments above and considered that they applied here. In the Panel's view weight would be a prognostic factor for SVR, particularly in very heavy patients. As above the Panel considered that the claim at issue was inaccurate and did not reflect all of the available evidence. A breach of the Code was ruled.

Roche alleged that the first bullet point of the claim 'ViraferonPeg + Rebetol provide the opportunity to individualise care by dosing according to weight: eliminating body weight as a prognostic factor; delivering high SVRs in a wide population', was exaggerated and inaccurate for reasons described above. With regard to the second bullet point, Roche referred to a previous case, Case AUTH/1474/6/03, in which Schering-Plough's claim that 'Individualised weight adjusted [ViraferonPeg] plus ribavirin therapy maximises the chance for SVR in the broadest HCV population' was ruled in breach of the Code on the basis that it exaggerated the data. Looking at subgroups of those patients

with genotype 2 or 3, those patients with high viral loads and those with fibrosis/cirrhosis, there was no evidence to claim superiority 'in the broadest population of HCV patients'.

Manns *et al* stated that 'the primary benefit of [ViraferonPeg] plus ribavirin for this group [genotype 2 or 3] may be convenience, ease of administration of a once-weekly injection compared with alternate-day injections, and the potential for better compliance'. In Case AUTH/1474/4/03 the Panel considered that this claim 'conflicted with the message of superiority in the 'broadest population of HCV patients' and 'maximises the chance for an SVR'. It now appeared that Schering-Plough had slightly watered down its message by claiming that 'ViraferonPeg + Rebetol provide the opportunity to individualise care by dosing according to weight … delivering high SVRs in a wide population'.

Given that the only subgroup in which ViraferonPeg had been shown to be superior to standard interferon was genotype 1, low viral load, ie approximately 25% of the UK HCV population, even claiming high SVRs in a wide population was misleading.

Roche was surprised that Schering-Plough had persisted with this kind of claim despite previous censure and undertaking not to use it. By slightly re-wording the claim as stated, Schering-Plough had not acted either within the spirit, or the letter of the Code. Roche alleged a breach of Clause 2 due to the breach of the previous undertakings.

The Panel noted its comments above and considered that they applied here with regard to the bullet point 'eliminating body weight as a prognostic factor'. The Panel considered that the claim was misleading and exaggerated as alleged. Breaches of the Code were ruled.

With regard to the second bullet point 'delivering high SVRs in a wide population' the Panel considered that it was sufficiently different from the claim 'Individualised weight adjusted [ViraferonPeg] plus ribavirin therapy maximises the chance for SVR in the broadest HCV population' which was ruled in breach of the Code in Case AUTH/1474/6/03 for it not to represent a breach of the undertaking given in that case. No breach of the Code was ruled. There could thus be no breach of Clause 2.

The Panel noted that the claim 'delivering high SVRs in a wide population' was not a comparative claim. The claim was referenced to Manns *et al*. The Panel accepted that ViraferonPeg/Rebetol had been used in a wide range of patients but noted that it had not been provided with the data to show that patients in each of the treated groups achieved a high SVR. On the basis of the data before it the Panel considered that the claim was exaggerated as alleged and ruled a breach of the Code.

Roche stated that the claim 'ViraferonPeg is the only pegylated interferon in a pre-filled pen to help encourage patient adherence' could be read to mean that ViraferonPeg was the only pegylated interferon presented in such a way as to encourage patient adherence by virtue of its pre-filled pen. This disparaged Pegasys by implication as Pegasys was presented in a pre-filled syringe. There were also no data to support the claim that the pre-filled pen helped encourage adherence. Compared to what? Roche alleged that the claim could not be substantiated.

The Panel noted that ViraferonPeg was, as stated in the claim, the only pegylated interferon to be presented in a pre-filled pen. No data had been submitted, however, to show that such a presentation helped encourage patient adherence. In that regard the Panel considered that the claim had not been substantiated. A breach of the Code was ruled. The Panel did not consider that the claim disparaged Pegasys. No breach of the Code was ruled in that regard.

Roche's allegation that the claim 'Weight-based dosing with ViraferonPeg and Rebetol makes a difference' was a hanging comparison was rejected by the Panel and no breach of the Code was ruled.

Roche alleged that claims 'Efficacy demonstrated in patients with bridging fibrosis/cirrhosis' and 'In a randomised, open label trial, 188 patients received ViraferonPeg 1.5mcg/ kg + Rebetol >10.6mg/kg for 48 weeks' incorrectly implied that ViraferonPeg + Rebetol >10.6mg/kg were prospectively investigated in a randomised, open label trial. The 188 patient cohort actually represented a retrospective sub-set analysis of pre-selected patients out of the intention to treat population of 511 patients.

The Panel considered that the way in which the claims had been presented implied that a discreet and separate trial of 188 patients with bridging fibrosis/cirrhosis had taken place which was not so. The claims were misleading in that regard. The Panel ruled a breach of the Code.

Roche alleged that the claim 'NICE states that people who weigh more than the average have a lower response rate to treatment than those who weigh less than the average when the doses of interferon alfa (and ribavirin for combination therapy) are fixed' had been used in a misleading manner. This was immediately followed by the claim 'ViraferonPeg and Rebetol, when dosed according to body weight in line with their licence, is the only pegylated interferon/ribavirin combination for which weight is no longer a prognostic factor for SVR'.

Roche considered that the order of these two claims implied extrapolation of the NICE statement on standard interferon to ViraferonPeg and Rebetol. There was no NICE consensus on the effect of weight, SVR and the use of any pegylated interferon. In addition, the NICE statement formed part of its clinical need and practice appraisal, and did not represent the actual NICE recommendation or guidance. As such this claim led the reader to believe that NICE concurred with or even endorsed Schering-Plough's marketing strategy whch aimed to leave health professionals with the impression that the different posologies of the two pegylated interferons could be extrapolated to differing efficacies.

The Panel noted that the statement from NICE regarding the influence of bodyweight on response to fixed doses of interferon alfa (and ribavirin for combination therapy) was immediately followed by a claim for ViraferonPeg and Rebetol being the only pegylated interferon/ribavirin combination for which weight was no longer a prognostic factor for SVR. The Panel considered that juxtaposing the two statements was misleading in that some readers would assume that the NICE statement related to *pegylated* (emphasis added) interferon alfa when it did not. The Panel ruled a breach of the Code.

Roche Products Limited complained about promotional materials for ViraferonPeg (pegylated interferon (peginterferon) alfa-2b) and Rebetol (ribavirin) issued by Schering-Plough Ltd. The items at issue were leavepieces entitled (i) 'When does weight matter?' (ref VPEG 03/210), (ii) 'How to get 63% SVR [sustained viral response] in Genotype 1 patients' (ref VPEG 03/211), (iii) 'Does fibrosis matter?' (ref VPEG 03/212) and (iv) 'NICE [National Institute for Clinical Excellence] weighs up which factors affect SVR rates in hepatitis C patients' (ref VPEG 04/227). Intercompany correspondence had failed to resolve the issues.

Roche supplied Pegasys (peginterferon alfa-2a).

The complaint involved, *inter alia*, an alleged a breach of undertaking and that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board. Thus in addition to those clauses cited by Roche, the Authority asked Schering-Plough to respond in relation to the requirements of Clause 22 of the Code.

Roche explained that Pegasys and ViraferonPeg were both pegylated interferons licensed for the treatment of chronic hepatitis C (HCV) and given as once weekly injections, usually in combination with ribavirin. The two products differed in the size and structure of their molecules and so they had different pharmacological properties and hence posologies. Pegasys was dosed at 180mcg for all patients, irrespective of weight. This flat dosing was one of the major competitive advantages of Pegasys. ViraferonPeg was given on a dose/bodyweight basis.

Schering-Plough explained that it had been in close discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) over the last year and had agreed the promotional messages that could be used for ViraferonPeg and Rebetol (ribavirin) based on the original clinical data dossier submitted to the European Medicines Evaluation Agency (EMEA). That submission resulted in Schering-Plough obtaining an authorization for the weight-based dosing of ViraferonPeg. Naturally, in the light of such regulatory endorsement, Schering-Plough was disappointed that Roche continued to question the rationale for its licence and, in particular, its promotional approach to the approved posology.

1 Claim 'When ViraferonPeg and Rebetol are dosed according to body weight, in line with their licence, weight ceases to be a prognostic factor for SVR'

This claim appeared in leavepieces (i), (ii) and (iii).

COMPLAINT

Roche stated that body weight was one of many (though by no means the most important) prognostic factors for SVR. In general heavier patients were less likely to obtain an SVR through interferon therapy, however weight might just be a surrogate for the fatty liver which was difficult to treat.

Roche noted that Manns *et al* (2001) stated quite clearly that in the registration study, on which the ViraferonPeg posology was based, '… logistic regression analysis showed that baseline weight was an important factor of SVR'. The authors went on to state that '… weight was no longer significant after controlling for ribavirin dose'. There was no mention of controlling for ViraferonPeg dosing. Also a publication by the Food and Drug Administration, Antiviral Drugs Advisory Committee December 12, 2001: Briefing Information – Peginterferon alfa-2b [ViraferonPeg] clearly showed higher SVR rates in patients who weighed less than 65kg than those who weighed more. Schering-Plough had overstated the case with respect to this claim whose credibility after all rested on a logistic regression on a subset of a cohort of patients. Roche did not consider that this was a sufficiently robust analysis.

Roche alleged that to state that body weight ceased to be a prognostic factor for SVR was not accurate, objective or based on an up-to-date evaluation of all evidence in breach of Clause 7.2 and exaggerated in breach of Clause 7.10.

RESPONSE

Schering-Plough stated that the objective of Manns *et al*, a multinational, randomised study, was to compare the safety and efficacy of two treatment regimens of interferon alfa-2b in patients naïve to interferon therapy; the treatments studied were ViraferonPeg plus ribavirin and Viraferon plus ribavirin. The primary endpoint of the study was SVR, as measured by loss of detectable serum HCV-RNA at a 24-week follow-up visit at the end of a 48-week treatment period.

The treatment groups were as follows:

1 ViraferonPeg, 1.5mcg/kg once weekly for 4 weeks and then reduced to 0.5mcg/kg once weekly for 44 weeks plus ribavirin 1000-2000mg/day for 48 weeks. Both ViraferonPeg and ribavirin were dosed according to body weight. This regimen was anticipated to have equal or slightly improved efficacy and possibly better tolerance than group 3 below. The higher starting dose was anticipated to induce more rapid reductions in viral titre.

2 ViraferonPeg 1.5mcg/kg once weekly plus ribavirin 800mg/day for 48 weeks. This dose was anticipated to have better activity than group 3. ViraferonPeg only was dosed according to body weight. The lower dose of ribavirin was selected to counter the side effects of the higher dose of ViraferonPeg.

3 Viraferon 3 MIU three times weekly plus ribavirin 1000-2000mg/day for 48 weeks (standard

Table 1 **SVR rates in Manns *et al***

Genotype	*SVR rate (%)*		
	ViraferonPeg 1.5mcg/kg + ribavirin (n=511)	*ViraferonPeg 0.5mcg/kg + ribavirin (n=514)*	*Viraferon 3 MIU + ribavirin (n=505)*
Overall	54a	47	47
Genotype 1	42b	34	33
Genotypes 2/3	82	80	79

a) p=0.01 vs Viraferon + ribavirin
b) p=0.02 vs Viraferon + ribavirin

regimen). Ribavirin only was dosed according to patient weight.

Demographics

Baseline characteristics were consistent in all three treatment groups. The mean age of the subjects was 43 years, 63% were male and 89% were Caucasian. There was a wide range of subject weights (38-181kg) the average being 82kg.

Sixty-eight percent of subjects were infected with HCV genotype 1 and 29% with genotype 2 or 3. The mean baseline serum HCV-RNA level was 2.7million copies/ml. Twenty-nine percent of the subjects had histological evidence of bridging fibrosis or cirrhosis (Knodell score 3/4 [Knodell *et al* 1981; Goodman *et al* 1995]); the source of exposure to HCV was mainly parenteral. The mean time from first exposure to study enrolment was 19.0-19.5 years.

Overall the study population was more likely to be refractory to treatment in that patients had a high incidence of genotype 1, high viral load, high incidence of cirrhosis and bridging fibrosis, and heavier weight.

Efficacy

ViraferonPeg 1.5mcg/kg once weekly plus ribavirin 800mg/day achieved a significantly better SVR rate (54%) compared with either ViraferonPeg 0.5mcg/kg once weekly or Viraferon three times weekly + ribavirin 1000-1200mg (both 47%; p=0.01) (Table 1).

Weight-based dosing

Notably, this further confirmed the importance of weight-based dosing of ViraferonPeg and ribavirin in optimising SVRs. A logistic regression analysis of the relationship between SVR and the dose of ViraferonPeg (categorical variable) and ribavirin (continuous variable) showed that weight-adjusted dosing of both medicines significantly predicted the likelihood of an SVR (p=0.01 for ViraferonPeg; p=0.013 for ribavirin). This analysis revealed the greatest efficacy in patients receiving ViraferonPeg 1.5mcg/kg once weekly plus ribavirin >10.6mg/kg/day.

Sixty-one percent of patients receiving weight-based ViraferonPeg and weight-based ribavirin had an SVR, compared to 54% where the ribavirin was not dosed according to weight and 47% in the group receiving Viraferon plus ribavirin (Table 2).

The benefits of weight-based dosing were also evident when the patients were grouped by genotype (Table 2). Thus, among patients with genotype 1 HCV, there was a 48% response rate to the weight-based ViraferonPeg and weight-based ribavirin dosing versus 34% for Viraferon and ribavirin. For patients with genotype 2/3 the SVR was 88% for weight-based ViraferonPeg and ribavirin dosing.

Further data were summarised in an appendix. Given the extent of relevant data on weight-based dosing, Schering-Plough did not consider the claim at issue breached Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted the findings of Manns *et al*; baseline weight was a predictive factor for SVR. Although a retrospective regression analysis found that weight was no longer a significant predictor of response after control for the Rebetol dose the Panel noted Roche's submission that there was no mention of control for ViraferonPeg dosing. Schering-Plough had not provided copies of the other studies referred to.

The Panel noted that the licensed dose of ViraferonPeg was 1.5mcg/kg/week when administered in combination with ribavirin capsules. The ViraferonPeg summary of product characteristics (SPC) included a table showing the dosing for combination therapy for patients of varying weights. For patients weighing >85kg the dose was given as 150mcg. There was no provision to give higher doses in heavier patients. The Panel thus noted that patients weighing more than 100kg would in effect receive a dose of less than 1.5mcg/kg.

Table 2 **Sustained SVR rates in Manns *et al* with weight-based dosing**

Genotype	*ViraferonPeg 1.5mcg/kg + ribavirin >10.6mg/kg/day*	*Viraferon 3 MIU + ribavirin >10.6mg/kg/day*
Overall	61% (114/188)	47% (229/483)
Genotype 1	48% (58/122)	34% (111/328)
Genotypes 2/3	88% (51/58)	80% (112/140)

Rebetol was only licensed to be used in combination with ViraferonPeg or interferon alpha-2b. The dose, based on bodyweight, was divided into three bands; 800mg for patients weighing <65kg; 1000mg for patients weighing 65-85kg and 1,200mg for patients weighing >85kg. Section 5.1 of the Rebetol SPC referred, *inter alia*, to Rebetol clinical trials and noted that in one trial response rates were shown to be dependent on the dose of Rebetol. In patients who received 10.6mg/kg, regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6mg/kg, while response rates in patients that received >13.2mg/kg Rebetol were even higher. This data appeared to be the same as that published by Manns *et al*. A bar chart in leavepiece (i), and a different one in leavepiece (ii) both referred to 'ViraferonPeg 1.5mcg/kg + Rebetol >10.6mg/kg'. The Panel noted that the Rebetol SPC did not refer to a larger dose than 1,200mg which was for patients of 85kg or more. Once a patient weighed more than 113.2kg, however, a dose of 1,200mg Rebetol would equate to less than 10.6mg/kg. The Panel considered that at that point weight would become a prognostic factor for SVR.

In the Panel's view the claim 'When ViraferonPeg and Rebetol are dosed according to bodyweight, in line with their licence, weight ceases to be a prognostic factor for SVR' ignored the fact that, given the dosage instructions in the SPC, in heavy patients (>100kg) the dose of ViraferonPeg would fall below 1.5mg/kg and in others (>113.2kg) the dose of Rebetol would be <10.6mg/kg. In these patients weight would be a prognostic factor. The Panel considered that the claim was misleading in that regard. A breach of Clause 7.2 was ruled. The Panel also considered that the claim was exaggerated in that it implied that in all patients, whatever their weight, weight was not a prognostic factor. A breach of Clause 7.10 was ruled.

2 Claim 'ViraferonPeg and Rebetol, when dosed according to body weight in line with their licence, is the only pegylated interferon/ ribavirin combination for which weight is no longer a prognostic factor for SVR'

This claim appeared in all four leavepieces.

COMPLAINT

Roche alleged that for much the same reason as in point 1 above, this claim was inaccurate and did not reflect all available evidence in breach of Clause 7.2. Indeed a peer-reviewed critique of weight-based dosing of pegylated interferons reinforced Roche's position that it was inaccurate to state that weight was no longer a prognostic factor with this combination (Ferenci 2003). Ferenci stated '… overweight US patients responded less well to [Pegasys]/ribavirin than patients with normal body weight …. A similar albeit less-pronounced effect of body weight was noted for standard interferon/ribavirin and [ViraferonPeg]/ribavirin therapy'. The author also stated 'What is clear, is that although body weight appears to be a negative predictor of response (albeit relatively minor when compared to viral factors such as genotype and viral load), the negative effects of increased body weight *cannot* [Roche's emphasis] be overcome by weight-based dosing' and 'The impact of weight-based dosing in general is overestimated and certainly not needed when [Pegasys] with a restricted volume of distribution is used. Whether weight-based dosing of [ViraferonPeg] provides any benefit over a flat dose of the drug remains to be studied'. Roche noted that Ferenci had received support from both Roche and Schering-Plough.

In intercompany dialogue Schering-Plough had defended its claims by referring to the following statements which Roche presumed were from its internal literature: 'In the pivotal study with 1219 patients looking at weight-based pegylated interferon alfa 2b therapy in patients with chronic hepatitis C, Lindsay *et al* performed a logistic regression analysis of independent predictive factors for cure. With weight-based dosing the weight of the patient did not influence their chance of cure.' and 'Similarly in the pivotal trial of combination therapy with pegylated interferon Manns *et al* concluded that when both components of the antiviral therapy were given according to patient's [sic] weight (in accordance with the UK summary of product characteristics (SPC)) patient's [sic] weight as a predictor of response 'was no longer significant''.

These two statements did not represent a consensus of opinion because they were based on a post-hoc analysis. The post-hoc analysis performed by the FDA showed something quite different. In addition, closer reading of Manns *et al* was clearly at odds with this second statement.

RESPONSE

Schering-Plough noted that this complaint stemmed from the fact that 'These two statements did not represent the consensus of opinion because they were based on post hoc analysis …'.

Schering-Plough's ViraferonPeg and Rebetol was the only pegylated interferon/ribavirin combination that was dosed according to weight. Secondly, as previously discussed, when dosed according to the licence, weight was removed as a prognostic factor (Manns *et al*). Additionally the data already supplied had satisfied the rigorous licensing processes of the EMEA and MHRA.

Schering-Plough repeated that it had provided clinical trial data and a copy of the FDA transcript November 2002. This substantial document laid out clearly the extensive discussions that took place at an Antiviral Drugs Advisory Committee meeting including substantial review on the question of dosing in relation to weight and its impact on both efficacy (SVR) and toxicity. The Chairman of the committee stated 'Weight is probably one of the more important variables because we can actually respond to it as opposed to other demographic factors'.

Therefore, on the basis of the substantial body of evidence available Schering-Plough did not consider the claim was in breach of Clause 7.2.

PANEL RULING

The Panel noted its comments at point 1 above and considered that they applied here. In the Panel's view weight would be a prognostic factor for SVR, particularly in very heavy patients. As in point 1 above the Panel considered that the claim at issue was inaccurate and did not reflect all of the available evidence. A breach of Clause 7.2 was ruled.

3 Claim 'ViraferonPeg + Rebetol provide the opportunity to individualise care by dosing according to weight:

- **eliminating body weight as a prognostic factor**
- **delivering high SVRs in a wide population'**

This claim appeared in leavepieces (i) and (ii).

COMPLAINT

Roche stated that the first bullet point was an exaggerated claim and was inaccurate in breach of Clauses 7.2 and 7.10 for reasons described above.

With regard to the second bullet point, Roche noted that in Case AUTH/1474/6/03 Schering-Plough's claim that 'Individualised weight adjusted [ViraferonPeg] plus ribavirin therapy maximises the chance for SVR in the broadest HCV population' was ruled in breach of Clause 7.10 of the Code on the basis that it exaggerated the data. Looking at subgroups of those patients with genotype 2 or 3, those patients with high viral loads and those with fibrosis/ cirrhosis, there was no evidence to claim superiority 'in the broadest population of HCV patients'.

Manns *et al* stated that 'the primary benefit of [ViraferonPeg] plus ribavirin for this group [genotype 2 or 3] may be convenience, ease of administration of a once-weekly injection compared with alternate-day injections, and the potential for better compliance'. In Case AUTH/1474/4/03 the Panel considered that this claim 'conflicted with the message of superiority in the 'broadest population of HCV patients' and 'maximises the chance for an SVR'. It now appeared that Schering-Plough had slightly watered down its message by claiming that 'ViraferonPeg + Rebetol provide the opportunity to individualise care by dosing according to weight … delivering high SVRs in a wide population'.

Given that the only subgroup in which ViraferonPeg had been shown to be superior to standard interferon was genotype 1, low viral load which represented approximately 25% of the UK HCV population, even claiming high SVRs in a wide population was misleading.

Roche was surprised however that Schering-Plough had persisted with this kind of claim despite previous censure and undertaking not to use this exaggerated claim. Roche also considered that by slightly re-wording the claim as stated, Schering-Plough was acting neither within the spirit, nor the letter of the Code. Roche alleged a breach of Clause 2 due to the breach of the previous undertakings.

RESPONSE

Schering-Plough stated that it had dealt with body weight as a prognostic factor previously and would now focus its attention on the claim 'delivering high SVRs in a wide population'.

Schering-Plough noted that Pegintron/ViraferonPeg for hepatitis C was licensed in at least 50 countries world wide as of July 2003 and provided a list of over 100 references on the differing populations investigated. These included 44 references for PegIFN and co-infection with HIV-HCV, 20 references for PegIFN and genotypes other than type 1, 11 references for PegIFN and racial differences, 4 references for the use of PegIFN and patients with renal dysfunction, 33 references for the use of PegIFN in liver transplant patients and 5 references for use of PegIFN alfa in high viral load patients.

Schering-Plough considered these data objectively and self-evidently supported its reference to a wide population. High SVRs had been achieved in this population. The SPC demonstrated a high SVR (up to 88% for genotype 2 or 3). Schering-Plough's promotional copy clearly and deliberately avoided the use of superlatives. The term 'wide population' was not an all-embracing claim.

Manns *et al* used pegylated interferon alfa-2b in patients with genotypes 1 through to 6. Although, as previously noted by Roche, most patients in the study were genotype 1, over 300 patients enrolled were of genotype non-1 (ie genotypes 2-6). Schering-Plough had provided the data on this for completeness and had briefly summarised the remaining references cited above.

Schering-Plough noted that Roche had stated that the only subgroup in which ViraferonPeg had been shown to be superior to standard interferon was genotype 1, low viral load which represented approximately 25% of the UK HCV population. Roche had therefore considered that claiming high SVRs in a wide population was misleading. However, Harris *et al* (1999) stated that the most prevalent HCV genotypes in England and Wales were types 1a (32%), 1b (15%) and 3a (37%). Hence, these data showed that 47% of patients were of genotype 1. This genotype was even more prevalent in areas such as the North East. Watson *et al* (1996) looked at the epidemiology and genotypes in the North East and found that 69% of patients were of genotype 1a. Therefore, Schering-Plough considered that along with the references presented, that the use of ViraferonPeg in genotype 1 and the varying genotypes represented in the cited literature constituted a wide population.

Schering-Plough concluded that the substantial data presented showed that ViraferonPeg and Rebetol were able to deliver high SVRs in a wide population. Consequently, Schering-Plough submitted that it was not in breach of Clause 2 or of Clause 7.10. Schering-Plough added that it had complied with the spirit and the letter of the previous rulings and that it had been assiduous in maintaining compliance with its undertakings as outlined in Clause 22 of the Code.

PANEL RULING

The Panel noted its comments at point 1 above and considered that they applied here with regard to the bullet point 'eliminating body weight as a prognostic factor'. The Panel considered that the claim was misleading and exaggerated as alleged. Breaches of Clauses 7.2 and 7.10 were ruled.

With regard to the second bullet point 'delivering high SVRs in a wide population' the Panel considered that it was sufficiently different from the claim 'Individualised weight adjusted [ViraferonPeg] plus ribavirin therapy maximises the chance for SVR in the broadest HCV population' which was ruled in breach of the Code in Case AUTH/1474/6/03 for it not to represent a breach of the undertaking given in that case. No breach of Clause 22 was ruled. There could thus be no breach of Clause 2 of the Code and the Panel ruled accordingly.

The Panel noted that the claim 'delivering high SVRs in a wide population' was not a comparative claim. The claim was referenced to Manns *et al*. The Panel noted that Schering-Plough had submitted lists of references which reported the use of ViraferonPeg/ Rebetol in patients with co-infection with HIV and in patients with previous organ transplantation; these two groups had been excluded from the study by Manns *et al*. The Panel accepted that ViraferonPeg/ Rebetol had been used in a wide range of patients but noted that it had not been provided with the data to show that patients in each of the treated groups achieved a high SVR. On the basis of the data before it the Panel considered that the claim was exaggerated as alleged and ruled a breach of Clause 7.10 of the Code.

4 Claim 'ViraferonPeg is the only pegylated interferon in a pre-filled pen to help encourage patient adherence'

This claim appeared in leavepiece (ii).

COMPLAINT

Roche stated that this claim could be read in a number of ways. One meaning was that ViraferonPeg was the only pegylated interferon that was presented in such a way as to encourage patient adherence by virtue of its pre-filled pen. This disparaged Pegasys by implication as Pegasys was presented in a pre-filled syringe. Roche alleged a breach of Clause 8.1. There were also no data to support the claim that the pre-filled pen helped encourage adherence. Compared to what? Roche alleged that the claim was not capable of substantiation in breach of Clause 7.4.

RESPONSE

Schering-Plough did not recognise the argument or logic behind Roche's 'interpretation' that the claim disparaged Pegasys. The claim was objectively and factually accurate in that only Schering-Plough supplied pegylated interferon in a pre-filled pen.

Schering-Plough noted Roche's additional point that 'there are no data to support the claim of encouraging patient adherence'. Giving patients choice, including the removal of part of the challenge of preparation for self-injection was a pragmatic approach designed to encourage patient adherence. In this regard Schering-Plough submitted it was not in breach of Clauses 7.4 or 8.1.

PANEL RULING

The Panel noted that ViraferonPeg was, as stated in the claim, the only pegylated interferon to be presented in a pre-filled pen. No data had been submitted, however, to show that such a presentation helped encourage patient adherence. In that regard the Panel considered that the claim had not been substantiated. A breach of Clause 7.4 was ruled. The Panel did not consider that the claim disparaged Pegasys. No breach of Clause 8.1 was ruled.

5 Claim 'Weight-based dosing with ViraferonPeg and Rebetol makes a difference'

This claim appeared in leavepiece (iii).

COMPLAINT

Roche alleged that this claim was a hanging comparison in breach of Clause 7.2.

RESPONSE

Schering-Plough stated that when it developed this leavepiece it reflected the clinical acceptance that when patients were treated with its products, in a manner consistent with its licences, such treatments made a difference to them, their underlying condition and to their prognosis. In addition, weight-based dosing with ViraferonPeg and Rebetol made a difference to physicians treating a serious pathology and Schering-Plough provided them with a choice to individualise dosing according to the weight of their patients.

Gish *et al* (2002) evaluated weight-based ViraferonPeg plus ribavirin and assessed its effects on health-related quality of life (HQL) during treatment and post therapy in treatment naïve patients with chronic HCV infection as compared to interferon alfa-2b plus ribavirin. Patients were followed for 48 weeks and self reported HQL was assessed using the generic SF-36 Health Survey administered at baseline, every 12 weeks during the 48-week treatment and 24-week follow-up period.

1530 patients were enrolled into this study and 1153 patients were included in the analysis of weight-based dosing. After 12 weeks of treatment, subjects in the ViraferonPeg group tolerated treatment better than those in the interferon alfa-2b group in all 8 domains (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning role, emotional and mental health) and in 7 out of 8 domains at the end of 48 weeks of treatment. Five out of the 8 domains showed a benefit in favour of the ViraferonPeg group were observed at 24 weeks post-treatment for SVR as well as relapse and non-responders. Overall HQL scores were similar for all

groups although the specific primary domain of vitality was statistically better at 12 weeks for the ViraferonPeg group. This difference in HQL scores during treatment reached statistical significance ($p<0.05$) for the pre-specified primary domain of vitality at 12 weeks of treatment. As reported with interferon alfa-2b and the combination of interferon alfa-2b plus ribavirin in CHC, HQL scores for sustained responders improved from pre-treatment levels while non-responders did not improve. The authors concluded that PegIFN plus ribavirin was more efficacious and had better HQL during treatment as well as post-therapy compared to interferon alfa-2b plus ribavirin for chronic hepatitis C.

While Schering-Plough believed that its claim could be substantiated it had acknowledged to Roche that it could be viewed as a hanging comparison. Consequently, Schering-Plough had advised Roche that it would, in the light of Roche's comments, modify this claim appropriately in the future to avoid such interpretation.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2, hanging comparisons, explained that hanging comparisons whereby a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared must not be made. The Panel did not consider that the claim now at issue 'Weight-based dosing with ViraferonPeg and Rebetol makes a difference' was a hanging comparison as described in the supplementary information. No breach of Clause 7.2 was ruled.

6 Claims 'Efficacy demonstrated in patients with bridging fibrosis/ cirrhosis'

'In a randomised, open label trial, 188 patients received ViraferonPeg 1.5mcg/ kg + Rebetol >10.6mg/kg for 48 weeks'

This claim appeared in leavepiece (iii).

COMPLAINT

Roche alleged a breach of Clause 7.2 as the claims incorrectly implied that ViraferonPeg + Rebetol >10.6mg/kg were prospectively investigated in a randomised, open label trial. The 188 patient cohort actually represented a retrospective sub-set analysis of pre-selected patients out of the intention to treat population of 511 patients.

RESPONSE

Schering-Plough considered that the claims factually described the circumstances under which the data were generated; in that respect it did not believe the claims were inaccurate or in breach of Clause 7.2. However, Schering-Plough had already communicated with Roche on this matter and taking its comments into account, had told Roche that future material would clearly indicate that the 188 patients with the bridging fibrosis/cirrhosis represented a sub-group of the larger study.

PANEL RULING

The Panel considered that the way in which the claims had been presented implied that a discreet and separate trial of 188 patients with bridging fibrosis/cirrhosis had taken place which was not so. The claims were misleading in that regard. The Panel ruled a breach of Clause 7.2.

7 Claim 'NICE states that people who weigh more than the average have a lower response rate to treatment than those who weigh less than the average when the doses of interferon alfa (and ribavirin for combination therapy) are fixed'

This claim appeared in leavepiece (iv).

COMPLAINT

Roche alleged that the claim had been used in a misleading manner in breach of Clause 7.2. The NICE statement on weight was relevant only to standard interferon alfa and not to pegylated interferons. The claim was immediately followed by 'ViraferonPeg and Rebetol, when dosed according to body weight in line with their licence, is the only pegylated interferon/ribavirin combination for which weight is no longer a prognostic factor for SVR'.

Roche considered that the order of these two claims implied extrapolation of the NICE statement on standard interferon to ViraferonPeg and Rebetol. There was no NICE consensus on the effect of weight, SVR and the use of any pegylated interferon. In addition, the NICE statement formed part of its clinical need and practice appraisal, and did not represent the actual NICE recommendation or guidance. As such this claim led the reader to believe that NICE concurred with or even endorsed Schering-Plough's well known marketing strategy. This aimed to differentiate the two pegylated interferons by attempting to confuse the medical community that the different posologies of the two medicines could be extrapolated to differing efficacies.

RESPONSE

Schering-Plough stated that Roche appeared to believe that this claim was misleading because it was 'relevant to standard interferon alfa and not to pegylated interferons'. The claim served to inform physicians clearly that with previous therapies for HCV, weight was a significant prognostic factor.

Schering-Plough had already discussed in depth the evidence for weight-based dosing and ViraferonPeg, and considered that there was no need to elaborate on this further here. Schering-Plough submitted that the page was intended to reinforce the previous statement that with previous therapies weight was one of the prognostic factors for cure. With the ViraferonPeg and Rebetol combination this was not so. The relative juxtaposition of the two statements was not intended to imply extrapolation of the NICE statement. Schering-Plough believed that physicians would be interested in NICE statements relevant to their prescribing choices and practice.

Schering-Plough stated that in its promotional materials it had clarified the importance of weight in addition to other significant predictors of response. It had confirmed the need to dose its products according to weight and in line with its licence. Schering Plough took this approach to ensure that physicians prescribed and dosed its products appropriately in order to optimise individual patient responses. Indeed, elsewhere Schering-Plough's materials listed nine factors that could affect efficacy in the treatment of HCV. Weight was among those listed and cited by NICE and as mentioned above was also a clear focus for discussion within the FDA's Antiviral Drugs Advisory Committee.

In summary, Schering-Plough had previously accepted some of Roche's comments and had advised it as such in previous correspondence. Schering-Plough confirmed once again that it had undertaken to amend its detail aids accordingly as outlined in points 5 and 6 above. That aside, Schering-Plough believed that its promotional material was consistent with the published data, clinical experience and the SPC. Furthermore Schering-Plough was fully cognisant of its agreements with the MHRA last year and with previous rulings under the Code.

Consequently, Schering-Plough considered sincerely that it had complied fully with the undertakings in relation to rulings under the Code and hoped that this response would allow closure to be brought satisfactorily to the issues detailed above.

PANEL RULING

The Panel noted that the statement from NICE regarding the influence of bodyweight on response to fixed doses of interferon alfa (and ribavirin for combination therapy) was immediately followed by a claim for ViraferonPeg and Rebetol being the only pegylated interferon/ribavirin combination for which weight was no longer a prognostic factor for SVR. The Panel considered that juxtaposing the two statements was misleading in that some readers would assume that the NICE statement related to **pegylated** (emphasis added) interferon alfa when it did not. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **10 August 2004**

Case completed **29 November 2004**

CASE AUTH/1618/8/04

CONSULTANT DERMATOLOGIST v SERONO

Efalizumab advisory board

A consultant dermatologist complained about an invitation sent to him on behalf of Serono to participate in an efalizumab advisory board. The invitation stated that those participating would input on various topics including the long-term management of psoriasis and provide a regional perspective on issues and considerations. An honorarium of £500 was offered in addition to reimbursement of any travel expenses and overnight accommodation if required.

The complainant stated that the invitation was clearly a poorly disguised attempt to get some support from dermatologists for the promotion of the new medicine efalizumab as a treatment for psoriasis. Efalizumab was a promising treatment as judged by recently published phase 3 trials. However, the description of the purpose of the meeting was not credible and there was over-generous hospitality offered. The complainant questioned whether this was an ethical or acceptable method for a pharmaceutical company to develop and promote its product.

The Panel noted that the meeting in question was one in a series of seven planned, each with ten attendees. The Panel did not accept Serono's submission that because the invitation was sent by its communications agency and did not use the brand name or specific indication it was not promotional. The invitation did, however, state the generic name of the medicine and referred to psoriasis in general. The invitation asked recipients to participate in the efalizumab advisory board series. Serono was described as developing innovative treatment solutions. The invitation continued 'Of particular interest is efalizumab, a long-term treatment for psoriasis …'. Reference was made to receipt of a positive opinion from the Committee for Human Medicinal Products (CHMP) which was described as a pivotal step towards the granting of the marketing authorization.

No agenda was sent with the invitation. From the agenda supplied by Serono the meeting would start at 6pm with refreshments, followed by an introduction to Serono and objectives for the meeting. This ten minute session was followed by a twenty minute overview of new biologics for psoriasis with ten minutes for questions, and an hour was spent on a group discussion. Fifteen minutes were allowed for a buffet dinner followed by an hour for participants to identify five key local issues for use and funding of new biological treatment. The meeting ended at 9pm after a twenty minute feedback session.

The Panel was concerned about the wording of the invitation. Efalizumab was linked to the phrase 'innovative treatment solutions'. The positive opinion of the CHMP was referred to. The Panel was concerned that by not including sufficient details the invitation gave the impression that the meeting was a promotional meeting. The Panel considered that the invitation was not sufficiently clear about the precise role of the invitees and how much work would be involved. The purpose of the meeting had not been made sufficiently clear.

The presentations included eight slides introducing the company and highlighting three therapeutic areas in which it was developing products and its commitment to dermatology. Details of the product were provided. The overview of biologics in psoriasis referred to some of the issues that Serono wanted information on, including funding issues and limitations of current treatments. A presentation 'Biologics in Psoriasis' gave details of the immunological basis of psoriasis, therapeutic targets, and the mode of action of efalizumab and a summary of its development.

Health professionals were to be paid £500 in respect of their participation. There was no prereading and very limited detail in the invitation of the contribution and information expected from attendees. The failure to send the agenda with the invitation added to the impression that the meeting was a promotional one.

On balance the Panel decided that the invitation was not sufficiently clear that the meeting was non promotional. It was not clear about the role and amount of work to be undertaken by participants. The offer to pay an honorarium in conjunction with the details as stated in the invitation was inappropriate and contrary to the requirements of the Code; a breach was ruled.

On balance the Panel thus decided that the invitation amounted to promotion prior to the grant of the marketing authorization. A breach of the Code was ruled. It was thus not disguised promotion as alleged; no breach of the Code was ruled in that regard.

The Panel noted its rulings and its comments on the agenda above. Whilst the Panel had considered that the impression given by the invitation was inappropriate, on balance, it did not consider that the actual meeting itself failed to meet the requirements of the Code. No breach was ruled.

A consultant dermatologist complained about an invitation which had been sent to him on behalf of Serono Limited to participate in an efalizumab advisory board.

The invitation from a communications agency stated that efalizumab had received a positive opinion as a pivotal step towards the granting of a marketing authorization. The invitation stated that those participating would input on various topics including the long-term management of psoriasis and provide a regional perspective on issues and considerations. The advisory board would be held from 6-9pm. A buffet dinner would be served during the meeting. An honorarium of £500 was offered in addition to reimbursement of any travel expenses and overnight accommodation if required.

When the complaint was received, efalizumab was awaiting the grant of its marketing authorization. The medicine would be marketed as Raptiva, a subcutaneous injection for the treatment of moderate to severe chronic plaque psoriasis.

COMPLAINT

The complainant stated that the invitation was clearly a poorly disguised attempt to get some support from dermatologists for the promotion of the new medicine efalizumab as a treatment for psoriasis. Efalizumab was a promising treatment as judged by recently published phase 3 trials. However, the description of the purpose of the meeting was not credible and there was over-generous hospitality offered. The complainant questioned whether this was an ethical or acceptable method for a pharmaceutical company to develop and promote its product. He also had some doubt about whether acceptance of the invitation would contravene the rules governing gifts and favours for NHS staff.

When writing to Serono, the Authority asked it to respond in relation to Clauses 3.1, 10.1, 18.1 and 19.1 of the Code.

RESPONSE

Serono noted that this advisory board meeting was scheduled to run in either September or October and the agenda had not yet been issued.

Raptiva (efalizumab) had recently received a positive opinion from the Committee for Human Medicinal Products (CHMP), and formal approval from the European Commission was awaited. Accordingly, it was not appropriate for Serono to supply the Raptiva summary of product characteristics (SPC) to the Authority at the present time.

Serono responded in relation to each of the clauses cited by the Authority as follows:

In relation to Clause 3.1 Serono stated that efalizumab was a new class of biological product representing a significant departure from current practice.

As psoriasis was a new therapeutic area for Serono, regional advisory boards were set up to collect information from leading clinicians on current issues in the disease area and enable the company to understand regional funding situations for dermatology. As stated in the invitation, the purpose of the meeting was to gain 'input on various topics including the long-term management of psoriasis and provide a regional perspective on issues and considerations'. One clinical issue concerned the route of administration [subcutaneous injection] of efalizumab which was different from current therapies and so the resource required to implement this needed to be assessed. Another key element was the funding of treatment. The future funding of efalizumab was expected to be complicated and variable across the UK in view of the ongoing National Institute for Clinical Excellence (NICE) appraisal of the product. There was particular uncertainty in this area as funding decisions were delegated to a local level and there was presently no published consensus regarding the use of biologicals for dermatology. Serono had no NHS team able to assess the funding situation and therefore it relied on advisory boards to understand the market.

To ensure that the format of the advisory boards was suitable for interactive discussion the numbers of clinicians were limited to ten. Both the invitation and meetings were non-promotional. In particular, the invitations were sent out by the communication agency so that a third party interacted with the health professionals, rather than Serono. Neither the proprietary name Raptiva nor the specific indication was mentioned in the invitation.

Serono did not consider that the invitation or the planned advisory board meetings were promotional in nature.

In relation to Clause 10.1 Serono stated that advisory boards had been used by pharmaceutical companies for many years to gain advice from a group of experts in their field. Consultant level physicians would be expected to be familiar with the remit of such advisory boards and it was anticipated that opinion-leading physicians would be members of several advisory boards at a given time. The invitation clearly stated the purpose of the meeting in the heading.

In relation to Clause 18.1 Serono stated that the honorarium of £500 was proposed to cover time spent travelling and at the board meeting. According to BMA guidelines the cost for a locum for half a day was approximately £300. As all of the attendees were senior full time consultant dermatologists and some could have travelled for $2^1/2$ hours a fee of £500 seemed reasonable. Serono noted that the attendees were expected to provide advice to the company, and were not simply attending a presentation.

In relation to Clause 19.1 Serono stated that at the advisory board meeting it intended to provide a buffet meal at £17.50/head to be taken as a working dinner. For those attendees travelling some distance, overnight accommodation (£120 per room) was to be provided in a 4 star hotel. Accordingly, the planned hospitality was secondary to the purpose of the meeting and the level of hospitality was appropriate and not out of proportion to the occasion. Also, taking into account the seniority of the attendees, Serono did not consider the cost to be in excess of that which they would normally pay for themselves.

Serono chose not to send any pre-reading as the product was unlicensed and the company did not consider it appropriate to send out clinical trial results at this stage.

The meetings were scheduled to last 3 hours, excluding a short break for a buffet dinner. The meetings followed a standard advisory board format, starting with an introduction to Serono as it was new to the disease area, a medical presentation on the clinical trial base for efalizumab, a discussion on the data presented, identification of unmet needs in the psoriasis market, current opinion on biologicals and local funding issues/requirements. Any information presented would be scientific in nature and any information collected would not be divulged further.

Seven meetings were to be held. The venues had been chosen based on the ease of travel to each. Dates had yet to be confirmed awaiting the response from Serono's invitation.

In response to a request for further information Serono stated that the purpose of the advisory boards

was not to discuss product-specific matters but to collect expert advice mainly on anticipated local funding issues for biologicals. Apart from a short presentation on the mode of action of the product there was no further emphasis on product-specific matters.

Serono stated that when Raptiva was introduced in UK it expected to be faced with regional funding shortages. It anticipated particular uncertainty in this area as funding decisions were delegated to a local level. This view was supported by two recent UK surveys. Firstly a major survey by the British League against Rheumatism and the British Association of Rheumatology showed that doctors were being prevented from prescribing the products they wanted to patients with rheumatoid arthritis. The survey revealed wide variations across the UK, across regions and even within trusts. Consultants in just one in six trusts stated that they had adequate funding to pay for the treatment. Almost one in three consultant rheumatologists in 185 trusts stated that they were prevented from prescribing registered anti-TNF medicines. These biotechnology products were similar to efalizumab. A second publication by Cancer BACUP revealed substantial differences throughout the UK in access to the breast cancer medicine Herceptin. The data showed that 14% of women in the Midlands had access to the treatment compared with 61% in the South West. Following publication of the report the Health Secretary announced a government investigation into postcode prescribing. Serono submitted that these surveys demonstrated regional funding differences in the presence of NICE guidelines on the products. In the case of Raptiva, the absence of NICE guidelines at the time of launch made regional funding a critical issue.

A copy of the agenda for the dermatology advisory board was provided as were copies of the two presentations prepared by the company.

Serono stated that the formal approval for Raptiva from the European commission was expected in approximately two weeks' time. It confirmed that most of the advisory boards would be held after the date of formal approval. In view of the licence status, at the present time it was not able to provide the UK SPC. The product was already approved in leading countries such as Switzerland and the US and a copy of the US SPC was provided.

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 on subjects such as management of a disease, regional factors, if relevant, and how their products should be promoted. The selection of attendees had to stand up to independent scrutiny and the arrangements had to comply with the Code.

The meeting in question was one in a series of seven planned each with ten attendees. The Panel noted Serono's submission that the purpose of the meeting was to collect information on current issues in the disease area and to understand the regional funding situation. The Panel did not accept Serono's submission that because the invitation was sent by its communications agency and did not use the brand name or specific indication it was not promotional. The invitation did, however, state the generic name of the medicine and referred to psoriasis in general. The invitation asked recipients to participate in the efalizumab advisory board series. Serono was described as developing innovative treatment solutions. The invitation continued 'Of particular interest is efalizumab, a long-term treatment for psoriasis …'. Reference was made to receipt of a positive opinion from the Committee for Human Medicinal Products (CHMP) which was described as a pivotal step towards the granting of the marketing authorization.

No agenda was sent with the invitation. From the agenda supplied by Serono the meeting would start at 6pm with refreshments followed by an introduction to Serono and objectives for the meeting. This ten minute session was followed by a twenty minute overview of new biologics for psoriasis with ten minutes for questions. An hour was spent on a group discussion on the limits of current treatments, local treatment protocols and current opinion on biologics within the local trust. Fifteen minutes were allowed for dinner followed by an hour for participants to identify five key local issues for use and funding of new biological treatment. The meeting ended at 9pm after a twenty minute feedback session.

The Panel was concerned about the wording of the invitation. Efalizumab was linked to the phrase 'innovative treatment solutions'. The positive opinion of the CHMP was referred to. The Panel was concerned that by not including sufficient details the invitation gave the impression that the meeting was a promotional meeting. The Panel considered that although the invitation mentioned the interactive nature of the meeting in general terms, it was not sufficiently clear about the precise role of the invitees and how much work would be involved. Given the limited information in the invitation and absence of an agenda the purpose of the meeting had not been made sufficiently clear.

The presentations included eight slides introducing the company, highlighting three therapeutic areas in which it was developing products and its commitment to dermatology. Details of the product were provided. The overview of biologics in psoriasis referred to some of the issues that Serono wanted information on, including funding issues and limitations of current treatments. A presentation 'Biologics in Psoriasis' gave details of the immunological basis of psoriasis, therapeutic targets, the mode of action of efalizumab and a summary of its development.

Health professionals were to be paid £500 in respect of their participation. There was no prereading and very limited detail in the invitation of the contribution and information expected from attendees. The failure to send the agenda with the invitation added to the impression that the meeting was a promotional one.

The Panel considered that it was difficult in such cases to determine precisely where the boundary lay. On

balance the Panel decided that the invitation was not sufficiently clear that the meeting was non promotional. It was not clear about the role and amount of work to be undertaken by participants. The offer to pay an honorarium in conjunction with the details as stated in the invitation was inappropriate and contrary to the requirements of Clause 18.1 of the Code; a breach of that clause was ruled.

On balance the Panel thus decided that the invitation amounted to promotion prior to the grant of the marketing authorization. A breach of Clause 3.1 was ruled. It was thus not disguised promotion as alleged; no breach of Clause 10.1 was ruled.

The Panel noted its ruling of a breach of Clause 18.1 and its comments on the agenda above. Whilst the Panel had considered that the impression given by the invitation was inappropriate, on balance, it did not consider that the actual meeting itself failed to meet the requirements of Clause 19.1.

Complaint received **10 August 2004**

Case completed **10 Devember 2004**

CASE AUTH/1619/8/04

NOVO NORDISK v AVENTIS PHARMA

Arrangements for insulin meeting

Novo Nordisk complained about a meeting arranged by Aventis Pharma for health professionals. The meeting, entitled 'Insulin in the management of type 2 diabetes', had taken place partly on a ferry between Fishguard and Rosslare and partly at a hotel in Rosslare.

On the first day, according to Aventis, there were presentations lasting two hours and 40 minutes on the ferry, followed by another one hour presentation in a hotel in Rosslare. On the second day, presentations lasted two hours on the ferry on its return trip to Fishguard.

Novo Nordisk did not consider that the venue and trip arrangements were appropriate. In Novo Nordisk's view health professionals might have been attracted to the trip itself rather than by the educational content. In addition, the level of hospitality was out of proportion to the educational content. The impression created by the arrangements could potentially bring disrepute to the industry in breach of Clause 2.

The Panel noted that the supplementary information to the Code stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues.

The Panel noted that the meeting agenda was educational and that its content had not been criticised. There had been five hours of presentations. In the Panel's view neither the mode of transport nor the hotel accommodation provided for the meeting could be considered extravagant; delegates would be attracted by the educational content rather than the trip to Rosslare. Delegates had left Rosslare by 09:00 on the Sunday morning. There had been very limited free time. In the Panel's view, Rosslare would not be considered an exotic location. The Panel did not consider that the cost was generally more than delegates would pay if they were paying themselves.

The Panel was surprised that no suitable accommodation was available in Pembrokeshire/Carmarthenshire. The meeting could have been held over the course of a working day.

Nonetheless, the Panel considered that, on balance, for the reasons listed above, the arrangements for the meeting were not unacceptable. The Panel ruled no breach of the Code.

Upon appeal by Novo Nordisk, the Appeal Board noted that Aventis' decision to use the ferry and travel to Ireland was a result of advice from a travel company that suitable hotel accommodation would not be available on the date of the meeting. The date of the meeting could not be changed as speakers had already been booked. However, Aventis had no knowledge of the extent of the travel company's search for a venue. The Appeal Board considered that the meeting could have been held at a number of venues, the choice was not limited to hotels or ferries. A group of UK health professionals had been taken outside the UK. There had to be valid and cogent reasons for holding meetings outside the UK. The Appeal Board considered that the delegates might have been attracted by the associated hospitality and the meeting could have been held locally over the course of a working day. The Appeal Board was concerned about inaccuracies and inconsistencies in Aventis' submissions which were unacceptable.

The Appeal Board noted from Aventis that the meeting invitation had been signed off in April and sent in June. The ferry ticket and refreshments on the ferry had been paid by card on the day of the meeting. The Appeal Board queried whether this was normal practice considering the invitation had been signed off some two months previously.

The Appeal Board considered that the cost of the meeting at £153.75 per head was not unreasonable, it would not exceed what delegates would pay if they were paying for themselves. The educational content at nearly six hours was not unreasonable and there was limited free time.

The Appeal Board considered, however, that Aventis had failed to provide valid and cogent reasons for

holding the meeting on the ferry and in Ireland. Thus the Appeal Board ruled a breach of the Code.

Novo Nordisk Limited complained about a meeting arranged by Aventis Pharma Ltd. The meeting, entitled 'Insulin in the management of type 2 diabetes', had taken place partly on a ferry between Fishguard in Wales and Rosslare in the Republic of Ireland and partly at a hotel in Rosslare.

COMPLAINT

Novo Nordisk stated that on 11-12 June Aventis Pharma took thirty-five health professionals from Fishguard to Rosslare on a boat, with an overnight stay in a hotel at Rosslare. On the first day, according to Aventis, there were presentations lasting two hours and 40 minutes on the boat, followed by another one hour presentation in a hotel in Rosslare. On the second day, presentations lasted two hours on the boat on its return trip to Fishguard.

Novo Nordisk asked the Authority to investigate how the event was advertised to the health professionals and how they were recruited to the trip. Novo Nordisk was also interested to know if the meeting was certified as part of it took place outside the UK. Aventis had submitted that the cost per head was £109 but this seemed rather low given the total cost of the boat, the overnight hotel accommodation and dinner involved. Novo Nordisk asked the Authority to also investigate whether there was other entertainment or hospitality involved. Novo Nordisk did not consider that the venue and trip arrangements were appropriate for educational purposes. In Novo Nordisk's view health professionals might have been attracted by the trip itself rather than by the educational content. In addition, the level of hospitality was out of proportion to the educational content. Novo Nordisk alleged a breach of Clause 19.1 of the Code. The company further alleged that the impression created by the arrangements could potentially bring disrepute to the industry in breach of Clause 2.

RESPONSE

Aventis stated that 28 attended the meeting (22 delegates, 4 speakers and 2 Aventis personnel). Half of the delegates were physicians, evenly split across primary and secondary care, the others were nurses. Sixty had been invited. The majority of delegates came from Pembrokeshire, the others were from Carmarthenshire.

No further materials were provided to delegates either in preparation for or during the meeting itself.

The meeting took place during a return sea voyage between Fishguard and Rosslare, as well as in Rosslare itself. Departure was from Fishguard at 14.30 on Saturday, 12 June, and the Chairman opened the meeting at 14.50. Three presentations by expert speakers followed until 17.30, at which time there was a question and answer session. Details of the three presentations were provided. Afternoon refreshments were served between two of the sessions.

The boat docked at 18.00 and the attendees were taken to the hotel by bus. A presentation took place between 20.00 and 21.00; details were provided. Tea and coffee were served during the session. Dinner was served at 21.00. All delegates stayed at the hotel.

At 09.00 on Sunday, 13 June, the boat departed Rosslare. Two speaker sessions took place between 09.30 and 11.30; details were provided. The boat docked at Fishguard at 12.00 and the meeting closed.

The meeting was certified and approved by Aventis which considered carefully the decision to run the meeting outside the UK. The intention had been to run the meeting in the Pembrokeshire/ Carmarthenshire area, ie in the vicinity of the practices and hospitals of the invitees. However no appropriate venue could be found. Venues further afield in Wales were considered; however the time required for travel ruled this option out.

Whilst exploring possible venues in the area, the travel agency retained by Aventis suggested the Rosslare ferry as having suitable room and facilities for the planned meeting. In addition, suitable hotel accommodation and conferences facilities were available in Rosslare itself. Aventis considered there were both valid and cogent reasons for conducting the meeting outside the UK.

Details of the costs for the meeting were provided by Aventis; the cost per planned delegate (30) was £153.75. This differed from the figure of £109 cited in Aventis' letter to Novo Nordisk, due to a simple accounting error in a spreadsheet.

Whilst part of the meeting took place outside the UK, based on the agenda and cost Aventis considered that the quality and quantity of the educational programme (a total of nearly 6 hours) was the reason for attendance by the health professionals, rather than the venue (standard ferry) and limited hospitality (refreshments, meals and accommodation only). Aventis was confident that the meeting was appropriate to the audience and within Clause 19.1 of the Code.

PANEL RULING

The Panel noted that the supplementary information to Clause 19.1 of the Code stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. Each case had to be judged on its own particular merits.

The Panel considered that the educational content of the meeting was not unreasonable. There had been five hours of presentations. In the Panel's view neither the mode of transport nor the hotel accommodation provided for the meeting could be considered extravagant; delegates would be attracted by the educational content rather than the associated hospitality, venue or location. Delegates arrived in Rosslare at 18.00 on the Saturday evening and left Rosslare at 09:00 on the Sunday morning. There had been very limited free time. The Panel did not consider that the cost was generally more than delegates would pay if they were paying for themselves.

The Panel was surprised that no suitable accommodation was available in Pembrokeshire/ Carmarthenshire. The meeting could have been held locally over the course of a working day. Nonetheless, the Panel considered that, on balance, for the reasons listed above, the arrangements for the meeting were not unacceptable. The Panel ruled no breach of Clause 19.1. The Panel did not consider that the arrangements were such as to bring the industry into disrepute. No breach of Clause 2 was ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk noted that the arrangement was unusual for a medical meeting. Health professionals might be attracted to the cruise and the overnight stay in Ireland, rather than the medical content of the meeting itself.

Novo Nordisk noted that a quick search on the internet had yielded a number of possible hotels. There were probably other venues such as hospital meeting rooms and GP surgeries which were suitable for the meeting. Alternatively numerous venues could be found in Swansea.

Novo Nordisk alleged that should there truly be no suitable venue in Pembrokeshire, a more reasonable arrangement would be to hold the meeting in neighbouring Carmarthenshire. As the meeting was on a Saturday and the medical content lasted six hours the meeting could be held within one day. It was not necessary to organise the meeting over two days, with an overnight stay at Rosslare in Ireland where dinner and alcohol were served.

Novo Nordisk noted that the actual cost of the meeting was £153.75 per head and not £109 as cited by Aventis in its first letter.

Novo Nordisk alleged that the impression created by the arrangements for this meeting was important in attracting health professionals to attend. Therefore in Novo Nordisk's view the arrangements were in breach of Clause 19.1 of the Code.

Novo Nordisk stated that there was an inconsistency in two of the Panel's recent rulings. In Case AUTH/1603/7/04, Aventis had complained about two medical meetings held by Novo Nordisk in conjunction with the launch of insulin detemir in the UK; one at a boat restaurant in London and another one at a football club. The cost per head for the meeting at the football club was £45.39. While the invitation had mentioned the England v Croatia football match, the meeting was arranged prior to the football match being known, and the match was broadcast live on national TV immediately after the meeting had finished, which would not have allowed participants to return home in time to watch the match. The Panel ruled in Case AUTH/1603/7/04 that 'the invitation was such that it sought to attract attendees to the meeting by virtue of the venue and the associated hospitality and not the educational content'. The Panel had further ruled that 'the hospitality provided was out of proportion to the occasion' and 'the impression created by the arrangements was important', a breach of Clause 19.1 was ruled.

In Novo Nordisk's view the same standards should apply to the current case, Case AUTH/1619/8/04; the per head cost was £153.75, the arrangement involved a boat trip across the Irish Sea and an overnight stay in Ireland, with dinner and wine. The impression created here was certainly important. The cost per head was three times what Novo Nordisk spent.

COMMENTS FROM AVENTIS

Aventis stated that its response to the original complaint explained fully the nature of the meeting including invitees and agenda together with details of the arrangements and associated cost. To summarise: delegates were physicians and nurses spread across both primary and secondary care; the educational content of the meeting was wide ranging in its scope and included presentations and workshops on: the new GMS contract, insulin initiation in type 2 diabetes, communications skills training for health professionals and motivating the patient with type 2 diabetes; the educational content lasted close to six hours; the amount of free time was very limited; the arrangements and cost were not excessive with a cost per delegate of £153; this venue was chosen as the company's travel consultants could find no appropriate venue in Carmarthenshire or Pembrokeshire.

Aventis agreed with Novo Nordisk's assertion that the impression created by the arrangements for a meeting was important in attracting health professionals to attend. The manner of the initial invitation to a meeting was therefore critical in creating that impression from the outset. The invitation to attend this meeting was posted to health professionals and clearly focused on the educational content of the agenda.

In addition, Aventis provided a letter received from a physician who was one of the speakers at the meeting. This letter was important as it represented an independent health professional's opinion of the meeting. The physician stated:

> 'I was delighted to be able to take part in this workshop, which I found well organised and very efficiently run. It was a novel use of time having the workshop on the ferry and the feedback I had from my fellow presenters, but also delegates, was very positive. The weekend was extremely useful educationally and also the level of hospitality was appropriate but not excessive.'

Aventis remained confident that it was the educational programme for this meeting that attracted the delegates to attend and not the associated ferry crossing or overnight stay.

Aventis noted that the parallels drawn by Novo Nordisk between the Panel's ruling in this case and its ruling in Case AUTH/1603/7/04 that two meetings organised by Novo Nordisk were in breach of Clause 19.1. Novo Nordisk argued that there was an inconsistency between the rulings and argued that similar standards should be applied and concluded that 'The impression created here (referring to the Aventis meeting) was certainly important. The cost per head was three times what Novo spent'.

Aventis submitted that it was important for the Appeal Board to be aware of the entirely different nature of the Novo Nordisk meetings compared to the Aventis meeting now being considered. One striking difference was the nature of the educational content, the Novo Nordisk meetings had focused on the promotion of insulin detemir, whilst the Aventis meeting was wide ranging including a variety of non-promotional topics. Further differences were apparent from the Panel's analysis of the Novo Nordisk meetings:

1) The arrangements for the meeting at the boat restaurant were considered to be unacceptable by the Panel because: the invitation advertised an educational programme to last 1 hour and 15 minutes; a reception and barbecue were advertised on the invitation; the cost per head was £116 and included the costs of musicians and two samba dancers.

2) The arrangements for the meeting at a football club were considered unacceptable by the Panel because: the invitation advertised an educational programme to last no more than one hour; a midsummer buffet dinner and drinks together with an invitation to watch the England v Croatia football match were advertised on the invitation; the impression created by the arrangements was that the evening was primarily a social and sporting event.

Aventis noted that the Panel had concluded that for both of these meetings the necessary balance of educational content against hospitality provided was not achieved. Whether or not this crucial balance was achieved in the Aventis meeting was the key issue to be considered here.

Aventis submitted that the comparison of relative costs per head between the meetings referred to by Novo Nordisk was ill-judged. If relative costs were to be considered, Aventis proposed the appropriate comparison was 'cost per head per hour of educational content'. The comparison under these circumstances would be thus: Aventis Insulin meeting: £25.50, Novo Nordisk boat restaurant meeting: £93 and Novo Nordisk football club meeting: £45.

Aventis remained confident that the initial invitation and subsequent educational programme were of good quality and that the associated hospitality was appropriate. The correct balance and high standards expected within the pharmaceutical industry were achieved and due care was given to create the correct impression with health professionals. Aventis was confident that the meeting was conducted within the guidance of Clause 19.1 of the Code.

FURTHER COMMENTS FROM NOVO NORDISK

Novo Nordisk noted that Aventis had stated in its first letter that the cost for the meeting was £109, this was subsequently revised to £153.75, an increase of 41%. Novo Nordisk submitted, however, that detailed evidence such as receipts for bar bills were not disclosed, which was in marked contrast with its transparent approach where full costs with receipts were shown to the Appeal Board recently. Novo Nordisk asked if this implied that it and the Appeal Board had to accept Aventis' cost declaration as stated?

Novo Nordisk considered that Aventis did not adequately address its concern that many hotels suitable for hosting meetings could be found locally in Wales; and that a boat cruise taking health professionals from Fishguard to Rosslare created the image that the cruise itself, rather than the medical content, was an inducement to attend the meeting.

Novo Nordisk considered that Aventis had not adequately explained why a meeting with medical content of 5 hours had to be split into two days, taking people from their local surgeries to a port to board a boat across the Irish Sea and back. The programme clearly indicated Stena Sealink and the trip to Ireland as an attraction.

Novo Nordisk noted Aventis' suggestion that the meeting was 'wide-ranging' but alleged that the meeting had a hidden agenda:

- GMS contract and 'Treat to Target Strategies to achieve this goal'. This was a promotional talk as it was well-known in the diabetes community that Aventis conducted clinical trials with 'Treat to Target' strategies with Lantus.
- 'The Insulin for Life programme' was also a promotional talk, as Lantus was the insulin used in the programme.

Novo Nordisk was unconvinced how claiming the programme as non-promotional would help justify the meeting, given that the cruise was the attraction to the meeting.

Novo Nordisk stated that it was important that the Panel and the Appeal Board apply, and be seen to apply, the same rigour in scrutinising two competing companies' activities; and that there was consistency in rulings. Novo Nordisk requested that the Appeal Board look into items in Aventis' meeting receipts to ascertain the level of alcoholic drinks consumed, both before and after dinner.

APPEAL BOARD RULING

The Appeal Board noted that Aventis' decision to use the ferry and travel to Ireland was a result of advice from an independent travel company that suitable hotel accommodation would not be available on the date of the meeting. The Aventis representatives submitted that the date of the meeting could not be changed as speakers had already been booked. However, the Appeal Board noted that Aventis had no knowledge of the extent of the travel company's search for a venue. The Appeal Board considered that the meeting could have been held at a number of venues, the choice was not limited to hotels or ferries. A group of UK health professionals had been taken outside the UK. The supplementary information to Clause 19.1 of the Code stated that there had to be valid and cogent reasons for holding meetings outside the UK. The Appeal Board considered that the delegates might have been attracted by the associated hospitality and the meeting could have been held locally over the course of a working day.

The Appeal Board was concerned that the cost of the meeting and number of delegates had changed upon further investigation by Aventis. The Appeal Board

was also concerned that at the appeal Aventis had referred to the meeting being held over a half day on Friday and Saturday. However, this was inaccurate and retracted by Aventis upon realisation that the meeting had been held on a Saturday and a Sunday. The Appeal Board considered that the inaccuracies and inconsistencies in Aventis' submissions were unacceptable.

The Appeal Board noted from Aventis that the meeting invitation had been signed off on 12 April and sent on 6 June. The ferry ticket and refreshments on the ferry provided by Aventis had been paid by card on the day of the meeting. The Appeal Board queried whether this was normal practice considering the invitation had been signed off some two months previous and that speakers had already been booked.

The Appeal Board expressed concern that Aventis had solicited feedback from one of the speakers at the meeting.

The Appeal Board considered that the cost of the meeting at £153.75 per head was not unreasonable, it would not exceed what delegates would pay if they were paying for themselves. The educational content at nearly six hours was not unreasonable and there was limited free time.

The Appeal Board considered, however, that Aventis had failed to provide valid and cogent reasons for holding the meeting on the ferry and in Ireland. Thus the Appeal Board ruled a breach of Clause 19.1 of the Code. The appeal was successful.

Complaint received **12 August 2004**

Case completed **30 November 2004**

CASE AUTH/1620/7/04

SERVIER v GLAXOSMITHKLINE

Avandamet leavepiece

Servier complained about a GP leavepiece for Avandamet (rosiglitazone/metformin) issued by GlaxoSmithKline. Servier supplied Diamicron (glicazide – a sulphonylurea).

Servier noted that the claim 'AVANDAMET maintains lasting glycaemic control' was the heading to a page which featured a graph showing the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin. The graph was referenced to Jariwala *et al* (2003). 'Stamped' over the lower right hand corner of the graph was the claim 'UKPDS Sulphonylurea: glycaemic control starts to deteriorate after 1 year'. This claim was referenced to the UK Prospective Diabetes Study 16 (UKPDS) (1995).

Servier alleged that overall the page was misleading as it implied that Avandamet offered lasting glycaemic control while sulphonylureas did not.

Servier stated that the current most relevant UK HbA_{1c} targets were those established in the new General Medical Services (GMS) contract which set two targets, 7.4 or less and 10 or less, requiring a lower percentage of patients to hit the lower target, and in the National Institute for Clinical Excellence (NICE) guidance, which recommended that target HbA_{1c} should be between 6.5 and 7.5. The average GP reader of the leavepiece was thus likely to interpret glycaemic control in relation to HbA_{1c} as reaching these target levels and then achieving consistent maintenance at or below these levels.

While it was clearly not possible to directly compare Avandamet and the sulphonylureas, as the data for each derived from separate and very different studies, the leavepiece specifically invited a comparison in relation to the maintenance of control.

The Avandamet data showed an initial reduction of HbA_{1c} to 7.4 and then maintenance at approximately this level for 30 months with a final level of 7.6.

The UKPDS data showed an initial reduction of HbA_{1c} to 6.3 and then a slow increase from the end of the first year throughout the 6-year study. However, even at the end of the UKPDS study, HbA_{1c} was 7.4 ie below all but the most stringent NICE target; 'glycaemic control', as it was likely to be understood by the readers, was thus maintained throughout the study. The statement 'glycaemic control starts to deteriorate after 1 year' was therefore accurate, but misleading, as, in the context of the claims for Avandamet, it gave the impression that glycaemic control was somehow lost.

The Panel noted that the data in the graph supporting the claim for lasting glycaemic control with Avandamet was taken from Jariwala *et al*. The aim of the study was to evaluate the long-term efficacy of rosiglitazone plus metformin in type 2 diabetics who had been inadequately controlled on metformin alone. The study showed that rosiglitazone, at doses of up to 8mg/day, added to metformin provided long-term improvements in HbA_{1c} for at least $2^1/_2$ years. HbA_{1c} fell from an initial level of a little over 8.5 to just under 7.5 after 9 months' therapy. At thirty months the levels had risen very slightly to just over 7.5. The authors stated that the study provided an initial insight into the long-term glycaemic control provided by rosiglitazone.

UKPDS evaluated glycaemic control in patients treated with a sulphonylurea. HbA_{1c} fell from an initial level of 6.9 to 6.1 at one year. During the next five years the levels rose to 7.1%.

The Panel noted that the claim 'UKPDS sulphonylurea: glycaemic control starts to deteriorate after 1 year' was 'stamped' across the bottom right-hand corner of the graph depicting the results of Jariwala *et al*. The Panel considered that, as presented, the claim implied a direct comparison of Avandamet and sulphonylureas in which, after 1 year's treatment with sulphonylureas, glycaemic control, as measured by the levels of HbA_{1c}, was inferior to that achieved with Avandamet and depicted in the graph. The Panel noted that, although HbA_{1c} rose after one year's treatment with sulphonylureas, and in that sense glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years' of treatment with sulphonylureas than after $2^1/_2$ years of Avandamet treatment (7.1% vs 7.5% respectively). In terms of HbA_{1c} targets set by the GMS contract and/or NICE both groups were controlled at the end of each study. The Panel disagreed with GlaxoSmithKline's submission that 'control' would be interpreted in a wide sense with no reference to a specific HbA_{1c} target. The graph, over which the claim in question was 'stamped', depicted specific HbA_{1c} levels and the claim would thus be read in the context of these levels.

The Panel noted that there were significant differences between the patient groups included in Jariwala *et al* and the UKPDS. The patients in Jariwala *et al* were older than those in the UKPDS (57 vs 53) and had had diabetes for longer (7 years vs newly diagnosed). Baseline levels of HbA_{1c} were also higher in Jariwala *et al* (8.5% vs 6.9%). The Panel did not consider that the two groups of patients were comparable.

The Panel considered that, as presented, page 2 of the leavepiece was misleading as alleged. A breach of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board noted that Section 5.1, Pharmacodynamic properties of the Avandamet summary of product characteristics (SPC) stated that 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control …'. The Appeal Board considered that 'sustained improvement in glycaemic control' referred to a directional move. The claim in the leavepiece, however, referred to maintenance of lasting glycaemic control which the Appeal Board considered implied achievement and maintenance of targets.

The Appeal Board considered that, as presented, page 2 of the leavepiece was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Servier noted that page 4 of the leavepiece headed 'Make a positive choice' presented a table which listed three features of therapy. The second feature 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control' was followed by a tick for Avandamet and a cross for sulphonylurea. Servier stated that the table implied that Avandamet helped patients reach targets and maintain control at or below these targets, while sulphonylureas did not.

Servier noted that the issue of lasting glycaemic control and HbA_{1c} target had been addressed in the first point and considered that the same arguments applied here. Servier alleged that the claim at issue was similarly misleading in relation to the duration and degree of HbA_{1c} control of sulphonylureas.

The Panel noted that page 4 of the leavepiece was part of a three page spread of pages 2, 4 and 5. Page 2, as considered above, would be clearly visible when reading page 4. The claim at issue on page 4 would thus be viewed as a summary of the information presented on page 2. In the Panel's view, the implication of the claim 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control', together with a tick for Avandamet and a cross for sulphonylurea, was that, in contrast to Avandamet, sulphonylureas did not achieve and/or maintain glycaemic control. The Panel noted its comments above and considered that they also applied here. The Panel considered that the claim, as presented, was misleading as alleged. A breach of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board considered that due to the layout of the leavepiece pages 4 and 2 would be viewed together. In the Appeal Board's view, the implication of the claim 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control', together with a tick for Avandamet and a cross for sulphonylurea, was that, in contrast to Avandamet, sulphonylureas did not achieve and/or maintain glycaemic control. The Appeal Board noted its comments above and considered that they also applied here. The Appeal Board considered that the claim, as presented, was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Servier Laboratories Ltd complained about a GP leavepiece (ref AVM/DAP/04/12799/1) for Avandamet (rosiglitazone/metformin) issued by GlaxoSmithKline UK Ltd. Correspondence between the parties had not resolved the issues. Servier supplied Diamicron (glicazide – a sulphonylurea).

1 Claims 'AVANDAMET maintains *lasting* glycaemic control', 'UKPDS, Sulphonylurea: glycaemic control starts to deteriorate after 1 year' and associated graph

The claim 'AVANDAMET maintains **lasting** glycaemic control' was the heading to page 2 which featured a graph showing the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin. The graph was referenced to Jariwala *et al* (2003). 'Stamped' over the lower right hand corner of the graph was the claim 'UKPDS Sulphonylurea: glycaemic control starts to deteriorate after 1 year'. This claim was referenced to the UK Prospective Diabetes Study 16 (UKPDS) (1995).

COMPLAINT

Servier considered that overall page two implied that Avandamet offered lasting glycaemic control while sulphonylureas did not. Servier alleged that this was misleading, in breach of Clause 7.2 of the Code.

Servier stated that the current gold standard for determining glycaemic control was the level of HbA_{1c} or glycosylated haemoglobin, which provided an index of the average blood glucose concentration over the life of the haemoglobin molecule (approximately 6 weeks). Therefore the measurement of this and its evolution over time gave an accurate long-term picture of blood sugar control, the most important measurable index of disease in a diabetic.

The current most relevant UK HbA_{1c} targets were those established in the new General Medical Services (GMS) contract and in National Institute for Clinical Excellence (NICE) guidance. The GMS contract set two targets, 7.4 or less and 10 or less, requiring a lower percentage of patients to hit the lower, more demanding target. NICE guidance on the management of blood sugar in type 2 diabetes recommended that target HbA_{1c} should be between 6.5 and 7.5. The average GP reader of the leavepiece was thus likely to interpret glycaemic control in relation to HbA_{1c} as reaching these target levels and then achieving consistent maintenance at or below these levels.

While it was clearly not possible to directly compare Avandamet and the sulphonylureas, as the data for each derived from separate and very different studies, the leavepiece specifically invited a comparison in relation to the maintenance of control. It therefore seemed reasonable that the data from the two studies should be compared in this regard.

The Avandamet data showed an initial reduction of HbA_{1c} to 7.4 and then maintenance at approximately this level for 30 months with a final level of 7.6.

The UKPDS data showed an initial reduction of HbA_{1c} to 6.3 and then a slow increase from the end of the first year throughout the 6-year study. However, even at the end of the UKPDS study, HbA_{1c} was 7.4 ie below all but the most stringent NICE target; 'glycaemic control', as it was likely to be understood by the readers, was thus maintained throughout the study. The statement 'glycaemic control starts to deteriorate after 1 year' was therefore accurate, but misleading, as, in the context of the claims for Avandamet, it gave the impression that glycaemic control was somehow lost.

RESPONSE

GlaxoSmithKline stated that with respect to the use of the word 'control', Servier's complaint was practically identical to that made by Takeda in a previous case concerning Avandia (Case AUTH/1123/1/01). GlaxoSmithKline's response at the time remained relevant:

> '… [the complainant has] chosen to interpret the word "control" in a highly specific sense, namely the Diabetes UK target level for HbA_{1c} 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 HbA_{1c} target, and [GlaxoSmithKline did] not claim that administration of Avandia would automatically result in such a target being attained'.

GlaxoSmithKline noted that Servier had referred to the GMS and NICE guidance on HbA_{1c} targets, rather than the Diabetes UK guidance, but the principle was identical.

In its ruling in Case AUTH/1123/1/01, the Panel had noted that the advertisement did not refer to any specific target level of HbA_{1c}, and considered that the word 'control' would be interpreted in the light of the clinical claims made in the material in question. As such, no breach of the Code was ruled. Given that the item in question in the current case equally made no reference to specific HbA_{1c} targets, and that the claims made in it were self-evidently intended to be taken in the context of a general comparison of the long-term glycaemic effects of Avandamet and sulphonylureas, GlaxoSmithKline believed that the ruling with respect to the use of the word 'control' in Case AUTH/1123/1/01 also applied in this case. The issue thus reduced to whether the comparison made, and the claims deriving from it, were fair, accurate, and not misleading.

The Avandamet summary of product characteristics (SPC) ('Pharmacodynamic properties') stated with regard to the rosiglitazone component in studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control (fasting plasma glucose and HbA_{1c}). As this SPC statement referred directly to a licensed indication of the product, it required no further substantiation, as recently confirmed by the Panel's ruling in Case AUTH/1533/10/03. Nevertheless, further substantiation was provided (Jariwala *et al*). In these pooled data from two double-blind trials and their open-label extensions, addition of rosiglitazone to metformin led to a drop in HbA_{1c} of approximately 1.2% (8.7% to 7.5% approximately) by nine months. This drop was sustained for up to $2^1/_2$ years. Although not cited in the material, similar results had been obtained with rosiglitazone monotherapy (Nadra *et al* 2004). Here, the reduction in HbA_{1c} was maintained, essentially unaltered, for up to three years.

GlaxoSmithKline stated that for a therapeutic class that had been available for over 40 years, there was a paucity of data on the long-term glycaemic effects of sulphonylureas. The best such data – indeed the best overall data available for the effects of traditional antidiabetic therapies – came from the UKPDS. The relevant graph from UKPDS 16, cited in the item in question, demonstrated that, in patients allocated to intensive sulphonylurea therapy, HbA_{1c} dropped overall by some 1% at one year, following which there was an essentially linear rise out to six years, with starting (baseline) levels being reached at between three and four years after starting therapy.

GlaxoSmithKline therefore believed that – by any generally accepted use of the word 'control' – it was accurate to state that glycaemic control with sulphonylureas began to deteriorate after one year.

Indeed, Servier had acknowledged that the statement was accurate in its complaint. Servier's assertion that it was also misleading – despite the fact that all available evidence, and the Avandamet SPC, clearly indicated that glycaemic control did not begin to deteriorate after one year with Avandamet – was rather mystifying.

GlaxoSmithKline submitted that if the baselines of the UKPDS sulphonylurea graph, and that obtained with Avandamet in Jariwala *et al*, were equated, and the curves superimposed, the results would suggest that, at $2^1/_2$ years, sulphonylurea-treated patients would have an average HbA_{1c} somewhat in excess of 0.5% greater than those treated with rosiglitazone, rising to around 1% at three years. These differences were of great clinical significance.

GlaxoSmithKline noted that Servier had correctly stated that there were methodological differences between the UKPDS and Jariwala *et al*. Servier did not mention, however, that these differences would be expected to weight the results heavily in favour of sulphonylureas. Thus, the UKPDS was carried out in newly diagnosed patients, in whom beta-cell function and disease progression would not be so advanced, and who would thus be expected to be more amenable to therapeutic intervention. In contrast, the patients in Jariwala *et al* had had diabetes for seven years on average, and were already inadequately controlled on metformin monotherapy. Similarly, the UKPDS mobilised vast resources in comparison to the two trials in Jariwala *et al* and UKPDS patients were more intensively monitored. Despite these differences, addition of rosiglitazone still led to markedly longer control than did sulphonylurea administration.

Although not cited, additional evidence was beginning to become available in which the effects of glitazones and sulphonylureas on long-term control were compared directly. Koro *et al* compared the Mediplus records of 1,999 patients taking metformin and sulphonylurea with 143 on metformin and rosiglitazone. The latter group had a statistically significant ($p<0.03$) slower rate of progression to insulin compared with the sulphonylurea-treated group (progression to insulin being directly correlated with duration of clinically adequate glycaemic control). Likewise, data from a two-year double-blind trial showed that pioglitazone (a similar product to rosiglitazone) was significantly better ($p<0.0001$) than a sulphonylurea in sustaining long-term glycaemic control (Tan *et al* 2004).

The differential effects of sulphonylureas and glitazones on duration of diabetic control were readily explained in terms of their modes of action. Thus, sulphonylureas further stimulated beta-cells that were already under significant stress. In contrast, glitazones, by improving insulin resistance, led to a corresponding improvement in beta-cell function, as evidenced directly and through such surrogate markers as the proinsulin-to-insulin ratio (an average indicator of beta-cell stress).

GlaxoSmithKline maintained that the claims and comparisons included in the leavepiece with respect to the differential effects of Avandamet and sulphonylureas on long-term glycaemic control were fair, balanced, accurate, and reflected the overwhelming weight of available evidence. As such, GlaxoSmithKline did not consider that the leavepiece was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the data in the graph supporting the claim for lasting glycaemic control with Avandamet was taken from Jariwala *et al*. The aim of the study was to evaluate the long-term efficacy of rosiglitazone plus metformin in type 2 diabetics who had been inadequately controlled on metformin alone. The average age of patients was 57 and they had had diabetes for over 7 years. HbA_{1c} levels were determined at baseline and every three months for 30 months. The study showed that rosiglitazone, at doses of up to 8mg/day, added to metformin provided long-term improvements in HbA_{1c} for at least $2^1/_2$ years. HbA_{1c} fell from an initial level of a little over 8.5 to just under 7.5 after 9 months' therapy. At thirty months the levels had risen very slightly to just over 7.5. The authors stated that the study provided an initial insight into the long-term glycaemic control provided by rosiglitazone. More definitive data would come from ongoing trials.

The patients included in the UKPDS were newly diagnosed type 2 diabetics; their average age was 53. The study, *inter alia*, evaluated glycaemic control in patients treated with a sulphonylurea. HbA_{1c} fell from an initial level of 6.9 to 6.1 at one year. During the next five years the levels rose to 7.1%.

The Panel noted that the claim 'UKPDS sulphonylurea: glycaemic control starts to deteriorate after 1 year' was 'stamped' across the bottom right-hand corner of the graph depicting the results of Jariwala *et al*. The Panel considered that, as presented, the claim implied a direct comparison of Avandamet and sulphonylureas in which, after one year's treatment with sulphonylureas, glycaemic control, as measured by the levels of HbA_{1c}, was inferior to that achieved with Avandamet and depicted in the graph. The Panel noted that, although HbA_{1c} rose after one year's treatment with sulphonylureas, and in that sense glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years' of treatment with sulphonylureas than after $2^1/_2$ years of Avandamet treatment (7.1% vs 7.5% respectively). In terms of HbA_{1c} targets set by the GMS contract and/or NICE both groups were controlled at the end of each study. The Panel disagreed with GlaxoSmithKline's submission that 'control' would be interpreted in a wide sense with no reference to a specific HbA_{1c} target. The graph, over which the claim in question was 'stamped', depicted specific HbA_{1c} levels and the claim would thus be read in the context of these levels.

The Panel noted that there were significant differences between the patient groups included in Jariwala *et al* and the UKPDS. The patients in Jariwala *et al* were older than those in the UKPDS (57 vs 53) and had had diabetes for longer (7 years vs newly diagnosed). Baseline levels of HbA_{1c} were also higher in Jariwala *et al* (8.5% vs 6.9%). The Panel did not consider that the two groups of patients were comparable.

The Panel considered that, as presented, page 2 of the leavepiece was misleading as alleged. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that it had four reasons to appeal:

- it did not accept that the phrase 'glycaemic control' necessarily, or even ordinarily, implied some pre-existing fixed glycaemia target;
- the correct interpretation of the comparison made in the leavepiece revolved around the profile or shape of the respective HbA_{1c} curves, rather than the absolute values contained therein;
- although there were differences between Jariwala *et al* and the UKPDS, in terms of the baseline characteristics of the respective study populations, these differences would, without exception, be expected to favour sulphonylureas over Avandamet;
- the findings of the UKPDS with respect to the long-term effects of sulphonylureas were representative of, and, if anything, more favourable than, the results of all other long-term studies in the general type 2 diabetes population. These included studies in which baseline characteristics were similar to those of Jariwala *et al*, and direct comparative studies between sulphonylureas and rosiglitazone. The UKPDS findings were thus consistent with the balance of available evidence, and hence not misleading.

With regard to its first point, GlaxoSmithKline submitted that irrespective of other considerations, the Panel's ruling on the interpretation of 'glycaemic control' in this case was inconsistent with that given in Case AUTH/1123/1/01 (Takeda vs SmithKlineBeecham). GlaxoSmithKline noted its response at the time was:

'… Takeda had chosen to interpret the word 'control' in a highly specific sense, namely the Diabetes UK target level for HbA_{1c} 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 HbA_{1c} target, and [GlaxoSmithKline] did not claim that administration of Avandia would automatically result in such a target being attained.'

GlaxoSmithKline stated that the Panel had endorsed this interpretation at the time and noted that the advertisement under review had not referred to any specific target level for HbA_{1c}, and considered that 'control' would be interpreted in the light of the clinical claims made.

GlaxoSmithKline submitted that in exactly analogous circumstances in the present case, however, the Panel 'disagreed with GlaxoSmithKline's submission that 'control' would be interpreted in a wide sense with no reference to a specific HbA_{1c} target'. The Panel noted that the graph from Jariwala *et al* depicted specific HbA_{1c} levels. However, no pre-set target level for glycaemia was mentioned (or included) in Jariwala *et al*; and it was impossible to reproduce an HbA_{1c} graph without depicting specific HbA_{1c} levels. While the UKPDS had a target HbA_{1c} level for determination of rigorous control (6%), the wording in the leavepiece was self-evidently intended to refer to the changes in HbA_{1c} over time, without reference to specific targets (and, in any event, the sulphonylureas-treated group in the UKPDS did not attain the 6% target level of HbA_{1c} at any point).

GlaxoSmithKline submitted that it was not unreasonable that, in deciding on the wording for promotional pieces, consideration was given to previous relevant Panel rulings. In this case, as noted, these rulings had been inconsistent.

GlaxoSmithKline submitted that specific rulings aside, the most cursory examination of the literature showed that, when phrases such as 'improved diabetic control' or 'deteriorating diabetic control' were used, without further qualification, they were evidently intended to refer simply to changes in HbA_{1c} and/or blood glucose levels. As any target was essentially a threshold, the words 'improvement' or 'deterioration' in relation to target levels could only be meaningful in the sense of the proportion of patients above or below that threshold at specific times. Neither the Jariwala graph, nor that in UKPDS 16, depicted such proportions.

GlaxoSmithKline submitted that if 'improved glycaemic control' necessarily equated to attainment of a target level of HbA_{1c}, its use would be very imprecise unless the particular target referred to was specified. Unfortunately several existed. The GMS target for HbA_{1c} was 7.4%. NICE guidelines suggested between 6.5% and 7%. The NSF target was <7%. As noted above, the UKPDS target for rigorous control was 6%. GlaxoSmithKline stated that the universally employed use in the literature supported its interpretation that 'control' was used loosely to refer to HbA_{1c} levels *per se*.

GlaxoSmithKline submitted that equating 'glycaemic control' with 'attainment of target' (whatever that target might be) would quickly lead to untenable conclusions. Thus, as previously noted, the SPC for Avandamet stated: 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control (FPG and HbA_{1c})'. GlaxoSmithKline asked if Servier would be happy for it to have claimed, on this basis, that Avandamet would lead to patients attaining glycaemic targets (however defined) for up to three years?

GlaxoSmithKline submitted that likewise, as noted above, the overall sulphonylureas-treated group in the UKPDS had not attained the target level of 6% pre-set as representing rigorous control. On Servier's definition of control, it was therefore possible to claim that, within the terms of reference of the UKPDS, sulphonylureas had not improved glycaemic control at all; an evidently absurd conclusion.

Turning to its second point, GlaxoSmithKline contended that the point at issue was not the absolute levels of HbA_{1c} attained with a particular medicine at one or several points, but rather the development of the glycaemic profile as a whole over an extended period; the profile or shape of the HbA_{1c} curve with respect to time.

In a chronic disease such as type 2 diabetes, the duration of effect of the medicines prescribed to reduce HbA_{1c} was of obvious significance. There was a clear difference in this respect between sulphonylureas and rosiglitazone/Avandamet. Taking only the evidence presented in the leavepiece, whatever the absolute values of glycaemia might have been in the UKPDS, it was clear that the initial fall in HbA_{1c} following administration of sulphonylureas was not sustained. Levels began to rise after one year of treatment and by three years had reached baseline values, ie the level at which it was deemed desirable to prescribe an oral antidiabetic in the first place. It was totally spurious for Servier to state that, even at the end of the UKPDS as a whole, HbA_{1c} levels were within GMS targets (albeit not within NICE, NSF or UKPDS targets). Baseline levels in the UKPDS, before administration of any product, were below GMS target. On the real point at issue, the UKPDS findings clearly indicated that it was not possible to maintain HbA_{1c} levels below baseline for more than three years with sulphonylureas; and that levels began to rise after one year. On the universally accepted understanding of the phrase 'diabetic control' referred to above, it was therefore accurate, and not misleading, to state that glycaemic control in the UKPDS began to deteriorate after one year with sulphonylureas.

In contrast, the profiles of the HbA_{1c} curves obtained over the longer term with rosiglitazone/Avandamet equally clearly demonstrated the lasting nature of the degree of control achieved. As noted above, the Avandamet SPC contained a categorical assertion of this fact, sufficient in itself to sustain a promotional claim. Jariwala *et al* provided evidence for two-and-a-half years' control with the rosiglitazone/metformin combination; and Nadra *et al* for three years' control with rosiglitazone monotherapy. In both cases, the initial drops were maintained practically without change for the specified periods, contrasting strongly with the profiles obtained with sulphonylureas.

With regard to its third point, GlaxoSmithKline noted that Servier had rightly stated that there were obvious differences between the designs and patient populations of the UKPDS and Jariwala *et al*. Nevertheless, as previously noted these differences would all be expected to operate in favour of sulphonylureas. Indeed, it would be hard to think of a set of circumstances more favourable to any antidiabetic medicine than that pertaining in the UKPDS.

GlaxoSmithKline noted that the patients in the UKPDS were newly diagnosed and hence medicine-naïve, with consequently a greater pancreatic reserve. Their baseline HbA_{1c} levels were considerably lower than that in Jariwala *et al*, actually below the GMS target emphasised so strongly by Servier. Furthermore, GlaxoSmithKline submitted that the UKPDS was undoubtedly the most rigorous and extensively monitored trial in type 2 diabetes conducted to date. Patients were seen regularly, given intensive lifestyle and dietary advice, and encouraged to take their medicine. In contrast, the patients in Jariwala *et al* had been diagnosed as diabetics for an average of seven years, already required additional control on metformin, had markedly higher baseline levels of HbA_{1c} on entry and were followed up in the fairly loose context of an open-label trial (once the initial 26-week double-blind period was completed).

Despite this raft of differences in favour of sulphonylureas, the results of the two trials were as already noted. The magnitude of the initial falls in HbA_{1c} seen in the two trials was similar, indicating that the different baseline values had no effect on the short-term antihyperglycaemic efficacy of the two classes of products. With the rosiglitazone/metformin combination, however, this drop was maintained whereas in the UKPDS, the initial fall with sulphonylureas was not, despite the favourable circumstances of the trial. As previously noted, if the baselines of the UKPDS sulphonylureas graph, and that obtained in Jariwala *et al*, were equated, and the curves superimposed, the results would suggest that, at two-and-a-half years, sulphonylureas-treated patients would have an average HbA_{1c} in excess of 0.5% greater than those treated with rosiglitazone, rising to around 1% at three years. These findings were of great clinical significance. GlaxoSmithKline submitted that the differences between the two trials were not such as to render a comparison of their results with respect to glycaemic profiles misleading.

Finally, GlaxoSmithKline submitted that in the leavepiece, the UKPDS was chosen to represent the long-term effects of sulphonylureas on glycaemia as being the most widely known and most robust data available. Nevertheless, data from all long-term sulphonylureas trials in the literature supported the conclusion stated in the leavepiece that glycaemic control with sulphonylureas (by which was meant HbA_{1c} and plasma glucose levels) began to deteriorate at or before 12 months after starting treatment. Indeed, in most of the trials, control started to worsen well before 12 months, so that the wording in the leavepiece (which related to the UKPDS alone) was, if anything, conservative with respect to sulphonylureas efficacy, when taken in the context of the full evidence base available.

GlaxoSmithKline provided a table of data summarising the long-term effects of sulphonylureas. The company noted all of the seven studies were randomised and five were double-blind; treatment durations ranged from 1 to 1.25 years; other than one study, Draeger *et al* (1996), in which sulphonylureas had no evident effect following titration, HbA_{1c} and/or plasma glucose levels began to increase at between 12 and 26 weeks following initiation of sulphonylureas treatment, with a median of 16 weeks (compared with 52 weeks for the UKPDS trial referenced in the leavepiece); the patient demographics (duration of diabetes, baseline HbA_{1c}) in the majority of the trials were comparable to those in Jariwala *et al*; two of the trials, Lönnqvist *et al*

(1999) and Bakris *et al* (1999), were direct comparisons between rosiglitazone and sulphonylureas. Lönnqvist *et al* concluded that 'Rosiglitazone maintains glycaemic control for at least 12 months, in contrast to glibenclamide [SU], which demonstrates a clear loss of effect after the titration period'. Similarly, Bakris *et al* noted that 'In glibenclamide-treated patients, FPG decreased between weeks 0 and 8, but increased gradually from week 16 through week 52'. GlaxoSmithKline stated that to the best of its knowledge, these trials represented all of the public-domain evidence on the long-term antihyperglycaemic effects of sulphonylureas in the general type 2 diabetic population.

GlaxoSmithKline contended that given these data, regardless of any other considerations, the UKPDS findings were representative of, and if anything more favourable than, the totality of evidence on the chronic antihyperglycaemic effects of sulphonylureas . On this basis, the referencing of the UKPDS in the leavepiece was balanced, fair, and not misleading, and thus not in breach of Clause 7.2 of the Code.

In summary GlaxoSmithKline submitted that the Panel's rulings on the meaning of glycaemic control were inconsistent; the universally accepted meaning, in the absence of other qualification, referred to changes in glycaemic parameters, rather than attainment of targets. Equating glycaemic control and targets was imprecise and led to absurd conclusions. Servier's insistence on the relevance of absolute HbA_{1c} values (particularly the GMS HbA_{1c} target of 7.4%) was itself misleading, inasmuch as the baseline values in the UKPDS, prior to sulphonylureas administration, were below this level. In contrast, the real point at issue was the profile of the HbA_{1c} curve over time, for which there were clear differences between rosiglitazone/Avandamet and sulphonylureas. Any differences in baseline characteristics between Jariwala *et al* and the UKPDS population were wholly in favour of sulphonylureas. Regardless of these differences, the UKPDS findings were representative of the totality of published evidence and if anything were more favourable to sulphonylureas than all other long-term trials (including comparative trials with rosiglitazone and trials with patient demographics in line with those of Jariwala *et al*).

COMMENTS FROM SERVIER

Servier alleged that the average GP would get the impression from page two of the leavepiece that Avandamet offered lasting glycaemic control while sulphonylureas did not.

Servier stated that it was clearly necessary to consider the interpretation of 'lasting glycaemic control'. Servier accepted that there was no mention of HbA_{1c} target levels on this page, but maintained that a GP was unlikely to read this claim without considering that 'glycaemic control' related to reaching a target HbA_{1c} level and maintaining it at this level.

Servier accepted that there was no reference to a specific HbA_{1c} target level. However it considered that a GP was likely to be aware of the HbA_{1c} targets established in the new GMS General Practice contract (HbA_{1c} of 7.4 or less and HbA_{1c} of 10 or less, with requirements for a lower percentage of patients to hit the lower, more demanding target) and recent NICE guidance (target HbA_{1c} between 6.5 and 7.5) and likely to interpret 'glycaemic control' in this context. When attempting to control a patient's disease, clinicians tended to intervene according to a predefined threshold.

Servier noted that the claim 'AVANDAMET maintains lasting glycaemic control' appeared above a graph illustrating the change in HbA_{1c} over time, in which the level of HbA_{1c}, from around 9 months to 30 months, remained roughly 7-7.5%. It seemed reasonable to assume that it was intended that this conveyed the impression that this level of HbA_{1c}, for this duration of time, represented 'lasting glycaemic control'.

Servier noted that the UKPDS was a study of 4209 patients that ran over 11 years and investigated the different outcomes between patients on conventional therapy, primarily diet, and more intensive therapy, including sulphonylureas. The UKPDS 16 paper quoted in the leavepiece was a report at 6 years. Results showed that throughout this entire 6 year study the sulphonylureas group was maintained at a consistently lower level than the conventional therapy group and the HbA_{1c} level of this group never exceeded the target levels seen in the new GMS contract or the higher NICE target.

Servier alleged that this view was not inconsistent with the case precedent cited by GlaxoSmithKline (Case AUTH/1123/1/01) in which the Panel considered that the word 'control' 'would be read in light of the clinical claims in the advertisement'.

Servier further noted that in its appeal GlaxoSmithKline had stated that the correct interpretation of the leavepiece revolved around the profile or shape of the respective HbA_{1c} curves and that, although there were obvious differences between the design and patient populations of the UKPDS and Jariwala *et al*, these would all be expected to operate in favour of sulphonylureas.

Servier did not accept that these differences operated entirely in favour of sulphonylureas. The patient populations were clearly markedly different and a comparison of the methodology did not stand up to scrutiny. The results from the UKPDS were all analysed on an intention-to-treat basis, meaning that all patients available for follow-up were included in the final analysis. In contrast, Jariwala *et al* excluded from its final analysis those patients who experienced adverse events (9.5% of the patients entered) and, probably more relevantly, those patients in whom a lack of efficacy was observed (13%, n=55).

With regard to the additional evidence submitted by GlaxoSmithKline, Servier agreed with GlaxoSmithKline that the UKPDS provided the most robust and relevant data on long-term therapy with the sulphonylureas available at the time of the study. Servier alleged furthermore that, since this was the study used in the leavepiece, any conclusions related to this case should be predominantly drawn from the UKPDS and that other studies were irrelevant to this case.

Servier noted, however, that two of the studies cited by GlaxoSmithKline were direct comparisons of rosiglitazone and sulphonylureas and could therefore be considered influential. In Lönnquist *et al* the dose of sulphonylureas was fixed after a titration period of 3 months, with no option to increase the dose should HbA_{1c} rise. It was only after this period that HbA_{1c} levels began to increase. Furthermore, at the end of the trial, the sulphonylureas had reduced HbA_{1c} more than rosiglitazone at a maximal dose of 8mg/day compared with baseline. This clearly did not represent inferior control. In Bakris *et al* the dose of sulphonylureas was similarly fixed after 8 weeks of the study. Once again HbA_{1c} only started to increase after the investigator had lost the option of further uptitrating the sulphonylureas (glibenclamide). The average dose of glibenclamide in this study was 10.5mg/day, or 70% of the maximum of 15mg/day, compared with the maximum dose of 8mg/day of rosiglitazone.

In summary, Servier stood by its assertion that the average GP reader of the leavepiece would relate glycaemic control to the maintenance of HbA_{1c} below a certain level and that the claim that sulphonylureas somehow did not fulfil this was misleading, in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted GlaxoSmithKline's comments about previous rulings but considered that the context in which a claim was made was very important. Each case had to be considered on its own merits.

The Appeal Board did not consider that the comparison of results from Jariwala *et al* and the UKPDS was fair. There were differences in, *inter alia*, the study population and the statistical analyses. Importantly results from the UKPDS were analysed on an intention-to-treat basis whilst Jariwala *et al* was a per protocol analysis.

The Appeal Board noted that Section 5.1, Pharmacodynamic properties of the Avandamet SPC stated that 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control …'. The Appeal Board considered that 'sustained improvement in glycaemic control' referred to a directional move. The claim in the leavepiece, however, referred to maintenance of lasting glycaemic control which the Appeal Board considered implied achievement and maintenance of targets.

The Appeal Board considered that, as presented, page 2 of the leavepiece was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

2 Claim 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control'

Page 4 of the leavepiece headed 'Make a positive choice' presented a table which listed three features of therapy. The second feature 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control' was followed by a tick for Avandamet and a cross for sulphonylurea.

COMPLAINT

Servier stated that the table implied that Avandamet helped patients reach targets and maintain control at or below these targets, while sulphonylureas did not. Servier noted that the issue of lasting glycaemic control and HbA_{1c} target had been addressed in point 1 above and considered that the same arguments applied here. Servier therefore alleged the claim at issue was similarly misleading in relation to the duration and degree of HbA_{1c} control of sulphonylureas, in breach of Clause 7.2 of the Code.

RESPONSE

With regard to the claim 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control', GlaxoSmithKline agreed that both Avandamet and sulphonylureas fulfilled the first part of the conjunction. In considering the second part, GlaxoSmithKline noted that Servier asserted that the clear impression was that Avandamet helped maintain control at or below target, while sulphonylureas did not. This was not, however, the wording used. GlaxoSmithKline considered that the phrase Avandamet 'Helps patients … maintain lasting glycaemic control', in contrast to sulphonylureas was an accurate and substantial claim, for the reasons mentioned above. The use of a conjunction of this kind in differentiating products had previously been deemed acceptable by the Panel (Case AUTH/1349/8/02). GlaxoSmithKline denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that page 4 of the leavepiece was part of a three page spread of pages 2, 4 and 5. Page 2, as considered in point 1 above, would be clearly visible when reading page 4. The claim at issue on page 4 would thus be viewed as a summary of the information presented on page 2. In the Panel's view, the implication of the claim, 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control', together with a tick for Avandamet and a cross for sulphonylurea, was that, in contrast to Avandamet, sulphonylureas did not achieve and/or maintain glycaemic control. The Panel noted its comments in point 1 above and considered that they also applied here. The Panel considered that the claim as presented, was misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline referred to its comments at point 1 above.

COMMENTS FROM SERVIER

Servier considered that its comments at point 1 applied here, but in the claim now at issue there was,

additionally, specific reference to 'HbA_{1c} target'. It was therefore difficult to argue other than that, in this context, 'maintain lasting glycaemic control' was intrinsically linked to target levels of HbA_{1c}.

Servier considered that the presentation as a table, with ticks and crosses, emphasised these as clear, strong statements. The impression was therefore that, unequivocally, Avandamet helped patients reach HbA_{1c} targets and maintained lasting control at or below these targets; sulphonylureas did not.

The claim was misleading in relation to the duration and degree of HbA_{1c} control of sulphonylureas, in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that due to the layout of the leavepiece pages 4 and 2 would be viewed together. In the Appeal Board's view, the implication of the claim, 'Helps patients reach HbA_{1c} target and maintain lasting glycaemic control', together with a tick for Avandamet and a cross for sulphonylurea, was that, in contrast to Avandamet, sulphonylureas did not achieve and/or maintain glycaemic control. The Appeal Board noted its comments in point 1 above and considered that they also applied here. The Appeal Board considered that the claim as presented, was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

Complaint received **12 August 2004**

Case completed **7 December 2004**

CASES AUTH/1623/8/04 and AUTH/1624/8/04

LILLY v BRISTOL MYERS-SQUIBB and OTSUKA

Promotion of Abilify

Lilly complained about the promotion of Abilify (aripiprazole) by Bristol-Myers Squibb and Otsuka. The complaint related to the availability of the summary of product characteristics (SPC) for Abilify and an Abilify leavepiece. Abilify was indicated for the treatment of schizophrenia. Lilly supplied Zyprexa (olanzapine).

Lilly received a copy of the leavepiece on 8 June and telephoned Bristol-Myers Squibb to request a copy of the Abilify SPC. Bristol-Myers Squibb stated that the SPC was not available to be sent out to customers at that stage. The next day the same response was received. Lilly first obtained a copy of the SPC on 14 June from the Electronic Medicines Compendium.

On 21 June Lilly received press materials about the launch of Abilify, the SPC enclosed did not include valid marketing authorization numbers or the date of first authorization. Lilly alleged that the use of an incomplete SPC in press briefing materials was a failure to maintain high standards.

The Panel noted that with regard to the draft SPC included in the Abilify launch press pack, the Code did not require SPCs to be included in press packs. The Panel queried why a draft SPC was included in a press pack embargoed until Monday, 21 June with a press meeting on Friday, 18 June when, according to the response from the companies, the SPC was available from 4 June. The draft SPC in the press pack omitted the marketing authorization number and the date of first authorization. The companies submitted that the factual information in the draft SPC was the same as in the final. Taking all the circumstances into account the Panel ruled no breach of the Code.

The first page of the four page leavepiece described Abilify as 'The first and only available dopamine system stabiliser'. Page 2 was headed 'Highly effective symptom control in acute psychosis' beneath which were two graphs. Page 3 was headed 'Long term symptom control in both acute and stable patients' and also included two graphs. The final page included bullet points and the prescribing information.

Lilly noted that the Abilify SPC stated that 'Abilify is indicated for the treatment of schizophrenia'. Schizophrenia was only one of the very many causes of psychosis, which also included disorders as diverse as mania, depression and drug abuse. Lilly alleged that the claims constituted promotion of Abilify outside the marketing authorization.

The Panel noted that the leavepiece announced the launch of Abilify but did not state at the outset that it was a treatment for schizophrenia. The claims at issue referred to the control of the symptoms of acute psychosis; acute psychosis could be caused by conditions other than schizophrenia. The only mention of schizophrenia was in the second of five bullet points on the outside back cover; this was insufficient to negate the impression that Abilify was licensed to treat psychotic conditions generally. The prescribing information on the final page of the leavepiece clearly stated that Abilify was indicated in schizophrenia but it was an established principle under the Code that otherwise misleading claims could not be qualified by, *inter alia*, the prescribing information. The claims about symptom control in psychosis were not placed within the context of treating schizophrenia, the licensed indication. The Panel decided that in the context in which they appeared the claims were inconsistent with the SPC and each was ruled in breach of the Code.

Lilly referred to the Abilify SPC and pointed out that the leavepiece described four studies, three of which used doses of Abilify that did not comply with the dosing regime recommended by the SPC.

A graph on page 1 of the leavepiece, referenced to data on file, compared the efficacy of placebo, haloperidol (10-20mg) and Abilify (2-30mg). The dose of Abilify 2mg was below the recommended starting and maintenance dose and there were no caveats to suggest that the subjects were elderly or also receiving liver enzyme inhibitors.

A graph on page 2 adapted from Potkin *et al* (2003) compared the efficacy of placebo, Abilify 20mg, Abilify 30mg and risperidone 6mg. The SPC did not recommend the use of Abilify 20mg at all and did not recommend the use of Abilify 30mg as a starting dose.

A graph on page 3 referenced to data on file compared the efficacy of Abilify 20-30mg with haloperidol 7-10mg in relation to the reduction in PANSS total score in acutely psychotic patients. Again, the SPC did not recommend the use of Abilify 20mg at all and did not recommend the use of Abilify 30mg as a starting dose. Furthermore, Abilify was indicated for the treatment of schizophrenia, not acute psychosis.

The Panel noted that the Abilify SPC stated that the recommended starting and maintenance dose was 15mg/day. Further that Abilify was effective in a dose range of 15 to 30mg/day. The SPC stated that for patients aged over 65 a lower starting dose should be considered when clinical factors warranted. When given with certain other medicines (potent CYP3A4 or CYP3D6 inhibitors) the dose of Abilify should be reduced; in the presence of potent CYP3A4 inducers the dose of Abilify should be increased. Abilify was available as 10mg, 15mg or 30mg tablets.

The Panel noted that none of the graphs used doses of Abilify higher than 30mg. Showing data for the 20mg dose of Abilify was not unreasonable as that dose was within the effective dose range (15 to 30mg). With regard to the data in graph 1 where Abilify was dosed at less than the recommended starting and maintenance dose, the Panel noted that the data was being used to demonstrate an efficacy difference with placebo. It was not being used to support adverse event data or such like. Further, the available dosage forms of Abilify meant that it would be difficult to administer a 2mg dose. In the circumstances the Panel did not consider that the doses used in any of the four graphs were not in compliance with the SPC dosing regimen as alleged. Thus the Panel ruled no breach of the Code.

The Panel considered that the use of the term 'acutely psychotic patients' was similar to a point above and thus ruled a breach of the Code in that regard.

The claim 'Abilify significantly improved symptoms over 52 weeks vs haloperidol' appeared on page 3 of the leavepiece next to a graph comparing the reduction in PANSS total score for Abilify 20-30mg and haloperidol (7-10mg) in acutely psychotic patients. The claim was referenced to data on file.

Lilly stated that the data showed that Abilify was superior to haloperidol at 3 time points out of 20. Lilly considered that it was misleading to claim that one medicine was superior to another when they were equivalent at the overwhelming majority of time points in the study.

The Panel noted that the data on file had not been provided. The leavepiece showed a statistically significant difference between Abilify at only three time points including at 52 weeks.

Kasper *et al* stated that aripiprazole and haloperidol were associated with similar improvements in symptoms as measured by changes from baseline on the total Positive and Negative Syndrome Scale (PANSS) score, PANNS positive symptoms subscale and the Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Global Improvement (CGI-I) scores. Aripiprazole was superior to haloperidol in improving the negative symptoms of schizophrenia as measured by changes from baseline on the PANSS negative subscale and in reducing depressive symptoms demonstrated on Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline.

The Panel noted the SPC stated that 'Abilify is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medication at 52 weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale, showed a significant improvement over haloperidol'.

The Panel considered that the claim 'Abilify significantly improved symptoms over 52 weeks vs haloperidol' in association with the graph was misleading. In this regard it noted Kasper *et al* and the SPC. Data in the leavepiece which showed statistically significant differences at 52 weeks but no such difference in all but two time points before then was not sufficient for a claim that Abilify significantly improved symptoms over 52 weeks. The claim implied that throughout the 52 weeks symptom scores were improved with Abilify compared with haloperidol which was not so. A breach of the Code was ruled.

The claim 'Abilify is weight and prolactin neutral and has minimal potential for sedation' appeared as the third bullet point on the back page of the leavepiece. The claim regarding weight was referenced to McQuade *et al* (2003) and the claim about prolactin was referenced to Carson *et al* (2002).

Lilly alleged that the claim 'weight neutral' implied that the medicine had no effect on weight; however, Section 5.1 of the Abilify SPC stated 'Weight gain: in clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26 week, olanzapine-controlled, double-blind, multi-national

study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly fewer patients had at least 7% weight gain over baseline (ie a gain of at least 5.6kg for a mean baseline weight of ~80.5kg) on aripiprazole (n=18 or 13% of evaluable patients), compared to olanzapine (n=45, or 33% of evaluable patients)'.

Lilly stated that if 13% of Abilify treated patients could be expected to gain at least 7% weight over baseline it was misleading to claim the medicine was weight neutral. Furthermore Potkin *et al* stated 'aripiprazole showed a low incidence of clinically significant weight gain' and described a statistically greater probability of clinically significant weight gain in aripiprazole-treated patients compared to placebo-treated patients (aripiprazole 20mg 13% and aripiprazole 30mg 9% vs placebo 2%, both p<0.05), demonstrating the medicine not to be 'weight neutral'.

The claim 'prolactin neutral' implied that Abilify had no effect on prolactin levels. The SPC did not comment on the effect of Abilify on prolactin levels. Data presented at Davos 2004 included a graph of the proportion of aripiprazole-treated patients who experienced 'significant elevations in prolactin levels' over 26 weeks. About 8% of aripiprazole-treated patients experienced significant elevation of prolactin levels. The conclusion stated that aripiprazole had a 'low liability' for hyperprolactinaemia. It was therefore misleading to claim the medicine was 'prolactin neutral'.

The Panel considered that the claim that Abilify was weight and prolactin neutral was unhelpful and open to interpretation. 'Weight neutral' could mean that as many patients lost weight as gained weight but it told the prescriber nothing about the amount of weight change in either direction nor of the expected incidence of such changes; only that the changes cancelled one another out.

The Panel noted that there was data in the Abilify SPC which showed that some patients, albeit a minority, did gain weight on Abilify. Pigott *et al* showed that overall patients lost weight while being treated with Abilify although again a minority (6%) gained clinically significant amounts of weight (≥ 7% increase from baseline). Darlene (poster 379) showed that at the end of a 26 week study there was a mean weight loss of 1.37kg with Abilify although once again a minority (about 12%) did gain clinically significant amounts of weight.

The Panel considered that the claim 'weight neutral' did not reflect the available evidence clearly enough such that prescribers would know what to expect when treating patients with Abilify. The Panel ruled a breach of the Code.

With regard to 'prolactin neutral' the Panel noted that the Abilify SPC did not refer to prolactin levels. Pigott *et al* stated that prolactin levels were within normal limits from week 6 to week 26 of the study and that aripiprazole was associated with a lower rate of potentially clinically significant increases in serum prolactin than placebo (5% v 13%). Darlene *et al* (poster 379) stated that the incidence of prolactin levels greater than the upper limit of normal was significantly higher in olanzapine-treated patients than in aripiprazole-treated patients. From a bar chart in the poster it appeared that about 8% of aripiprazole patients experienced elevated prolactin compared to about 37% of olanzapine patients. Kasper *et al* stated that significantly fewer patients on aripiprazole (3.4%) had prolactin elevations greater than the upper limit of normal regardless of baseline vs haloperidol (61%).

The Panel noted its comments above regarding the claim 'weight neutral' and considered that they also applied to the claim 'prolactin neutral'. A breach of the Code was ruled.

Lilly requested the Panel's opinion as to whether these matters constituted a breach of Clause 2, in view of the fact that the complaints were about misleading safety, dosage and indication claims and because Bristol-Myers Squibb and Otsuka appeared to be running a promotional campaign which was consistently in breach of the Code.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

Eli Lilly and Company Limited complained about the promotion of Abilify (aripiprazole) by Bristol-Myers Squibb Pharmaceuticals Limited and Otsuka Pharmaceuticals (UK) Ltd. The complaint related to the availability of the summary of product characteristics (SPC) for Abilify and an Abilify leavepiece (ref ABI/04-04/0297/03-06). Correspondence between the parties had failed to resolve the matter. Abilify was indicated for the treatment of schizophrenia.

Lilly supplied Zyprexa (olanzapine).

Bristol-Myers Squibb and Otsuka submitted a joint response.

A Inability to supply an Abilify SPC upon request

COMPLAINT

Lilly received a copy of the leavepiece on 8 June and a member of its medical information department telephoned the Bristol-Myers Squibb medical information department to request a copy of the Abilify SPC. The named Lilly employee was told by a named Bristol-Myers Squibb employee that the SPC was not available to be sent out to customers at that stage. The telephone call was repeated on 9 June and the same response was received. Lilly first obtained a copy of the SPC on 14 June from the Electronic Medicines Compendium. Lilly alleged that the inability to supply a copy of the SPC for a promoted medicine was a breach of Clause 15.8.

The statement from the Bristol-Myers Squibb employee that the SPC was not available to give out on 8 or 9 June was supported by a copy of the SPC Lilly received on 21 June to support press materials about the launch of Abilify. The SPC enclosed in the press pack did not include valid marketing authorization numbers or the date of first authorization. Lilly alleged that the use of an incomplete SPC in press briefing materials was a failure to maintain high standards in breach of Clause 9.1.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the marketing authorization for Abilify was received on 4 June. As of that date, an Abilify SPC was available. No promotion of Abilify occurred prior to the availability of the SPC. As such, Clause 15.8 of the Code had not been breached.

In addition, although Lilly was correct that the SPC included in a launch press pack was a draft SPC, which did not include a valid marketing authorization number or date of first authorization, the factual information contained in that draft SPC was the same as that contained in the final SPC. As an SPC was not a formal requirement in a press pack, the inclusion of such a draft could not be viewed as unacceptable. The companies, therefore, also rejected the alleged breach of Clause 9.1.

PANEL RULING

The Panel noted that Clause 15.8 required representatives to provide, or have available to provide if requested, a copy of the SPC for each medicine promoted. There was no allegation that a representative as defined under Clause 1.6 of the Code, ie a representative calling upon health professionals and administrative staff in relation to the promotion of medicines, had failed to supply an SPC on request. The Panel thus ruled no breach of Clause 15.8 of the Code.

The Panel noted that Clause 7.1 stated that upon reasonable request a company must promptly provide health professionals and appropriate administrative staff with accurate and relevant information about the medicines it marketed.

The Panel noted that the SPC was available from 4 June. This should have been provided to Lilly following its request on 8 June. There was however no allegation of a breach of Clause 7.1 of the Code.

With regard to the draft SPC included in the Abilify launch press pack, the Panel noted that the Code did not require SPCs to be included in press packs. The supplementary information to Clause 20.2 of the Code stated that it was good practice to include an SPC with a press release or a press pack relating to a medicine. The Panel queried why a draft SPC was included in a press pack embargoed until Monday, 21 June with a press meeting on Friday, 18 June when, according to the response from the companies, the SPC was available from 4 June. The draft SPC in the press pack omitted the marketing authorization number and the date of first authorization. The companies submitted that the factual information in the draft SPC was the same as in the final. Taking all the circumstances into account the Panel ruled no breach of Clause 9.1 of the Code.

B Leavepiece

The first page of the four page leavepiece described Abilify as 'The first and only available dopamine system stabiliser'. Page 2 was headed 'Highly effective symptom control in acute psychosis' beneath which were two graphs. Page 3 was headed 'Long term symptom control in both acute and stable patients' and also included two graphs. The final page included bullet points and the prescribing information.

1 Claims 'Highly effective symptom control in acute psychosis' and 'Abilify helped to control the symptoms of acute psychosis as early as week 1'

The claims appeared on page 2 of the leavepiece.

COMPLAINT

Lilly noted that the Abilify SPC stated that 'Abilify is indicated for the treatment of schizophrenia'. Schizophrenia was only one of the very many causes of psychosis, which also included disorders as diverse as mania, depression and drug abuse. Lilly alleged that the claims constituted promotion of Abilify outside the marketing authorization in breach of Clause 3.2.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the reference to 'acute psychosis' in the leavepiece could only be confusing if it was taken out of context. However the leavepiece was designed to be left as a reminder of a call from a medical representative, in which the entire discussion was focused on schizophrenia; the prescribing information, on the final page of the leavepiece, clearly stated that Abilify was indicated for the treatment of schizophrenia; and the second bullet point on the final page also stated that Abilify addressed the symptoms of *schizophrenia*. In view of the above, the companies did not believe the claims constituted promotion of Abilify outside its marketing authorization and consequently there was no breach of Clause 3.2.

The companies reiterated that they had not attempted to promote indications not covered by the marketing authorization. However, in an attempt to reconcile the views of both parties, they had already acknowledged in their correspondence with Lilly that the clarity of this item could be improved. The companies had already agreed that when this leavepiece was revised, the indication would be stated more prominently. They were, therefore, disappointed that Lilly had chosen to draw this point to the Authority's attention.

PANEL RULING

The Panel noted that the leavepiece announced the launch of Abilify but did not state at the outset that it was a treatment for schizophrenia. The claims at issue referred to the control of the symptoms of acute psychosis; acute psychosis could be caused by conditions other than schizophrenia. It was irrelevant that the leavepiece was designed to be left as a reminder following a call from a representative. Each piece of promotional material had to stand alone. The only mention of schizophrenia was in the second of five bullet points on the outside back cover; this was insufficient to negate the impression that Abilify was

licensed to treat psychotic conditions generally. The prescribing information on the final page of the leavepiece clearly stated that Abilify was indicated in schizophrenia but it was an established principle under the Code that otherwise misleading claims could not be qualified by, *inter alia*, the prescribing information. The claims about symptom control in psychosis were not placed within the context of treating schizophrenia, the licensed indication. The Panel decided that in the context in which they appeared the claims were inconsistent with the SPC and each was ruled in breach of Clause 3.2 of the Code.

2 Alleged promotion of unlicensed doses of Abilify

COMPLAINT

Lilly noted that the Abilify SPC stated that 'The recommended starting and maintenance dose for Abilify is 15mg/day administered on a once-a-day schedule without regard to meals. Abilify is effective in a dose range of 15 to 30mg/day. Enhanced efficacy at doses higher than the recommended daily dose of 15mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30mg'. The only exceptions to these recommendations were when treating the elderly or when Abilify was administered concomitantly with potent CYP3A4 or CYP2D6 inhibitors, when a lower starting dose should be considered.

The leavepiece described four studies, three of which used doses of Abilify that did not comply with the dosing regime recommended by the SPC.

A graph on page 1 of the leavepiece, referenced to data on file, compared the efficacy of placebo, haloperidol (10-20mg) and Abilify (2-30mg). The dose of Abilify 2mg was below the recommended starting and maintenance dose and there were no caveats to suggest that the subjects were elderly or also receiving liver enzyme inhibitors. Lilly alleged a breach of Clause 3.2.

A graph on page 2 adapted from Potkin *et al* (2003) compared the efficacy of placebo, Abilify 20mg, Abilify 30mg and risperidone 6mg. The SPC did not recommend the use of Abilify 20mg at all and did not recommend the use of Abilify 30mg as a starting dose. Lilly alleged a breach of Clause 3.2.

A graph on page 3 referenced to data on file compared the efficacy of Abilify 20-30mg with haloperidol 7-10mg in relation to the reduction in PANSS total score in acutely psychotic patients. Again, the SPC did not recommend the use of Abilify 20mg at all and did not recommend the use of Abilify 30mg as a starting dose. Furthermore, Abilify was indicated for the treatment of schizophrenia, not acute psychosis. Lilly alleged a breach of Clause 3.2.

RESPONSE

Bristol-Myers Squibb and Otsuka did not consider that the dosages in the leavepiece were inconsistent with the Abilify SPC. The recommended starting and maintenance dose for Abilify was 15mg/day and the effective dose range was 15-30mg/day. However, the SPC clearly allowed for variation in dosage of Abilify beyond this range. Certain clinical situations would require lower doses than 15mg. Conversely, some patients might require higher doses with certain concomitant medications. Furthermore, the doses shown were an accurate reflection of efficacy associated with all doses of Abilify in the clinical trials.

Data was provided from a meta-analysis of five short-term studies. This included a dose-finding study which was part of the marketing authorization application. Certain clinical situations, admittedly rare, might warrant the use of a 2mg dose. It was, therefore, important that such data was available. The 20mg and 30mg doses were within the effective dose range of Abilify (Potkin *et al*). A physician could start at either of the two doses above and not be prescribing outside the effective 15-30mg/day dose recommended in the SPC. The same point also applied to the graph comparing the efficacy of Abilify 20-30mg to haloperidol 7-10mg in acutely psychotic patients.

Importantly, the SPC for Abilify was referenced in part by a study which only used 30mg/day (Kasper *et al*).

In summary, the companies did not consider the dosages shown were inconsistent with the particulars listed in the Abilify SPC. Therefore, they strongly refuted a breach of Clause 3.2.

PANEL RULING

The Panel noted that the Abilify SPC stated that the recommended starting and maintenance dose was 15mg/day. Further that Abilify was effective in a dose range of 15 to 30mg/day. The SPC stated that for patients aged over 65 a lower starting dose should be considered when clinical factors warranted. When given with certain other medicines (potent CYP3A4 or CYP3D6 inhibitors) the dose of Abilify should be reduced; in the presence of potent CYP3A4 inducers the dose of Abilify should be increased. Abilify was available as 10mg, 15mg or 30mg tablets.

The Panel noted that none of the graphs used doses of Abilify higher than 30mg. Showing data for the 20mg dose of Abilify was not unreasonable as that dose was within the effective dose range (15 to 30mg). With regard to the data in graph 1 where Abilify was dosed at less than the recommended starting and maintenance dose, the Panel noted that the data was being used to demonstrate an efficacy difference with placebo. It was not being used to support adverse event data or such like. Further, the available dosage forms of Abilify meant that it would be difficult to administer a 2mg dose. In the circumstances the Panel did not consider that the doses used in any of the four graphs were not in compliance with the SPC dosing regimen as alleged. Thus the Panel ruled no breach of Clause 3.2 of the Code.

The Panel considered that the use of the term 'acutely psychotic patients' was similar to point B1 above and

thus ruled a breach of Clause 3.2 of the Code in that regard.

During the consideration of this matter the Panel noted that nowhere in the leavepiece, other than in the prescribing information, was the recommended dosing regimen stated clearly. Given that Abilify was a new medicine and doses had been referred to, the Panel considered that the leavepiece should have clearly stated the recommended dosing information so that the graphs could be considered in context. The failure to clearly state the dosing regimen was in the Panel's view misleading. It asked that Bristol-Myers Squibb and Otsuka be advised of its concerns in this regard.

3 Claim 'Abilify significantly improved symptoms over 52 weeks vs haloperidol'

This claim appeared on page 3 of the leavepiece next to a graph comparing the reduction in PANSS total score for Abilify 20-30mg and haloperidol (7-10mg) in acutely psychotic patients. The claim was referenced to data on file.

COMPLAINT

Lilly stated that the data showed that Abilify was superior to haloperidol at 3 time points out of 20. Lilly considered that it was misleading to claim that one medicine was superior to another when they were equivalent at the overwhelming majority of time points in the study. A breach of Clause 7.2 was alleged.

RESPONSE

The companies stated there was a statistically significant improvement in Abilify treated patients at weeks 26, 37 and 52 as compared to haloperidol. In addition, the SPC stated that Abilify was superior to haloperidol in the 52 week study in both negative and depressive symptoms. The data on file used to support this claim was consistent with published data (Kasper *et al*). The companies denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the data on file had not been provided. A copy of Kasper *et al* (2003) was supplied. The leavepiece showed a statistically significant difference between Abilify at only three time points including at 52 weeks.

Kasper *et al* stated that aripiprazole and haloperidol were associated with similar improvements in symptoms as measured by changes from baseline on the total Positive and Negative Syndrome Scale (PANSS) score, PANNS positive symptoms subscale and the Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Global Improvement (CGI-I) scores. Aripiprazole was superior to haloperidol in improving the negative symptoms of schizophrenia as measured by changes from baseline on the PANSS negative subscale and in reducing depressive symptoms demonstrated on Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline.

The Panel noted the SPC stated that 'Abilify is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medication at 52 weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale, showed a significant improvement over haloperidol'.

The Panel considered that the claim 'Abilify significantly improved symptoms over 52 weeks vs haloperidol' in association with the graph was misleading. In this regard it noted Kasper *et al* and the SPC. Data in the leavepiece which showed statistically significant differences at 52 weeks but no such difference in all but two time points before then was not sufficient for a claim that Abilify significantly improved symptoms over 52 weeks. The claim implied that throughout the 52 weeks symptom scores were improved with Abilify compared with haloperidol which was not so. The claim was misleading as alleged and a breach of Clause 7.2 was ruled.

4 Claim 'Abilify is weight and prolactin neutral and has minimal potential for sedation'

This claim appeared as the third bullet point on the back page of the leavepiece. The claim regarding weight was referenced to McQuade *et al* (2003) and the claim about prolactin was referenced to Carson *et al* (2002).

COMPLAINT

Lilly alleged that the claims regarding weight and prolactin were misleading.

The claim 'weight neutral' implied that the medicine had no effect on weight; however, Section 5.1 of the Abilify SPC stated 'Weight gain: in clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26 week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly fewer patients had at least 7% weight gain over baseline (ie a gain of at least 5.6kg for a mean baseline weight of ~80.5kg) on aripiprazole (n=18 or 13% of evaluable patients), compared to olanzapine (n=45, or 33% of evaluable patients)'.

Lilly stated that if 13% of Abilify treated patients could be expected to gain at least 7% weight over baseline it was misleading to claim the medicine was weight neutral. Furthermore Potkin *et al* stated 'aripiprazole showed a low incidence of clinically significant weight gain' and described a statistically greater probability of clinically significant weight gain in aripiprazole-treated patients compared to placebo-treated patients (aripiprazole 20mg 13% and aripiprazole 30mg 9% vs placebo 2%, both $p<0.05$),

demonstrating the medicine not to be 'weight neutral'. Lilly alleged a breach of Clause 7.9.

The claim 'prolactin neutral' implied that Abilify had no effect on prolactin levels. The SPC did not comment on the effect of Abilify on prolactin levels. Data presented at Davos 2004 included a graph of the proportion of aripiprazole-treated patients who experienced 'significant elevations in prolactin levels' over 26 weeks. About 8% of aripiprazole-treated patients experienced significant elevation of prolactin levels. The conclusion stated that aripiprazole had a 'low liability' for hyperprolactinaemia. It was therefore misleading to claim the medicine was 'prolactin neutral'. Lilly alleged a breach of Clause 7.9.

RESPONSE

Bristol-Myers Squibb and Otsuka stated that the data supported the claim that Abilify was both weight and prolactin neutral (Pigott *et al*, 2003). Firstly, placebo controls were used as standard in clinical trials to calibrate against non-medicine effects in treatment arms. Secondly, as a feature of most biological parameters, there was variation around any mean value. Therefore, the only valid comparison was to the mean placebo effect. The Oxford English Dictionary defined the term 'neutral' as 'having no strongly marked characteristics'. Within normal clinical variation neither weight gain nor prolactin elevation were observed as mean effects of Abilify when compared to placebo. The companies, therefore, concluded that 'neutral' legitimately described the effects of Abilify on weight gain and prolactin elevation. They denied a breach of Clause 7.9.

PANEL RULING

The Panel considered that the claim that Abilify was weight and prolactin neutral was unhelpful and open to interpretation. 'Weight neutral' could mean that as many patients lost weight as gained weight but it told the prescriber nothing about the amount of weight change in either direction nor of the expected incidence of such changes; only that the changes cancelled one another out.

The Panel noted that there was data in the Abilify SPC which showed that some patients, albeit a minority, did gain weight on Abilify. Pigott *et al* showed that overall patients lost weight while being treated with Abilify although again a minority (6%) gained clinically significant amounts of weight (≥ 7% increase from baseline). Darlene (poster 379) showed that at the end of a 26 week study there was a mean weight loss of 1.37kg with Abilify although once again a minority (about 12%) did gain clinically significant amounts of weight.

The Panel considered that the claim 'weight neutral' did not reflect the available evidence clearly enough such that prescribers would know what to expect when treating patients with Abilify. The Panel ruled a breach of Clause 7.9.

With regard to 'prolactin neutral' the Panel noted that the Abilify SPC did not refer to prolactin levels. Pigott *et al* stated that prolactin levels were within normal limits from week 6 to week 26 of the study and that aripiprazole was associated with a lower rate of potentially clinically significant increases in serum prolactin than placebo (5% v 13%). Darlene *et al* (poster 379) stated that the incidence of prolactin levels greater than the upper limit of normal was significantly higher in olanzapine-treated patients than in aripiprazole-treated patients. From a bar chart in the poster it appeared that about 8% of aripiprazole patients experienced elevated prolactin compared to about 37% of olanzapine patients. Kasper *et al* stated that significantly fewer patients on aripiprazole (3.4%) had prolactin elevations greater than the upper limit of normal regardless of baseline vs haloperidol (61%).

The Panel noted its comments above regarding the claim 'weight neutral' and considered that they also applied to the claim 'prolactin neutral'. A breach of Clause 7.9 was ruled.

5 Alleged Breach of Clause 2

COMPLAINT

Lilly stated that in conclusion it requested the Panel's opinion as to whether these matters constituted a breach of Clause 2, in view of the fact that the complaints were about misleading safety, dosage and indication claims and because Bristol-Myers Squibb and Otsuka appeared to be running a promotional campaign which was consistently in breach of the Code.

RESPONSE

Bristol-Myers Squibb and Otsuka stated in conclusion that the: information on safety and dosage was factually supported by the SPC; as already agreed, the future use of the wording 'acute psychosis' would be in conjunction with the word 'schizophrenia' and; the claim of superiority over haloperidol was fully supported by the SPC. Bristol-Myers Squibb and Otsuka therefore strongly rejected the allegation that they had breached Clause 2.

PANEL RULING

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

Complaint received	**20 August 2004**
Case completed	**26 October 2004**

CASE AUTH/1627/8/04

PRIMARY CARE NHS TRUST PRESCRIBING ADVISER v GLAXOSMITHKLINE

'Dear Healthcare Professional' letter about Avandia

A prescribing adviser to a primary care NHS trust complained on behalf of the prescribing team about a 'Dear Healthcare Professional' letter sent by GlaxoSmithKline. The logo for Avandamet (rosiglitazone/metformin) appeared in the top right hand corner of the letter and the heading to the text of the letter stated 'Scottish Medicines Consortium (SMC) accepts rosiglitazone monotherapy (AVANDIA) for use within NHS Scotland for the treatment of Type 2 diabetes mellitus'.

The complainant considered that the letter heading selectively quoted the recommendation of the SMC and noted that the body of the letter and the logo displayed in the top right hand corner referred to Avandamet, not Avandia as suggested in the heading. As a consequence the letter was confusing, could be misinterpreted and might result in prescribing outwith the recommendations.

The Panel considered that the prominent display of the Avandamet logo and the repeated use of the product name on a letter which presented the SMC's advice on Avandia was misleading and confusing. The background colour of the boxed text which presented the SMC guidance was similar to that of the Avandamet logo, thus visually linking the two. Readers would not unreasonably assume that the SMC advice related to Avandamet and not to Avandia. The Panel ruled a breach of the Code. The letter did not compare the products as such and thus there was no misleading comparison; no breach was ruled.

The Panel considered that the heading to the letter 'Scottish Medicines Consortium (SMC) accepts [Avandia] for use within NHS Scotland' selectively quoted the SMC recommendation as alleged. The full recommendation, which was reproduced beneath the heading in the boxed text, stated that Avandia had been accepted for *restricted* use in NHS Scotland (emphasis added). The Panel ruled a breach of the Code in this regard.

A prescribing adviser to a primary care NHS trust complained on behalf of the prescribing team about a 'Dear Healthcare Professional' letter (ref AVC/LTR/04/13723/1) sent by GlaxoSmithKline UK Ltd.

The logo for Avandamet (rosiglitazone/metformin) appeared in the top right hand corner of the letter. The heading to the text of the letter stated 'Scottish Medicines Consortium (SMC) accepts rosiglitazone monotherapy (AVANDIA) for use within NHS Scotland for the treatment of Type 2 diabetes mellitus'. A black triangle appeared after the name Avandia.

COMPLAINT

The complainant believed that the letter might be in breach of the Code and raised the following issues:

- the graphic used did not directly relate to the agent cited in the body of the letter;
- the title selectively quoted the recommendation of the advisory body and
- the commentary provided again referred to a related agent, not that suggested in the title.

As a consequence the letter was confusing, could be misinterpreted and might result in prescribing outwith the recommendations. Therefore, the complainant alleged that the letter might be in breach of Clause 7.3 of the Code in that it was misleading.

The Authority asked GlaxoSmithKline to respond in relation to Clause 7.2 in addition to Clause 7.3 cited by the complainant.

RESPONSE

GlaxoSmithKline stated that the letter, which was widely distributed to health professionals in Scotland, was clearly intended to be promotional, as evidenced by the prominent use of the Avandamet logo, and the inclusion of prescribing information for both Avandia and Avandamet. The main purpose of the mailing was to draw attention to the SMC advice on rosiglitazone monotherapy. Following this, the reader was reminded of the prior SMC advice relating to Avandamet use, together with some general promotional statements.

In line with GlaxoSmithKline's current promotional strategy, only the Avandamet logo was included in the mailing. The Code did not prohibit reference to more than one medicine in a single communication; nor did it mandate that logos should be given for each product mentioned. In this case, the wording of the mailing clearly and unambiguously differentiated between the two products and the separate advice issued by the SMC. Thus: 'The guidance for rosiglitazone as monotherapy *follows the SMC's recommendation earlier this year for the use of AVANDAMET …'* and '*Both* these recommendations can be accessed …' and 'If you would like further information on AVANDAMET *or* rosiglitazone as monotherapy …' (emphasis added in italics by GlaxoSmithKline). GlaxoSmithKline therefore did not consider that, as regards the copy text, the letter was misleading or confusing.

The heading or title alerted the reader to the general subject of the mailing. The full wording of the SMC advice was given immediately below, in a pink-coloured box with an emboldened sub-heading. It was difficult to see how the advice could have been presented in a more prominent manner.

Clause 7.3 of the Code related only to comparisons between medicines. No such comparisons were made in the letter, and this clause did not apply. For the reasons already given, GlaxoSmithKline maintained that the mailing was not misleading, and thus not in breach of Clause 7.2.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that the main purpose of the letter was to draw attention to the SMC's advice on rosiglitazone monotherapy. The Avandamet logo appeared prominently in the top right-hand corner of the letter in bold, pink type. In the Panel's view this would be seen first and would catch the reader's attention. The heading to the letter referred to the SMC advice on Avandia and the advice itself was reproduced in a highlighted pink box of text in the main body of the letter. Immediately following the boxed text was a statement that the SMC guidance for rosiglitazone as monotherapy followed the SMC recommendation for the use of Avandamet in a broader group of patients. The letter ended with a description of how Avandamet therapy could benefit patients. The Panel noted that the letter referred to Avandamet four times – once in logo type and otherwise in upper case type. Avandia was only mentioned twice – once in upper case type and once in lower case; the product was otherwise referred to as rosiglitazone.

The Panel accepted GlaxoSmithKline's submission that promotional material could refer to more than one product. It must be clear however which claims related to which of the products so promoted.

The Panel considered that the prominent display of the Avandamet logo and the repeated use of the product name on a letter which presented the SMC's advice on Avandia was misleading and confusing. The background colour of the boxed text which presented the SMC guidance was similar to that of the Avandamet logo, thus visually linking the two. The letter was otherwise black type face on a white background. Readers would not unreasonably assume that the SMC advice related to Avandamet and not to Avandia.

The Panel ruled a breach of Clause 7.2 of the Code. The letter did not compare the products as such and therefore no breach of Clause 7.3 was ruled.

The Panel considered that the heading to the letter 'Scottish Medicines Consortium (SMC) accepts [Avandia] for use within NHS Scotland' selectively quoted the SMC recommendation as alleged. The full recommendation, which was reproduced beneath the heading in the boxed text, stated that Avandia had been accepted for *restricted* use in NHS Scotland (emphasis added). The Panel ruled a breach of Clause 7.2 in this regard.

Complaint received **24 August 2004**

Case completed **11 October 2004**

CASE AUTH/1630/8/04

PRIMARY CARE TRUST PHARMACIST v ASTRAZENECA

Nexium cost comparison chart

A pharmacist at a primary care trust alleged that a cost comparison chart for Nexium (esomeprazole) which appeared in a booklet entitled 'Further Evidence' issued by AstraZeneca was misleading.

The complainant noted that the chart compared the cost of Nexium 20mg with alternative full dose proton pump inhibitors (PPIs) to which it was therapeutically equivalent and showed it to be the least expensive. However the chart omitted the price of generic omeprazole 20mg which, in February 2004 (about the time the chart seemed to have been produced), cost less. The chart thus did not provide a balanced and fair reflection of the cost of Nexium in relation to the equivalent PPIs available. The fact that it stated the prices shown were for 'branded' PPIs was immaterial as the significance of this was not appreciated by prescribers, many of whom would not know that omeprazole was available generically.

The Panel noted that the cost comparison chart appeared on a page headed 'What is the cost of failing to maintain RO [reflux oesophagitis] patients on other low dose PPIs?'. Below the page heading was the title of the chart 'Cost of branded PPIs (licensed maintenance doses) in RO therapy cost of 28 days' therapy' and then the chart itself. The Panel noted that the chart compared the cost variance of 28 days' therapy of rabeprazole (£12.43 – £22.75), pantoprazole (£12.88 – £23.65), lansoprazole capsules (£12.98 – £23.75), lansoprazole oro-dispersible tablets (£11.35 – £21.38) and Losec (£19.34 – £29.22) with Nexium 20mg od at £18.50.

The Panel considered that the prominence of the page heading 'What is the cost of failing to maintain RO patients on other low dose PPIs?', compared with that of the title of the chart, was such that readers would gain the initial impression that comparative data was presented for all other low dose PPIs but that was not so. The Panel noted that whilst the chart title referred to 'branded' PPIs this was not sufficiently prominent to negate the overall visual impression created by the page. The chart title was in a small font size and black typeface in contrast to the purple typeface and larger font of the page heading. The design of the page was such that the reader's eye was drawn straight from the page heading to 'Nexium 20mg' which appeared in a purple block at the bottom of the cost comparison chart. The Panel also noted that although the chart title referred to branded PPIs the only brand name used was Losec. All of the other PPIs were referred to by their generic names which might have increased the complainant's expectation that generic omeprazole should have been included. The Panel considered the cost comparison chart misleading as alleged. Breaches of the Code were ruled.

A pharmacist at a primary care trust complained about a cost comparison chart for Nexium (esomeprazole) which appeared in a booklet entitled 'Further Evidence' (ref NEX13664) issued by AstraZeneca UK Ltd.

COMPLAINT

The complainant alleged that the cost comparison chart contravened Clauses 7.2 and 7.3 of the Code in relation to the comparison of the cost of Nexium 20mg with the cost of alternative full dose proton pump inhibitors (PPIs) to which it was therapeutically equivalent. The chart showed Nexium 20mg to be the least expensive compared to other full dose PPIs but omitted the price of generic omeprazole 20mg which, in February 2004 (about the time the chart seemed to have been produced), cost less (£12.75 compared to £18.15 for 28 days' therapy). The chart thus did not provide a balanced and fair reflection of the cost of Nexium in relation to the equivalent PPIs available, and so misled prescribers. The fact that it stated the prices shown were for 'branded' PPIs was immaterial as the significance of this was not appreciated by prescribers, many of whom would not know that omeprazole was available generically. The whole purpose of the chart was to show that Nexium 20mg was cheaper than the equivalent dose of alternative PPIs, when it was not, as it was possible to prescribe omeprazole 20mg for less cost.

RESPONSE

AstraZeneca stated that the cost comparison chart was included as a single page in a Sales Force Opportunities Handling document for Nexium which was used by representatives to address specific concerns raised by health professionals regarding Nexium. The chart compared the cost of branded PPIs used in reflux oesophagitis (RO) at their licensed dosages for maintenance treatment.

Nexium was licensed at a specific dose of 20mg for maintenance treatment in patients with RO. The cost of Nexium 20mg was compared to the cost of 28 days' therapy of the other available branded PPIs at their respective licensed doses for maintenance treatment as indicated by the title of the chart 'Cost of branded PPIs (licensed maintenance doses) in RO therapy'. The recent National Institute of Clinical Excellence (NICE) Clinical Guideline on dyspepsia considered low dose Nexium 20mg to be as effective and hence equivalent to all other PPIs at their full dose and so the chart compared the cost of low dose Nexium 20mg versus both low and full doses of the other available PPIs for this indication.

As it was clearly stated that the chart compared the cost of 'branded' PPIs, the cost of generic omeprazole had not been included, but branded omeprazole, Losec, was. This was to clearly indicate that the comparison was with branded omeprazole and not generic omeprazole. Losec was manufactured and marketed by AstraZeneca.

Generic omeprazole had been available since early 2003. Through medical communications and the influence of pharmaceutical and prescribing advisers, prescribers knew that omeprazole could be prescribed generically as opposed to the branded version. This was reflected by the rising UK market share of generic omeprazole. In July 2004 sales of generic omeprazole had increased to 87% of total omeprazole pack sales with 96% of total omeprazole prescriptions being written generically.

AstraZeneca did not consider that the chart was in breach of Clauses 7.2 and 7.3 of the Code as it was clearly stated that it compared the cost of Nexium in relation to other branded PPIs and all prices were accurate at the time of preparation. In addition, AstraZeneca did not consider that prescribers did not know of the availability of generic omeprazole, as outlined above. Moreover, the purpose of the chart was not to indicate that Nexium 20mg was the 'cheapest' PPI, but to accurately depict the price of Nexium compared to branded PPIs in maintaining RO patients on long-term therapy at their respective licensed doses in the context of the new NICE Guideline.

AstraZeneca stated that the cost comparison chart was used to address specific concerns about the price of Nexium compared to other branded PPIs. Should a representative be asked about the price of generic omeprazole, they would be able to provide information on that too.

PANEL RULING

The cost comparison chart appeared on a page headed 'What is the cost of failing to maintain RO patients on other low dose PPIs?'. Below the page heading was the title of the chart 'Cost of branded PPIs (licensed maintenance doses) in RO therapy cost of 28 days' therapy' and then the chart itself. The Panel noted that the chart compared the cost variance of 28 days' therapy of rabeprazole (£12.43 – £22.75), pantoprazole (£12.88 – £23.65), lansoprazole capsules (£12.98 – £23.75), lansoprazole oro-dispersible tablets (£11.35 – £21.38) and Losec (£19.34 – £29.22) with Nexium 20mg od at £18.50.

The Panel considered that the prominence of the page heading 'What is the cost of failing to maintain RO patients on other low dose PPIs?', compared with that of the title of the chart, was such that readers would gain the initial impression that comparative data was presented for all other low dose PPIs but that was not so. The Panel noted that whilst the chart title referred to 'branded' PPIs this was not sufficiently prominent to negate the overall visual impression created by the page. The chart title was in a small font size and black typeface in contrast to the purple typeface and larger font of the page heading. The design of the page was such that the reader's eye was drawn straight from the page heading to 'Nexium 20mg' which appeared in a purple block at the bottom of the cost comparison chart. The Panel also noted that although the chart title referred to branded PPIs the only brand name used was Losec. All of the other PPIs were referred to by their generic names which might have increased the complainant's expectation that generic omeprazole should have been included. The Panel considered the cost comparison chart misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **9 September 2004**

Case completed **8 November 2004**

CASE AUTH/1631/9/04

CONSULTANT ANAESTHETIST v ROCHE

Conduct of representative

A consultant anaesthetist and lead consultant for acute pain complained about the promotion of Kytril (granisetron) by a Roche representative.

Earlier in 2004, the complainant had organised a multidisciplinary clinical governance meeting for the anaesthetic departments and pharmacy across the division to discuss prevention and management of post-operative nausea and vomiting (PONV). A standard policy was agreed. The medicine of choice was agreed as ondansetron. The Roche representative was told of this decision and that it had been agreed across the division.

It had recently come to the complainant's attention that this representative had approached nurses and advised them that the PONV policy had changed to granisetron from ondansetron and encouraged them to order the medicine for ward stock. Granisetron promotional material was also found beside the new local wall chart guideline for PONV. This representative was clearly aware that granisetron was not the medicine of choice for the management of PONV, but appeared to have misinformed staff of its place in the guideline. This could lead to confusion. It was also inappropriate that the representative had approached members of the nursing staff and encouraged them to keep stocks of granisetron on the ward.

The Panel noted that the parties' accounts of what took place differed. The complainant alleged that the representative had misinformed nurses on various wards that the PONV policy had changed to granisetron from ondansetron and that he had encouraged the nurses to order granisetron for ward stock. The representative denied that he had advised nurses that the local policy had changed. Roche had not commented on whether or not the representative had encouraged nurses to keep or order stocks for the ward. The representative had informed the nursing staff that Kytril was used in the theatres by some anaesthetists and left promotional material with the nurses he had seen.

The Panel noted that even if a company's medicine was not the medicine of choice within a hospital the company's representatives could still promote the product within the hospital providing that such promotion met the requirements of the Code. In this particular case the representative was aware that ondansetron was the product of choice in PONV. It did not appear, however, from the account of either party that the representative had taken sufficient notice of the PONV policy when promoting Kytril to nursing staff on the wards. Overall the Panel decided that the representative had not maintained a high standard of ethical conduct. A breach of the Code was ruled.

A consultant anaesthetist and lead consultant for acute pain at a local hospital, complained about the promotion of Kytril (granisetron) by a representative of Roche Products Limited.

COMPLAINT

The complainant had met the representative a number of times over the past year to discuss Kytril's merits and demerits compared with other 5-HT_3 antagonists.

Earlier in 2004, the complainant had organised a multidisciplinary clinical governance meeting for the anaesthetic departments and pharmacy across the division to discuss prevention and management of post-operative nausea and vomiting (PONV). A standard policy was agreed along with guidelines which were implemented. The medicine of choice was agreed as ondansetron. The Roche representative was told of this decision and that it had been agreed across the division.

It had come to the complainant's attention that this representative had approached nurses on various wards across both hospital sites and advised them that the PONV policy had changed to granisetron from ondansetron and encouraged them to order the medicine for ward stock. Promotional material relating to granisetron was also found beside the new local wall chart guideline for PONV. This representative was clearly aware that granisetron was not the local medicine of choice for the management of PONV, but appeared to have mis-informed staff of its place in the guideline. This could lead to confusion amongst nurses and trainee doctors. It was also inappropriate that the representative had approached members of the nursing staff and encouraged them to keep stocks of granisetron on the ward.

The complainant alleged that the actions of the representative appeared to be highly inappropriate and in breach of Clause 15 of the Code.

When writing to Roche, the Authority asked it to respond in relation to Clauses 9.1 and 15.2 of the Code.

RESPONSE

Roche was very sorry to learn that a consultant anaesthetist had found cause to complain about its representative. In respect of his promotion of Kytril the representative was very experienced and had received regular training on the Code and had passed the ABPI representatives examination.

Kytril was included within the greater local formulary, and therefore was available for use throughout all hospitals within its domain. Kytril was a stock item within the pharmacy department and, according to the representative, was used in neuro-surgical, maxillo-facial, ENT and various other surgical procedures throughout the hospital. Many of these patients, therefore, were returned to the wards having received Kytril in theatre. The representative thus considered justified in informing the nursing staff about Kytril as some of their patients might have received this medicine or might require a subsequent

dose of a 5-HT_3 antagonist after surgery. The representative was aware of the decision that ondansetron was the medicine of choice for PONV within the division and denied that he had advised nurses that the policy had changed.

Roche noted that its representative had sought, and been given, permission by a nurse co-ordinator for the hospital to go into the wards, where he informed the nursing staff that Kytril was used in the theatres by some anaesthetists. He now realised the consequences of this action and the confusion that had been caused. He very much regretted that his action had been considered to undermine the decision taken by the complainant, which was certainly not his intention. He merely intended to inform relevant staff that Kytril was used in theatre and he left several pieces of Kytril literature with dosing details with the nurses he saw. He denied putting such literature on the wall next to the current protocols.

Roche stated that its representative had been reprimanded and reminded of the requirements of the Code and the need to maintain a high standard of ethical conduct throughout the discharge of his duties. He apologised for any distress caused to the complainant and any uncertainty or confusion that this might have caused in the wards.

FURTHER COMMENTS FROM THE COMPLAINANT

Roche's response was sent to the complainant for comment.

The complainant stated that granisetron was included in the local health board formulary under Section 4.6; Drugs used in Nausea and Vertigo as one of two 5-HT_3 atagonists for refractory PONV. However not all formulary medicines were kept in stock in either theatres or the ward areas.

At a consensus meeting of all anaesthetists in the local area it was decided to rationalise treatments for PONV at which time the avantages and disadvantages of both granisetron and ondansetron were discussed. The decision was that ondansetron was the medicine of choice and therefore should be included as a stock medicine on surgical wards and in theatres. The complainant was aware that some colleagues chose to use granisetron in certain cases where it was available in particular theatres within the local university hospitals division but granisetron was not routinely stocked on the wards unless there was a particular indication for treatment for nausea or vomiting not associated with anaesthesia and operation.

The response from Roche indicated that its representative had intended to inform the nursing staff that granisetron was being used in theatres by some anaesthetists. However he also included areas such as gynaecology and orthopaedics where granisetron was not being used and thus informing the staff caused confusion.

The decision to use ondansetron was a collective one and the complainant was eager that companies and their representatives respected such decisions and restricted their promotional activities in those areas where such agreements had been made.

The complainant noted that the representative had been reprimanded and reminded of the Code and hoped that this guaranteed that his actions outlined above would not be repeated. The complainant would keep the issue under review and not hesitate to reopen the issue if there were any need to do so.

PANEL RULING

The Panel noted that the parties' accounts of what took place differed. The complainant alleged that the representative had misinformed nurses on various wards that the PONV policy had changed to granisetron from ondansetron and that he had encouraged the nurses to order granisetron for ward stock. The representative denied that he had advised nurses that the local policy had changed. Roche had not commented on whether the representative had encouraged nurses to keep or order stocks for the ward. The representative had informed the nursing staff that Kytril was used in the theatres by some anaesthetists and left promotional material with the nurses he had seen.

The Panel noted that even if a company's medicine was not the medicine of choice within a hospital the company's representatives could still promote the product within the hospital providing that such promotion met the requirements of the Code, paying particular attention to Clause 15.4 which stated that the arrangements in force at a particular establishment must be observed. It was beholden upon the representative in such circumstances not to undermine or misleadingly represent the stated hospital policy. In this particular case the representative was aware that ondansetron was the product of choice in PONV. It did not appear, however, from the account of either party that the representative had taken sufficient notice of the PONV policy when promoting Kytril to nursing staff on the wards. Overall the Panel decided that the representative had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled. The Panel considered that the matter of high standards was covered by this ruling such that an additional ruling of a breach of Clause 9.1 was not required. The Panel thus ruled no breach of Clause 9.1.

Complaint received **10 September 2004**

Case completed **17 November 2004**

CASE AUTH/1632/9/04

NOVO NORDISK v AVENTIS PHARMA

Lantus folder

Novo Nordisk complained about a four page folder for Lantus (insulin glargine) issued by Aventis Pharma. The front page of the folder was headed 'It's Lantus Time. All the time'. The title of Riddle *et al* (2003) 'The treat-to-target trial: randomised addition of Lantus or human NPH insulin to oral therapy of type 2 diabetic patients' appeared beneath the subheading 'Landmark Study'. Brief details of the authors were also given on the front page along with the paper's citation. Page two discussed data from Riddle *et al*, a reprint of which was provided in a pocket on page 3.

Novo Nordisk noted that, importantly, Riddle *et al* had included overweight men and women with inadequate glycaemic control. 'Overweight' was defined in the study as a body mass index (BMI) between 26 to 40kg/m2. The claim 'It's Lantus Time. All the time' implied that the trial results could be generalised to all patients and did not point out the limitation of the trial. The claim 'It's Lantus Time. All the time', however, was all-inclusive and exaggerated as it implied that all patients could be treated with Lantus. This was not substantiated by Riddle *et al* which clearly referred to patients with type 2 diabetes who were overweight. In intercompany correspondence Novo Nordisk had noted that it was important to clarify this inclusion criterion in promotional material.

Novo Nordisk further noted that patients in the study had to have had diabetes for ≥ 2 years, and have been treated with stable doses of one or two oral antihyperglycaemic agents for ≥ 3 months. In other words newly diagnosed patients and those patients who had not been treated with oral antihyperglycaemic agents beforehand could not participate in this study. Hence the results of this study could not be generalised; and the claim 'It's Lantus time. All the time' was exaggerated.

Novo Nordisk alleged that the claim was inaccurate, ambiguous, over-inclusive and did not reflect the evidence clearly.

The Panel did not consider that the claim 'It's Lantus Time. All the time' was linked specifically to the results of Riddle *et al*. The front page of the folder gave no details about the results of the study, these were given on page two where the claim did not appear. The Panel noted that Riddle *et al* was a randomized, open label, parallel, 24 week multicentre trial in 756 overweight patients which compared the abilities and associated hypoglycaemic risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}. Inclusion criteria included BMI between 26 and 40kg/m^2. The Panel noted Aventis' submission that approximately 80% of people with type 2 diabetes were obese and that the population studied in Riddle *et al* was representative of those with the condition.

The Panel noted that although the folder stated that the patient population in Riddle *et al* had type 2 diabetes the weight inclusion criterion was not discussed. The Panel did not consider that this omission was misleading; the patient population was representative of those with type 2 diabetes. Nor did the Panel consider that the claim 'It's Lantus Time. All the time' otherwise rendered the omission misleading or exaggerated as alleged. No breach of the Code was ruled. This ruling was upheld on appeal by Novo Nordisk.

The Panel noted that the front page of the folder referred to the 'addition of Lantus or human NPH insulin to oral therapy of type 2 diabetic patients', a similar description appeared on page two. The Panel considered that it was thus sufficiently clear that the patients in Riddle *et al* were already receiving antihyperglycaemic agents and were thus not newly diagnosed. Nor did the Panel consider that the claim 'It's Lantus Time. All the time' gave an otherwise misleading or exaggerated impression of the patient population in Riddle *et al* in this regard. No breach of the Code was ruled. This ruling was upheld on appeal by Novo Nordisk.

Novo Nordisk noted that Riddle *et al* had, importantly, included patients on stable doses of one or two oral antihyperglycaemic agents which could include pioglitazone or rosiglitazone. Both pioglitazone and rosiglitazone were contraindicated with concomitant use of insulin, including insulin glargine. Novo Nordisk stated that this important safety point should be noted in all promotional materials and alleged that omission of information was in breach of the Code as it was ambiguous and failed to reflect available evidence on safety and side effects.

The Panel noted that subjects in Riddle *et al* were treated with stable doses of one or two oral antihyperglycaemic agents (sulphonylureas, metformin, pioglitazone or rosiglitazone) for ≥ 3 months. Both pioglitazone and rosiglitazone, however, were contraindicated in combination with insulin but neither product was mentioned by name in the folder which referred to 'oral therapy of type 2 diabetes'. The Panel noted that this description included sulphonylureas and metformin in addition to pioglitazone and rosiglitazone. On balance, the Panel considered that the folder gave the impression that Lantus could be added to any standard oral therapy for type 2 diabetes which was not so. The folder was misleading in this regard. A breach of the Code was ruled.

Novo Nordisk Limited complained about a four page folder (ref LAN 4101103) for Lantus (insulin glargine) issued by Aventis Pharma Ltd. The front page of the folder was headed 'It's Lantus Time. All the time'. The title of Riddle *et al* (2003) 'The treat-to-target trial: randomised addition of Lantus or human NPH insulin to oral therapy of type 2 diabetic patients' appeared beneath the subheading 'Landmark Study'. Brief details of the authors were also given on the front page along with the paper's citation. Page two discussed data from Riddle *et al*, a reprint of which was provided in a pocket on page 3.

Correspondence between the parties had failed to resolve Novo Nordisk's concerns. Novo Nordisk supplied a range of insulins.

1 Inclusion criteria of Riddle *et al* and the claim 'It's Lantus Time. All the time'

COMPLAINT

Novo Nordisk stated that Riddle *et al* had a number of important inclusion criteria: overweight men and women with inadequate glycaemic control.

'Overweight' was defined in the study as a body mass index (BMI) between 26 to 40kg/m^2. The claim 'It's Lantus Time. All the time', implied, however, that the trial results could be generalised to all patients and did not point out the limitation of the trial.

In intercompany correspondence Novo Nordisk had noted that it was important to clarify this inclusion criterion in promotional material. Aventis replied that a reprint of the paper was attached and therefore there was no need to list specific inclusion criteria.

Novo Nordisk considered that the folder should be a stand-alone piece; the reprint was loose and detachable.

The claim 'It's Lantus Time. All the time' was all-inclusive and covered all patients which was exaggerated. This was not substantiated by Riddle *et al*, which clearly referred to patients with type 2 diabetes who were overweight.

The inclusion criteria of the study also stated that patients had to have had diabetes for ≥ 2 years, and have been treated with stable doses of one or two oral antihyperglycaemic agents for ≥ 3 months. These criteria were highly time-specific: ie Lantus was used in this study for patients who had diabetes for *a period of time*, and *not newly diagnosed* diabetes; and that these patients had to *have been treated for a period of time* with stable doses of antihyperglycaemic agents. In other words newly diagnosed patients and those patients who had not been treated with oral antihyperglycaemic agents beforehand could not participate in this study. Hence the results of this study could not be generalised; and the claim 'It's Lantus time. All the time' was an exaggeration.

The claim was inaccurate, ambiguous and did not reflect the evidence clearly; a breach of Clause 7.2 was alleged. This claim was over-inclusive; a breach of Clause 7.10 was alleged.

RESPONSE

Aventis stated that Lantus was well understood to be a once daily product with a 24 hour duration of action. The claim 'It's Lantus time. All the time', together with the time based clock graphics that incorporated the imagery of the number seven to represent the accepted target HbA_{1c} level, clearly related to time. It did not refer to who might use Lantus, but what duration of action those people who used Lantus could reasonably expect from the product. The jump in logic that Novo Nordisk appeared to make from the stated notion of time, to the suggestion that the three word sentence 'All the time' referred in some way to a patient population was in Aventis' view at best ill-thought through.

Aventis noted that Novo Nordisk had alleged that the lack of explicit mention of the inclusion criteria, and one presumed the exclusion criteria of the study, implied that the trial results could be generalised to all patients. Aventis disagreed and was surprised that Novo Nordisk took this stance, which appeared to be exceedingly narrow and not in keeping with its own practices. Notwithstanding this, Aventis considered that the piece was a fair and balanced summary of the data and capable of substantiation.

Concerning the issue of weight and the fact that the study recruited overweight people, a review of type 2 diabetes published in the Handbook of Diabetes, stated that approximately 80% of type 2 diabetics were obese, defined in this review as a BMI >30. The mean BMI of the subjects in this study was approximately 32kg/m^2. This evidence showed that the population studied in Riddle *et al* was representative of the population of people with type 2 diabetes. Aventis did not agree that this folder breached the Code as alleged.

Aventis noted that the basis of Novo Nordisk's concerns with regard to inadequate glycaemic control appeared to be centred on the suggestion that: because the patients in Riddle *et al* had to have been receiving treatment for their diabetes before entry into the trial the results could not be generalised to other patient groups. In particular Novo Nordisk cited newly diagnosed patients and those who had not been treated with oral hypoglycaemic agents. Aventis stated that the allegation that it was making an exaggerated claim was again based on Novo Nordisk's view that the folder was about all patients with type 2 diabetes as discussed above.

The title of Riddle *et al* was on the front page of the folder and stated that the trial looked at the effects of the addition of Lantus or human NPH to oral therapy. Aventis considered that it was obvious that as the study was in patients already receiving treatment for diabetes, they would not be newly diagnosed and that the addition of therapy would mean that they were inadequately controlled. Aventis did not consider that it had either stated or suggested, that people with type 2 diabetes who were adequately controlled should be switched to Lantus.

Aventis agreed that the reprint might become detached from the piece and with this in mind it had taken particular care to ensure that the folder was self-contained and balanced as a stand-alone document. Nowhere had Aventis implied that Riddle *et al* supported the notion that Lantus could be used for all patients with type 2 diabetes. Aventis was clear in its view that within the practice of medicine there would always be an exception to any absolute statement made. This was why Aventis stated 'For patients with type 2 diabetes' on the back page of the document rather than a phrase which Novo Nordisk was somehow trying to suggest that Aventis had included, or implied such as 'for all patients with type 2 diabetes' or 'It's Lantus time for everyone'.

Aventis did not agree that this folder breached the Code as alleged.

PANEL RULING

The Panel did not consider that the claim 'It's Lantus Time. All the time' was linked specifically to the results of Riddle *et al*. The front page of the folder gave no details about the results of the study; these were given on page two where the claim did not appear. The Panel noted that Riddle *et al* was a randomized, open label, parallel, 24 week multicentre trial in 756 overweight patients which compared the abilities and associated hypoglycaemic risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}. Inclusion criteria included BMI between 26 and 40kg/m^2.

The Panel noted Aventis' submission that approximately 80% of people with type 2 diabetes were obese and that the population studied in Riddle *et al* was representative of those with the condition.

The Panel noted that although the folder stated that the patient population in Riddle *et al* had type 2 diabetes the weight inclusion criterion was not discussed. The Panel did not consider that this omission was misleading; the patient population was representative of those with type 2 diabetes. Nor did the Panel consider that the claim 'It's Lantus Time. All the time' otherwise rendered the omission misleading or exaggerated as alleged. No breach of Clauses 7.2 and 7.10 was ruled. This ruling was appealed by Novo Nordisk.

The Panel noted that the front page of the folder referred to the 'addition of Lantus or human NPH insulin to oral therapy of type 2 diabetic patients', a similar description appeared on page two. The Panel considered that it was thus sufficiently clear that the patients in Riddle *et al* were already receiving antihyperglycaemic agents and were thus not newly diagnosed. Nor did the Panel consider that the claim 'It's Lantus Time. All the time' gave an otherwise misleading or exaggerated impression of the patient population in Riddle *et al* in this regard. No breach of Clauses 7.2 and 7.10 were ruled. This ruling was appealed by Novo Nordisk.

APPEAL BY NOVO NORDISK

Novo Nordisk alleged that it was unclear as to what and to whom the claim 'It's Lantus Time. All the time' referred. Whilst Aventis stated that its intention was to refer to time, the Panel had interpreted it as patients with type 2 diabetes. Readers could interpret the claim to imply that one could treat type 2 diabetics with Lantus all the time, rather than referring to duration of action *per se*. This statement therefore was ambiguous in breach of Clause 7.2 of the Code.

In addition, Aventis had also pointed out that 'Lantus was well understood to be a once daily product'. Hence the statement 'It's Lantus Time. All the time' could also be taken to imply that once daily injection of Lantus would be sufficient for all types of diabetic patients.

Novo Nordisk noted that Garg *et al* (2004) showed that 104 out of 292 patients with type 1 diabetes required twice daily injection of Lantus in order to achieve a similar change of HbA_{1c} from baseline compared with those on once daily doses of Lantus. This showed that once daily Lantus was certainly not sufficient for some patients all the time; and certainly not all patients all the time. The claim 'It's Lantus Time. All the time' was therefore exaggerated and all-embracing in breach of Clause 7.10 of the Code.

Novo Nordisk noted that physiologically, Lantus was a basal insulin and did not provide cover for meal-related rises in blood glucose. This had to be addressed with short- or rapid-acting insulin (such as insulin aspart). Basal-bolus regimen in type 1 diabetes (a basal insulin plus a meal-time short-acting insulin) illustrated this point. Hence to claim 'It's Lantus Time. All the time' was exaggerated in breach of Clause 7.10.

Novo Nordisk noted that Riddle *et al* had two important inclusion criteria: 'overweight men and women with inadequate glycaemic control'. The term 'overweight' referred to people with a BMI between 26 to 40 kg/m^2. This was made clear by the authors in the opening sentence of the section 'Research Design and Methods', the second paragraph of the abstract. The claim 'It's Lantus Time. All the time', however, implied that the trial results could be generalised to all patients all of the time.

Novo Nordisk alleged that not all type 2 diabetics were overweight. By Aventis' submission, 20% of type 2 diabetes patients did not fit into this category. To claim 'It's Lantus Time. All the time' was all embracing and would mislead the readers.

Novo Nordisk alleged that equally, many patients were adequately controlled with oral hypoglycaemic agents without the need for insulin (such as Lantus). For this group of well-controlled patients, there was no justification to put them onto an injectible medicine such as insulin. Therefore Riddle *et al* could not be used to substantiate the claim 'It's Lantus Time. All the time' for this group of patients.

Novo Nordisk alleged that furthermore, the inclusion criteria of the study stated that patients had to have been diabetic for ≥ 2 years, and have been treated with stable doses of one or two oral antihyperglycaemic agents for ≥ 3 months. These criteria were highly time-specific: ie Lantus was used in this study for patients who had diabetes for a period of time, and not newly diagnosed diabetes; and that these patients had to have been treated for a period of time with stable doses of antihyperglycaemic agents.

Novo Nordisk noted that it was estimated that there were 1.8 million type 2 diabetics in the UK. Many of these patients were on oral antidiabetic agents; their disease had not progressed to the point where they needed insulin. Hence the claim 'It's Lantus time. All the time' stretched the applicability of the study to a very important group of patients not covered in the study. Novo Nordisk alleged that the claim was exaggerated in breach of Clause 7.10 of the Code; it was also inaccurate and not balanced, in breach of Clause 7.2.

Novo Nordisk noted the NICE Final Appraisal Determination on insulin glargine stated that:

'Insulin glargine is not recommended for routine use for people with type 2 diabetes who require insulin therapy. Insulin glargine treatment should be considered only for those people with type 2 diabetes who require insulin therapy and who fall into one of the following categories.

Those who require assistance from a carer or healthcare professional to administer their insulin injections.

Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.

Those who would otherwise need twice-daily insulin injections to maintain basal insulin levels in combination with oral antidiabetic drugs.'

Novo Nordisk alleged that the claim 'It's Lantus Time. All the time' in the folder was specific for type 2 diabetes, in direct contradiction of NICE guidelines. This claim was over-inclusive in breach of Clause 7.10. It was also in breach of Clause 7.2 as it was neither accurate nor unambiguous and it did not reflect the evidence clearly.

COMMENTS FROM AVENTIS

Aventis submitted that Novo Nordisk had linked the claim 'It's Lantus Time. All the time.' with Riddle *et al*. The Panel had to investigate the complaint made by Novo Nordisk and concluded that it did not consider there to be a link between the two; no breach was ruled. This view was consistent with Aventis' assertion that the intention was to refer to time. Aventis accepted the Panel's ruling and it was confident that readers would not find this ambiguous.

Aventis noted that in an attempt to show that Lantus was not a once daily injection, Novo Nordisk had cited Garg *et al*. Novo Nordisk claimed that 104 of the 292 patients with type 1 diabetes enrolled in the study received a split dose in order to achieve similar change of HbA_{1c} from baseline compared with those on single dose which proved that Lantus was not a once daily insulin. Novo Nordisk had, however, been selective in its reference and had misrepresented the study: the aim of the study was to see if insulin glargine improved control in a clinical setting; this was not a study comparing once daily and twice daily insulin glargine injections; the different regimens, namely morning dosing, evening dosing or split between the two were chosen for a number of reasons and not, as implied by Novo Nordisk, only to achieve similar change in Hb1A1c. The authors' conclusions included: 'Splitting the glargine dose did not offer any advantages in glycaemic control parameters'; 'This suggests that splitting the glargine dose may not be the treatment of choice'; 'We recommend that proper time and effort be put into a single injection of glargine before deciding to split the dose'.

Aventis submitted that the wealth of clinical data on insulin glargine's duration of action overwhelmingly supported the claim that it was an effective treatment given once daily. This was endorsed by the European Medicines Evaluation Agency (EMEA) in the wording of the summary of product characteristics (SPC): 'Lantus contains insulin glargine, an insulin analogue with a prolonged duration of action. It should be administered once daily at any time, but at the same time each day'.

Aventis noted that Novo Nordisk had stated that Lantus was a basal insulin and did not provide cover for meal-related rises in blood sugar, therefore the statement was an exaggeration.

Aventis submitted that the claim referred to the duration of action of Lantus and did not refer to how many insulins were needed as part of a basal-bolus regimen. Aventis considered that health professionals involved in the use of insulin were aware that Lantus was a basal insulin. Notwithstanding that, Lantus could be used as a sole insulin with or without oral antihyperglycaemic treatments, with the exception of glitazones.

Aventis noted that Novo Nordisk continued to insist that Riddle *et al* did not support the claim as patients in the study could not be generalised. As previously stated, the claim referred to the duration of action of Lantus and was not specifically linked to the study or to type 2 patients.

Aventis submitted that based on the above, the reference to the NICE guidance was not relevant to this case.

In summary, Aventis submitted that it had clearly shown that the claim 'It's Lantus Time. All the time.' referred to the duration of action of Lantus. The data available, including the EMEA public assessment report and the SPC supported the once daily use of insulin glargine.

FURTHER COMMENTS FROM NOVO NORDISK

Novo Nordisk reiterated much of its appeal adding that it had noted that Aventis had pointed out that Lantus could be used as a sole insulin with or without oral antihyperglycaemic treatments. This statement applied to type 2 diabetes, a point not made clear by Aventis.

Novo Nordisk also added that concomitant use of insulin and glitazones was contraindicated in Europe. 'It's Lantus Time. All the time' extended the claim to patients on glitazones. In point 2 of this case the Panel had ruled that Aventis was in breach of Clause 7.2 for not making this contraindication clear, Aventis had not appealed this ruling.

Novo Nordisk noted that Aventis had stated that 'Lantus contains insulin glargine, an insulin analogue with a prolonged duration of action. It should be administered once or twice daily at any time, but at the same time each day'.

Novo Nordisk alleged that crucially, Aventis had not mentioned the therapeutic indications of Lantus:

'For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required'. The Lantus SPC implied that there were age restrictions and 'It's Lantus Time. All the time' was exaggerated.

Novo Nordisk again noted that the Lantus SPC implied that Lantus was only indicated for those patients who required insulin and not all patients with diabetes, implicitly acknowledging that patients might not need insulin or could be adequately managed with oral medicines. In short, 'It's Lantus Time. All the time' was inaccurate, ambiguous, misleading, over-inclusive and all-embracing in breach of Clauses 7.2 and 7.10.

APPEAL BOARD RULING

The Appeal Board noted the ambit of the complaint; Novo Nordisk had complained that with reference to Riddle *et al* the claim 'It's Lantus Time. All the time' on the folder at issue was misleading and exaggerated. The complaint had thus been very specific.

The Appeal Board noted that although the folder stated that the patient population in Riddle *et al* had type 2 diabetes the weight inclusion criterion was not discussed. The Appeal Board did not consider that this omission was misleading; the patient population was representative of those with type 2 diabetes. Nor did the Appeal Board consider that the claim 'It's Lantus Time. All the time' otherwise rendered the omission misleading or exaggerated on the narrow grounds alleged. The Appeal Board considered that on the narrow basis of the complaint there was no breach of the Code and it upheld the Panel's rulings of no breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted that the front page of the folder referred to the 'addition of Lantus or human NPH insulin to oral therapy of type 2 diabetic patients', a similar description appeared on page two. The Appeal Board considered that it was thus sufficiently clear that the patients in Riddle *et al* were already receiving antihyperglycaemic agents and were thus not newly diagnosed. Nor did the Appeal Board consider that the claim 'It's Lantus Time. All the time' gave an otherwise misleading or exaggerated impression of the patient population in Riddle *et al* in this regard. The Appeal Board again considered that on the narrow basis of the complaint there was no breach of the Code and it upheld the Panel's rulings of no breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

2 Concomitant use of glitazones and insulin

COMPLAINT

Novo Nordisk stated that Riddle *et al* had a very important inclusion criterion: patients treated with stable doses of one or two oral antihyperglycaemic agents (sulfonylureas, metformin, pioglitazone or rosiglitazone). Both pioglitazone and rosiglitazone were contraindicated with concomitant use of insulin (including insulin glargine). These were clearly listed in the glitazones' SPCs in Europe. This was an important safety point that should be noted in all promotional materials.

Novo Nordisk noted this concern to Aventis which had replied that in its view health professionals were well aware of the contraindication to the use of glitazones with insulin and therefore it did not need to list the contraindication. Novo Nordisk considered that pharmaceutical companies had a duty to adequately inform health professionals whenever there was a safety risk involved in the prescribing of medicines, especially when such risk was clearly listed as a contraindication and the company was fully aware of the fact. Novo Nordisk considered that Aventis' suggestion that all health professionals were well aware of the contraindication was a bold assumption and might put patients at risk.

Novo Nordisk alleged that omitting such important safety information was a breach of Clause 7.2 of the Code as it was ambiguous. It was also in breach of Clause 7.9 which required information on safety and side-effects to reflect available evidence.

RESPONSE

Aventis stated that the concomitant use of glitazones and insulin was contraindicated and stated as such in the SPCs of rosiglitazone and pioglitazone.

There was a narrow point being made here, in that Novo Nordisk asserted that Aventis should include contraindication information for products that it was not promoting for use with Lantus in its piece. Moreover Novo Nordisk asserted that Aventis was bold, perhaps bordering on reckless in its assumption that prescribers were aware of the important limitations of the products they used. Aventis strongly refuted this assertion.

Aventis was committed to ensuring the safe use of its medicines. It did not believe that any competent prescriber would be unaware of the limitations of the use of glitazones, particularly given the advice on their use that had been issued to doctors by the authorities. Importantly, nowhere in the folder did Aventis suggest and/or imply the use of glitazones with Lantus. As a consequence Aventis did not see the relevance of including a statement that such a combination was contraindicated when Aventis was neither promoting it nor was it in the Lantus SPC.

PANEL RULING

The Panel noted that enrolled subjects in Riddle *et al* were treated with stable doses of one or two oral antihyperglycaemic agents (sulphonylureas, metformin, pioglitazone or rosiglitazone) for ≥ 3 months. The Panel noted that Section 4.3 Contraindications of the pioglitazone SPC stated 'Pioglitazone is also contraindicated for use in combination with insulin'. A similar reference also appeared in the rosiglitazone SPC.

The Panel noted that references to competitor products in promotional material had to comply, *inter alia*, with Clause 7.2. The Panel noted that neither pioglitazone nor rosiglitazone were mentioned by name in the folder which referred to 'oral therapy of type 2 diabetes'. The Panel noted that this description included sulphonylureas and metformin in addition to pioglitazone and rosiglitazone. On balance, the Panel considered that the folder gave the impression that Lantus could be added to any standard oral therapy for type 2 diabetes and that was not so given the contraindication in the SPCs of rosiglitazone and pioglitazone. The folder was misleading in this regard. Breaches of Clauses 7.2 and 7.9 were ruled.

Complaint received **20 September 2004**

Case completed **10 January 2005**

CASE AUTH/1633/9/04

MERCK SHARP & DOHME v GLAXOSMITHKLINE

Promotion of Imigran Radis

Merck Sharp & Dohme complained about the promotion of Imigran Radis (sumatriptan) by GlaxoSmithKline. Imigran Radis was indicated for the acute relief of migraine attacks. The items at issue were a launch mailing, a leavepiece and a guidelines leavepiece. Merck Sharp & Dohme supplied Maxalt (rizatriptan).

Merck Sharp & Dohme alleged that the claim 'The only triptan proven to get patients back to their normal lives from just 45 minutes', based on Cruccu *et al* (2004) in which patients treated a migraine attack within 1 hour of onset whilst the pain was still mild, was misleading and exaggerated. Only the 100mg dose resulted in a significant improvement ($p<0.05$) at 45 minutes, allowing return to normal function. It was clear from the summary of product characteristics (SPC) for Imigran Radis that the recommended dose was 50mg. At this dose, there was no significant improvement until 1 hour post administration. This should have been made clear.

Merck Sharp & Dohme further noted that Cruccu *et al* compared Imigran Radis with placebo. There was a wealth of evidence from previous studies involving comparator triptans. In a meta analysis of 53 trials by Ferrari *et al* (2001) both rizatriptan 10mg and eletriptan 80mg showed higher response and pain free rates at 2 hours compared to sumatriptan 100mg. It was difficult to conceive that a medicine able to get patients back to their 'normal function from 45 minutes' would somehow be less efficacious at two hours than these two comparator triptans.

Furthermore, previous studies of triptans specified that pain should be treated when moderate or severe rather than mild, as in this case. Cady *et al* (2000) stated that early treatment of mild pain with sumatriptan resulted in higher rates of 'pain-free response' at 2 hours compared with treatment of moderate or severe pain. Therefore, although a move to treat early was admirable and should be adopted in future trials, it could not be erroneously used to justify the phrase 'only triptan' for sumatriptan as this unusual endpoint had not been investigated for the other products.

A recent randomized, double blind, placebo-controlled study compared rizatriptan 10mg with sumatriptan 50mg and rizatriptan 5mg with sumatriptan 25mg (Kolodny *et al* 2004). Rizatriptan 10mg was the only treatment that provided significant pain relief compared with placebo at 30 minutes. At all time intervals from 30 minutes, the percentage of patients taking rizatriptan 10mg who reported pain relief was greater than that of sumatriptan; at 1 hour this reached a significant level ($p=0.04$). In terms of functional disability, rizatriptan resulted in improvement compared with the corresponding dose of sumatriptan; the 5mg dose reached statistical significance ($p=0.004$).

Given the wealth of evidence indicating that sumatriptan 50mg was less efficacious than other triptans, Merck Sharp & Dohme suggested that a 45 minute claim was not valid as Imigran Radis had not been assessed against comparator triptans for this endpoint.

The Panel considered that the claim 'The only triptan proven to get patients back to their normal lives from just 45 minutes' implied that other triptans had been proven not to get patients back to their normal lives from just 45 minutes. This was not so. The Panel noted GlaxoSmithKline's submission that functional recovery from 45 minutes had not been studied or reported for other triptans. The Panel considered that the implied comparison with other triptans was misleading and exaggerated. Breaches of the Code were ruled.

The Panel noted that the Imigran Radis SPC stated that 'The recommended dose of oral Imigran is a single 50mg tablet. Some patients may require 100mg'. Cruccu *et al* evaluated patients' ability to function following treatment with Imigran Radis 50mg and 100mg, administered during the mild pain phase of a single migraine attack. At 45 minutes 29% of patients receiving Imigran Radis 100mg reported normal ability to perform work or usual activities ($p \leq 0.05$ vs placebo). The same percentage of patients receiving the 50mg dose also reported normal functioning but the result was not statistically significant.

The Panel considered that the claim 'The only triptan proven to get patients back to their normal lives from just 45 minutes' implied that most patients would report normal functioning at 45 minutes, when taking any dose of Imigran Radis, which was not so. Statistical significance was only reported at 45 minutes for the 100mg dose and not the recommended dose of 50mg. The Imigran Radis SPC stated that only some patients would require treatment with 100mg. At 45 minutes only 1 in 3 patients reported normal functioning after taking 100mg. Given the results of Cruccu *et al* the Panel considered that the claim at issue was misleading and exaggerated. Breaches of the Code were ruled.

Merck Sharp & Dohme Limited complained about the promotion of Imigran Radis (sumatriptan) by GlaxoSmithKline UK Ltd. Imigran Radis was designed to disperse rapidly and was indicated for the acute relief of migraine attacks. The items at issue were a launch mailing (ref IMG/MLP/04/12740/1), a main leavepiece (ref IMG/LVP/04/13005/1) and an MIPCA (migraine in primary care advisors) Guidelines leavepiece (ref IMG/LVP/04/12916/1). Discussions between the parties had not resolved the matter. Merck Sharp & Dohme supplied Maxalt (rizatriptan).

COMPLAINT

Merck Sharp & Dohme alleged that the claim 'The only triptan proven to get patients back to their normal lives from just 45 minutes' was misleading and exaggerated in breach of Clauses 7.2, 7.3 and 7.10 of the Code.

The claim was based on Cruccu *et al* (2004) in which patients treated a migraine attack within 1 hour of

onset whilst the pain was still mild. Only the 100mg dose resulted in a significant improvement ($p<0.05$) at 45 minutes, allowing return to normal function. It was clear from the summary of product characteristics (SPC) for Imigran Radis that the recommended dose was 50mg. At this dose, there was no significant improvement until 1 hour post administration. This should have been made clear. GlaxoSmithKline had stated that this was the reason for the use of the word 'from' in the claim but Merck Sharp & Dohme considered that this qualification was inadequate to allow full understanding by the reader. Furthermore, GlaxoSmithKline quoted figures from Scriptcount which showed that almost equal numbers of patients were prescribed the 100mg and the 50mg doses of Imigran Radis. Merck Sharp & Dohme considered this data was irrelevant as its objection was based on the licensed dose of Imigran.

Merck Sharp & Dohme further noted that in Cruccu *et al* Imigran Radis was compared only with placebo. There was a wealth of evidence from previous studies involving comparator triptans. In a meta analysis of 53 trials by Ferrari *et al* (2001) both rizatriptan 10mg and eletriptan 80mg showed higher response and pain free rates at 2 hours compared to sumatriptan 100mg. It was difficult to conceive that a medicine able to get patients back to their 'normal function from 45 minutes' would somehow be less efficacious at two hours than these two comparator triptans.

Furthermore, previous studies of triptans specified that pain should be treated when moderate or severe rather than mild, as in this case. Cady *et al* (2000) unsurprisingly stated that early treatment of mild pain with sumatriptan resulted in higher rates of 'pain-free response' at 2 hours compared with treatment of moderate or severe pain. Therefore, although a move to treat early was admirable and should be adopted in future trials, it could not be erroneously used to justify the phrase 'only triptan' for sumatriptan as this unusual endpoint had not been investigated for the other products.

In a recent randomized, double blind, placebo-controlled study rizatriptan 10mg was compared with sumatriptan 50mg and rizatriptan 5mg with sumatriptan 25mg (Kolodny *et al* 2004). Rizatriptan 10mg was the only treatment that provided significant pain relief compared with placebo at 30 minutes. At all time intervals from 30 minutes, the percentage of patients taking rizatriptan 10mg who reported pain relief was greater than that of sumatriptan; at 1 hour this reached a significant level ($p=0.04$). In terms of functional disability, rizatriptan resulted in improvement compared with the corresponding dose of sumatriptan; the 5mg dose reached statistical significance ($p=0.004$).

Given the wealth of evidence indicating that sumatriptan 50mg was less efficacious than other triptans, Merck Sharp & Dohme suggested that a 45 minute claim was not valid as Imigran Radis had not been assessed against comparator triptans for this endpoint.

RESPONSE

GlaxoSmithKline noted that according to its SPC, Imigran Radis could be prescribed at a dose of either 50mg or 100mg, both doses being licensed for the acute relief of migraine attacks with or without aura. Scriptcount data indicated that the 50mg and 100mg tablets were prescribed in approximately equal proportions.

Contrary to Merck Sharp & Dohme's suggestion, the claim at issue was not based solely on a single data point from Cruccu *et al* ie the 100mg dose at 45 minutes. The claim was in fact based on all data points from all arms of the study which was why it stipulated that functional recovery could be expected from 45 minutes, ie 45 minutes being the time point at which significant functional recovery was first observed when using Imigran Radis within its licensed indication and at licensed doses. GlaxoSmithKline therefore denied that the claim was either misleading or exaggerated.

Cruccu *et al* was the only study so far to use functional recovery at 30, 45, 60 and 120 minutes as clinical endpoints, furthermore, this was the only published clinical trial that had been conducted using Imigran Radis. GlaxoSmithKline considered that it was acceptable to use placebo-controlled data taken from a pivotal study in order to support a claim about Imigran Radis, especially since no direct comparisons to other triptans had been made. Therefore the meta-analysis and study referred to by Merck Sharp & Dohme, one of which was significantly out of date and neither of which included Imigran Radis as a comparator or functional recovery from 45 minutes as an endpoint, were irrelevant to the complaint. Indeed, far from being exaggerated, the claim was very specific and conveyed the fact that no data existed for any triptan other than Imigran Radis where a variable representing return to premorbid functional status had been measured and found significantly different compared with either placebo or baseline. In fact these very specific conditions were fulfilled only in Cruccu *et al*, not least because functional recovery from 45 minutes had not been studied or reported for other triptans. As such it represented the entirety of the evidence available on functional recovery.

Regarding the point made about the administration of Imigran Radis in the early mild pain phase of the attack, GlaxoSmithKline noted that Section 4.2 of the Imigran Radis SPC stated 'It is advisable that Imigran be given as early as possible after the onset of migraine attack but it is equally effective at whatever stage of the attack it is administered'. Thus, the study by Cruccu *et al* replicated the SPC recommendations as to the timing of administration. Furthermore, since Imigran Radis was equally effective at whatever stage of the attack it was administered, GlaxoSmithKline did not consider that use of these data or the claim derived from them was exaggerated or misled as to the expected outcomes of prescribing the medicine.

In conclusion, GlaxoSmithKline therefore denied that the claim at issue breached Clauses 7.2, 7.3 and 7.10 of the Code.

PANEL RULING

The Panel considered that the claim 'The only triptan

proven to get patients back to their normal lives from just 45 minutes' implied that other triptans had been proven not to get patients back to their normal lives from just 45 minutes. This was not so. The Panel noted GlaxoSmithKline's submission that functional recovery from 45 minutes had not been studied or reported for other triptans. The Panel considered that the implied comparison with other triptans was misleading and exaggerated. Breaches of Clauses 7.2, 7.10 and 7.3 were ruled.

The Panel noted that the Imigran Radis SPC stated that 'The recommended dose of oral Imigran is a single 50mg tablet. Some patients may require 100mg'. Cruccu *et al* evaluated patients' ability to function following treatment with Imigran Radis 50mg and 100mg, administered during the mild pain phase of a single migraine attack. The authors reported that more subjects treated with Imigran Radis returned to normal ability to perform work or usual activities compared with placebo. At 45 minutes 29% of patients receiving Imigran Radis 100mg reported normal ability to perform work or usual activities ($p \leq 0.05$ vs placebo). The same percentage of patients receiving the 50mg dose also reported normal functioning but the result was not statistically significant. It was only at 1 hour that the results for 50mg became statistically significant ($p \leq 0.01$) with 41% of patients so treated reporting normal ability to function. At two hours 60% of patients taking 100mg and 53% of those on 50mg Imigran Radis reported normal functioning ($p < 0.001$).

The Panel considered that the claim 'The only triptan proven to get patients back to their normal lives from just 45 minutes' implied that most patients would report normal functioning at 45 minutes, when taking any dose of Imigran Radis, which was not so. Statistical significance was only reported at 45 minutes for the 100mg dose and not the recommended dose of 50mg. The Imigran Radis SPC stated that only **some** (emphasis added) patients would require treatment with 100mg. At 45 minutes only 1 in 3 patients reported normal functioning after taking 100mg. Given the results of Cruccu *et al* the Panel considered that the claim at issue was misleading and exaggerated. Breaches of Clauses 7.2, 7.10 and 7.3 were ruled.

Complaint received **20 September 2004**

Case completed **22 November 2004**

CASE AUTH/1636/10/04 *NO BREACH OF THE CODE*

IVAX v PROCTER & GAMBLE

Asacol letter referring to Code of Practice ruling

Ivax alleged that a letter sent to dispensing pharmacists by Procter & Gamble reporting the rulings in Case AUTH/1547/1/04 was inaccurate and misleading. The letter bore the prescribing information for Asacol (mesalazine 400mg, modified release) on the reverse and was headed 'Switching of mesalazine 400mg preparations – Prescription Medicines Code of Practice Authority Ruling' and referred to the outcome of Case AUTH/1547/1/04. In that case Procter & Gamble had complained that in the promotion of Mesren MR (mesalazine 400mg, modified release) by Ivax the claim 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence' implied that the two products were clinically equivalent. On appeal by Ivax the Panel's rulings that the claim was misleading and could not be substantiated had been upheld.

Ivax noted that the letter opened with the statement 'A recent ruling by the Prescription Medicines Code of Practice Authority highlighted that different mesalazine 400mg preparations cannot be considered interchangeable'. The Appeal Board ruled, however, that the claim that Mesren and Asacol could be interchanged with confidence was misleading because there was no clinical data offered to substantiate it. The ruling did not state or highlight that different mesalazine 400mg preparations could not be considered interchangeable. The ruling simply stated that there was no clinical data offered to back up the claim that Mesren and Asacol could be interchanged with confidence. These were completely different conclusions. The lack of clinical data to support a claim did not necessarily mean that the claim was incorrect or unverifiable. Procter & Gamble's assertion was not a direct quote from the ruling, nor was it an accurate summation of the ruling and was therefore misleading.

Ivax stated that it was extremely unlikely that the pharmacists to whom this letter had been addressed would have read the ruling and would therefore realise the error in the reporting of it. Consequently they would be under a false impression as to their ability to interchange any mesalazine 400mg preparation which had already had an adverse effect on the sales of Mesren by pharmacists.

The Panel noted that the letter was headed 'Switching of mesalazine 400mg preparations – Prescription Medicines Code of Practice Authority Ruling'. The first paragraph and the statement at issue read 'A recent ruling by the Prescription Medicines Code of Practice Authority highlighted that different mesalazine 400mg preparations cannot be considered interchangeable'. The second paragraph noted that three oral mesalazine 400mg preparations were available and referred to guidance that such preparations should not be considered interchangeable and should be prescribed by brand name. This was followed by further discussion of

Case AUTH/1547/1/04: 'In a recent letter and promotion for Mesren MR, a claim was made that; Mesren could be interchanged with Asacol with confidence. The Prescription Medicines Code of Practice Authority have subsequently investigated this claim and made the following ruling; the Panel considered the letter and advertisement were misleading in this regard and could not be substantiated. This was subsequently upheld on appeal'.

The Panel noted that in Case AUTH/1547/1/04 it had considered, *inter alia*, that in the context in which it appeared the claim that Asacol and Mesren 'can therefore be interchanged with confidence' implied that Mesren MR could be given to patients who had previously received Asacol ie the two products were clinically equivalent. There was no clinical data to show that this was so. The Panel had considered that the letter and advertisement were misleading in this regard and could not be substantiated. Breaches of the Code had been ruled in respect of each item. These rulings had been upheld by the Appeal Board.

Turning to the present case, Case AUTH/1636/10/04, the Panel noted that the statement at issue was not a quotation from the ruling in Case AUTH/1547/1/04 and nor was it presented as such. The Panel noted that few details about the ruling were given in the body of the letter. Nonetheless, the Panel did not consider the statement was an unreasonable summary of the ruling made in Case AUTH/1547/1/04 and so was not misleading as alleged. No breach of the Code was ruled.

The Panel was concerned that Ivax had stated that 'The lack of clinical data to support a claim did not necessarily mean that the claim was incorrect or unverifiable'. The Panel noted that the Code stated, *inter alia*, that all claims must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. All claims had to be capable of substantiation. Thus if there was no data to support a claim then the claim was not substantiable and its use in promotional material would be in breach of the Code.

Ivax Pharmaceuticals UK Limited complained about a letter sent to all dispensing pharmacists (ref AS2584a) by Procter & Gamble Pharmaceuticals UK Limited. The letter bore the prescribing information for Asacol (mesalazine 400mg, modified release) on the reverse and was headed 'Switching of mesalazine 400mg preparations – Prescription Medicines Code of Practice Authority Ruling' and referred to the outcome of a previous case, Case AUTH/1547/1/04. In Case AUTH/1547/1/04 Procter & Gamble had complained that in the promotion of Mesren MR (mesalazine 400mg, modified release) by Ivax the claim 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence' implied that the two products were clinically equivalent. On appeal by Ivax the Panel's rulings that the claim was misleading and could not be substantiated had been upheld.

COMPLAINT

Ivax alleged that Procter & Gamble's reporting of the rulings in Case AUTH/1547/1/04 was inaccurate and misleading in breach of Clause 7.2 of the Code.

Ivax noted that the letter sent by Procter & Gamble opened with the statement 'A recent ruling by the Prescription Medicines Code of Practice Authority highlighted that different mesalazine 400mg preparations cannot be considered interchangeable'. The Appeal Board's ruling, however, was that the claim that Mesren and Asacol could be interchanged with confidence was misleading because there was no clinical data offered to substantiate it. Nowhere in the ruling was it stated or even highlighted that different mesalazine 400mg preparations could not be considered interchangeable. The ruling simply stated that there was no clinical data offered to back up the claim that Mesren and Asacol could be interchanged with confidence. These were completely different conclusions. The lack of clinical data to support a claim did not necessarily mean that the claim was incorrect or unverifiable.

Ivax stated that Procter & Gamble's assertion was not a direct quote from the ruling, nor was it an accurate summation of the ruling and was therefore misleading in that regard.

Ivax stated that it was extremely unlikely that the pharmacists to whom this letter had been addressed would have read the ruling and would therefore realise the error in the reporting of it. Consequently they would be under a false impression as to their ability to interchange any mesalazine 400mg preparation which had already had an adverse effect on the sales of Mesren by pharmacists.

RESPONSE

Procter & Gamble noted that the point at issue was whether the statement 'A recent ruling by the Prescription Medicines Code of Practice Authority highlighted that different mesalazine 400mg preparations cannot be considered interchangeable' was misleading as to the ruling in Case AUTH/1547/1/04. Procter & Gamble considered that a reader of the entire ruling and a reader of the letter would take similar action as a result of the information presented, and hence the letter was not misleading, and accurately reflected the outcome of the ruling. No one was misled and no false prescribing or dispensing decisions would be made based on the letter.

The original ruling concluded that the claim 'interchangeable with confidence' implied that Mesren and Asacol were clinically equivalent, and that in the absence of clinical data, this claim was misleading and unsubstantiated.

In conclusion, Procter & Gamble considered that the sentence used in the letter whilst not a direct quote from the ruling, accurately reported the Panel's ruling and was not misleading. The additional detail contained within the letter further clarified the specific case ruling.

PANEL RULING

The Panel noted that the letter was headed 'Switching of mesalazine 400mg preparations – Prescription Medicines Code of Practice Authority Ruling'. The first paragraph and the statement at issue read 'A recent ruling by the Prescription Medicines Code of Practice Authority highlighted that different mesalazine 400mg preparations cannot be considered interchangeable'. The second paragraph noted that three oral mesalazine 400mg preparations were available and referred to guidance that such preparations should not be considered interchangeable and should be prescribed by brand name. This was followed by further discussion of Case AUTH/1547/1/04: 'In a recent letter and promotion for Mesren MR, a claim was made that; Mesren could be interchanged with Asacol with confidence. The Prescription Medicines Code of Practice Authority have subsequently investigated this claim and made the following ruling; the Panel considered the letter and advertisement were misleading in this regard and could not be substantiated. This was subsequently upheld on appeal'.

The Panel noted that in Case AUTH/1547/1/04 it had considered, *inter alia*, that in the context in which it appeared the claim that Asacol and Mesren 'can therefore be interchanged with confidence' implied that Mesren MR could be given to patients who had previously received Asacol ie the two products were clinically equivalent. There was no clinical data to show that this was so. The Panel had considered that the letter and advertisement were misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 had been ruled in respect of each item. These rulings had been upheld by the Code of Practice Appeal Board upon appeal by Ivax.

Turning to the present case, Case AUTH/1636/10/04, the Panel noted that the statement at issue was not a quotation from the ruling in Case AUTH/1547/1/04 and nor was it presented as such. The Panel noted that few details about the ruling were given in the body of the letter. Nonetheless, the Panel did not consider the statement was an unreasonable summary of the ruling made in Case AUTH/1547/1/04 and so was not misleading as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case the Panel was concerned that Ivax had stated that 'The lack of clinical data to support a claim did not necessarily mean that the claim was incorrect or unverifiable'. The Panel noted that Clause 7.2 stated, *inter alia*, that all claims must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. Clause 7.4 required all claims to be capable of substantiation. Thus if there was no data to support a claim then the claim was not substantiable and its use in promotional material would be in breach of the Code. The Panel requested that Ivax be advised of its concerns in this regard.

Complaint received **1 October 2004**

Case completed **17 November 2004**

CASE AUTH/1639/10/04

PRIMARY CARE PRESCRIBING GROUP v PFIZER

Cardura XL information sheet

Two lead pharmacists complained on behalf of a primary care prescribing group about a one page information sheet about Cardura XL (doxazosin XL) issued by Pfizer and sent in response to prescribers' requests for information about how to switch from standard doxazosin to Cardura XL and vice versa.

The information stated that 'Titration is *recommended* … when switching from Cardura XL to standard doxazosin', however, in the diagram following this it was stated that 're-titration is necessary'. As 'recommended' implied an optional course of action and 'necessary' an essential course of action, this wording appeared to the complainants to be contradictory and misleading. Pfizer's Medical Information Department had assured the complainants that it had no clinical information as to whether patients should or should not be titrated, when switching from Cardura XL to standard doxazosin.

The Panel noted the Cardura (standard doxazosin) summary of product characteristics (SPC) stated that the initial dose was 1mg, thereafter dosage might be increased to 2mg after an additional one or two weeks of therapy and thereafter, if necessary, to 4mg. The maximum recommended dose in hypertension was 16mg. The Panel noted Pfizer's submission that it had no option but to recommend titration in the usual way, commencing at 1mg. The Panel considered that stating that titration was recommended and also that re-titration was necessary was contradictory and misleading as alleged; it was not sufficiently clear whether titration was optional or obligatory; breaches of the Code were ruled.

The Panel considered that the overall impression of the information sheet was that there was clinical data to support the advice on titration when switching from Cardura XL to standard doxazosin. That was not so. This impression was reinforced by the heading 'Important information doxazosin' and the bold statement in red typeface 'Re-titration is necessary'. In the absence of clinical data Pfizer had reproduced the titration recommendations in the Cardura SPC. The information sheet was misleading as to the clinical status of the information provided. Breaches of the Code were ruled.

Two lead pharmacists complained on behalf of a primary care prescribing group about a one page information sheet (ref CAR 689r) about Cardura XL (doxazosin XL) issued by Pfizer Limited. The sheet was sent in response to prescribers' requests for information about how to switch from standard doxazosin to Cardura XL and *vice versa*.

COMPLAINT

The complainants noted that the information sheet, which was being distributed to GPs, referred to the issue of titration. It stated that 'Titration is *recommended* … when switching from Cardura XL to standard doxazosin', however, in the diagram following this it stated that 're-titration is *necessary*'. As 'recommended' implied an optional course of action and 'necessary' an essential course of action, this wording appeared contradictory and misleading. The complainants had been assured by Pfizer's Medical Information Department that it had no clinical information as to whether patients should or should not be titrated, when switching from Cardura XL to standard doxazosin. The complainants stated that their analysis of the clinical data confirmed this view.

The complainants alleged breaches of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Pfizer explained that the issue of switching from standard doxazosin to Cardura XL and from Cardura XL to standard doxazosin had caused some confusion with its customers and so the information sheet in question was produced to clarify the situation.

Pfizer explained that the starting dose of standard doxazosin was 1mg. The dosage might then be increased after one or two weeks of therapy to 2mg and later to 4mg and so on. The starting dose of Cardura XL was 4mg which might be later increased after four weeks to 8mg (two tablets). Thus no titration was required to start on Cardura XL (4mg) but titration was required to achieve a dose of more than 1mg of standard doxazosin. Pfizer understood that this was regardless of a patient's previous or existing medication.

Pfizer was often asked by prescribers how patients stopping Cardura XL should be changed over to standard doxazosin at doses in excess of 1mg. Within the constraints of the posology on the summary of product characteristics (SPC) for standard doxazosin, Pfizer had no option but to recommend titration in the usual way, commencing at 1mg. There were no data to support any other method of administration. Clearly, should prescribers wish to introduce standard doxazosin in any other way, they were in a position to do so, although Pfizer could not advise them in this way.

The specific issue raised by the complainants was that the words 'recommended' and 'necessary' had apparently been used interchangeably. The term 'titration is recommended' was Pfizer's way of referring to the posology in the SPC for standard doxazosin. 'Recommended' was a term used to represent the instructions of the licensing authority and so Pfizer did not agree that its use was incompatible with the use of the word 'necessary'. Pfizer considered that prescribers in general were fully aware of the specific meaning in this context of the word 'recommended' and so did not consider that this information sheet was in breach of Clauses 7.2 or 7.4 as it was not inaccurate, unbalanced, unfair or ambiguous and was capable of substantiation.

Furthermore, it was fairly based on all the evidence, namely the respective SPCs, and on the lack of data to support any other method of introduction of standard doxazosin.

In the light of the misunderstanding expressed by the complainants Pfizer, whilst it did not accept that it had breached the Code, had decided to amend the information sheet and review all other promotional materials for Cardura XL with this in mind.

PANEL RULING

The Panel noted that the information sheet at issue was headed 'Important information on doxazosin' beneath which appeared 'Titration is recommended … when switching from Cardura XL to standard doxazosin'. There followed a highlighted box headed 'Switching from Cardura XL 4mg to standard doxazosin' which featured a diagrammatic representation of a switch from Cardura XL 4mg to 1mg doxazosin and, in a prominent red typeface, the statement 're-titration necessary'. Subsequent text reproduced the relevant section of the Cardura (standard doxazosin) SPC titration regimen.

The Panel noted the Cardura SPC stated that the initial dose was 1mg, thereafter dosage might be increased to 2mg after an additional one or two weeks of therapy and thereafter, if necessary, to 4mg. The maximum recommended dose in hypertension was 16mg. The Panel noted Pfizer's submission that it had no option but to recommend titration in the usual way, commencing at 1mg. The Panel considered that stating that titration was recommended and also that re-titration was necessary was contradictory and misleading as alleged; it was not sufficiently clear whether titration was optional or obligatory; breaches of Clauses 7.2 and 7.4 were ruled.

The Panel considered that the overall impression of the information sheet was that there was clinical data to support the advice on titration when switching from Cardura XL to standard doxazosin. That was not so. This impression was reinforced by the heading 'Important information doxazosin' and the bold statement in red typeface 're-titration is necessary'. In the absence of clinical data Pfizer had reproduced the titration recommendations in the Cardura SPC. The information sheet was misleading as to the clinical status of the information provided. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **11 October 2004**

Case completed **24 November 2004**

CASE AUTH/1640/10/04 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST PHARMACEUTICAL ADVISER v AMDIPHARM

Gift of memory stick

The pharmaceutical adviser to a primary care trust complained about the provision of a 64MB memory stick as a promotional aid for Detrunorm (propiverine) by Amdipharm. The memory sticks bore the product name.

The complainant noted the requirements of the Code with respect to the provision of gifts or prizes, provided that such were inexpensive and relevant to the practice of the recipient's profession or employment. The complainant questioned whether guidance was given with regard to the interpretation of 'inexpensive'. The complainant noted that 64MB memory sticks currently retailed for around £25.

The Panel noted that the complainant had queried the provision of the memory sticks on the grounds of cost. The Code stated, *inter alia*, that promotional aids must be inexpensive and supplementary information defined an inexpensive gift as one which had cost the donor company no more than £6, excluding VAT. Amdipharm had provided a copy of the invoice for the memory sticks showing that each one cost £6, excluding VAT. The Panel thus ruled no breach of the Code with regard to the memory sticks.

The Panel did not consider whether the memory sticks were relevant to the practice of medicine as it had not received a complaint in that regard.

The pharmaceutical adviser to a primary care trust complained about the provision of a 64MB memory stick as a promotional aid for Detrunorm (propiverine) by Amdipharm Plc. The memory sticks bore the product name.

COMPLAINT

The complainant noted the requirements of Clause 18.2 of the Code with respect to the provision of gifts or prizes, provided that such were inexpensive and relevant to the practice to the recipient's profession or employment. The complainant questioned whether guidance was given with regard to the interpretation of 'inexpensive'. The complainant noted that 64MB memory sticks currently retailed for around £25.

RESPONSE

Amdipharm submitted that a 64MB memory stick was of particular relevance to the practice of medicine as it provided a lightweight method of accessing 64MB of possible clinical data eg word documents, including summaries of product characteristics (SPCs), patient information leaflets (PILs) or patient orientated literature. The company provided an original receipted invoice to show that each memory stick had cost it £6, excluding VAT.

PANEL RULING

The Panel noted that the complainant had queried the provision of the memory sticks on the grounds of cost. Clause 18.2 of the Code stated, *inter alia*, that promotional aids must be inexpensive and supplementary information to that clause defined an inexpensive gift as one which had cost the donor company no more than £6, excluding VAT. Amdipharm had provided a copy of the invoice for the memory sticks showing that each one cost £6, excluding VAT. The Panel thus ruled no breach of Clause 18.1 of the Code with regard to the cost of the memory sticks.

The Panel noted that it had not been required to consider whether the memory sticks were relevant to the practice of medicine, as it had not received a complaint in that regard.

Complaint received	**11 October 2004**
Case completed	**2 December 2004**

CASE AUTH/1642/10/04 *NO BREACH OF THE CODE*

HOSPITAL CLINICAL PHARMACIST v AVENTIS PHARMA

'Dear Healthcare Professional' letter about Clexane

A principal hospital clinical pharmacist and director of research governance complained about a 'Dear Healthcare Professional' letter issued by Aventis Pharma and headed 'New prescribing advice for enoxaparin/Clexane' and 'Dose adjustment recommendation for patients with severe renal failure (creatinine clearance <30ml/min)'. The letter stated that the summary of product characteristics (SPC) for Clexane had recently been revised to include a recommended dose reduction for patients with severe renal failure. Details of the new doses were provided.

The complainant was extremely concerned about the poor coverage of the 'Dear Healthcare Professional' letter in question; it only came to his attention through a more junior colleague. To the complainant's knowledge few, if any, of his medical colleagues had received the letter. The complainant considered that deliberately providing poor information coverage was a rather cynical attempt to lessen the impact of 'bad news'. This lack of coverage potentially risked patients receiving the wrong dose; although pharmacists were often involved in dosing patients they were not available to check everyone requiring low molecular weight heparin (LMWH). The complainant was also concerned that no notice of the new dosage recommendations had been found in either The Pharmaceutical Journal or the BMJ.

The complainant was further concerned that the guidance, suggesting that dose alteration was only required in 'severe' renal impairment, did not accord with standard descriptions of renal function such as that set out in the British National Formulary (BNF) where 30ml/min would be classed as mild renal failure. The use of the term 'severe' was clearly obfuscating and there was the very real potential that patients might not be assessed unless they were symptomatic; many patients were more or less asymptomatic at a glomerular filtration rate (GFR) of 30ml/min. Moreover, Aventis' medical information department advised careful monitoring of patients with a GFR of between 30 and 80 ml/min – presumably for anti-Xa activity. As far as the complainant was aware this was not a routine test that would be readily available from pathology departments for all (or most patients) receiving prophylaxis or treatment with enoxaparin.

The prescribing of enoxaparin, and errors on the estimation of GFR were likely to lead to dosing errors. The complainant noted that the main attraction of choosing enoxaparin from a trust and clinical governance perspective, the range of indications and the simplicity of dose calculations, had been eradicated by the new recommendations; enoxaparin now was one of the most difficult of LMWHs to prescribe rather than the easiest.

The Panel noted that the letter in question had been sent as a result of discussions between Aventis and the Medicines and Healthcare products Regulatory Agency (MHRA). The letter had been sent to consultant cardiologists, consultant haematologists and consultants in care of the elderly. In addition it had been addressed to heads of pharmacies. Relevant information was also published in the Committee on Safety of Medicines (CSM)/MHRA publication Current Problems in Pharmacovigilance. This was published as necessary and circulated to all doctors, dentists, pharmacists and coroners in the UK.

The Panel did not consider that Aventis had deliberately provided poor information coverage as alleged. The letter had been sent to relevant consultants. The decision not to send the letter to every health professional had been agreed with the MHRA. Aventis' promotion of Clexane must not be inconsistent with the SPC.

Taking all the circumstances into account, the Panel did not consider that Aventis had failed to maintain high standards and ruled no breach of the Code.

The Panel noted that both the Clexane SPC and the letter in question referred to severe renal impairment as creatinine clearance <30ml/min. The Panel also noted Aventis' submission that this definition of severe renal failure was based on the data that it had. The Panel noted the complainant's comments regarding the disparity between the BNF and the letter in question with regard to the definition of severe renal failure. The preface to the BNF, however, stated, *inter alia*, that the publication should be supplemented as necessary by reference to the manufacturer's product literature. A product's SPC represented the agreed information about a medicine, the BNF did not.

The Panel noted that the letter defined what was meant by severe renal failure. Taking all the circumstances into account the Panel did not consider that the letter was misleading in this regard. No breach of the Code was ruled.

The principal hospital clinical pharmacist and director of research governance at a hospitals NHS trust, complained to about a 'Dear Healthcare Professional' letter Aventis Pharma Ltd had sent about Clexane (enoxaparin). The letter in question was dated 18 August 2004 and headed 'New prescribing advice for enoxaparin/Clexane' and 'Dose adjustment recommendation for patients with severe renal failure (creatinine clearance <30ml/min).' The letter stated that the summary of product characteristics (SPC) for Clexane had recently been revised to include a recommended dose reduction for patients with severe renal failure. Details of the new doses were provided. The complainant sent the Authority a copy of his letter to Aventis.

COMPLAINT

The complainant stated that two years ago the hospitals trust decided to move to enoxaparin as the low molecular weight heparin (LMWH) of choice at two of its sites and had subsequently moved to trust-wide enoxaparin-only prescribing during the past 12 months. The complainant was sure that this decision had influenced other local trusts to stock only enoxaparin.

The first issue that had concerned colleagues was the poor coverage of the 'Dear Healthcare Professional' letter in question; anecdotally, few people had received it. It only came to the complainant's attention through a more junior colleague. To the complainant's knowledge few, if any, of his medical colleagues had received the letter. Rather worryingly this included at least one consultant haematologist for the trust. The complainant was extremely concerned about the lack of coverage to prescribers and advisers about the changes in dosage recommendation. Colleagues from other trusts seemed to be in the same position, in that few of them had been informed about these recommendations.

The complainant considered that this approach was a rather cynical attempt to lessen the impact of 'bad news' by deliberately providing poor information coverage. This lack of coverage was potentially dangerous putting patients at risk of receiving the wrong dose; although pharmacists were often involved in dosing patients they were not available to check every patient requiring LMWH. It was also of concern that no reference was found in either The Pharmaceutical Journal or the BMJ, the two most commonly used journal sources for pharmacists and doctors relating to the changes or advertising that there were new dosage recommendations.

The second issue was that the guidance, suggesting that dose alteration was only required in 'severe' renal impairment, did not accord with standard descriptions of renal function such as that set out in the British National Formulary (BNF) where 30ml/min would be classed as mild renal failure. As the majority of the complainant's patients were elderly, the likelihood of finding glomerular filtration rates (GFRs) of 30ml/min was significant; indeed, an audit was currently being conducted to establish the rate at which dosages would have to be altered in light of Aventis' recommendations, and at first glance the worries seemed justified. The use of the term 'severe' was clearly obfuscating and there was the very real potential that patients might not be assessed unless they were symptomatic; many patients were more or less asymptomatic at a GFR of 30ml/min. Moreover, Aventis' medical information department advised careful monitoring of patients with a GFR of between 30 and 80 ml/min – presumably for anti-Xa activity. As far as the complainant was aware this was not a routine test that would be readily available from pathology departments for all (or most patients) receiving prophylaxis or treatment with enoxaparin.

The prescribing of enoxaparin, and errors on the estimation of GFR were likely to lead to dosing errors. The complainant noted that the main attraction of choosing enoxaparin from a trust and clinical governance perspective, the range of indications and the simplicity of dose calculations, had been eradicated by the recommendations; enoxaparin now was one of the most difficult of LMWHs to prescribe rather than the easiest.

In writing to Aventis attention was drawn to the requirements of Clauses 7 and 9.1 of the Code.

RESPONSE

Aventis stated that it was well known that enoxaparin was cleared by the renal route. What was not well known was the effect that renal failure had on the change in relative risk of bleeding in patients who were treated with recommended doses of enoxaparin. No study had looked at the effect of renal failure on the change in risk of bleeding. This would be a complex challenge. What Aventis had done was to closely look at a series of pharmacokinetic modelling analyses to try and assess the impact of renal failure on the risk of bleeding.

Aventis wrote to the Medicines Control Agency, now the Medicines and Healthcare products Regulatory Agency (MHRA) to request a change in the SPC to include advice on dose reduction in patients with severe renal failure as a result of the work it had conducted. It supplied several expert reports and data analyses to the MHRA to support the request. To conclude the marketing authorization variation agreement Aventis held a meeting in late July with the MHRA and it was agreed and that Aventis should send a 'Dear Doctor Letter' (DDL) to alert people to the changes. Aventis spent a considerable amount of time during the meeting assessing the evidence and deciding what it could and could not reasonably state. The wording of the DDL in question was agreed with the MHRA.

The test for anti-Xa activity not only had wide inter-laboratory standard results, but also was not universally, or perhaps more accurately, even commonly available. When researching the use and range of anti-Xa monitoring Aventis' findings suggested that, even where the test was available, the turn around time for receipt of a result could be as long as 48 hours after taking the sample from a patient. Notwithstanding the obvious variance in the test standards and the availability of the test, the interpretation of any particular result was difficult as no particularly meaningful information could be drawn from a single spot test result. The dose response effect of all LMWH activities could only be meaningfully interpreted from exposure data relating to the area under the concentration or anti-Xa activity curve.

Given that there was not a reliable monitoring test for any LMWH, Aventis had been concerned to inform health professionals of the existence and also the limitations of the anti-Xa test when renal clearance was severely compromised. Using anti-Xa activity monitoring tests to check on the normal or even raised level of anti-Xa activity was unhelpful unless multipoint and exposure assessments were made. This was why the following paragraph was included in the letter.

> 'In addition, the product information for enoxaparin now emphasises the need to consider risk factors for bleeding and need for appropriate clinical monitoring whenever LMWH such as enoxaparin is administered. Anti-Factor Xa monitoring is not normally required, but may be considered in those patients who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.'

In total 8,456 letters were sent, 1,088 to cardiologists, 2,028 to care of the elderly physicians, 785 to haematologists and 4,525 to heads of pharmacy and hospital pharmacists. The list of the specialities that the letter was sent to was agreed with the MHRA. A commercial mailing house generated the final list of recipients. Aventis did not consider that it restricted dissemination of the information.

Achieving the right distribution of a DDL letter was an important consideration. DDLs contained information that must be read and to achieve this they must retain a good degree of impact and not be so common as to be relegated to routine correspondence. This was why, together with the MHRA, Aventis decided not to mail every health professional (orthopaedic surgeons, GPs and the like), but to limit the distribution to the specialties listed above.

In addition to the letter in question the MHRA also included an article on the Clexane dose adjustment in Current Problems in Pharmacovigilance. This was done so that Aventis could be confident that all of those who needed to know were informed.

Aventis stated that it had not been cynical over the provision and distribution of the information. Indeed, the only thing that it would like to have done was to have the letter agreed with the regulatory authorities earlier. Providing safety information was not 'bad news', instead Aventis considered that failing to provide safety information was bad news, particularly if a medicine was used incorrectly.

Aventis stated the use of grades of renal failure such as mild, moderate and severe, were difficult to define. The BNF stated that:

> 'For prescribing purposes renal impairment is arbitrarily divided into three grades (definitions vary for grades of renal impairment therefore, where the product literature does not correspond with this grading values for creatinine clearance or another measure of renal function are included).'

It was true that Aventis had not used a definition of severe as <10 ml/ min; it had defined severe as a clearance of <30 ml/min, based on its own data. Aventis stated that it had tried to be as informative as possible by providing numerical values as well as common nomenclature terms. By giving this data Aventis stated it was not trying to hide anything. Quite the contrary, it was trying to be helpful.

In response to a request for further information Aventis confirmed that the need to send the letter was a joint decision by the MHRA and Aventis as both thought that it was the best way to get this important information to the people who needed to know.

The distribution was to the doctors and pharmacists mentioned above. Aventis did not distribute it to other specialties. This was a decision taken by the MHRA and Aventis together as Aventis wanted to make sure that the information went to those who needed to know and/or who were responsible for policy making and governance with regard to LMWH use.

Aventis deliberately decided not to undertake a universal mailing because it did not want to reduce the currency of a DDL. The MHRA and Aventis were concerned that if too many DDLs were sent to health professionals that did not directly relate to their daily practice they would not retain the necessary impact and importance and as a consequence might start to be considered as just another mass mailing. The danger was that when a relevant DDL for their own medical practice was received it might not be read or acted upon.

The final recipient list was produced by a leading mailing house. Aventis crosschecked the list to see who was recorded as being a specialist in which area. Using this analysis Aventis showed that at least 94% of consultant cardiologists, haematologists and geriatricians had received the mailing; 100% of NHS and private hospital principal pharmacists/ pharmacies had been mailed.

With specific regard to the complainant's trust, Aventis wrote to: a haematologist and two geriatricians, care of the elderly. It did not have a list of the names of the heads of pharmacies in all of the trusts and hospitals, including the complainant's trust. All letters to pharmacists were addressed to the head of pharmacy.

PANEL RULING

The Panel noted that the letter in question had been sent as a result of discussions between Aventis and the MHRA. The letter had been sent to consultant cardiologists, haematologists and geriatricians. In addition it had been addressed to heads of pharmacies.

Relevant information was also published in the Committee on Safety of Medicines (CSM)/MHRA publication Current Problems in Pharmacovigilance. This was published as necessary and circulated to all doctors, dentists, pharmacists and coroners in the UK.

The Panel did not consider that Aventis had deliberately provided poor information coverage as alleged. The letter had been sent to relevant consultants. The decision not to send the letter to every health professional had been agreed with the MHRA. Aventis' promotion of Clexane must not be inconsistent with the SPC as required by Clause 3.2 of the Code.

Taking all the circumstances into account, the Panel did not consider that Aventis had failed to maintain high standards and ruled no breach of Clause 9.1 of the Code.

The Panel noted that the Clexane SPC referred to severe renal impairment as creatinine clearance <30ml/min. The definition of severe renal failure as stated in the letter in question was the same as that used in the Clexane SPC. The Panel also noted Aventis' submission that the definition of severe renal failure as a creatinine clearance of <30ml/min was based on the data that it had. The Panel noted the complainant's comments regarding the disparity between the BNF and the letter in question with regard to the definition of severe renal failure. The preface to the BNF, however, stated, *inter alia*, that the publication should be supplemented as necessary by reference to the manufacturer's product literature. A product's SPC represented the agreed information about a medicine, the BNF did not.

The Panel noted that the letter defined what was meant by severe renal failure. Taking all the circumstances into account the Panel did not consider that the letter was misleading in this regard. No breach of Clause 7.2 of the Code was ruled.

Complaint received **19 October 2004**

Case completed **21 December 2004**

CASE AUTH/1643/10/04

GENERAL PRACTITIONER v PFIZER

Envelope for Celebrex mailing

A general practitioner complained about a Celebrex (celecoxib) mailing sent by Pfizer. The complainant had recently returned from holiday to find a huge volume of mail, but he opened one particular letter as a priority because it was labelled 'IMPORTANT PRODUCT INFORMATION ENCLOSED'. The top left hand corner of the front of the envelope gave a return address for Pfizer; the complainant thus assumed it must contain important information on one of its COX-2 inhibitor products as he was aware of the withdrawal of Vioxx (Merck Sharp & Dohme's product) for safety reasons.

The complainant was disgusted to find that the envelope contained only advertising material (albeit in the form of a letter) for Celebrex. The complainant felt conned by the message on the envelope into opening it quickly instead of despatching it in the same way as other advertising material. This was not an appropriate way for advertisements to be mailed to doctors.

The complainant also noticed in a recent GP newspaper that there had been concerns raised in a recent study about increased risk of myocardial infarctions with another Pfizer product, Bextra. It was ironic that Pfizer had not sent any 'Important Product Information' about this new finding.

The Panel considered that many of the recipients of the mailing in question, on reading the statement on the envelope 'IMPORTANT PRODUCT INFORMATION ENCLOSED', would not have expected its contents to be promotional, particularly given that the mailing was from Pfizer and the recent withdrawal of Vioxx by Merck Sharp & Dohme. The Panel considered that the promotional nature of the mailing was thus disguised and a breach of the Code was ruled.

The Panel noted the complainant's comments about increased risk of myocardial infarction with Bextra and Pfizer's response that the data had been sent to the EMEA and FDA for review. Once discussions with the EMEA had concluded the company would assess what health professionals needed to be told. The Panel did not consider it had a complaint in this regard and therefore no ruling was made.

A general practitioner complained about a Celebrex (celecoxib) mailing sent by Pfizer Limited. The bottom of the mailing envelope stated 'IMPORTANT PRODUCT INFORMATION ENCLOSED'. The top left hand corner of the front of the envelope gave a return address for Pfizer.

COMPLAINT

The complainant had recently returned from holiday to find a huge volume of mail, but he opened one particular letter as a priority because it was labelled 'IMPORTANT PRODUCT INFORMATION ENCLOSED'. Noting that it was from Pfizer he assumed it must contain important information on one of its COX-2 inhibitor products as he was aware of the withdrawal of Vioxx (Merck Sharp & Dohme's product) for safety reasons.

The complainant was disgusted to find that the envelope contained only advertising material (albeit in the form of a letter) for Celebrex. The complainant felt conned by the message on the envelope into opening it quickly instead of despatching it in the same way as other advertising material. This was not an appropriate way for advertisements to be mailed to doctors.

The complainant also noticed in a recent GP newspaper that there had been concerns raised in a recent study about increased risk of myocardial infarctions with another Pfizer product, Bextra. It was ironic that Pfizer had not sent any 'Important Product Information' about this new finding.

RESPONSE

Pfizer apologised for any inconvenience caused and regretted the annoyance felt by the complainant.

The letter in question addressed specific concerns about celecoxib that were raised by health practitioners and patients by the withdrawal of Vioxx on 30 September. The company noted that its medical information department had reported a 16-fold increase in enquiries about Celebrex, from health practitioners, between 29 September and 1 October. In light of the circumstances and the questions received from prescribers, Pfizer considered the content of the letter to be important product information and that it was justified in stating this on the envelope. The information was particularly relevant in light of the level of attention COX-2s were receiving in the healthcare and lay press and the confusion that this was causing amongst doctors and patients.

Unless GPs were fully up to date with all the relevant literature, Pfizer considered they would not be able to

address the concerns of patients taking Celebrex and so the company considered it was its responsibility to send a letter covering the relevant data. The letter presented a balanced and clinically orientated summary of the celecoxib cardiovascular data in a serious and matter of fact style. The prescribing information was included as omitting it would have been incorrect and in breach of the Code.

The letter in question did not consider Bextra due to ongoing licensing discussions about it with the European Medicines Evaluation Agency (EMEA). Once these discussions had progressed Pfizer would be able to assess what health practitioners needed to be told. Pfizer noted that the recent study referred to by the complainant had been passed to the EMEA (and FDA) for review and that the Bextra summary of product characteristics already reflected the findings of a previous coronary artery bypass graft surgery study (increased cardiovascular events in this patient population) and a warning about severe cutaneous reactions as noticed in periodic safety update reviews.

Pfizer apologised again for the negative impact that the letter had had on the complainant and it understood the level of frustration that many health practitioners felt due to the unheralded withdrawal of Vioxx.

Whilst Pfizer accepted that most prescribers were immediately aware of the withdrawal of Vioxx, it suggested that many health providers and patients were not so well informed about the continued availability of Celebrex.

Pfizer believed that it had maintained high standards. It had acted in good faith against a background of some confusion and believed that the importance of the information regarding the ongoing availability of Celecoxib warranted the wording on the letter and envelope. Pfizer therefore denied breaches of Clauses 9.1 and 10.1 of the Code.

PANEL RULING

The Panel considered that many of the recipients of the mailing in question, on reading the statement on the envelope 'IMPORTANT PRODUCT INFORMATION ENCLOSED', would not have expected its contents to be promotional, particularly given that the mailing was from Pfizer and the recent withdrawal of Vioxx by Merck Sharp & Dohme. The Panel considered that the promotional nature of the mailing was thus disguised and a breach of Clause 10.1 of the Code was ruled. The Panel considered that the circumstances were adequately addressed by this ruling such that an additional ruling of a breach of Clause 9.1 was not required.

The Panel noted the complainant's comments about increased risk of myocardial infarction with Bextra and Pfizer's response that the data had been sent to the EMEA and FDA for review. Once discussions with the EMEA had concluded the company would assess what health professionals needed to be told. The Panel did not consider it had a complaint in this regard and therefore no ruling was made.

Complaint received **26 October 2004**

Case completed **6 December 2004**

CASE AUTH/1644/10/04

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Sunday Times Asthma Supplement

A general practitioner complained about a supplement on asthma which appeared in The Sunday Times. The front cover stated 'New approaches for the chance of a life without symptoms'; 'In association with GlaxoSmithKline' and the GlaxoSmithKline logo appeared in the bottom right-hand corner.

The supplement was a mixture of articles about asthma, advice on what to ask health professionals and case studies from patients/carers. The supplement focussed on combination therapy including details of the recently published GOAL (Gaining Optimal Asthma controL) study.

The only asthma medicine named in the supplement was GlaxoSmithKline's fixed combination product for asthma Seretide (salmeterol/fluticasone). The GOAL study compared Seretide with an inhaled corticosteroid. The supplement included a photograph of a patient holding a Seretide inhaler. The four case studies all featured patients taking Seretide.

The complainant alleged that the supplement advertised Seretide to the public.

The Panel noted that the supplement had been sponsored by GlaxoSmithKline; it had been initiated by the company which had provided detailed direction as to the subject area to be covered as well as what was not to be covered. A copy of GlaxoSmithKline's overview and objectives document was given to all writers and sub-editors. GlaxoSmithKline had planned to distribute further copies of the supplement but on seeing the final item had decided not to proceed.

The Panel considered that GlaxoSmithKline was inextricably linked to the content of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation and content of the supplement. The Panel considered that GlaxoSmithKline was responsible for the content of the supplement in relation to compliance with the Code.

The Panel noted the summaries of discussions between GlaxoSmithKline's agency and The Sunday Times and considered that the discussions and approach were not consistent with the requirements of the Code that material for the general public must not promote a specific medicine and must be balanced. Notes from one meeting between the agency and The Sunday Times stated that the objective of the supplement was to provide a guaranteed communications platform from which to disseminate key Seretide/GOAL messages following publication of the [GOAL] data to consumers and health professionals. The supplement focussed on combination therapy but mention of competitor products was by generic name and there had to be no mention of flexible dosing, which was a feature of AstraZeneca's combination product Symbicort (formeterol/budesonide), or of Symbicort trial data.

The supplement discussed the GOAL study; Seretide was mentioned. One case study headed 'Free to play netball' highlighted the effect of Seretide on a young patient's life and included a photograph of her holding a Seretide inhaler. The Panel considered that the photograph of the patient with the Seretide inhaler together with the content of the supplement meant that it was an advertisement for a prescription only medicine to the public. The Panel ruled a breach of the Code as acknowledged by GlaxoSmithKline.

The Panel did not consider that the supplement presented the information in a balanced way and it would encourage members of the public to ask their doctor to prescribe a specific medicine. Thus the Panel ruled a breach of the Code as acknowledged by GlaxoSmithKline.

A general practitioner complained about a supplement on asthma which formed part of The Sunday Times of 24 October. The cover of the 12 page supplement stated 'New approaches for the chance of a life without symptoms'; 'In association with GlaxoSmithKline' and the GlaxoSmithKline logo appeared in the bottom right-hand corner.

The supplement was a mixture of articles about the disease, advice on what to ask health professionals and case studies from patients/carers. The supplement focussed on combination therapy including details of the recently published GOAL (The Gaining Optimal Asthma controL) study.

The supplement did not mention medicines by name apart from Seretide (salmeterol/fluticasone) which was GlaxoSmithKline's fixed combination product for asthma. The GOAL study compared Seretide with an inhaled corticosteroid.

The supplement included a photograph of a patient holding a Seretide inhaler. The four case studies all featured patients taking Seretide.

COMPLAINT

The complainant was concerned that the supplement, which bore the endorsement of GlaxoSmithKline, advertised Seretide to the public.

When writing to GlaxoSmithKline UK Ltd the Authority asked it to respond in relation to the requirements of Clauses 20.1 and 20.2 of the Code.

RESPONSE

GlaxoSmithKline stated that after seeing a previous industry sponsored supplement, it approached The Sunday Times, via a public relations (PR) agency at the beginning of 2004 to propose that a similar asthma supplement be produced later in the year. The objectives were to provide a media platform from which to highlight suboptimal asthma management in the UK and communicate to patients and health professionals that more could and should now be achieved. In addition, GlaxoSmithKline wished to refer to the findings of a landmark trial in asthma. This trial demonstrated that a greater level of asthma

symptom control than previously seen with any clinical study could be achieved, and would, therefore, provide context for an improved standard of asthma management to both patients and health professionals by demonstrating what might be possible in asthma management in the future. The PR agency was to provide The Sunday Times with information on GlaxoSmithKline (in terms of what the company did and what it wanted to achieve with the asthma supplement), why it had chosen The Sunday Times and why the article might interest its readership. Throughout the process, the PR agency liaised between GlaxoSmithKline and The Sunday Times. GlaxoSmithKline recognised that it was responsible under the Code for the conduct of agencies acting on its behalf.

Code considerations and copy approval
From the outset, it was made clear to the PR agency that GlaxoSmithKline was fully committed to the Code. This was to be an overriding consideration throughout all activities, and this requirement should clearly be communicated to The Sunday Times.

Notes from an initial meeting between the PR agency and The Sunday Times clearly confirmed the above. The sections describing 'Key points' and 'Copy approval', specifically noted that the final copy of the asthma supplement be reviewed for ABPI approval by an independent, Times-appointed, panel.

'Key points
1. All editorial content is at the discretion of the Supplement Editor
2. The briefing stage is critical – once the brief has been signed off, GSK/[the PR agency] will have no influence over content
3. The copy will receive final ABPI approval from an independent review panel appointed by The Times
4. Need to decide whether to discuss treatments in terms of class or product (must mention all brands)

Copy approval
- Copy can not leave The Times building until publication
- Representatives from GSK/[the PR agency] [an asthma charity] can preview copy on-site
  - o Overall content cannot be changed
- Final copy will be reviewed by independent Times appointed panel
  - o Professor
  - o Representative from ABPI'

This intent was echoed in notes from a second meeting between the PR agency and The Sunday Times, outlining the process and content, which stated the following:

'Implementation
- If Seretide is mentioned within the supplement, details of all competitor brands will also be mentioned. GSK/[the PR agency] must therefore establish if the supplement should discuss treatment in terms of class or product. If possible, mentioning of combination therapies would be the ideal route for the copy.
- The final supplement will receive ABPI approval by an independent review panel, appointed by the title. The appointed panel will include a Professor and a representative from the ABPI.
- Upon completion of the final copy GSK/[the PR agency]/third party group can preview the copy on-site at the titles offices, however, the copy can not leave the building until publication. *NB. At this stage of the process the overall content/angle of the supplement can not be amended but any inaccuracies or possible medicolegal problems can be amended.*

Supplement content
The title will want to ensure that the supplement is well-balanced and not overtly promotional towards Seretide. As such, clearly defined expectations should be set regarding what 'must' be included in the supplement in order to fulfil our objectives and what would be 'nice to have'.'

An Overview and Objectives document, dated 18 August, which summarised the discussions, specifically stated:

'Product positioning
In line with the ABPI, Seretide and competitor products should be mentioned in a balanced way in appropriate sections. Any competitor products mentioned in the supplement should be mentioned by generic name only. Seretide should be mentioned in association with the new landmark clinical trial data.

Within the supplement there should be **no** mention of the following:

- GOAL without a reference to Seretide (as this is required by ABPI guidance).
- Mention of other combination treatments in relation to GOAL.
- Concept of flexible dosing.
- Any Symbicort trial data.
- Any other trial data that is not strongly relevant to the story.

Considerations
- In order to proceed with the development of the supplement GSK/[the PR agency] would like to be notified of the individuals who will form the independent ABPI approval panel.
- Once the objectives and content of the supplement are agreed and put into writing, they should be adhered to by both GSK/[the PR agency] and The Sunday Times.
- As previously discussed we understand that GSK/[the PR agency] will have full control over the design and layout of the front cover.
- We would like to discuss the choice of author for the supplement.

GSK strictly adhere to the ABPI code of practice. The contents of this brief have been reviewed and

approved by GSK medical therefore we do not anticipate that the independent review panel should highlight any ABPI issues.'

GlaxoSmithKline noted that an email sent by The Sunday Times demonstrated that The Sunday Times understood that the primary intent of the asthma supplement was to inform readers about the condition, to raise awareness regarding treatment aims and to do so within the Code:

> 'The focus of the supplement is to educate and inform readers (patients and medical professionals) about what asthma is, how badly it affects lives in the UK, how asthma treatment can be improved to a level where sufferers can live symptom-free. This is due to a medical regime using Seretide, but, in accordance with the guidelines, we will not use the brand-name Seretide unless we are writing about what GOAL says about it, the rest of the time we will use generic names. I have a copy of your 'overview and objectives' document, which will be given to all writers and sub-editors, and the Glaxo team will provide the final checks, so I am confident we will meet all your objectives safely within the ABPI guidelines.'

GlaxoSmithKline submitted that this was re-iterated in the Final Brief document dated 1 September 2004. From the above it could be seen that the intent of the piece was to provide balanced information as well as setting expectations regarding improvements in asthma management. This correspondence was conducted in the context of internal GlaxoSmithKline guidance on preparation and approval of PR materials.

As agreed, GlaxoSmithKline was permitted to review the written copy at The Sunday Times offices on 7 October to check for factual inaccuracies, bearing in mind that editorial content was at the discretion of the supplement editor, and that there would be a further check for compliance with the Code by an independent ABPI review panel prior to the anticipated print date of 17 October.

GlaxoSmithKline submitted that reasonable steps were taken to ensure that all parties involved in the production of the asthma supplement understood the importance of adherence to the Code. In retrospect, however, GlaxoSmithKline acknowledged that there were several areas where it could have been more robust in its adherence to the Code and its internal guidance. Specifically [ABPI] approval should not have been delegated to The Sunday Times, and although the intent was to achieve a balanced picture of asthma and possibilities for new treatments while setting the new data from the GOAL study in context, the delegation of final responsibility did not allow GlaxoSmithKline sufficient control to be able to ensure this.

GlaxoSmithKline noted that there was an error in the briefing document where it stated that there should be no reference to GOAL without reference to Seretide. This should have read, 'no reference to Seretide without reference to GOAL.' GlaxoSmithKline acknowledged that this might have contributed to the confusion in the minds of the journalists.

Authorship of asthma supplement

All articles in the supplement were written by the authors themselves. None were ghost written by either GlaxoSmithKline or a third party, and there was no known relationship between the authors and either GlaxoSmithKline or the PR agency. The Sunday Times commissioned the authors; notes from a meeting on the 21 July stated 'The title will commission an author to develop the supplement'. In these notes, the PR agency suggested an author known to GlaxoSmithKline; however The Sunday Times was not obliged to engage this author. In fact, this author wrote two articles for the supplement neither of which mentioned Seretide, the GOAL study or any other GlaxoSmithKline medicine. The Overview of Objectives document noted that the PR agency wished to discuss the choice of author for the supplement with The Sunday Times, however the email sent by The Sunday Times confirmed that The Sunday Times made the choice of authors:

> 'The supplement will be written mainly by [a named author], he and I will choose suitably qualified journalists for the bits he can't do. They will talk to experts in medicine, asthma charities, etc, for our information. Anyone you can suggest/provide will be helpful, though I am sure [the author] has an excellent contacts book already. Though we will need your help with case studies'

Four case studies were used. The PR agency approached the individuals to ask if they would be prepared to be interviewed by The Sunday Times for an asthma supplement. If they were, then the PR agency forwarded their contact details to The Sunday Times, and took no further part in the proceedings. No copy or pictures relating to the case studies, or any other article included in the asthma supplement, were provided by either the PR agency or GlaxoSmithKline.

Pictures in asthma supplement

The image, title and subtitle for the front cover only were chosen in consultation with the PR agency, acting on behalf of GlaxoSmithKline. The front cover was reviewed by GlaxoSmithKline at The Sunday Times offices on 7 October, and considered to comply with the Code. The written copy was reviewed for factual accuracy at that time, and only factual inaccuracies were permitted to be changed by the editorial team at The Sunday Times. No images other than those on the front cover were available for review by GlaxoSmithKline at that time, and therefore, it was a matter of grave concern and disappointment to GlaxoSmithKline to discover a photograph of a Seretide Accuhaler in the supplement, that was so clearly outwith the Code. This was an unwitting error for which GlaxoSmithKline recognised its accountability.

Financing of asthma supplement

The asthma supplement was commissioned by GlaxoSmithKline, via its PR agency. Details of the costs were provided. Once GlaxoSmithKline saw the published asthma supplement, it did not proceed with the online version, or any further distribution.

Explanation of the meaning 'In association with GlaxoSmithKline'
This was considered the most appropriate term since GlaxoSmithKline had commissioned the supplement, but did not have editorial control. This term had been used for the previously referred to industry sponsored supplement, and was therefore considered acceptable.

Conclusions
GlaxoSmithKline remained fully committed to the Code and this was its overriding consideration throughout all activities associated with the production of the asthma supplement. GlaxoSmithKline submitted that reasonable steps were taken to ensure that the supplement would comply with the Code, however in retrospect it recognised that in trying to remain distant from final editorial control, and allowing third parties to undertake these activities that this was not achieved. Additionally it recognised that an error within the briefing document might have resulted in a different objective in the minds of the journalists. As such it recognised that Seretide might have been given greater prominence than intended by the journalists who authored articles according to GlaxoSmithKline's brief. GlaxoSmithKline however re-emphasised that at the point of final review it was only permitted to correct factual inaccuracies, and that no images other than the cover image were seen by GlaxoSmithKline in advance of publication.

GlaxoSmithKline recognised that the article did not achieve the desired level of balance and as such it admitted a breach of Clause 20.2 of the Code. In breaching Clause 20.2 it recognised that there was greater prominence of Seretide than intended and regretfully also admitted a breach of Clause 20.1.

Key learnings and remedial actions
GlaxoSmithKline decided to remain as 'hands off' as possible once the article had been briefed to journalists and it was anticipating that the content would, after review by GlaxoSmithKline, be checked once more for Code compliance prior to print. In reality, the error in the briefing material and the inability to finally approve the written copy left GlaxoSmithKline exposed as liable for breaches of the Code, because it did not have access to the final version of the asthma supplement. It acknowledged its responsibilities and duties in connection with this issue and had therefore investigated in detail all steps of the process and its relationship with the agency and the Sunday Times.

Summary
GlaxoSmithKline intended to commission an ethical, balanced, educational article. It played no part in the writing of the supplement, nor did it provide any photographs or visual materials. Editorial control was completely in the hands of The Sunday Times. GlaxoSmithKline attempted to ensure that appropriate control and sign off would occur at each stage of development. The initial expectation of an independent approval panel (provided by The Sunday Times) did not materialise. By respecting journalistic independence (insisted upon by The Sunday Times) GlaxoSmithKline ultimately had limited power to amend copy apart from factual inaccuracy, and was not given the opportunity to approve the full and complete final version. GlaxoSmithKline saw the final supplement when it was too late to stop distribution. Unintentionally the item had a promotional appearance. GlaxoSmithKline accepted that the final version was in breach of Clauses 20.1 and 20.2. This was not the intention. GlaxoSmithKline accepted its responsibility in commissioning this supplement and had undertaken an appropriate internal investigation and review.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes. In the case of sponsored material aimed at the general public consideration would also have to be given to the requirements of Clause 20.

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

The supplement in question had been sponsored by GlaxoSmithKline. The supplement had been initiated by the company which had provided detailed direction as to the subject area to be covered as well as what was not to be covered. A copy of GlaxoSmithKline's overview and objectives document was given to all writers and sub-editors. GlaxoSmithKline had planned to distribute further copies of the supplement but once seeing the final item had decided not to proceed.

The Panel considered that GlaxoSmithKline was inextricably linked to the content of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation and content of the supplement. The Panel considered that GlaxoSmithKline was responsible for the content of the supplement in relation to compliance with the Code.

The Panel noted the summaries of discussions between GlaxoSmithKline's agency and The Sunday Times and considered that the discussions and approach were not consistent with the requirements

of either Clause 20.1 or Clause 20.2 that material for the general public must not promote a specific medicine and must be balanced. The Panel noted that the outline of process and content document dated 21 July stated that the objective of the supplement was to provide a guaranteed communications platform from which to disseminate key Seretide/GOAL messages following publication of the [GOAL] data to consumers and health professionals. The supplement focussed on combination therapy but mention of competitor products was by generic name and there had to be no mention of flexible dosing which was a feature of AstraZeneca's combination product Symbicort (formeterol/budesonide) or Symbicort trial data.

The supplement discussed the GOAL study; Seretide was mentioned. One case study headed 'Free to play netball' highlighted the effect of Seretide on a young patient's life and included a photograph of her holding a Seretide inhaler.

The Panel considered that the photograph of the patient with the Seretide inhaler in the supplement together with the content of the supplement meant that it was an advertisement for a prescription only medicine to the public. The Panel ruled a breach of Clause 20.1 of the Code as acknowledged by GlaxoSmithKline.

The Panel did not consider that the supplement presented the information in a balanced way and it would encourage members of the public to ask their doctor to prescribe a specific medicine. Thus the Panel ruled a breach of Clause 20.2 of the Code as acknowledged by GlaxoSmithKline.

Complaint received **27 October 2004**

Case completed **24 December 2004**

CODE OF PRACTICE REVIEW – FEBRUARY 2005

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1557/2/04	**Pierre Fabre/Director v Aventis Pharma**	**Breach of undertaking**	**Breaches Clauses 2, 3.2, 9.1 and 22**	**Report from Panel to Appeal Board** **Report to ABPI Board**	**Page 3**
1593/6/04	**Novo Nordisk v Aventis Pharma**	**Lantus leavepieces**	**Seven breaches Clause 7.2 Two breaches Clause 7.3 Four breaches Clause 7.4 Two breaches Clause 7.8**	**Appeal by respondent**	**Page 7**
1597/6/04	**General Practitioner v GlaxoSmithKline**	**Patient review services**	**Breaches Clauses 9.1 and 18.1**	**No appeal**	**Page 19**
1604/7/04	**Voluntary admission by Takeda**	**Hospitality for health professionals**	**Two breaches Clause 2 Three breaches Clause 9.1 Three breaches Clause 19.1** **Audit required by Appeal Board** **Further audit in July 2005 required by Appeal Board**	**Report from Panel to Appeal Board**	**Page 25**
1606/7/04	General Practitioner/Director v Wyeth	Alleged breach of undertaking	No breach	No appeal	Page 31
1607/7/04	**General Practitioner v GlaxoSmithKline**	**Airways Integrated Management Service**	**Breaches Clauses 9.2 and 18.1**	**No appeal**	**Page 35**
1608/7/04	**Roche v Novartis**	**Promotion of Zometa**	**Two breaches Clause 7.2**	**No appeal**	**Page 38**
1610/7/04	**Primary Care Trust Advisor v Roche**	**Letter about Xenical sent to patients**	**Breaches Clauses 9.1, 20.1 and 20.2**	**Report from Panel to Appeal Board**	**Page 44**
1616/8/04	**Roche/Director v Schering-Plough**	**ViraferonPeg and Rebetol leavepieces**	**Three breaches Clause 7.2 Breach Clause 7.4 Two breaches Clause 7.10**	**No appeal**	**Page 47**
1618/8/04	**Consultant Dermatologist v Serono**	**Efalizumab advisory board**	**Breaches Clauses 3.1 and 18.1**	**No appeal**	**Page 56**
1619/8/04	**Novo Nordisk v Aventis Pharma**	**Arrangements for insulin Meeting**	**Breach Clause 19.1**	**Appeal by complainant**	**Page 59**
1620/8/04	**Servier v GlaxoSmithKline**	**Avandamet leavepiece**	**Two breaches Clause 7.2**	**Appeal by respondent**	**Page 63**

1623/8/04 & 1624/8/04	**Lilly v Bristol-Myers Squibb and Otsuka**	**Promotion of Abilify**	**Three breaches Clause 3.2 Breach Clause 7.2 Two breaches Clause 7.9**	**No appeal**	**Page 71**
1627/8/04	**Primary Care NHS Trust Prescribing Adviser v GlaxoSmithKline**	**'Dear Healthcare Professional' letter about Avandia**	**Two breaches Clauses 7.2**	**No appeal**	**Page 78**
1630/9/04	**Primary Care Trust Pharmacist v AstraZeneca**	**Nexium cost comparison chart**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 80**
1631/9/04	**Consultant Anaesthetist v Roche**	**Conduct of representative**	**Breach Clause 15.2**	**No appeal**	**Page 82**
1632/9/04	**Novo Nordisk v Aventis Pharma**	**Lantus folder**	**Breaches Clauses 7.2 and 7.9**	**Appeal by complainant**	**Page 84**
1633/9/04	**Merck Sharp & Dohme v GlaxoSmithKline**	**Promotion of Imigran Radis**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Two breaches Clause 7.10**	**No appeal**	**Page 89**
1636/10/04	Ivax v Procter & Gamble	Asacol letter referring to Code of Practice ruling	No breach	No appeal	Page 91
1639/10/04	**Primary Care Prescribing Group v Pfizer**	**Cardura XL information sheet**	**Two breaches Clause 7.2 Two breaches Clause 7.4**	**No appeal**	**Page 94**
1640/10/04	Primary Care Trust Pharmaceutical Adviser v Amdipharm	Gift of memory stick	No breach	No appeal	Page 96
1642/10/04	Hospital Clinical Pharmacist v Aventis Pharma	'Dear Healthcare Professional' letter about Clexane	No breach	No appeal	Page 97
1643/10/04	**General Practitioner v Pfizer**	**Envelope for Celebrex mailing**	**Breach Clause 10.1**	**No appeal**	**Page 100**
1644/10/04	**General Practitioner v GlaxoSmithKline**	**Sunday Times Asthma supplement**	**Breaches Clauses 20.1 and 20.2**	**No appeal**	**Page 102**

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 sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, 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).

February 2005